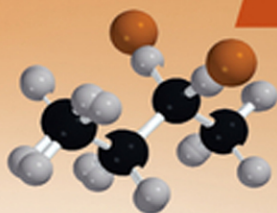
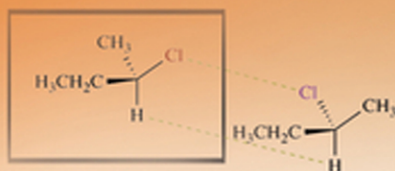


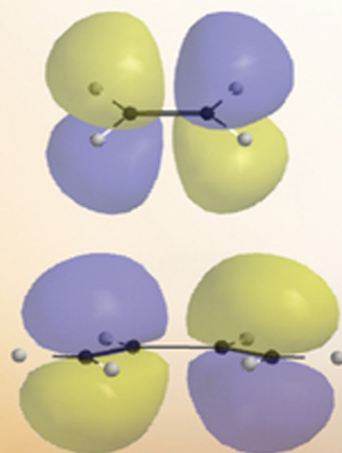
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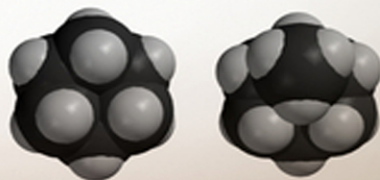
March's Advanced Organic Chemistry



Reactions, Mechanisms, and Structure



Michael B. Smith



WILEY

**MARCH'S ADVANCED
ORGANIC CHEMISTRY**

MARCH'S ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

SEVENTH EDITION

Michael B. Smith
Professor of Chemistry

WILEY

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PREFACE

This seventh edition of *March's Advanced Organic Chemistry* has been thoroughly updated to include new advances in areas of Organic chemistry published between 2005 and 2010. Every topic retained from the sixth edition has been brought up to date if there was activity in that area during that five year period. Changes also include a significant rewrite of most of the book. More than 5500 new references have been added for work published since 2005. As with the sixth edition, many older references were deleted to make room for new ones, and in cases where a series of papers by the same principal author were cited, all but the most recent were deleted. The older citations are usually found by referring to the more recent publication(s). Many of the figures relating to molecular orbitals dated to the 1960s. In all cases possible, they have been replaced by molecular orbitals drawings using Spartan software from Wavefunction, Inc. The fundamental structure of the seventh edition is essentially the same as that of all previous ones.

The goal, as in previous editions is to give equal weight to the three fundamental aspects of the study of organic chemistry: reactions, mechanisms, and structure. A student who has completed a course based on this book should be able to approach the literature directly, with a sound knowledge of modern organic chemistry. Major special areas of organic chemistry: terpenes, carbohydrates, proteins, many organometallic reagents, combinatorial chemistry, polymerization and electrochemical reactions, steroids, and so on, have been treated lightly or ignored completely. The use of this book in the first year of graduate study should help master the fundamentals. It is hoped that this book will lead a student to consult the many excellent books and review articles cited for various topics in order to understand the subject in more detail. Indeed, many of these topics are so vast, they cannot be explained completely in this book.

The organization is based on reaction types, and a relatively few principles suffice to explain nearly all of them despite the large number of organic reactions. Accordingly, the reactions-mechanisms section of this book (Part II) is divided into 10 chapters (10–19), each concerned with a different type of reaction. In the first part of each chapter, the appropriate basic mechanisms are discussed along with considerations of reactivity and orientation, while the second part consists of numbered sections devoted to individual reactions, where the scope and the mechanism of each reaction are discussed. Numbered sections are used for the reactions and are set in boldface. Since the methods for the preparation of individual classes of compounds (ketones, nitriles, etc.) are not treated all in one place, an updated and revised index has been provided (Appendix B) by use of which the synthesis of a given type of compound will be found. It is important to note that the numbers for each reaction in the 7th edition are *different* from editions 1–5 in many cases, but are the same as found in the 6th edition. For this reason, a correlation table is included at the end of this Preface that directly correlates the sections found in the 5th edition with the new ones in both the 6th and 7th editions.

The structure of organic compounds is discussed in Chapters 1–5 (Part I). This section provides a necessary background for understanding mechanisms and is also important in its own right. The discussion begins with chemical bonding (Chapt. 1) and ends with a chapter on stereochemistry (Chapt. 4). Two chapters follow (Chapt 6–7) on reaction mechanisms in general, one for ordinary reactions and the other for photochemical reactions. Part 1 concludes with two more chapters (Chapt 8 and 9) that give further background to the study of mechanisms.

The IUPAC names for many organic transformations are included, first introduced in the 3rd edition. Since then the rules have been broadened to cover additional cases; hence more such names are given in this edition. Furthermore, International Union of Pure and Applied Chemistry (IUPAC) has now published a system for designating reaction mechanisms, and some of the simpler designations are included.

Appendix A is devoted to the literature of organic chemistry.

In treating subjects as broad as structure, reactions, and mechanisms of organic chemistry, it is impossible to cover each topic in great depth, and this would not be desirable even if possible. This book is intended to point the reader to the primary literature of the areas it covers. To this end, there are >20,000 references to original papers. Secondary literature sources including reviews, books, and monographs have been included as well. Appendix A provides a brief introduction to using computer-based search engines (e.g., *Reaxys*[®] and *SciFinder*[®]).

Although basically designed as a reference text for a one-year course on the graduate level, this book can also be used in advanced undergraduate courses, but only after completion of a one-year course in organic chemistry. A one year course in both inorganic and physical chemistry would be most helpful. It has been my experience that students who have completed the first-year courses often have a hazy recollection of the material and greatly profit from a representation of the material if it is easily accessible. The material in the first nine chapters, particularly Chapters 1, 2, 4, 6, and 8 may be helpful for reviewing such material when this book is used in connection with a course.

This book is probably most valuable as a reasonably up-to-date reference work. Students preparing for qualifying examinations and practicing organic chemists will find that Part II contains a survey of what is known about the mechanism and scope of a large number of reactions, arranged in an orderly manner based on reaction type and on which bonds are broken and formed.

For units of energy, IUPAC mandates joules, and many journals do use this unit exclusively. However, organic chemists who publish in United States journals commonly use calories. Virtually all energy values are presented in both calories and joules. Although IUPAC does not recommend angstrom units for bond distances, but rather picometers (pm), a vast number of bond distances published in the literature are in angstrom units, and this book therefore uses angstrom units.

I would like to acknowledge the contributions of those chemists cited and thanked by Professor March in the first-four editions, and those I thanked in the 5th and 6th editions. This book would not be possible without their contributions. For the 7th edition, I thank Lou Allinger for pointing out the deficiencies in the hyperconjugation section, and graciously helping me write the new section appearing in this new edition. I thank Warren Hehre for his invaluable help in calculating and presenting the molecular orbital drawings using Spartan. I also thank Adrian Shell (Elsevier) for facilitating the transfer of material relating to the program *Reaxys*, discussed in Appendix A. I thank the many people who have contributed comments or have pointed out errors in the 6th edition that were

invaluable to putting together the 7th edition. I thank Warren Hehre and Sean Ohlinger of Wavefunction, Inc., Irvine, CA (www.wavefun.com) for providing Spartan 10 Macintosh (v. 1.0.1), allowing the incorporation of Spartan models for selected molecules and intermediates. All structures and line drawings in this book were done using ChemDraw[®] Ultra 11.0.1 (350440), graciously provided by CambridgeSoft Corporation, Cambridge, MA (www.cambridgesoft.com).

Special thanks are due to the Interscience division of John Wiley & Sons and to Jonathan Rose. Special thanks are also given to Kristen Parrish and Amanda Amanullah, at Wiley for their fine work as editors in turning the manuscript into the finished book as well as Sanchari Sil of Thomson Digital. I also thank Jeanette Stiefel for an excellent job of copy editing the manuscript.

With gratitude, I acknowledge the work of Jerry March, upon whose work this new edition is built, and who is responsible for the concept of this book and for carrying it through four very successful editions. I used Jerry's book as a student and it is an honor to continue this tradition.

I encourage those who read and use the 7th edition to contact me directly with comments, errors, and with publications that might be appropriate for future editions. I hope that this new edition will due justice to the tradition that Professor March began with the first edition.

My Email address is
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Finally, I want to thank my wife Sarah for her patience and understanding during the preparation of this manuscript. I also thank my son Steven for his support. Without their support, this work would not have been possible.

MICHAEL B. SMITH
May, 2012

Correlation Table
5th edition → 7th edition Reactions

10-1 → 10-1	10-18 → 10-14	10-35 → 16-68
10-2 → 10-2	10-19 → 10-15	10-36 → 10-24
10-3 → 10-3	10-20 → 10-16	10-37 → 10-25
10-4 → 10-4	10-21 → 16-61	10-38 → 10-26
10-5 → 10-5	10-22 → 16-62	10-39 → 16-69
10-6 → 10-6	10-23 → 16-63	10-40 → 10-27
10-7 → 10-7	10-24 → 16-64	10-41 → 10-28
10-8 → 16-57	10-25 → 16-65	10-42 → 10-29
10-9 → 16-58	10-26 → 10-17	10-43 → 10-30
10-10 → 16-59	10-27 → 10-18	10-44 → 10-31
10-11 → 16-60	10-28 → 10-19	10-46 → 10-32
10-12 → 10-8	10-29 → 16-66	10-47 → 10-33
10-13 → 10-9	10-30 → 16-67	10-48 → 16-70
10-14 → 10-10	10-31 → 10-20	10-49 → 10-34
10-15 → 10-11	10-32 → 10-21	10-50 → 10-35
10-16 → 10-12	10-33 → 10-22	10-51 → 10-37
10-17 → 10-13	10-34 → 10-23	10-52 → 10-38

10-53 → 10-39	10-101 → 10-64	11-18 - deleted
10-54 → 10-40	10-102 → 10-65	11-19 → 11-19
10-55 → 16-72	10-103 → 10-66	11-20 → 11-20
10-56 → 16-73	10-104 → 10-67	11-21 → 11-21
10-57 → 16-74	10-105 → 10-68	11-22 → 11-12
10-58 → 16-75	10-106 → 10-70	11-23 → 11-13
10-59 → 16-76	10-107 → 10-71	11-24 → 11-14
10-60 → 16-77	10-108 → 10-72	11-25 → 11-22
10-61 → 10-41	10-109 → 10-73	11-26 → 11-23
10-62 → 10-42	10-110 → 10-74	11-27 → 11-24
10-63 → 10-36	10-111 → 10-75	11-28 → 11-25
10-64 → 10-42	10-112 → 10-76	11-29 → 11-26
10-65 → 10-43	10-113 → 10-77	11-30 → 11-27
10-66 → 10-44	10-114 → 16-81	11-31 → 11-28
10-67 → 10-45	10-115 → 16-82	11-32 → 11-29
10-68 → 10-46	10-116 → 16-83	11-33 → 11-30
10-69 → 10-47	10-117 → 16-84	11-34 → 11-31
10-70 → 10-48	10-118 → 16-85	11-35 → 11-32
10-71 → 10-49	10-119 → 16-86	11-36 → 11-33
10-72 → 10-50	10-120 → 16-87	11-37 → 11-34
10-73 → 10-51	10-121 → 16-88	11-38 → 11-35
10-74 → 10-52	10-122 → 16-89	11-39 → 11-36
10-75 → 10-53	10-123 → 16-90	11-40 → 11-37
10-76 → 10-54	10-124 → 16-100	11-41 → 11-38
10-77 → 16-79	10-125 → 16-101	11-42 → 11-39
10-78 → 16-80	10-126 → 16-102	11-43 → 11-40
10-79 → 19-53	10-127 → 16-103	11-44 → 11-41
10-80 → 19-57	10-128 → 16-104	
10-81 → 19-54	10-129 → 16-105	
10-82 → 19-58		12-1 → 12-1
10-83 → 19-66	11-1 → 11-1	12-2 → 12-2
10-84 → 19-56	11-2 → 11-2	12-3 → 12-3
10-85 → 19-35	11-3 → 11-3	12-4 → 12-4
10-86 → 19-59	11-4 → 11-4	12-5 → 12-5
10-87 → 19-67	11-5 → 11-5	12-6 → 12-6
10-88 → 19-70	11-6 → 11-6	12-7 → 12-7
10-89 → 19-39	11-7 → 11-7	12-8 → 12-8
10-90 → 19-40	11-8 → 11-8	12-9 → 12-10
10-91 → 19-41	11-9	12-10 → 12-11
10-92 → 10-55	11-10 → 11-9	12-11 → 12-12
10-93 → 10-56	11-11 → 11-10	12-12 → 12-13
10-94 → 10-57	11-12 → 11-11	12-13 → 12-14
10-95 → 10-58	11-13 → 11-15	12-14 → 12-16
10-96 → 10-59	11-14 → 11-17	12-15 → 12-18
10-98 → 10-61	11-15 → 11-18	12-16 → 12-19
10-99 → 10-63	11-16 - deleted	12-17 → 12-20
10-100 → 10-60	11-17 - deleted	12-18 → 10-69
		12-19 → 12-21

12-20 → 12-22
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 12-34 → 12-37
 12-35 deleted
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 12-52 → 12-52
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13-1 → 13-1
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 13-7 → 13-7
 13-8 → 19-55
 13-9 deleted
 13-10 → 13-8
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13-14 → 13-11
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15-1 → 15-1
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 15-62 → 15-64
 15-63 → 15-65
 15-64 → 15-66

16-1 → 16-1
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16-27 → 16-24
 16-28 → 16-25
 16-29 → 16-26
 16-30 → 16-27
 16-31 → 16-28
 16-32 → 16-29
 16-33 deleted
 combined
 with 10-115
 16-34 → 16-30
 16-35 → 16-31
 16-36 → 16-32
 16-37 → 16-33
 16-38 → 16-34
 16-39 → 16-35
 16-40 → 16-36
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 16-57 → 16-6
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 16-60 → 16-94
 16-61 → 16-46
 16-62 → 16-48
 16-63 → 16-95
 16-64 → 16-96
 16-65 → 16-97
 16-66 → 16-98
 16-67 → 16-99

17-1 → 17-1
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 17-14 → 17-15
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 17-20 → 17-20
 17-21 → 17-21
 17-22 → 17-22
 17-23 → 17-23
 17-24 → 17-24
 17-25 → 17-25
 17-26 deleted
 combined
 with 17-25
 17-27 → 17-26
 17-28 → 17-27
 17-29 → 17-28
 17-30 → 17-29
 17-31 deleted
 combined
 with 17-30
 17-32 → 17-30
 17-33 → 17-31
 17-34 → 17-32
 17-35 → 17-33
 17-36 → 17-34
 17-37 → 17-35
 17-38 → 17-36
 17-39 → 17-37
 17-40 → 17-38

18-1 → 18-1
 18-2 → 18-2
 18-3 → 18-3
 18-4 → 18-4
 18-5 → 18-5

18-6 → 18-6	18-43 → 18-43	19-32 → 19-34
18-7 → 18-7	18-44 → 18-44	19-33 → 19-61
18-8 → 18-8		19-34 → 19-37
18-9 → 18-9	19-1 → 19-1	19-35 → 19-64
18-10 → 18-10	19-2 → 19-2	19-36 → 19-62
18-11 → 18-11	19-3 → 19-3	19-37 → 19-63
18-12 → 18-12	19-4 → 19-4	19-38 → 19-38
18-13 → 18-13	19-5 → 19-5	19-39 → 19-65
18-14 → 18-14	19-6 → 19-6	19-40 deleted
18-15 → 18-15	19-7 → 19-7	incorporated
18-16 → 18-16	19-8 → 19-8	into 10-85
18-17 → 18-17	19-9 → 19-9	19-41 → 19-45
18-18 → 18-18	19-10 → 19-10	19-42 → 19-46
18-19 → 18-19	19-11 → 19-11	19-43 → 19-47
18-20 → 18-20	19-12 → 19-12	19-44 → 19-48
18-21 → 18-21	19-13 → 19-13	19-45 → 19-50
18-22 → 18-22	19-14 → 19-17	19-46 → 19-51
18-23 → 18-23	19-15 → 19-15	19-47 → 19-71
18-24 → 18-24	19-16 → 19-18	19-48 → 19-68
18-25 → 18-25	19-17 deleted	19-49 → 19-72
18-26 → 18-26	incorporated	19-50 → 19-60
18-27 → 18-27	in 19-14	19-51 → 19-49
18-28 → 18-28	19-18 → 19-19	19-52 → 19-73
18-29 → 18-29	19-19 → 19-20	19-53 → 19-74
18-30 → 18-30	19-20 → 19-21	19-54 → 19-75
18-31 → 18-31	19-21 → 19-22	19-55 → 19-76
18-32 → 18-32	19-22 → 19-25	19-56 → 19-77
18-33 → 18-33	19-23 → 19-27	19-57 → 19-78
18-34 → 18-34	19-24 → 19-28	19-58 → 19-79
18-35 → 18-35	19-25 → 19-30	19-59 → 19-80
18-36 → 18-36	19-26 → 19-26	19-60 → 19-81
18-37 → 18-37	19-27 → 19-29	19-61 → 19-82
18-38 → 18-38	19-28 → 19-31	19-62 → 19-83
18-39 → 18-39	19-29 → 19-24	19-63 → 19-84
18-40 → 18-40	19-30 → 19-32	
18-42 → 18-42	19-31 → 19-33	

COMMON ABBREVIATIONS

Other, less common abbreviations are given in the text when the term is used.

Ac
acac
AIBN
aq
ARC
Ax

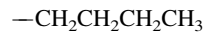
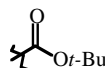
Acetyl
Acetylacetonate (ligand)
Azobisisobutyronitrile
Aqueous
Anion relay chemistry
Axial
9-Borabicyclo[3.3.1]nonylboryl



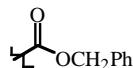
9-BBN 9-Borabicyclo[3.3.1]nonane
BDE Bond dissociation energy
BER Borohydride exchange resin
BINAP (2*R*,3*S*)-2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl
BINOL 1,1'-Bi-2-naphthol
BMS Borane methyl sulfide
Bn Benzyl




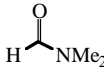
Boc *tert*-Butoxycarbonyl
Bpy (Bipy) 2,2'-Bipyridyl
BSA *N*-*O*-Bis(trimethylsilyl)acetamide
Bu *n*-Butyl
Bs Brosylate, *O*-(4-Bromophenyl) sulfenate
Bz Benzoyl
CAN Ceric ammonium nitrate
cat Catalytic






Cbz *N*-Carbobenzyloxy
CD Circular dichroism
Chap Chapter(s)
Chirald (2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methylbutan-2-ol
CIDNIP Chemically induced dynamic nuclear polarization
CIP Cahn-Ingold-Prelog
CNDO Complete Neglect of Differential Overlap
cod 1,5-Cyclooctadienyl (ligand)



xxii COMMON ABBREVIATIONS

cot	1,3,5-Cyclooctatrienyl (ligand)	
Cp	Cyclopentadienyl	
Cy	Cyclohexyl	
°C	Temperature in degrees Celcius	
3D	Three dimensional	
DABCO	1,4-Diazabicyclo[2.2.2]octane	
DAST	Diethylammoniumsulfur trifluoride	Et ₂ NSF ₃
dba	Dibenzylidene acetone	
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene	
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	
DCC	1,3-Dicyclohexylcarbodiimide	<i>c</i> -C ₆ H ₁₁ —N=C=N— <i>c</i> -C ₆ H ₁₁
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	
DDT	1,1,1-Trichloro-2,2'-bis(<i>p</i> -chlorophenyl)ethane	
DEA	Diethylamine	HN(CH ₂ CH ₃) ₂
DEAD	Diethylazodicarboxylate	EtO ₂ C—N=NCO ₂ Et
DHAD	Dihydroquinidine	
DHU	Dicyclohexylurea	
DIAD	Diisopropylazodicarboxylate	
Dibal-H	Diisobutylaluminum hydride	(Me ₂ CHCH ₂) ₂ AlH
DMA	Dimethylacetamide	
DMAP	4-Dimethylaminopyridine	
DME	Dimethoxyethane	MeOCH ₂ CH ₂ OMe
DMEAD	Di-2-methoxyethyl azodicarboxylate	
DMF	<i>N,N'</i> -Dimethylformamide	
DMS	Dimethyl sulfide	
DMSO	Dimethyl sulfoxide (ligand)	
DNA	Deoxyribonucleic acid	
DOSY	Diffusion-ordered NMR Spectroscopy	
dppb	1,4-Bis-(Diphenylphosphino) butane	Ph ₂ P(CH ₂) ₄ PPh ₂
dppe	1,2-Bis-(Diphenylphosphino)ethane; see also Diphos	Ph ₂ PCH ₂ CH ₂ PPh ₂
dppf	Bis(Diphenylphosphino)ferrocene	
dpm	1,1-Bis(diphenylphosphino)methane	
dppp	1,3-Bis(Diphenylphosphino)propane	Ph ₂ P(CH ₂) ₃ PPh ₂
e [−]	Transfer of electrons	
% ee	% Enantiomeric excess	
EE	1-Ethoxyethoxy	EtO(Me)CH— —CH ₂ CH ₃
Et	Ethyl	
EDA	Electron donor–acceptor orbital	
EDTA	Ethylenediaminetetraacetic acid	
Equiv	Equivalent(s)	
EPR	Electron paramagnetic resonance spectroscopy	
ESR	Electron spin resonance spectroscopy	
FMO	Frontier molecular orbital	
FVP	Flash vacuum pyrolysis	
GC	Gas chromatography	
h	Hour (hours)	
<i>hν</i>	Irradiation with light	
HF	Hartree–Fock	

HMO	Hückel molecular orbital	
HMPA	Hexamethylphosphoramide	$(\text{Me}_2\text{N})_3\text{P}=\text{O}$
HMPT	Hexamethylphosphorus triamide	$(\text{Me}_2\text{N})_3\text{P}$
^1H NMR	Proton nuclear magnetic resonance spectroscopy	
HOMO	Highest occupied molecular orbital	
HPLC	High-performance liquid chromatography	
HSAB	Hard–Soft Acid–Base	
IBX	<i>o</i> -Iodoxybenzoic acid	
<i>i</i> -Pr	Isopropyl	$-\text{CH}(\text{Me})_2$
IR	Infrared spectroscopy	
IUPAC	International Union of Pure and Applied Chemistry	
ISC	Intersystem crossing	
LCAO	Linear combination of atomic orbitals	
LICA	Lithium <i>N</i> -isopropyl- <i>N</i> -cyclohexylamide	
(LIPCA)		
LDA	Lithium diisopropylamide	$\text{LiN}(\textit{i}\text{-Pr})_2$
LHMDS	Lithium hexamethyl disilazide	$\text{LiN}(\text{SiMe}_3)_2$
LTMP	Lithium 2,2,6,6-tetramethylpiperidide	
LUMO	Lowest unoccupied molecular orbital	
Mcpba	<i>m</i> -Chloroperoxybenzoic acid	
Me	Methyl	$-\text{CH}_3$ or Me
MEM	β -Methoxyethoxymethyl	$\text{MeOCH}_2\text{CH}_2\text{OCH}_2-$
Mes	Mesityl	2,4,6-tri-Me- C_6H_2
min	minutes	
MMPP	Magnesium monoperoxyphthalate	
MO	Molecular Orbital	
MOM	Methoxymethyl	MeOCH_2-
Ms	Methanesulfonyl	MeSO_2-
MTO	Methyl trioxorhenium	
NBS	<i>N</i> -Bromosuccinimide	
NCS	<i>N</i> -Chlorosuccinimide	
NHS	<i>N</i> -Hydroxysuccinimide	
NIS	<i>N</i> -Iodosuccinimide	
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide	
NMP	<i>N</i> -Methylpyrrolidinone	
NMR	Nuclear magnetic resonance	
NOESY	Nuclear overhauser effect spectroscopy	
NOE	Nuclear overhauser effect	
Nu (Nuc)	Nucleophile	
OBs	<i>O</i> -(4-Bromophenyl)sulfinate	
Oxone [®]	2 $\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$	
	Polymeric backbone	
PCC	Pyridinium chlorochromate	
PDC	Pyridinium dichromate	
PEG	Polyethylene glycol	
PES	Photoelectron spectroscopy	
Ph	Phenyl	
PhH	Benzene	
PhMe	Toluene	

PIFA	Phenyliodine (III)-bis-(trifluoroacetate)	
PPHF	Pyridinium poly(hydrogen fluoride)	
PMHS	Polymethylhydrosiloxane	
Pr	<i>n</i> -Propyl	$-\text{CH}_2\text{CH}_2\text{CH}_3$
Py	Pyridine	
Quant	Quantitative yield	
Red-Al	$[(\text{MeOCH}_2\text{CH}_2\text{O})_2\text{AlH}_2]\text{Na}$	
ROESY	Rotating-frame NOE spectroscopy	
rt	Room temperature	
<i>s</i> BuLi	<i>sec</i> -Butyllithium	$\text{CH}_3\text{CH}_2\text{CH}(\text{Li})\text{CH}_3$
s	seconds	
salen	Bis (salicylidene) ethylenediamine	
sc CO ₂	supercritical CO ₂	
SCF	self-consistent field	
SDS	Sodium dodecyl sulfate	
Sec.	Section(s)	
SET	Single electron transfer	
Siamyl		
(Sia) ₂ BH	Disiamylborane <i>sec</i> -Isoamyl	
SOMO	Singly occupied molecular orbital	
Tr	Tritium	
TBAF	Tetrabutylammonium fluoride	$n\text{-Bu}_4\text{N}^+ \text{F}^-$
<i>t</i> -Bu	<i>tert</i> -Butyl	$-\text{CMe}_3$
TEAB	Tetraethylammonium bromide	
TEBA	Triethylbenzylammonium	$\text{Bn}(\text{Et}_3)_3\text{N}^+$
TED	Tetraethylenediamine	
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy free radical	
TFA	Trifluoroacetic acid (solvent)	CF_3COOH
tfa	Trifluoroacetic acid (ligand)	$(\text{CF}_3\text{CO})_2\text{O}$
Tf (OTf)	Triflate	$-\text{SO}_2\text{CF}_3$ ($-\text{OSO}_2\text{CF}_3$)
THF	Tetrahydrofuran (solvent)	
THP	Tetrahydropyran	
TMEDA	Tetramethylethylenediamine	$\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$
TMS	Trimethylsilyl or tetramethylsilane	$-\text{Si}(\text{CH}_3)_3$
Tol	Tolyl	$4\text{-(Me)C}_6\text{H}_4$
TOSMIC	Toluenesulfonylmethyl isocyanide	
TPAP	Tetrapropylammonium perruthenate	$\text{Pr}_4\text{N}^+ \text{RuO}_4^-$
TPP	Triphenylphosphine (solvent)	
tpp	Triphenylphosphine (ligand)	pPh_3
Ts(Tos)	Tosyl = <i>p</i> -Toluenesulfonyl	$4\text{-(Me)C}_6\text{H}_4\text{SO}_2$
UV	Ultraviolet spectroscopy	
VCD	Vibrational circular dichroism	
VDW	van der Waals	
vis	Visible	
XPS	X-ray photoelectron spectroscopy	

BIOGRAPHICAL STATEMENT

Professor Michael B. Smith was born in Detroit, Michigan in 1946. In 1957, he and his family moved to Madison Heights, Virginia. After graduation from Amherst County high school, he entered Ferrum Jr. College and graduated with an A.A. Professor Smith transferred to Virginia Polytechnic Institute (Virginia Tech), where he did undergraduate research with Professor Harold Bell, and graduated with a B.S in chemistry in 1969. After working as an analytical chemist at the Newport News Shipbuilding and Dry Dock Co. (Tenneco) in Newport News, Virginia for three years, he began graduate studies at Purdue University under the mentorship of Professor Joseph Wolinsky. Professor Smith graduated with a Ph.D. in Organic chemistry in 1977. He spent one year as a faculty research associate at the Arizona State University in the Cancer Research Institute, directed by Professor George R. Pettit, and a second year doing postdoctoral work at the Massachusetts Institute of Technology under the mentorship of Professor Sidney Hecht. In 1979 he began his independent academic career, where he now holds the rank of full professor.

Professor Smith is the author of approximately 90 independent research articles, and 20 published books. The books include the 5th and 6th edition of *March's Advanced Organic Chemistry* (Wiley), volumes 6–12 of the *Compendium of Organic Synthetic Methods* (Wiley), *Organic Chemistry a Two Semester Course* (HarperCollins) into its 2nd edition, and *Organic Synthesis* (Elsevier) in its 3rd edition. A new undergraduate organic chemistry book, *Organic Chemistry: An Acid-Base Approach*, was published in 2011 by the CRC Press.

Professor Smith's current research involves the synthesis and structural verification of lipids obtained from the dental pathogen *Porphyromonas gingivalis*, which show inflammatory activity, induce bone degeneration and are involved in triggering multiple sclerosis. A main area of research is the synthesis of fluorescent dye-heterocyclic conjugates that target hypoxic cancerous tumors, allowing non-invasive fluorescence imaging in the near IR. The synthesis of anti-cancer alkaloids is also ongoing.

INTRODUCTION

This book contains 19 chapters. Chapters 1–9 may be thought of as an introduction to Part II. The first-five chapters deal with the structure of organic compounds. These chapters discuss the kinds of bonding important in organic chemistry, the fundamental principles of conformation and stereochemistry of organic molecules, and reactive intermediates in organic chemistry. Chapters 6–9 are concerned with general principles of mechanism in organic chemistry, including acids and bases, photochemistry, sonochemistry and microwave irradiation, and finally the relationship between structure and reactivity.

Chapters 10–19, which make up Part II, are directly concerned with the nature and the scope of organic reactions and their mechanisms.

Localized Chemical Bonding

Localized chemical bonding may be defined as bonding in which the electrons are shared by two and only two nuclei. Such bonding is the essential feature associated with the structure of organic molecules.¹ Chapter 2 will discuss *delocalized bonding*, in which electrons are shared by more than two nuclei.

1.A. COVALENT BONDING²

Wave mechanics is based on the fundamental principle that electrons behave as waves (e.g., they can be diffracted). Consequently, a wave equation can be written for electrons, in the same sense that light waves, sound waves, and so on, can be described by wave equations. The equation that serves as a mathematical model for electrons is known as the *Schrödinger equation*, which for a one-electron system is

$$\frac{\delta^2\psi}{\delta x^2} + \frac{\delta^2\psi}{\delta y^2} + \frac{\delta^2\psi}{\delta z^2} + \frac{8\pi^2m}{h^2}(E - V)\psi = 0$$

where m is the mass of the electron, E is its total energy, V is its potential energy, and h is Planck's constant. In physical terms, the function (Ψ) expresses the square root of the probability of finding the electron at any position defined by the coordinates x , y , and z , where the origin is at the nucleus. For systems containing more than one electron, the equation is similar, but more complicated.

The Schrödinger equation is a differential equation, so solutions to it are themselves equations, but the solutions are not differential equations. They are just simple equations for which graphs can be drawn. Such graphs are essentially three-dimensional (3D)

¹ See Hoffmann, R.; Schleyer, P.v.R.; Schaefer, III, H.F. *Angew. Chem. Int. Ed. (Engl.)* **2008**, 47, 7164.

² This treatment of orbitals is simplified by necessity. For more detailed treatments of orbital theory, as applied to organic chemistry, see Matthews, P.S.C. *Quantum Chemistry of Atoms and Molecules*, Cambridge University Press, Cambridge, **1986**; Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, **1985**; Albright, T.A.; Burdett, J.K.; Whangbo, M. *Orbital Interactions in Chemistry*, Wiley, NY, **1985**; MacWeeny, R.M. *Coulson's Valence*, Oxford University Press, Oxford, **1980**; Murrell, J.N.; Kettle, S.F.A.; Tedder, J.M. *The Chemical Bond*, Wiley, NY, **1978**; Dewar, M.J.S.; Dougherty, R.C. *The PMO Theory of Organic Chemistry*, Plenum, NY, **1975**; Zimmerman, H.E. *Quantum Mechanics for Organic Chemists*, Academic Press, NY, **1975**; Borden, W.T. *Modern Molecular Orbital Theory for Organic Chemists*, Prentice-Hall, Englewood Cliffs, NJ, **1975**.

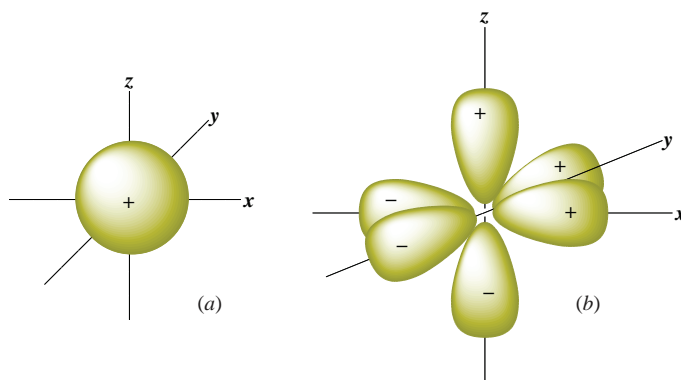


FIG. 1.1. (a) The 1s orbital. (b) The three 2p orbitals.

pictures that show the electron density, and these pictures are called *orbitals* or electron clouds. Most students are familiar with the shapes of the *s* and *p* atomic orbitals (Fig. 1.1). Note that each *p* orbital has a *node*: A region in space where the probability of finding the electron is extremely small.³ Also note that in Fig. 1.1 some lobes of the orbitals are labeled + and others -. These signs do not refer to positive or negative *charges*, since both lobes of an electron cloud must be negatively charged. They are the signs of the wave function Ψ . When a node separates two parts of an orbital, a point of zero electron density, Ψ always has opposite signs on the two sides of the node. According to the *Pauli exclusion principle*, no more than two electrons can be present in any orbital, and they must have opposite spins.

Unfortunately, the Schrödinger equation can be solved exactly only for one-electron systems (e.g., the hydrogen atom). If it could be solved exactly for molecules containing two or more electrons,⁴ a precise picture of the shape of the orbitals available to each electron (especially for the important ground state) would become available, as well as the energy for each orbital. Since exact solutions are not available, drastic approximations must be made. There are two chief general methods of approximation: the molecular orbital (MO) method and the valence bond method.

In the MO method, bonding is considered to arise from the overlap of atomic orbitals. When any number of atomic orbitals overlap, they combine to form an equal number of new orbitals, called *molecular orbitals*. Molecular orbitals differ from atomic orbitals in that an electron cloud effectively surrounds the nuclei of two or more atoms, rather than just one atom. In other words, the electrons are shared by two atoms rather than being localized on one atom. In localized bonding for a single covalent bond, the number of atomic orbitals that overlap is two (each containing one electron), so that two molecular orbitals are generated. One of these, called a *bonding orbital*, has a lower energy than the original atomic orbitals (otherwise a bond would not form), and the other, called an *antibonding orbital*, has a higher

³ When wave mechanical calculations are made according to the Schrödinger equation, the probability of finding the electron in a node is zero, but this treatment ignores relativistic considerations. When such considerations are applied, Dirac has shown that nodes do have a very small electron density: Powell, R.E. *J. Chem. Educ.* **1968**, 45, 558. See also, Ellison, F.O.; Hollingsworth, C.A. *J. Chem. Educ.* **1976**, 53, 767; McKelvey, D.R. *J. Chem. Educ.* **1983**, 60, 112; Nelson, P.G. *J. Chem. Educ.* **1990**, 67, 643. For a general review of relativistic effects on chemical structures, see Pyykkö, P. *Chem. Rev.* **1988**, 88, 563.

⁴ See Roothaan, C.C.J.; Weiss, A.W. *Rev. Mod. Phys.* **1960**, 32, 194; Kolos, W.; Roothaan, C.C.J. *Rev. Mod. Phys.* **1960**, 32, 219. For a review, see Clark, R.G.; Stewart, E.T. *Q. Rev. Chem. Soc.* **1970**, 24, 95.

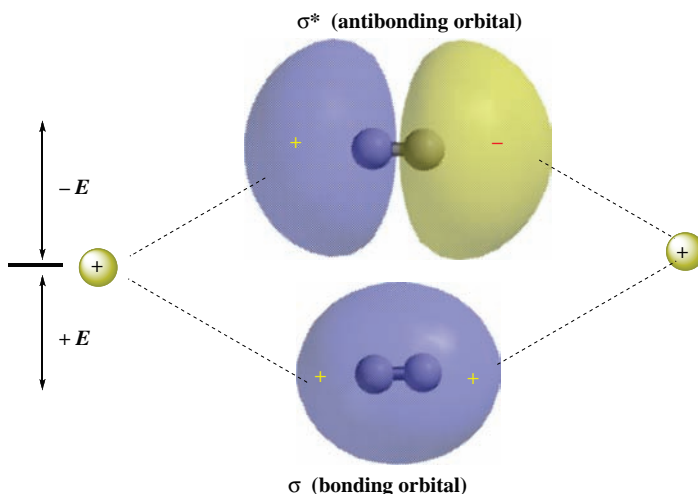


FIG. 1.2. Overlap of two 1s orbitals gives rise to a σ and a σ^* orbital.

energy. Orbitals of lower energy fill first. Since the two original atomic orbitals each held one electron, both of these electrons will reside in the new molecular *bonding* orbital, which is lower in energy. Remember that any orbital can hold two electrons. The higher energy antibonding orbital remains empty in the ground state.

The strength of a bond is determined by the amount of electron density that resides between the two nuclei. The greater the overlap of the orbitals, the stronger the bond, but total overlap is prevented by repulsion between the nuclei. Figure 1.2 shows the bonding and antibonding orbitals that arise by the overlap of two 1s electrons. Note that since the antibonding orbital has a node between the nuclei, there is practically no electron density in that area, so that this orbital cannot be expected to bond very well. When the centers of electron density are on the axis common to the two nuclei, the molecular orbitals formed by the overlap of two atomic orbitals are called σ (*sigma*) orbitals, and the bonds are called σ bonds. The corresponding antibonding orbitals are designated σ^* . Sigma orbitals may be formed by the overlap of any of the atomic orbital (*s*, *p*, *d*, or *f*) whether the same or different, not only by the overlap of two *s* orbitals. However, the two lobes that overlap must have the same sign: A positive *s* orbital can form a bond only by overlapping with another positive *s* orbital or with a positive lobe of a *p*, *d*, or *f* orbital. Any σ molecular orbital may be represented as approximately ellipsoidal in shape.

Orbitals are frequently designated by their symmetry properties. The σ orbital of hydrogen is often written ψ_g . The *g* stands for *gerade*. A *gerade* orbital is one in which the sign on the orbital does not change when it is inverted through its center of symmetry. The σ^* orbital is *ungerade* (designated ψ_u). An *ungerade* orbital changes sign when inverted through its center of symmetry.

In MO calculations, the *linear combination of atomic orbitals* (known as LCAO) generates a wave function from a linear combination of overlapped atomic orbitals. Addition of the atomic orbitals gives the bonding MO:

$$\psi = c_A\psi_A + c_B\psi_B \quad (1-1)$$

The functions ψ_A and ψ_B are the functions for the atomic orbitals of atoms A and B, respectively, and c_A and c_B represent weighting factors. Subtraction is also a linear combination:

$$\psi = c_A\psi_A - c_B\psi_B \quad (1-2)$$

This gives rise to the antibonding molecular orbital.

In the valence bond method, a wave equation is written for each of various possible electronic structures that a molecule may have (each of these is called a *canonical form*), and the total ψ is obtained by summation of as many of these as seem plausible, each with its weighting factor:

$$\psi = c_1\psi_1 + c_2\psi_2 + \cdots \quad (1-3)$$

This resembles Eq. (1-1), but here each ψ represents a wave equation for an imaginary canonical form and each c is the amount contributed to the total picture by that form. For example, a wave function can be written for each of the following canonical forms of the hydrogen molecule⁵:



Values for c in each method are obtained by solving the equation for various values of each c , and choosing the solution of lowest energy. In practice, both methods give similar solutions for molecules that contain only localized electrons, and these are in agreement with the Lewis structures long familiar to the organic chemist. Delocalized systems are considered in Chapter 2. Note that orbital functions can indeed be reconstructed from measured data using several different approaches. Often, however, the results are still less accurate than those achieved with purely theoretical methods.⁶

1.B. MULTIPLE VALENCE

A univalent atom has only one orbital available for bonding. But atoms with a valence of 2 or more must form bonds by using at least two orbitals. An oxygen atom has two half-filled orbitals, giving it a valence of 2. It forms single bonds by the overlap of these with the orbitals of two other atoms. According to the principle of maximum overlap, the other two nuclei should form an angle of 90° with the oxygen nucleus, since the two available orbitals on oxygen are p orbitals, which are perpendicular. If this is correct, nitrogen, which has three mutually perpendicular p orbitals, would have bond angles of 90° when it forms three single bonds. However, these are not the observed bond angles. The bond angles in water are,⁷ $104^\circ 27'$, and in ammonia, $106^\circ 46'$. For alcohols and ethers, the angles are even larger (see Sec. 1.K). A discussion of this will be deferred to Section 1.K, but it is important to note that covalent compounds do have definite bond angles. Although the atoms are continuously vibrating, the mean position is the same for each molecule of a given compound.

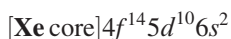
⁵ In this book, a pair of electrons in a bond is represented by two dots.

⁶ Schwarz, W.H.E. *Angew. Chem. Int. Ed.* **2006**, *45*, 1508. For the ball-in-box model, see Pierrefixe, S.C.A.H.; Guerra, C.F.; Bickelhaupt, F.M. *Chem. Eur. J.* **2008**, *14*, 819; Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *J. Phys. Chem. A* **2008**, *112*, 12816.

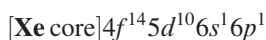
⁷ Bent, H.A. *Chem. Rev.* **1961**, *61*, 275, 277.

1.C. HYBRIDIZATION

Consider the case of mercury. Its electronic structure is



Although it has no half-filled orbitals, it has a valence of 2 and forms two covalent bonds. This result can be explained by imagining that one of the $6s$ electrons is promoted to a vacant $6p$ orbital to give the excited configuration



In this state, the atom has two half-filled orbitals, but they are not equivalent. If bonding were to occur by the overlap of these orbitals with the orbitals of external atoms, the two bonds would not be equivalent. The bond formed from the $6p$ orbital would be more stable than the one formed from the $6s$ orbital, since a larger amount of overlap is possible with the former. A more stable situation is achieved when, in the course of bond formation, the $6s$ and $6p$ orbitals combine to form two new orbitals that *are* equivalent; these are shown in Fig. 1.3.

The new molecular orbitals are a mixture of the two original orbitals, so they are called *hybrid orbitals*. Each orbital is a merger of an s and p orbital and is called an sp orbital. The sp orbitals, each of which consists of a large lobe and a very small one, arise only in the bonding process and do not represent a possible structure for the free atom. A mercury atom forms its two bonds by overlapping each of the large lobes shown in Fig. 1.3 with an orbital from an external atom. The orbital of this external atom may be any of the atomic orbitals previously considered (s , p , d , or f), or it may be another hybrid orbital. Note that only lobes of the same sign can overlap. In any of these cases, the molecular orbital that arises is called a σ orbital since it fits the previous definition of a σ orbital.

In general, equivalent orbitals lie as far away from each other as possible because of mutual repulsion, so two sp orbitals form an angle of 180° . In other words, an atom that forms only two σ bonds uses two sp orbitals so HgCl_2 , for example, should be a linear molecule, and it is. This kind of hybridization is called *digonal hybridization*. An sp hybrid orbital forms a stronger covalent bond than either an s or a p orbital because it extends out in space in the direction of the other atom's orbital farther than the s or the p and permits

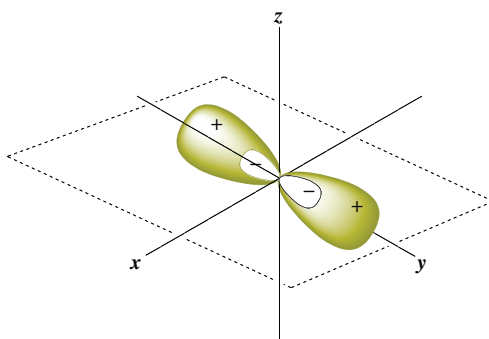
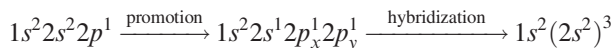


FIG. 1.3. The two sp orbitals formed by mercury.

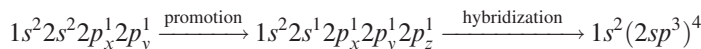
greater overlap. Compare HgCl_2 with water (OH_2). It is known that the shape of HgCl_2 is linear, but water is angular. This fact suggests that the hybrid orbitals utilized by oxygen in water is different from those used by mercury in HgCl_2 .

Many other kinds of hybridization are possible. Consider boron, which has the electronic configuration $1s^2 2s^2 2p^1$ yet has a valence of 3. To begin, boron has only three valence electrons available to form bonds, hence the valence of three. Any hybridization model must take this into account. As before, imagine promotion of an electron and hybridization:



In this case, there are three equivalent hybrid orbitals, each called sp^2 (*trigonal hybridization*). This method of designating hybrid orbitals is perhaps unfortunate since nonhybrid orbitals are designated by single letters, but keep in mind that *each* of the three orbitals is called sp^2 . The key is to understand that the atom forms two σ bonds for sp hybridization and three σ bonds for sp^2 hybridization. The sp^2 hybrid orbitals just noted are shown in Fig. 1.4. The three axes are all in one plane and point to the corners of an equilateral triangle. This accords with the known structure of BF_3 , a planar molecule with angles of 120° .

Another type of hybrid orbital is possible, formed by atoms that can form four σ bonds. Carbon is an important atom that can form four single bonds (four σ bonds). Imagine promotion of an electron and hybridization that leads to



There are four equivalent molecular orbitals, each called sp^3 , and electron repulsion leads to a shape in which the orbitals point to the corners of a regular tetrahedron (Fig. 1.4). A typical molecule is methane (CH_4) and assuming that carbon forms four bonds with sp^3 hybrid orbitals, the bond angles of methane would thus be expected to be $109^\circ 28'$, which is the angle for a regular tetrahedron. In reality, electrons are not “promoted” in atomic orbitals, but atomic orbitals are different from molecular orbitals (e.g., those found in methane). The model of promoting an electron is a mathematical device to describe molecular orbitals using the atomic orbitals.

The hybrid orbitals discussed in this section stem from only one possible approximate solution of the Schrödinger equation. The s and the three p atomic orbitals used to form sp^3 orbitals, for example, can be combined in other equally valid ways. As will be seen in Section 1.E, the four C—H bonds of methane do not always behave as if they are

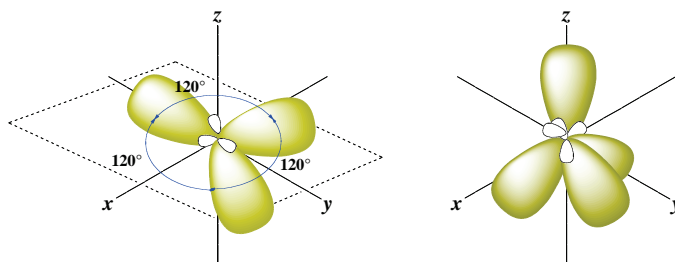


FIG. 1.4. The three sp^2 and the four sp^3 orbitals.

equivalent. Bickelhaupt⁶ has proposed an alternative approach to the bonding in carbon suggesting that the maximum coordination number of carbon cannot exceed four because it is too small to allow more than four substituents approach and form the appropriate bonds.

1.D. MULTIPLE BONDS

If ethylene ($\text{H}_2\text{C}=\text{CH}_2$) is examined in terms of the MO concepts discussed so far, each carbon has three σ bonds, one to each of the three atoms. Therefore, sp^2 orbitals are used to form those three bonds. These sp^2 orbitals arise from hybridization of the $2s^1$, $2p_x^1$, and $2p_y^1$ electrons after promotion of electrons (Sec. 1.C). In general, any carbon atom that is bonded to only three different atoms uses sp^2 orbitals for this bonding. The three σ bonds of ethylene are one to each of two hydrogen atoms and one to the other carbon. Each carbon therefore has another electron in the $2p_z$ orbital that is perpendicular to the plane of the sp^2 orbitals. The two parallel $2p_z$ orbitals, one on each of the two adjacent carbon atoms, can overlap sideways to generate a bonding and an antibonding orbital (Fig. 1.5). In the ground state, both electrons go into the bonding orbital and the antibonding orbital remains vacant. In other words, a new bond is formed, but it is formed by sideways overlap of adjacent p orbitals rather than direct overlap of σ orbitals. Molecular orbitals formed by the overlap of atomic

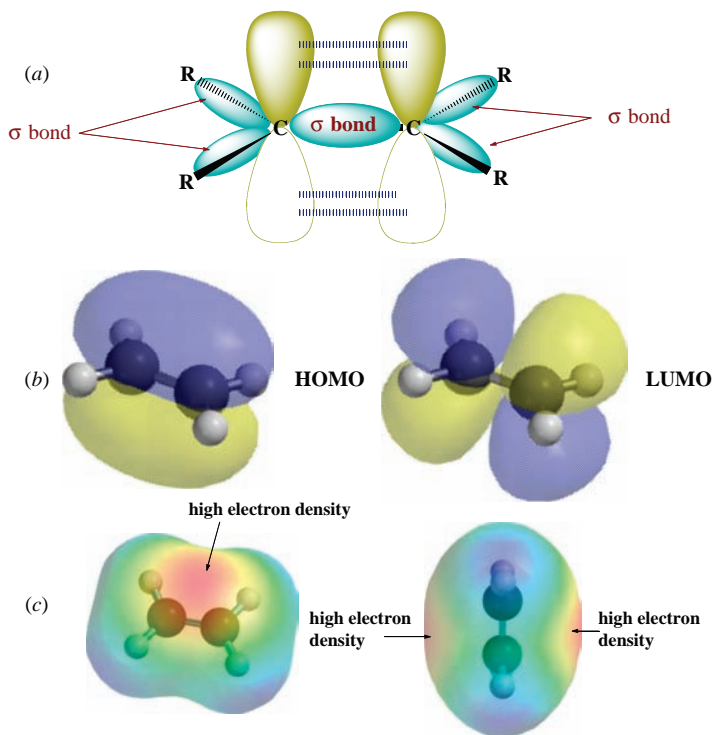
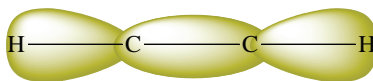


FIG. 1.5. (a) Overlapping p orbitals form a π and a π^* orbital. The σ orbitals are shown in (a). The π orbitals are shown in (b) as the highest occupied molecular orbital (HOMO) (on the left) and the LUMO. In (c), the electron potential map of ethylene shows the concentration of electron density above and below the plane of the atoms, consistent with a π bond.

FIG. 1.6. The σ orbitals of acetylene.

orbitals whose axes are parallel are called π orbitals if they are bonding and π^* if they are antibonding.

In this picture of ethylene, there are two bonds connecting the adjacent carbon atoms, but the two orbitals that make up the double bond are not equivalent.⁸ This means that the two bonds are different one from the other. The σ orbital is ellipsoidal and symmetrical about the C—C axis, and this is the familiar σ bond. The π orbital is in the shape of two ellipsoids, one above the plane and one below, and forms the second bond, a π bond. The plane itself represents a node for the π orbital. In order for the p orbitals to maintain maximum overlap, they must be parallel. Since both a σ bond and the π bond connect the two carbon atoms, free rotation is not possible about the double bond. In other words, the two p orbitals would have to reduce their overlap to allow one H—C—H plane to rotate with respect to the other (i.e., the π bond would have to disappear). With two sp^2 hybrid carbon atoms in ethylene, the six atoms associated with the double bond ($H_2C=CH_2$) are in a plane with angles that should be $\sim 120^\circ$. Double bonds are shorter than the corresponding single bonds because maximum stability is obtained when the p orbitals overlap as much as possible (see Sec. 1.J). Double bonds between carbon and oxygen (C=O) or nitrogen (C=N) similarly consist of one σ and one π orbital.

When carbon is connected to another carbon atom by a triple bond, as in acetylene ($HC\equiv CH$), each carbon is connected to only two other atoms by a σ bond, and hence uses sp hybridization. This fact requires that the four atoms of acetylene (2H and 2C) are in a straight line (Fig. 1.6).⁹ Each carbon has two p orbitals remaining, with one electron in each. These orbitals are perpendicular to each other and also to the C—C axis. They overlap in the manner shown in Fig. 1.7 to form two π orbitals. A triple bond is thus composed of one σ and two π orbitals. Triple bonds between carbon and nitrogen can be represented in a similar manner, $C\equiv N$.

For most organic molecules, double and triple bonds typically involve the first-row elements carbon, nitrogen, and oxygen.¹⁰ Second-row elements tend to form weaker π bonds than do the first-row elements,¹¹ so multiple bonds are less common and compounds containing them are generally less stable.¹² Compounds with C=S bonds are known, for example, and C=S compounds are generally much less stable than the corresponding C=O compounds (however, see $p\pi-d\pi$ bonding in Sec. 2.H). Stable compounds with

⁸ For an alternative representation, see Pauling, L. *Theoretical Organic Chemistry, The Kekulé Symposium*, Butterworth, London, **1959**, pp. 2–5; Palke, W.E. *J. Am. Chem. Soc.* **1986**, *108*, 6543.

⁹ See Simonetta, M.; Gavezzotti, A., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, **1978**, pp. 1–56; Dale, J., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 3–96.

¹⁰ For a review of metal–metal multiple bonds, see Cotton, F.A. *J. Chem. Educ.* **1983**, *60*, 713.

¹¹ For discussions, see Schmidt, M.W.; Truong, P.N.; Gordon, M.S. *J. Am. Chem. Soc.* **1987**, *109*, 5217; Schleyer, P. von R.; Kost, D. *J. Am. Chem. Soc.* **1988**, *110*, 2105.

¹² For double bonds between carbon and elements other than C, N, S, or O, see Jutzi, P. *Angew. Chem. Int. Ed.* **1975**, *14*, 232; Raabe, G.; Michl, J. *Chem. Rev.* **1985**, *85*, 419 (Si only); Wiberg, N. *J. Organomet. Chem.* **1984**, *273*, 141 (Si only); Gordon, M.S. *Mol. Struct. Energ.* **1986**, *1*, 101. For reviews of C=P and C≡P bonds, see Regitz, M. *Chem. Rev.* **1990**, *90*, 191; Appel, R.; Knoll, F. *Adv. Inorg. Chem.* **1989**, *33*, 259; Markovski, L.N.; Romanenko, V.D. *Tetrahedron* **1989**, *45*, 6019.

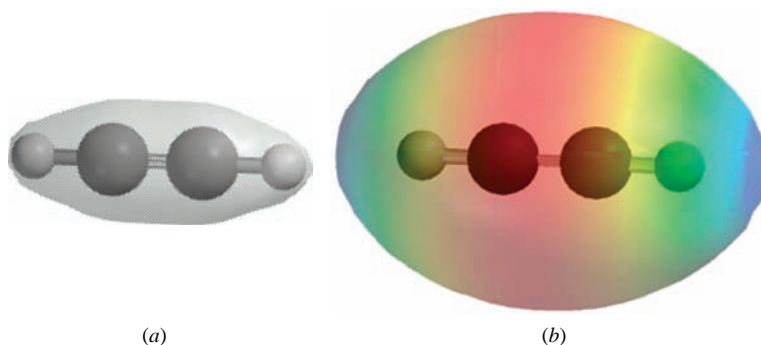


FIG. 1.7. (a) The electron density map of acetylene. Note the concentration of electron density along a line between the nuclei of each atom, consistent with overlap of σ orbitals in a triple bond. (b) Electron potential map of acetylene showing the concentration of electron density between the carbon atoms, consistent with two orthogonal π bonds.

$\text{Si}=\text{C}$ and $\text{Si}=\text{Si}$ bonds are rare, but examples have been reported,¹³ including a pair of *cis* and *trans* $\text{Si}=\text{Si}$ isomers.¹⁴

There is at least one report of a so-called two-electron, four-center C—C bond for the dimer of tetracyanoethylene.¹⁵ While such multi-center bonding is not formally an example of the multiple bonding described in this section, it constitutes a different type of bonding when compared to the simple C—C bonds described earlier.

1.E. PHOTOELECTRON SPECTROSCOPY

Based on the hybridization model, methane is expected to have four equivalent σ bonds. Indeed, the four bonds of methane are equivalent according to most physical and chemical methods of detection. The *nuclear magnetic resonance* (NMR) and the *infrared* (IR) spectrum of methane show *no* peaks that can be attributed to different kinds of C—H bonds. However, there is one physical technique showing that the eight valence electrons of methane can be differentiated. In this technique, called *photoelectron spectroscopy* (PES),¹⁶ a molecule or free atom is bombarded with vacuum *ultraviolet* (UV) radiation, causing an electron to be ejected. The energy of the ejected electron can be measured, and the difference between the energy of the radiation used and that of the ejected electron is

¹³ For $\text{Si}=\text{C}$ bonds, see Fink, M.J.; DeYoung, D.J.; West, R.; Michl, J. *J. Am. Chem. Soc.* **1983**, *105*, 1070; Fink, M.J.; Michalczyk, M.J.; Haller, K.J.; West, R.; Michl, J. *Organometallics* **1984**, *3*, 793; West, R. *Pure Appl. Chem.* **1984**, *56*, 163; Masamune, S.; Eriyama, Y.; Kawase, T. *Angew. Chem. Int. Ed.* **1987**, *26*, 584; Shepherd, B.D.; Campana, C.F.; West, R. *Heteroat. Chem.* **1990**, *1*, 1.

¹⁴ Michalczyk, M.J.; West, R.; Michl, J. *J. Am. Chem. Soc.* **1984**, *106*, 821, *Organometallics* **1985**, *4*, 826.

¹⁵ Miller, J.S.; Novoa, J.J. *Acc. Chem. Res.* **2007**, *40*, 189.

¹⁶ See Ballard, R.E. *Photoelectron Spectroscopy and Molecular Orbital Theory*, Wiley, NY, **1978**; Rabalais, J.W. *Principles of Ultraviolet Photoelectron Spectroscopy*, Wiley, NY, **1977**; Baker, A.D.; Betteridge, D. *Photoelectron Spectroscopy*, Pergamon, Elmsford, NY, **1972**; Turner, D.W.; Baker, A.D.; Baker, C.; Brundle, C.R. *High Resolution Molecular Photoelectron Spectroscopy*, Wiley, NY, **1970**. For reviews, see Westwood, N.P.C. *Chem. Soc. Rev.* **1989**, *18*, 317; Baker, C.; Brundle, C.R.; Thompson, M. *Chem. Soc. Rev.* **1972**, *1*, 355; Bock, H.; Ramsey, B.G. *Angew. Chem. Int. Ed.* **1973**, *12*, 734; Turner, D.W. *Adv. Phys. Org. Chem.* **1966**, *4*, 31. For the IUPAC descriptive classification of various electron spectroscopy techniques, see Porter, H.Q.; Turner, D.W. *Pure Appl. Chem.* **1987**, *59*, 1343.

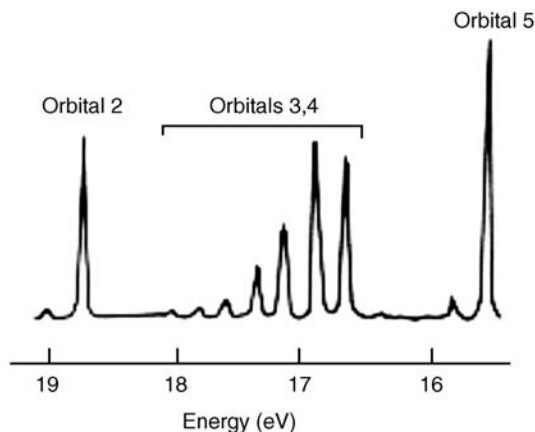


FIG. 1.8. Photoelectron spectrum of N₂.¹⁸ [Reprinted with permission from Brundle, C.R.; Robin, M.B. in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, **1971**, p. 18. Copyright © 1971, with permission from Elsevier Science. With permission of C. Richard Brundle, 2012.]

the *ionization potential* of that electron. A molecule that contains several electrons of differing energies can lose any one of them as long as its ionization potential is less than the energy of the radiation used. A single molecule loses only one electron; the loss of two electrons by any individual molecule almost never occurs. Since electrons reside in orbitals, a photoelectron spectrum consists of a series of bands, each corresponding to an orbital of a different energy. The spectrum gives a direct experimental picture of all orbitals that are present, and they are ejected in ascending order of their energies, provided that radiation of sufficiently high energy is used.¹⁷ Broad bands usually correspond to strongly bonding electrons and narrow bands to weakly bonding or nonbonding electrons.

Using PES, it is possible to probe the validity of the hybridization model for bonding. Dinitrogen (N₂) is a typical diatomic molecule and is shown in Fig. 1.8.¹⁸ The N₂ molecule has the electronic structure shown in Fig. 1.9: The two 2s orbitals of the nitrogen atoms combine to give the two orbitals marked 1 (bonding) and 2 (antibonding), while the six 2p orbitals combine to give six orbitals, three of which (marked 3, 4, and 5) are bonding. The three antibonding orbitals (not indicated in Fig. 1.9) are unoccupied. Electrons ejected from orbital 1 are not found in Fig. 1.8 because the ionization potential of these electrons is greater than the energy of the light used (they can be seen when higher energy light is used). The broad band in Fig. 1.8 corresponds to the four electrons in the degenerate orbitals 3 and 4. The individual peaks within this band are caused by different vibrational levels (see Chap. 7). The triple bond of N₂ is therefore composed of these two orbitals and orbital 1. The bands corresponding to orbitals 2 and 5 are narrow; hence these orbitals contribute little to the bonding and may be regarded as the two unshared pairs of $\tilde{N} \equiv \tilde{N}$. Note that this result is contrary to that expected from a naive consideration of orbital overlaps, where it

¹⁷ The correlation is not perfect, but the limitations do not seriously detract from the usefulness of the method. The technique is not limited to vacuum UV radiation. Higher energy radiation can also be used.

¹⁸ From Brundle, C.R.; Robin, M.B., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, **1971**, p. 18.

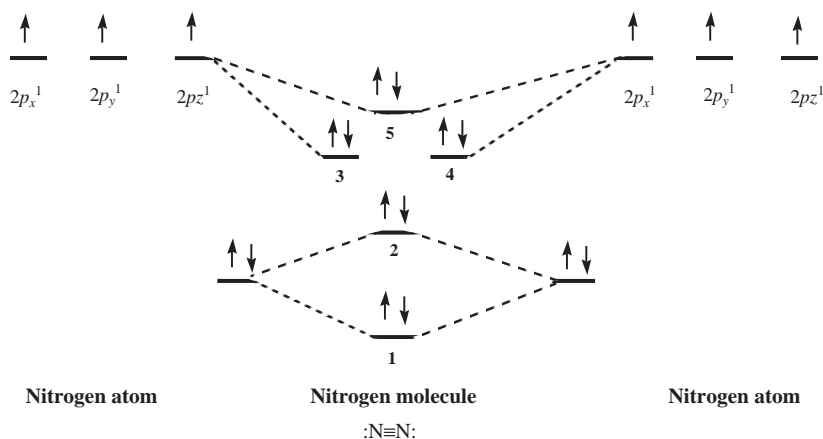


FIG. 1.9. Electronic structure of N_2 (inner-shell electrons omitted).

would be expected that the two unshared pairs would be those of orbitals 1 and 2, resulting from the overlap of the filled $2s$ orbitals. In addition, the triple bond would be composed of orbitals 3, 4, and 5, resulting from overlap of the p orbitals. This example is one illustration of the value of PES.

The photoelectron spectrum of methane¹⁹ in Fig. 1.10 shows two bands,²⁰ at ~ 23 and 14 eV, and not the single band expected from the equivalency of the four C—H bonds. Indeed, Fig. 1.10 suggests that carbon uses the available orbitals to form four bonds and the electrons in the bonds are distributed between carbon and the four atoms involved in the bonds. Remember that the hybridization model predicts four identical σ bonds made by overlap of four identical hybrid orbitals. The band at 23 eV comes from two electrons in a low-energy

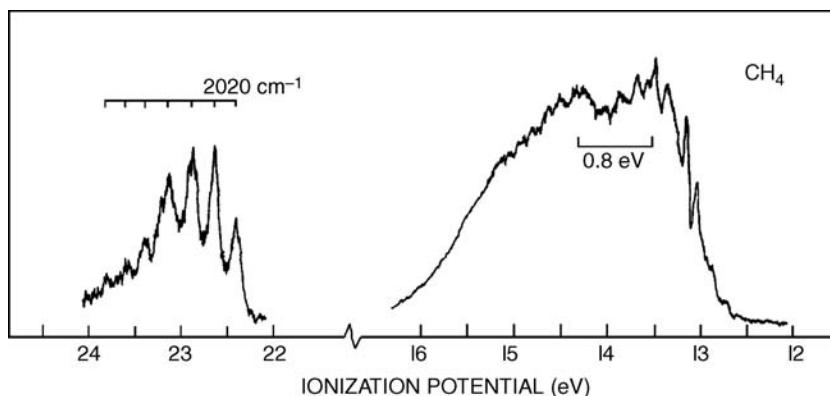


FIG. 1.10. Photoelectron spectroscopy scan of methane. [Reprinted with permission from Brundle, C.R.; Robin, M.B. *J. Chem. Phys.* **1970**, 53, 2196. Copyright © 1970, American Institute of Physics.]

¹⁹ Brundle, C.R.; Robin, M.B.; Basch, H. *J. Chem. Phys.* **1970**, 53, 2196; Baker, A.D.; Betteridge, D.; Kemp, N.R.; Kirby, R.E. *J. Mol. Struct.* **1971**, 8, 75; Potts, A.W.; Price, W.C. *Proc. R. Soc. London, Ser. A* **1972**, 326, 165.

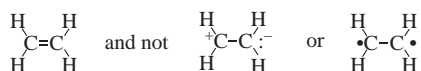
²⁰ A third band, at 290 eV, caused by the $1s$ electrons of carbon, can also be found if radiation of sufficiently high energy is used.

level (called the a_1 level), which can be regarded as arising from a combination of the $2s$ orbital of carbon with an appropriate combination of hydrogen $1s$ orbitals. The band at 14 eV comes from six electrons in a triply degenerate level (the t_2 level), arising from a combination of the three $2p$ orbitals of carbon with other combinations of $1s$ hydrogen orbitals. As mentioned above, most physical and chemical processes cannot distinguish these levels, but PES can. The photoelectron spectra of many other organic molecules are known as well,²¹ including monocyclic alkenes, in which bands < 10 eV are due to π -orbital ionization and those > 10 eV originate from ionization of σ orbitals only.²² Note that ordinary sp^3 hybridization is not adequate to explain phenomena involving ionized molecules (e.g., the $\text{CH}_4^{\bullet+}$ radical ion, which is left behind when an electron is ejected from methane). For these phenomena, it is necessary to use other combinations of atomic orbitals (see Sec. 1.C).

1.F. ELECTRONIC STRUCTURES OF MOLECULES

For each molecule, ion, or free radical that has only localized electrons, it is possible to draw an electronic formula, called a *Lewis structure*, which shows the location of these electrons. Only the valence electrons are shown. Valence electrons may be found in covalent bonds connecting two atoms or they may be unshared.²³ Drawing these structures correctly is essential, since the position of electrons changes in the course of a reaction, and it is necessary to know where the electrons are initially before one can follow where they are going. To this end, the following rules operate:

1. The total number of valence electrons in the molecule (or ion or free radical) must be the sum of all outer-shell electrons “contributed” to the molecule by each atom plus the negative charge or minus the positive charge, for the case of ions. Thus, for H_2SO_4 , there are 2 (one for each hydrogen) + 6 (for the sulfur) + 24 (6 for each oxygen) = 32; while for SO_4^{2-} , the number is also 32, since each atom “contributes” 6 plus 2 for the negative charge.
2. Once the number of valence electrons has been ascertained, it is necessary to determine which of them are found in covalent bonds and which are unshared. Unshared electrons (either a single electron or a pair) form part of the outer shell of just one atom, but electrons in a covalent bond are part of the outer shell of both atoms of the bond. *First-row atoms* (B, C, N, O, F) *can have a maximum of eight valence electrons*, and usually have this number, although some cases are known where a first-row atom has only six or seven. Where there is a choice between a structure that has six or seven electrons around a first-row atom and one in which all such atoms have an octet, the structure based on the octet is generally lower in energy than the one that is observed. For example, ethylene is



²¹ See Robinson, J.W., *Practical Handbook of Spectroscopy*, CRC Press, Boca Raton, FL, **1991**, p. 178.

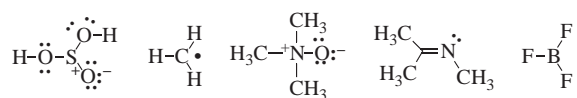
²² Novak, I.; Potts, A.W. *Tetrahedron* **1997**, 53, 14713.

²³ It has been argued that although the Lewis picture of two electrons making up a covalent bond may work well for organic compounds, it cannot be successfully applied to the majority of inorganic compounds: Jørgensen, C.K. *Top. Curr. Chem.* **1984**, 124, 1.

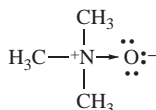
There are a few exceptions. For the molecule O_2 , the structure $\dot{O}-\dot{O}$ has a lower energy than $\ddot{O}=\ddot{O}$. Although first-row atoms are limited to 8 valence electrons, this is not so for second-row atoms, which can accommodate 10 or even 12 because empty d orbitals may be utilized.²⁴ For example, PCl_5 and SF_6 are stable compounds, and the hybridization model can be used to explain this fact. In SF_6 , one s and one p electron from the ground state $3s^2 3p^4$ of the sulfur are promoted to empty d orbitals, and the six orbitals hybridize to give six $sp^3 d^2$ orbitals, which point to the corners of a regular octahedron.

3. It is customary to show the formal charge on each atom. For this purpose, an atom is considered to “own” all unshared electrons, but only *one-half of the electrons in covalent bonds*. The sum of electrons that thus “belong” to an atom is compared with the number “contributed” by the atom. An excess belonging to the atom results in a negative charge, and a deficiency results in a positive charge. The total of the formal charges on all atoms equals the charge on the whole molecule or ion. Note that the counting procedure is not the same for determining formal charge as for determining the number of valence electrons. For both purposes, an atom “owns” all unshared electrons, but for outer-shell purposes it “owns” both the electrons of the covalent bond, while for formal-charge purposes it “owns” only one-half of these electrons.

Examples of electronic structures are



A coordinate-covalent bond (sometimes called a dative bond), represented by an arrow, is one in which both electrons come from the same atom; that is, the bond can be regarded as being formed by the overlap of an orbital containing two electrons with an empty one. Thus trimethylamine *N*-oxide would be represented:



For a coordinate-covalent bond, the rule concerning formal charge is amended so that both electrons count for the donor and neither for the recipient. Thus the nitrogen and oxygen atoms of trimethylamine oxide bear no formal charges. However, it is apparent that the electronic picture is exactly the same as the picture of trimethylamine *N*-oxide given just above, and there is a choice of drawing an arrowhead or a charge separation. Some compounds (e.g., amine *N*-oxides) must be drawn one way or the other. It is usually simpler to use charge separation.

1.G. ELECTRONEGATIVITY

The electron cloud that bonds two atoms is not symmetrical (with respect to the plane that is the perpendicular bisector of the bond) except when the two atoms are the same and have the same substituents. A symmetrical electron cloud typically occurs when there is a bond

²⁴ For a review concerning sulfur compounds with a valence shell larger than eight, see Salmond, W.G. *Q. Rev. Chem. Soc.* **1968**, 22, 235.

between two identical atoms, and an unsymmetrical electron cloud occurs when there are two different atoms. When there are two different atoms, and one is more electronegative than the other, the electron cloud is necessarily distorted toward one side of the bond or the other, depending on which atom (nucleus plus electrons) maintains the greater attraction for the cloud. This attraction is called *electronegativity*;²⁵ and it is greatest for atoms in the upper-right corner of the periodic table and lowest for atoms in the lower-left corner. Thus a bond between fluorine and carbon (C—F) shows distortion of the electron cloud associated with the bond, so that there is a higher probability of finding the electrons near the fluorine than near the carbon. Such a bond is said to be *polarized*, and the C—F bond is an example of a polarized covalent bond. The polarization gives the fluorine a partial negative charge (δ^-) and the carbon a partial positive charge (δ^+).

A number of attempts have been made to set up quantitative tables of electronegativity that will indicate the direction and extent of electron-cloud distortion for a bond between any pair of atoms. The most popular of these scales, devised by Pauling, is based on bond energies (see Sec. 1.L) of diatomic molecules. It is rationalized that if the electron distribution were symmetrical in a molecule A—B, the bond energy would be the mean of the energies of A—A and B—B, since in these cases the cloud must be undistorted. If the actual bond energy of A—B is higher than this (and it usually is), it is the result of the partial charges (the charges attract each other and make a stronger bond, which requires more energy to break). It is necessary to assign a value to one element arbitrarily ($F = 4.0$). Then the electronegativity of another is obtained from the difference between the actual energy of A—B and the mean of A—A and B—B (this difference is called Δ) by the formula

$$x_A - x_B = \sqrt{\frac{\Delta}{23.06}}$$

where x_A and x_B are the electronegativities of the known and unknown atoms and 23.06 is an arbitrary constant. Part of the scale derived from this treatment is shown in Table 1.1.^{26,27}

Other treatments²⁸ have led to scales that are based on different principles, for example, the average of the ionization potential and the electron affinity,²⁹ the average one-electron energy of valence-shell electrons in ground-state free atoms,³⁰ or the “compactness” of an atom’s electron cloud.²⁴ In some of these treatments, electronegativities can be calculated for different valence states, for different hybridizations (e.g., *sp* carbon atoms are more electronegative than *sp*², which are still more electronegative than *sp*³),³¹ and even

²⁵ For a collection of articles on this topic, see Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*), Springer, NY, **1987**. For a review, see Batsanov, S.S. *Russ. Chem. Rev.* **1968**, 37, 332.

²⁶ Taken from Pauling, L. *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, NY, **1960**, p. 93, except for the value for Na, which is from Sanderson, R.T. *J. Am. Chem. Soc.* **1983**, 105, 2259; *J. Chem. Educ.* **1988**, 65, 112, 223.

²⁷ See Sanderson, R.T. *J. Am. Chem. Soc.* **1983**, 105, 2259; *J. Chem. Educ.* **1988**, 65, 112, 223.

²⁸ See Huheey, J.E. *Inorganic Chemistry*, 3rd ed., Harper and Row, NY, **1983**, pp. 146–148; Mullay, J., in Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*), Springer, NY, **1987**, p. 9.

²⁹ Hinze, J.; Jaffé, H.H. *J. Am. Chem. Soc.* **1962**, 84, 540; Rienstra-Kiracofe, J.C.; Tschumper, G.S.; Schaefer, III, H.F.; Nandi, S.; Ellison, G.B. *Chem. Rev.* **2002**, 102, 231.

³⁰ Allen, L.C. *J. Am. Chem. Soc.* **1989**, 111, 9003.

³¹ Walsh, A.D. *Discuss. Faraday Soc.* **1947**, 2, 18; Bergmann, D.; Hinze, J., in Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*), Springer, NY, **1987**, pp. 146–190.

TABLE 1.1 Electronegativities of Some Atoms on the Pauling²⁶ and Sanderson²⁷ Scales

Element	Pauling	Sanderson	Element	Pauling	Sanderson
F	4.0	4.000	H	2.1	2.592
O	3.5	3.654	P	2.1	2.515
Cl	3.0	3.475	B	2.0	2.275
N	3.0	3.194	Si	1.8	2.138
Br	2.8	3.219	Mg	1.2	1.318
S	2.5	2.957	Na	0.9	0.835
I	2.5	2.778	Cs	0.7	0.220
C	2.5	2.746			

[Adapted material from *The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry*, 3rd edition, edited by Linus Pauling. Copyright © 1960 by Cornell University. Used by permission of the publisher, Cornell University Press. Reprinted with permission Sanderson, R.T. *J. Am. Chem. Soc.* **1983**, *105*, 2259. Copyright © 1983 American Chemical Society.]

TABLE 1.2 Some Group Electronegativities Relative to H = 2.176³²

CH₃	2.472	CCl₃	2.666
CH₃CH₂	2.482	C₆H₅	2.717
CH₂Cl	2.538	CF₃	2.985
CBr₃	2.561	C≡N	3.208
CHCl₂	2.602	NO₂	3.421

[Reprinted with permission from Inamoto, N.; Masuda, S. *Chem. Lett.* **1982**, 1003. Copyright © 1982 The Chemical Society of Japan.]

differently for primary, secondary, and tertiary carbon atoms. Also, electronegativity values can be calculated for groups rather than atoms (Table 1.2).³²

Electronegativity information can be obtained from NMR spectra. In the absence of a magnetically anisotropic group³³ the chemical shift of a ¹H or a ¹³C nucleus is approximately proportional to the electron density around it, and hence to the electronegativity of the atom or group to which it is attached. The greater the electronegativity of the atom or group, the lower the electron density around the proton, and the further downfield the chemical shift [relative to tetramethylsilane (TMS) as zero ppm]. An example of the use of this correlation is found in the variation of chemical shift of the *ring* protons in the series toluene, ethylbenzene, isopropylbenzene, and *tert*-butylbenzene (there is a magnetically anisotropic group here, but its effect should be constant throughout the series). The electron density surrounding the ring protons decreases³⁴ in the order given.³⁵ However, this type of correlation is by no means perfect, since all the measurements are made in a powerful field, which itself may affect the electron density distribution.

³² Inamoto, N.; Masuda, S. *Chem. Lett.* **1982**, 1003. See also, Bratsch, S.G. *J. Chem. Educ.* **1988**, *65*, 223; Mulla, J. *J. Am. Chem. Soc.* **1985**, *107*, 7271; Zefirov, N.S.; Kirpichenok, M.A.; Izmailov, F.F.; Trofimov, M.I. *Dokl. Chem.* **1987**, *296*, 440; Boyd, R.J.; Edgecombe, K.E. *J. Am. Chem. Soc.* **1988**, *110*, 4182.

³³ A magnetically anisotropic group is one that is not equally magnetized along all three axes. The most common such groups are benzene rings (see Sec. 2.I) and triple bonds.

³⁴ This order is opposite to that expected from the field effect (Sec. 1.I). It is an example of the *Baker–Nathan order* (Sec. 2.M).

³⁵ Moodie, R.B.; Connor, T.M.; Stewart, R. *Can. J. Chem.* **1960**, *38*, 626.

Coupling constants between the two protons of a system $-\text{CH}-\text{CH}-\text{X}$ have also been found to depend on the electronegativity of X.³⁶

When the difference in electronegativities is great, the electron density in an orbital may be effectively localized on only one nucleus. This is an *ionic bond*, which is seen to arise naturally out of the previous discussion. It is possible to view polarized covalent bonds as intermediates between ionic and covalent bonds. With this view, the extent of electron-cloud distortion is expressed as the percent ionic character of a bond. In this model, there is a continuous gradation from ionic to covalent bonds.

1.H. DIPOLE MOMENT

The *dipole moment* is a property of a molecule that results from charge separations like those discussed above. However, it is not possible to measure the dipole moment of an individual bond within a molecule. Only the total moment of the molecule may be measured, and it is the vectorial sum of the individual bond moments.³⁷ These individual moments are roughly the same from molecule to molecule,³⁸ but this constancy is by no means universal. Thus, from the dipole moments of toluene and nitrobenzene (Fig. 1.11)³⁹ the moment of *p*-nitrotoluene is predicted to be ~ 4.36 D. The actual value 4.39 D is reasonable. However, the moment of

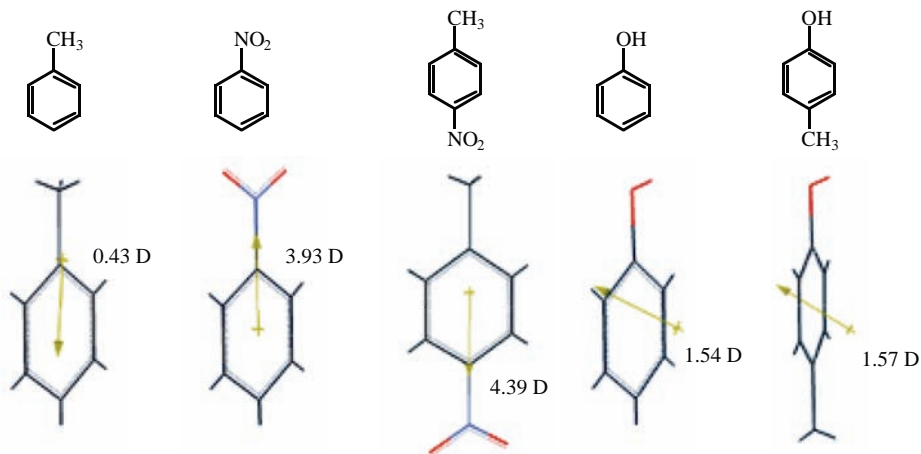


FIG. 1.11. Some dipole moments, in Debye units, measured in benzene. In the 3D model, the arrow indicates the direction of the dipole moment for the molecule, pointing to the negative part of the molecule.³⁹

³⁶ Williamson, K.L. *J. Am. Chem. Soc.* **1963**, 85, 516; Laszlo, P.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1963**, 85, 2709; Niwa, J. *Bull. Chem. Soc. Jpn.* **1967**, 40, 2192.

³⁷ See Exner, O. *Dipole Moments in Organic Chemistry*, Georg Thieme Publishers, Stuttgart, **1975**; McClellan, A. L. *Tables of Experimental Dipole Moments*, Vol. 1, W.H. Freeman, San Francisco, **1963**; Vol. 2, Rahara Enterprises, El Cerrito, CA, **1974**.

³⁸ For example, see Koudelka, J.; Exner, O. *Collect. Czech. Chem. Commun.* **1985**, 50, 188, 200.

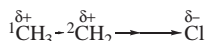
³⁹ The values for toluene, nitrobenzene, and *p*-nitrotoluene are from McClellan, A.L., *Tables of Experimental Dipole Moments*, Vol. 1, W.H. Freeman: San Francisco, **1963**; Vol. 2, Rahara Enterprises, El Cerrito, CA, **1974**. The values for phenol and *p*-cresol were determined by Goode, E.V.; Ibbitson, D.A. *J. Chem. Soc.* **1960**, 4265.

p-cresol (1.57 D) is quite far from the predicted value of 1.11 D. In some cases, molecules may have substantial individual bond moments, but no total moments at all because the individual moments are canceled out by the overall symmetry of the molecule. Some examples are CCl₄, *trans*-1,2-dibromoethene, and *p*-dinitrobenzene.

Because of the small difference between the electronegativities of carbon and hydrogen, alkanes have very small dipole moments, so small that they are difficult to measure. For example, the dipole moment of isobutane is 0.132 D⁴⁰ and that of propane is 0.085 D.⁴¹ Of course, methane and ethane, because of their symmetry, have no dipole moments.⁴² Few organic molecules have dipole moments > 7 D.

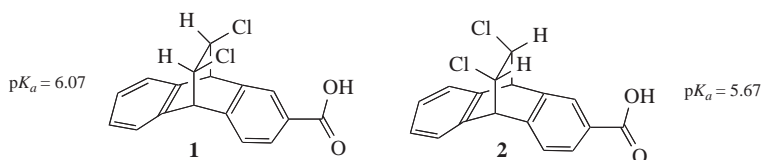
1.1. INDUCTIVE AND FIELD EFFECTS

The C—C bond in ethane has no polarity because it connects two equivalent atoms, with identical electronegativities. The presence of a more electronegative atom attached to one of the carbon atoms will lead to bond polarization, however, in what is known as an induced dipole. The C—C bond in chloroethane, for example, is polarized by the presence of the electronegative chlorine atom. This polarization is actually the sum



of two effects. In the first of these, the C-1 atom is deprived of some of its electron density by the greater electronegativity of Cl, and this effect is partially compensated by drawing the C—C electrons closer to itself. The result is a polarization of this bond and a slightly positive charge on the C-2 atom: an induced dipole. This polarization of one bond caused by the polarization of an adjacent bond is known as an *inductive effect*. The effect is greatest for adjacent bonds but may also be felt farther away; thus the polarization of the C—C bond causes a (slight) polarization of the three methyl C—H bonds. As a practical matter, the effect is negligible if the polarizing group is more than three bonds away.

The other effect operates not through bonds, but directly through space or solvent molecules, and is called a *field effect*.⁴³ It is often very difficult to separate the two kinds of effect, but a number of cases have been reported. This is generally accomplished by taking advantage of the fact that the field effect depends on the geometry of the molecule, but the inductive effect depends only on the nature of the bonds. For example, in isomers, **1** and **2**⁴⁴ the inductive effect of the chlorine atoms on the position of the electrons in the COOH group (and hence on the



⁴⁰ Lide Jr., D.R.; Mann, D.E. *J. Chem. Phys.* **1958**, 29, 914.

⁴¹ Muentner, J.S.; Laurie, V.W. *J. Chem. Phys.* **1966**, 45, 855.

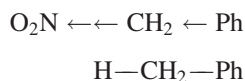
⁴² Actually, symmetrical tetrahedral molecules like methane do have extremely small dipole moments, caused by centrifugal distortion effects; these moments are so small that they can be ignored for all practical purposes. For CH₄, μ is $\sim 5.4 \times 10^{-6}$ D: Ozier, I. *Phys. Rev. Lett.* **1971**, 27, 1329; Rosenberg, A.; Ozier, I.; Kudian, A.K. *J. Chem. Phys.* **1972**, 57, 568.

⁴³ Roberts, J.D.; Moreland, Jr., W.T. *J. Am. Chem. Soc.* **1953**, 75, 2167.

⁴⁴ This example is from Grubbs, E.J.; Fitzgerald, R.; Phillips, R.E.; Petty, R. *Tetrahedron* **1971**, 27, 935.

acidity, see Chap. 8) should be the same since the same bonds intervene. The field effect is different, however, because the chlorine atoms are closer in space to the COOH in **1** than they are in **2**. Thus, a comparison of the acidity of **1** and **2** should reveal whether a field effect is truly operating. The evidence obtained from such experiments is overwhelming that field effects are much more important than inductive effects.⁴⁵ In most cases, the two types of effect are considered together; in this book, they will not be separated but will use the name *field effect* to refer to their combined action.⁴⁶ Note that the field effect for **1** may be viewed as internal hydrogen bonding (see Sec. 3.A).

Functional groups can be classified as electron withdrawing ($-I$) or electron donating ($+I$) groups relative to hydrogen. This means, for example, that NO₂, a $-I$ group, will draw electrons to itself more than a hydrogen atom would if it occupied the same position in the molecule.



Thus, in α -nitrotoluene, the electrons in the N—C bond are farther away from the carbon atom than the electrons in the H—C bond of toluene. Similarly, the electrons of the C—Ph bond are farther away from the ring in α -nitrotoluene than they are in toluene. Field effects are always comparison effects. For example, compare the $-I$ or $+I$ effect of one group with another (usually hydrogen). Therefore, it may be said that, compared with hydrogen, the NO₂ group is electron withdrawing and the O[−] group is electron donating or electron releasing. However, there is no actual donation or withdrawal of electrons, but rather electron distortion or electron redistribution. While withdrawing and releasing terms are convenient to use, the terms merely represent a difference in the position of electrons due to the difference in electronegativity between H and NO₂ or between H and O[−].

Table 1.3 lists a number of the most common $-I$ and $+I$ groups.⁴⁷ It can be seen that compared with hydrogen, most groups are electron withdrawing. The only electron-donating groups are those with a formal negative charge (but not even all these), atoms of low electronegativity (Si,⁴⁸ Mg, etc., and perhaps alkyl groups). Alkyl groups⁴⁹ were formerly regarded as electron donating, but many examples of behavior have been found that can be interpreted only by the conclusion that alkyl groups are electron withdrawing compared with hydrogen.⁵⁰ In accord with this is the value of 2.472 for the group electronegativity of CH₃ (Table 1.2) compared with 2.176 for H. When an alkyl group is attached to an unsaturated or trivalent carbon (or other atom), its behavior is best explained by assuming it is $+I$ (see, e.g., Sec. 5.A.ii, 5.B.i, 8.E, 11.B.i), but when it is

⁴⁵ See Schneider, H.; Becker, N. *J. Phys. Org. Chem.* **1989**, 2, 214; Bowden, K.; Ghadir, K.D.F. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1333. Also see Exner, O.; Fiedler, P. *Collect. Czech. Chem. Commun.* **1980**, 45, 1251; Li, Y.; Schuster, G.B. *J. Org. Chem.* **1987**, 52, 3975.

⁴⁶ There has been some question as to whether it is even meaningful to maintain the distinction between the two types of effect: see Grob, C.A. *Helv. Chim. Acta* **1985**, 68, 882; Lenoir, D.; Frank, R.M. *Chem. Ber.* **1985**, 118, 753; Sacher, E. *Tetrahedron Lett.* **1986**, 27, 4683.

⁴⁷ See also, Ceppi, E.; Eckhardt, W.; Grob, C.A. *Tetrahedron Lett.* **1973**, 3627.

⁴⁸ For a review of field and other effects of silicon-containing groups, see Bassindale, A.R.; Taylor, P.G., in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 2, Wiley, NY, **1989**, pp. 893–963.

⁴⁹ See Levitt, L.S.; Widing, H.F. *Prog. Phys. Org. Chem.* **1976**, 12, 119.

⁵⁰ See Sebastian, J.F. *J. Chem. Educ.* **1971**, 48, 97.

TABLE 1.3 Field Effects of Various Groups Relative to Hydrogen^a

+I		-I	
O ⁻	NR ₃ ⁺	COOH	OR
COO ⁻	SR ₂ ⁺	F	COR
CR ₃	NH ₃ ⁺	Cl	SH
CHR ₂	NO ₂	Br	SR
CH ₂ R	SO ₂ R	I	OH
CH ₃	CN	OAr	C≡CR
D	SO ₂ Ar	COOR	Ar
			C≡CR ₂

^aThe groups are listed approximately in order of decreasing strength for both -I and +I groups. [Reprinted with permission from Ceppi, E.; Eckhardt, W.; Grob, C.A. *Tetrahedron Lett.* **1973**, 3627. Copyright © 1973, with permission from Elsevier Science.]

connected to a saturated atom, the results are not as clear, and alkyl groups seem to be +I in some cases and -I in others⁵¹ (see also, Sec. 8.F). When connected to a positive carbon, alkyl groups are clearly electron releasing.

It is clear that the field-effect order of alkyl groups attached to unsaturated systems is tertiary > secondary > primary > CH₃, but this order is not always maintained when the groups are attached to saturated systems. Deuterium is electron donating with respect to hydrogen.⁵² Other things being equal, atoms with *sp* bonding generally have a greater electron-withdrawing power than those with *sp*² bonding, which in turn have more electron-withdrawing power than those with *sp*³ bonding.⁵³ This accounts for the fact that aryl, vinylic, and alkynyl groups are -I. Field effects always decrease with increasing distance, and in most cases (except when a very powerful +I or -I group is involved), cause very little difference in a bond four bonds away or more. There is evidence that field effects can be affected by the solvent.⁵⁴

For discussions of field effects on acid and base strength and on reactivity, see Chapters 8 and 9, respectively.

1.J. BOND DISTANCES⁵⁵

The distances between atoms in a molecule are characteristic properties of the molecule and can give information if compared with the same bond in different molecules. The chief methods of determining bond distances and angles are X-ray diffraction (only for solids),

⁵¹ See Wahl, Jr., G.H.; Peterson, Jr., M.R. *J. Am. Chem. Soc.* **1970**, 92, 7238; Minot, C.; Eisenstein, O.; Hiberty, P. C.; Anh, N.T. *Bull. Soc. Chim. Fr.* **1980**, II-119.

⁵² Streitwieser, Jr., A.; Klein, H.S. *J. Am. Chem. Soc.* **1963**, 85, 2759.

⁵³ Bent, H.A. *Chem. Rev.* **1961**, 61, 275, p. 281.

⁵⁴ See Laurence, C.; Berthelot, M.; Lucon, M.; Helbert, M.; Morris, D.G.; Gal, J. *J. Chem. Soc. Perkin Trans. 2* **1984**, 705.

⁵⁵ For tables of bond distances and angles, see Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, S1-S19 (follows p. 1914); Tables of Interatomic Distances and Configurations in Molecules and Ions *Chem. Soc. Spec. Publ. No. 11*, **1958**; Interatomic Distances Supplement *Chem. Soc. Spec. Publ. No. 18*, **1965**; Harmony, M.D.; Laurie, V.W.; Kuczkowski, R.L.; Schwendeman, R.H.; Ramsay, D.A.; Lovas, F.J.; Lafferty, W.J.; Maki, A.G. *J. Phys. Chem. Ref. Data* **1979**, 8, 619-721. See Lathan, W.A.; Curtiss, L.A.; Hehre, W.J.; Lisle, J.B.; Pople, J.A. *Prog. Phys. Org. Chem.* **1974**, 11, 175; Topsom, R.D. *Prog. Phys. Org. Chem.* **1987**, 16, 85.

TABLE 1.4 Bond Lengths between sp^3 Carbons in Some Compounds

C—C Bond in	Reference	Bond Length (Å)
Diamond	58	1.544
C ₂ H ₆	59	1.5324 ± 0.0011
C ₂ H ₅ Cl	60	1.5495 ± 0.0005
C ₃ H ₈	61	1.532 ± 0.003
Cyclohexane	62	1.540 ± 0.015
<i>tert</i> -Butyl chloride	63	1.532
<i>n</i> -Butane to <i>n</i> -heptane	64	1.531–1.534
Isobutane	65	1.535 ± 0.001

electron diffraction (only for gases), and spectroscopic methods, especially microwave spectroscopy. The distance between the atoms of a bond is not constant, since the molecule is always vibrating; the measurements obtained are therefore average values, so that different methods give different results.⁵⁶ However, this must be taken into account only when fine distinctions are made.

Measurements vary in accuracy, but indications are that similar bonds have fairly constant lengths from one molecule to the next. While exceptions are known,⁵⁷ the variation is generally < 1%. Table 1.4 shows distances for single bonds between two sp^3 carbons.^{58–65} However, an analysis of C—OR bond distances in >2000 ethers and carboxylic esters (all with sp^3 carbon) shows that this distance increases with increasing electron withdrawal in the R group and as the C changes from primary to secondary to tertiary.⁶⁶ For these compounds, mean bond lengths of the various types ranged from 1.418 to 1.475 Å. Certain substituents can also influence bond length. The presence of a silyl substituent β^- to a C—O (ester) linkage can lengthen the C—O, thereby weakening it.⁶⁷ This finding is believed to result from $\sigma-\sigma^*$ interactions in which the C—Si σ bonding orbital acts as the donor and the C—O σ^* orbitals acts as the receptor.

⁵⁶ Burkert, U.; Allinger, N.L. *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington, **1982**, pp. 6–9; Whiffen, D.H. *Chem. Ber.* **1971**, 7, 57–61; Stals, J. *Rev. Pure Appl. Chem.* **1970**, 20, 1, pp. 2–5.

⁵⁷ Schleyer, P.v.R.; Bremer, M. *Angew. Chem. Int. Ed.* **1989**, 28, 1226.

⁵⁸ Lonsdale, K. *Philos. Trans. R. Soc. London* **1947**, A240, 219.

⁵⁹ Bartell, L.S.; Higginbotham, H.K. *J. Chem. Phys.* **1965**, 42, 851.

⁶⁰ Wagner, R.S.; Dailey, B.P. *J. Chem. Phys.* **1957**, 26, 1588.

⁶¹ Iijima, T. *Bull. Chem. Soc. Jpn.* **1972**, 45, 1291.

⁶² Tables of Interatomic Distances, Ref. 55.

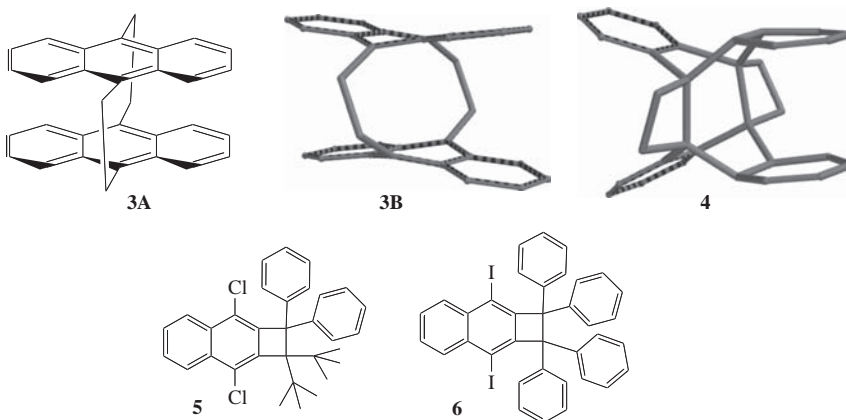
⁶³ Momany, F.A.; Bonham, R.A.; Druelinger, M.L. *J. Am. Chem. Soc.* **1963**, 85, 3075. Also see, Lide, Jr., D.R.; Jen, M. *J. Chem. Phys.* **1963**, 38, 1504.

⁶⁴ Bonham, R.A.; Bartell, L.S.; Kohl, D.A. *J. Am. Chem. Soc.* **1959**, 81, 4765.

⁶⁵ Hilderbrandt, R.L.; Wieser, J.D. *J. Mol. Struct.* **1973**, 15, 27.

⁶⁶ Allen, F.H.; Kirby, A.J. *J. Am. Chem. Soc.* **1984**, 106, 6197; Jones, P.G.; Kirby, A.J. *J. Am. Chem. Soc.* **1984**, 106, 6207.

⁶⁷ White, J.M.; Robertson, G.B. *J. Org. Chem.* **1992**, 57, 4638.



Bond distances for some important bond types are given in Table 1.5.⁶⁸ Although a typical carbon–carbon single bond has a bond length of ~ 1.54 Å, certain molecules are known that have significantly longer bond lengths.⁶⁹ Calculations have been done for unstable molecules that showed them to have long bond lengths, and an analysis of the X-ray structure for a photoisomer (**4**) of [2.2]-tetrabenzoparacyclophane, **3A** (also see Sec. 2.G), showed a C—C bond length of 1.77 Å.^{69,70} Note that **3A** is shown as the molecular model **3B** for comparison with photoisomer **4**, which has the two four-membered ring moieties. Long bond lengths have been observed in stable molecules (e.g., benzocyclobutane derivatives).⁷¹ A bond length of 1.729 Å was reliably measured in 1,1-di-*tert*-butyl-2,2-diphenyl-3,8-dichlorocyclobutan[*b*]naphthalene, **5**.⁷² X-ray analysis of several of these derivations confirmed the presence of long C—C bonds, with **6** having a confirmed bond length of 1.734 Å.⁷³

A theoretical study has been reported, using computer simulation to apply encapsulation, strapping back, and stiffening to “squeeze” C—C bonds, leading to shorter bonds than would be observed if hybridization and conjugative effects operated alone.⁷⁴ The additional strain caused by threefold symmetric geometry constraints is believed responsible for this effect rather than changes in hybridization alone, as postulated by others.^{75–82}

⁶⁸ Except where noted, values are from Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, S1–S19 (follows p. 1914). In this source, values are given to three significant figures.

⁶⁹ Kaupp, G.; Boy, J. *Angew. Chem. Int. Ed.* **1997**, 36, 48.

⁷⁰ Ehrenberg, M. *Acta Crystallogr.* **1966**, 20, 182.

⁷¹ Toda, F.; Tanaka, K.; Stein, Z.; Goldberg, I. *Acta Crystallogr., Sect. C* **1996**, 52, 177.

⁷² Toda, F.; Tanaka, K.; Watanabe, M.; Taura, K.; Miyahara, I.; Nakai, T.; Hirotsu, K. *J. Org. Chem.* **1999**, 64, 3102.

⁷³ Tanaka, K.; Takamoto, N.; Tezuka, Y.; Kato, M.; Toda, F. *Tetrahedron* **2001**, 57, 3761.

⁷⁴ Huntley, D.R.; Markopoulos, G.; Donovan, P.M.; Scott, L.T.; Hoffmann, R. *Angew. Chem. Int. Ed.* **2005**, 44, 7549.

⁷⁵ See Tanaka, M.; Sekiguchi, A. *Angew. Chem. Int. Ed.* **2005**, 44, 5821–5823.

⁷⁶ Costain, C.C.; Stoicheff, B.P. *J. Chem. Phys.* **1959**, 30, 777.

⁷⁷ For a full discussion of alkyne bond distances, see Simonetta, M.; Gavezzotti, A. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, **1978**.

⁷⁸ See Henry, B.R. *Acc. Chem. Res.* **1987**, 20, 429.

⁷⁹ Bartell, L.S.; Roth, E.A.; Hollowell, C.D.; Kuchitsu, K.; Young, Jr., J.E. *J. Chem. Phys.* **1965**, 42, 2683.

⁸⁰ For reviews of carbon–halogen bonds, see Trotter, J. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1; Wiley, NY, **1973**, pp. 49–62; Mikhailov, B.M. *Russ. Chem. Rev.* **1971**, 40, 983.

⁸¹ Lide, Jr., D.R. *Tetrahedron* **1962**, 17, 125.

⁸² Rajput, A.S.; Chandra, S. *Bull. Chem. Soc. Jpn.* **1966**, 39, 1854.

TABLE 1.5 Bond Distances^a

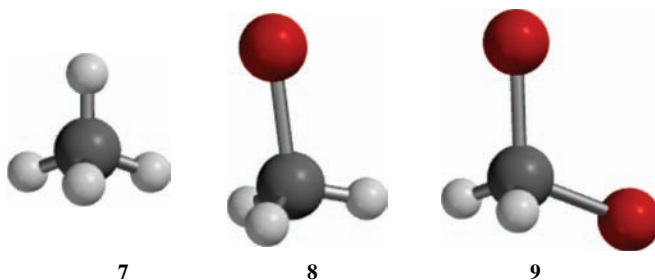
Bond Type	Length (Å)	Typical Compounds		
C—C				
sp^3-sp^3	1.53			
sp^3-sp^2	1.51	Acetaldehyde, toluene, propene		
sp^3-sp	1.47	Acetonitrile, propyne		
sp^2-sp^2	1.48	Butadiene, glyoxal, biphenyl		
sp^2-sp	1.43	Acrylonitrile, vinylacetylene		
$sp-sp$	1.38	Cyanoacetylene, butadiyne		
C=C				
sp^2-sp^2	1.32	Ethylene		
sp^2-sp	1.31	Ketene, allenes		
$sp-sp$ ⁷⁶	1.28	Butatriene, carbon suboxide		
C≡C ⁷⁷				
$sp-sp$	1.18	Acetylene		
C—H ⁷⁸				
sp^3-H	1.09	Methane		
sp^2-H	1.08	Benzene, ethylene		
$sp-H$ ⁷⁹	1.08	HCN , acetylene		
C—O				
sp^3-O	1.43	Dimethyl ether, ethanol		
sp^2-O	1.34	Formic acid		
C=O				
sp^2-O	1.21	Formaldehyde, formic acid		
$sp-O$ ⁶²	1.16	CO₂		
C—N				
sp^3-N	1.47	Methylamine		
sp^2-N	1.38	Formamide		
C=N				
sp^2-N	1.28	Oximes, imines		
C≡N				
$sp-N$	1.14	HCN		
C—S				
sp^3-S	1.82	Methanethiol		
sp^2-S	1.75	Diphenyl sulfide		
$sp-S$	1.68	CH ₃ SCN		
C=S				
$sp-S$	1.67	CS₂		
C—halogen ⁸⁰	F	Cl	Br	I
sp^3 -halogen	1.40	1.79	1.97	2.16
sp^2 -halogen	1.34	1.73	1.88	2.10
sp -halogen	1.27 ⁸¹	1.63	1.79 ⁸²	1.99 ⁸²

^aThe values given are average lengths and do not necessarily apply exactly to the compounds mentioned.⁸⁰
 [Reproduced from Allen F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor R. *J. Chem. Soc. Perkin Trans. 2* **1987**, S1–S19 with permission from the Royal Society of Chemistry.]

There are indications that a C—D bond is slightly shorter than a corresponding C—H bond. Thus, electron-diffraction measurements of C₂H₆ and C₂D₆ showed a C—H bond distance of 1.1122 ± 0.0012 Å and a C—D distance of 1.1071 ± 0.0012 Å.⁵⁹

As seen in Table 1.5, carbon bonds are shortened by increasing *s* character. This is most often explained by the fact that, as the percentage of *s* character in a hybrid orbital

increases, the orbital becomes more like an s orbital and hence is held more tightly by the nucleus than an orbital with less s character. However, other explanations have also been offered (see Sec. 2.C), and the matter is not completely settled. In general, molecules with one π bond ($X=X$) have shorter bond distances when compared to single bonds, $X-X$, and molecules with two π bonds ($X\equiv X$) have even shorter bond lengths. Indeed, the bond length clearly decreases in the molecules H_3C-CH_3 , $H_2C=CH_2$, and $HC\equiv CH$: C—C bond lengths of 1.538, 1.338, and 1.203 Å.⁸³ There is work that suggests the absence of σ bonds may play a role in producing short bond distances in molecules that contain only π bonds.⁸⁴ This suggests that σ bonds prevent π bonds from adopting their optimal shorter distances. Such bonds occur in some organometallic compounds.



1.K. BOND ANGLES

The bond angles of sp^3 carbon should be the tetrahedral angle $109^\circ 28'$ when the four atoms or groups are relatively small and identical, as in methane, neopentane, or carbon tetrachloride. As atoms or groups become larger, bond angles are distorted to accommodate the larger size of the attached units. In most cases, the angles deviate a little from the pure tetrahedral value unless two or more units are very large. Molecular models 7–9 illustrate this phenomenon. The H—C—H bond angles in methane (7) are calculated for the model to be $109^\circ 47'$, whereas the Br—C—H bond angle in 8 is calculated to be 108.08° and the Br—C—Br bond angle in 9 is calculated to be 113.38° . Note that the C—Br bond length is longer than the C—H bond lengths. As the bond angles expand to accommodate the larger atoms, the H—C—H bond angles in 8 and 9 must compress to a smaller angle. In 2-bromopropane, the bromine atom also has a methyl group (compare with bromomethane 8 where Br competes with H) and, the C—C—Br angle in 2-bromopropane is 114.2° .⁸⁵

Variations are generally found from the ideal values of 120° and 180° for sp^2 and sp carbon, respectively. These deviations occur because of slightly different hybridizations; that is, a carbon bonded to four other atoms hybridizes one s and three p orbitals, but the four hybrid orbitals thus formed are generally not exactly equivalent, nor does each contain exactly 25% s and 75% p character. Because the four atoms have (in the most general case) different electronegativities, each makes its own demand for electrons from the carbon atom.⁸⁶ The carbon atom supplies more p character when it is bonded to more

⁸³ Vannes, G.J.H.; Vos, A. *Acta Crystallogr. Sect. B* **1978**, B34, 1947; Vannes, G.J.H.; Vos, A. *Acta Crystallogr. Sect. B*, **1979**, B35, 2593; McMullan, R.K.; Kwick, A. *Acta Crystallogr. Sect. B*, **1992**, B48, 726.

⁸⁴ Jemmis, E.D.; Pathak, B.; King, R.B.; Schaefer, III, H.F. *Chem. Commun.* **2006**, 2164.

⁸⁵ Schwendeman, R.H.; Tobiasson, F.L. *J. Chem. Phys.* **1965**, 43, 201.

⁸⁶ For a review of this concept, see Bingel, W.A.; Lüttke, W. *Angew. Chem. Int. Ed.* **1981**, 20, 899.

TABLE 1.6 Oxygen, Sulfur, and Nitrogen Bond Angles in Some Compounds

Angle	Value	Compound	Reference
H—O—H	104°27'	Water	7
C—O—H	107–109°	Methanol	62
C—O—C	111°43'	Dimethyl ether	88
C—O—C	124° ± 5°	Diphenyl ether	89
H—S—H	92.1°	Hydrogen sulfide	82
C—S—H	99.4°	Methanethiol	82
C—S—C	99.1°	Dimethyl sulfide	90
H—N—H	106°46'	Ammonia	7
H—N—H	106°	Methylamine	91
C—N—H	112°	Methylamine	83
C—N—C	108.7°	Trimethylamine	92

electronegative atoms, so that in chloromethane, for example, the bond to chlorine has somewhat $> 75\%$ p character, which of course requires that the other three bonds have somewhat less, since there are only three p orbitals (and one s) to be divided among the four hybrid orbitals.⁸⁷ Of course, in strained molecules (e.g., **3–6**), the bond angles may be greatly distorted from the ideal values (also see Sec. 4.Q).

For molecules that contain oxygen and nitrogen, angles of 90° are predicted from p^2 bonding. However, as seen in Section 1.B, the angles of water and ammonia are much larger than this, as are the angles of other organic molecules that contain oxygen and nitrogen (Table 1.6).^{88–92} In fact, they are much closer to the tetrahedral angle of $109^\circ 28'$ than to 90° . These facts have led to the suggestion that in these compounds oxygen and nitrogen use sp^3 bonding. Using the hybridization model, these atoms are said to form bonds by the overlap of two (or three) p orbitals with $1s$ orbitals of the hydrogen atoms, which means that they hybridize their $2s$ and $2p$ orbitals to form four sp^3 orbitals and then use only two (or three) of these for bonding with hydrogen, the others remaining occupied by unshared pairs (also called *lone pairs*). If this description is valid, and it is generally accepted by most chemists today,⁹³ it becomes necessary to explain why the angles of these two compounds are in fact not $109^\circ 28'$ but a few degrees smaller. One explanation that has been offered is that the unshared electron pair actually has a greater steric requirement (see Sec. 4.Q) than the electrons in a bond, since there is no second nucleus to draw away some of the electron density and the bonds are thus crowded together. However, most evidence is that unshared pairs have smaller steric requirements than bonds⁹⁴ and the explanation most commonly

⁸⁷ This assumption has been challenged: see Pomerantz, M.; Liebman, J.F. *Tetrahedron Lett.* **1975**, 2385.

⁸⁸ Blukis, V.; Kasai, P.H.; Myers, R.J. *J. Chem. Phys.* **1963**, 38, 2753.

⁸⁹ Abrahams, S.C. *Q. Rev. Chem. Soc.* **1956**, 10, 407.

⁹⁰ Iijima, T.; Tsuchiya, S.; Kimura, M. *Bull. Chem. Soc. Jpn.* **1977**, 50, 2564.

⁹¹ Lide, Jr., D.R. *J. Chem. Phys.* **1957**, 27, 343.

⁹² Lide, Jr., D.R.; Mann, D.E. *J. Chem. Phys.* **1958**, 28, 572.

⁹³ The O—H bonding is between 2 H $1s$ and 2 O p orbitals, and that the increased angles come from repulsion of the hydrogen or carbon atoms. See Laing, M., *J. Chem. Educ.* **1987**, 64, 124.

⁹⁴ See Blackburne, I.D.; Katritzky, A.R.; Takeuchi, Y. *Acc. Chem. Res.* **1975**, 8, 300; Aaron, H.S.; Ferguson, C.P. *J. Am. Chem. Soc.* **1976**, 98, 7013; Anet, F.A.L.; Yavari, I. *J. Am. Chem. Soc.* **1977**, 99, 2794; Vierhapper, F.W.; Eliel, E.L. *J. Org. Chem.* **1979**, 44, 1081; Gust, D.; Fagan, M.W. *J. Org. Chem.* **1980**, 45, 2511. For other views, see Lambert, J.B.; Featherman, S.I. *Chem. Rev.* **1975**, 75, 611; Breuker, K.; Kos, N.J.; van der Plas, H.C.; van Veldhuizen, B. *J. Org. Chem.* **1982**, 47, 963.

accepted is that the hybridization is not pure sp^3 . As seen above, an atom supplies more p character when it is bonded to more electronegative atoms. An unshared pair may be considered to be an “atom” of the lowest possible electronegativity, since there is no attracting power at all. Consequently, the unshared pairs have more s and the bonds more p character than pure sp^3 orbitals, making the bonds somewhat more like p^2 bonds and reducing the angle. However, these arguments ignore the steric effect of the atoms or groups attached to oxygen or nitrogen. As seen in Table 1.6, oxygen, nitrogen, and sulfur angles generally increase with decreasing electronegativity of the substituents. Note that the explanation given above cannot explain why some of these angles are *greater* than the tetrahedral angle.

1.L. BOND ENERGIES⁹⁵

There are two kinds of bond energy. The energy necessary to cleave a bond to give the constituent radicals is called the *dissociation energy* (D). For example, D for $\text{H}_2\text{O} \rightarrow \text{HO} + \text{H}$ is $118 \text{ kcal mol}^{-1}$ (494 kJ mol^{-1}). However, this is not taken as the energy of the O—H bond in water, since D for $\text{H—O} \rightarrow \text{H} + \text{O}$ is $100 \text{ kcal mol}^{-1}$ (418 kJ mol^{-1}). The average of these two values, $109 \text{ kcal mol}^{-1}$ (456 kJ mol^{-1}), is taken as the *bond energy* (E). In diatomic molecules, of course, $D = E$.

The D values may be easy or difficult to measure. They can be estimated by various techniques.⁹⁶ When properly applied, “Pauling’s original electronegativity equation accurately describes homolytic bond dissociation enthalpies of common covalent bonds, including highly polar ones, with an average deviation of ($1.5 \text{ kcal mol}^{-1}$ ($\sim 6.3 \text{ kJ mol}^{-1}$) from literature values)”.⁹⁷ Whether measured or calculated, there is no question as to what D values mean. With E values the matter is not so simple. For methane, the total energy of conversion from CH_4 to $\text{C} + 4\text{H}$ (at 0 K) is $393 \text{ kcal mol}^{-1}$ (1644 kJ mol^{-1}).⁹⁸ Consequently, E for the C—H bond in methane is 98 kcal mol^{-1} (411 kJ mol^{-1}) at 0 K. The more usual practice is not to measure the heat of atomization (i.e., the energy necessary to convert a compound to its atoms) directly, but to calculate it from the heat of combustion. Such a calculation is shown in Fig. 1.12.

Heats of combustion are very accurately known for hydrocarbons.⁹⁹ For methane, the value at 25°C is $212.8 \text{ kcal mol}^{-1}$ ($890.4 \text{ kJ mol}^{-1}$), which leads to a heat of atomization of $398.0 \text{ kcal mol}^{-1}$ (1665 kJ mol^{-1}) or a value of E for the C—H bond at 25°C of $99.5 \text{ kcal mol}^{-1}$ (416 kJ mol^{-1}). This method is fine for molecules like methane in which all the

⁹⁵ Blanksby, S.J.; Ellison, G.B. *Acc. Chem. Res.* **2003**, *36*, 255. For reviews including methods of determination, see Wayner, D.D.M.; Griller, D. *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, *1*, 159; Kerr, J.A. *Chem. Rev.* **1966**, *66*, 465; Wiberg, K.B., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, **1971**, pp. 207–245.

⁹⁶ Cohen, N.; Benson, S.W. *Chem. Rev.* **1993**, *93*, 2419; Korth, H.-G.; Sicking, W. *J. Chem. Soc. Perkin Trans. 2* **1997**, 715.

⁹⁷ Matsunaga, N.; Rogers, D.W.; Zavitsas, A.A. *J. Org. Chem.* **2003**, *68*, 3158.

⁹⁸ For the four steps, D values are 101–102, 88, 124, and 80 kcal mol^{-1} (423–427, 368, 519, and 335 kJ mol^{-1}), respectively, though the middle values are much less reliable than the other two: Knox, B.E.; Palmer, H.B. *Chem. Rev.* **1961**, *61*, 247; Brewer, R.G.; Kester, F.L. *J. Chem. Phys.* **1964**, *40*, 812; Linevsky, M.J. *J. Chem. Phys.* **1967**, *47*, 3485.

⁹⁹ See Cox, J.D.; Pilcher, G., *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, **1970**; Domalski, E.S. *J. Phys. Chem. Ref. Data* **1972**, *1*, 221–277; Stull, D.R.; Westrum Jr., E.F.; Sinke, G.C. *The Chemical Thermodynamics of Organic Compounds*, Wiley, NY, **1969**.

				kcal	kJ
C_2H_6 (gas)	+ 3.5 O_2	= 2 CO_2 (gas)	+ 3 H_2O (liq)	+372.9	+1560
	2 CO_2 (gas)	= 2 C (graphite)	+ 2 O_2 (gas)	-188.2	-787
	3 H_2O (liq)	= 3 H_2 (gas)	+ 1.5 O_2 (gas)	-204.9	-857
	3 H_2 (gas)	= 6 H (gas)		-312.5	-1308
	2 C (graphite)	= 2 C (gas)		-343.4	-1437
<hr/>					
C_2H_6 (gas)		= 6 H (gas)	+ 2 C (gas)	-676.1 kcal	-2829 kJ

FIG. 1.12. Calculation of the heat of atomization of ethane at 25 °C.

bonds are equivalent, but for more complicated molecules, assumptions must be made. Thus for ethane, the heat of atomization at 25 °C is 676.1 kcal mol⁻¹ or 2829 kJ mol⁻¹ (Fig. 1.12), and it must be decided how much of this energy is due to the C—C bond and how much to the six C—H bonds. Any assumption must be artificial, since there is no way of actually obtaining this information, and indeed the question has no real meaning. If the assumption is made that E for each of the C—H bonds is the same as E for the C—H bond in methane (99.5 kcal mol⁻¹ or 416 kJ mol⁻¹), then 6×99.5 (or 416) = 597.0 (or 2498), leaving 79.1 kcal mol⁻¹ (331 kJ mol⁻¹) for the C—C bond. However, a similar calculation for propane gives a value of 80.3 (or 336) for the C—C bond, and for isobutane, the value is 81.6 (or 341). A consideration of heats of atomization of isomers also illustrates the difficulty. The E values for the C—C bonds in pentane, isopentane, and neopentane, similarly calculated from heats of atomization, are (at 25 °C) 81.1, 81.8, and 82.4 kcal mol⁻¹ (339, 342, 345 kJ mol⁻¹), respectively, even though all of them have twelve C—H bonds and four C—C bonds.

These differences have been attributed to various factors caused by the introduction of new structural features. Thus isopentane has a tertiary carbon whose C—H bond does not have exactly the same amount of s character as the C—H bond in pentane, which for that matter contains secondary carbons not possessed by methane. It is known that D values, which *can* be measured, are not the same for primary, secondary, and tertiary C—H bonds (see Table 5.2). There is also the steric factor (see Sec. 4.Q). Hence it is certainly incorrect to use the value of 99.5 kcal mol⁻¹ (416 kJ mol⁻¹) from methane as the E value for all C—H bonds. Several empirical equations have been devised that account for these factors; the total energy can be computed¹⁰⁰ if the proper set of parameters (one for each structural feature) is inserted. Of course, these parameters are originally calculated from the known total energies of some molecules that contain the structural feature.

Table 1.7 gives E values for various bonds.^{101–104} The values given are averaged over a large series of compounds. The literature contains charts that take hybridization into account (thus an sp^3 C—H bond does not have the same energy as an sp^2 C—H bond).¹⁰⁵ Bond dissociation

¹⁰⁰ For a review, see Cox, J.D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, **1970**, pp. 531–597. See also, Gasteiger, J.; Jacob, P.; Strauss, U. *Tetrahedron* **1979**, *35*, 139.

¹⁰¹ These values, except where noted, are from Lovering, E.G.; Laidler, K.J. *Can. J. Chem.* **1960**, *38*, 2367; Levi, G.I.; Balandin, A.A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1960**, 149.

¹⁰² Grelbig, T.; Pötter, B.; Seppelt, K. *Chem. Ber.* **1987**, *120*, 815.

¹⁰³ Bedford, A.F.; Edmondson, P.B.; Mortimer, C.T. *J. Chem. Soc.* **1962**, 2927.

¹⁰⁴ The average of the values obtained was $DH^\circ(\text{O—O})$. dos Santos, R.M.B.; Muralha, V.S.F.; Correia, C.F.; Simões, J.A.M. *J. Am. Chem. Soc.* **2001**, *123*, 12670.

¹⁰⁵ Cox, J.D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, **1970**, pp. 531–597; Cox, J.D. *Tetrahedron* **1962**, *18*, 1337.

TABLE 1.7 Bond Energy (*E*) Values at 25 °C for Some Important Bond Types^{a,b}

Bond	kcal mol ⁻¹	kJ mol ⁻¹	Bond	kcal mol ⁻¹	kJ mol ⁻¹
O—H	110–111	460–464	C—S ¹⁰²	61	255
C—H	96–99	400–415	C—I	52	220
N—H	93	390	C≡C	199–200	835
S—H	82	340	C=C	146–151	610–630
C—F			C—C	83–85	345–355
C—H	96–99	400–415	C≡N	204	854
C—O	85–91	355–380	C=O	173–81	724–757
C—C	83–85	345–355	C=N ¹⁰³	143	598
C—Cl	79	330	O—O ¹⁰⁴	42.9	179.6 ± 4.5
C—N ¹⁰³	69–75	290–315			
C—Br	66	275			

^aThe *E* values are arranged within each group in order of decreasing strength. The values are averaged over a large series of compounds.

^bSee Ref. 101.

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energies, both calculated and experientially determined, are constantly being refined. Improved values are available for the O—O bond of peroxides,¹⁰⁶ the C—H bond in alkyl amines,¹⁰⁷ the N—H bond in aniline derivatives,¹⁰⁸ the N—H bond in protonated amines,¹⁰⁹ the O—H bond in phenols,¹¹⁰ the C—H bond in alkenes,¹¹¹ amides and ketones,¹¹² and in CH₂X₂ and CH₃X derivatives (X = COOR, C=O, SR, NO₂, etc.),¹¹³ the O—H and S—H bonds of alcohols and thiols,¹¹⁴ and the C—Si bond of aromatic silanes.¹¹⁵ Solvent plays a role in the *E* values. When phenols bearing electron-releasing groups are in aqueous media, calculations show that the bond dissociation energies decrease due to hydrogen-bonding interactions with water molecules, while electron-withdrawing substituents on the phenol increase the bond dissociation energies.¹¹⁶

Certain generalizations can be derived from the data in Table 1.7.

1. There is a correlation of bond strengths with bond distances. A comparison of Tables 1.5 and 1.7 shows that, in general, *shorter bonds are stronger bonds*. Since it is

¹⁰⁶ Bach, R.D.; Ayala, P.Y.; Schlegel, H.B. *J. Am. Chem. Soc.* **1996**, 118, 12758.

¹⁰⁷ Wayner, D.D.M.; Clark, K.B.; Rauk, A.; Yu, D.; Armstrong, D.A. *J. Am. Chem. Soc.* **1997**, 119, 8925. For the α C—H bond of tertiary amines, see Dombrowski, G.W.; Dinnocenzo, J.P.; Farid, S.; Goodman, J.L. *J. Org. Chem.* **1999**, 64, 427.

¹⁰⁸ Bordwell, F.G.; Zhang, X.-M.; Cheng, J.-P. *J. Org. Chem.* **1993**, 58, 6410. See also, Li, Z.; Cheng, J.-P. *J. Org. Chem.* **2003**, 68, 7350.

¹⁰⁹ Liu, W.-Z.; Bordwell, F.G. *J. Org. Chem.* **1996**, 61, 4778.

¹¹⁰ Lucarini, M.; Pedrielli, P.; Pedulli, G.F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, 61, 9259. For the O—H, *E* of polymethylphenols, see de Heer, M.I.; Korth, H.-G.; Mulder, P. *J. Org. Chem.* **1999**, 64, 6969.

¹¹¹ Zhang, X.-M. *J. Org. Chem.* **1998**, 63, 1872.

¹¹² Bordwell, F.G.; Zhang, X.-M.; Filler, R. *J. Org. Chem.* **1993**, 58, 6067.

¹¹³ Brocks, J.J.; Beckhaus, H.-D.; Beckwith, A.L.J.; Rüchardt, C. *J. Org. Chem.* **1998**, 63, 1935.

¹¹⁴ Hadad, C.M.; Rablen, P.R.; Wiberg, K.B. *J. Org. Chem.* **1998**, 63, 8668.

¹¹⁵ Cheng, Y.-H.; Zhao, X.; Song, K.-S.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* **2002**, 67, 6638.

¹¹⁶ Guerra, M.; Amorati, R.; Pedulli, G.F. *J. Org. Chem.* **2004**, 69, 5460.

- known that increasing s character shortens bonds (Sec. 1.J), it follows that bond strengths increase with increasing s character. Calculations show that ring strain has a significant effect on bond dissociation energy, particularly the C—H bond of hydrocarbons, because it forces the compound to adopt an undesirable hybridization.¹¹⁷
2. Bonds become weaker moving down the periodic table. Compare C—O and C—S, or the carbon–halogen bonds C—F, C—Cl, C—Br, C—I. This is a consequence of the first generalization, since bond distances must increase going down the periodic table because the number of inner electrons increases. However, note that “high-level *ab initio* molecular orbital calculations confirm that the effect of alkyl substituents on R—X bond dissociation energies varies according to the nature of X (the stabilizing influence of the ionic configurations to increase in the order Me < Et < *i*-Pr < *t*-Bu), accounting for the *increase* (rather than expected decrease) in the R—X bond dissociation energies with increasing alkylation in the R—OCH₃, R—OH, and R—F molecules. This effect of X has been explained in terms of the increasing contribution of the ionic R⁺X[−] configuration for electronegative X substituents.”¹¹⁸
 3. Double bonds are both shorter and stronger than the corresponding single bonds, but not twice as strong, because π overlap is < σ overlap. This means that a σ bond is stronger than a π bond. The difference in energy between a single bond, say C—C, and the corresponding double bond is the amount of energy necessary to cause rotation around the double bond.¹¹⁹

Calculations suggest that covalent bond strength and also equilibrium bond length are not determined by maximum overlap of the σ valence orbitals, as described in previous sections.¹²⁰ Rather, orbital interactions, Pauli repulsion, and quasiclassical electrostatic attraction determine both.

Solvents are thought to play a role in bond dissociation energy of molecules, as noted for phenol above, and also for intermediates (see Chap 5). It has been assumed that the solvation enthalpies were small and they have been largely ignored in calculations involving various reactions. Solvent effects on the bond dissociation energy of a molecule may arise from the difference in solvation enthalpies between the molecule and the key intermediate. For radical reactions that involve polar molecules, the radical–solvent interaction may be larger.¹²¹

¹¹⁷ Feng, Y.; Liu, L.; Wang, J.-T.; Zhao, S.-W.; Guo, Q.X. *J. Org. Chem.* **2004**, 69, 3129; Song, K.-S.; Liu, L.; Guo, Q.X. *Tetrahedron* **2004**, 60, 9909.

¹¹⁸ Coote, M.L.; Pross, A.; Radom, L. *Org. Lett.* **2003**, 5, 4689.

¹¹⁹ See Miller, S.I. *J. Chem. Educ.* **1978**, 55, 778.

¹²⁰ Krapp, A.; Bickelhaupt, F.M.; Frenking, G. *Chem.: Eur. J.* **2006**, 12, 9196.

¹²¹ Borges dos Santos, R.M.; Costa Cabral, B.J.; Martinho Simões, J.A. *Pure Appl. Chem.* **2007**, 79, 1369.

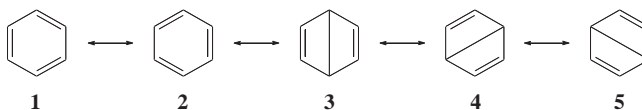
Delocalized Chemical Bonding

Although the bonding of many compounds can be adequately described by a single Lewis structure (Sec. 1.F), this is insufficient for many other compounds. Such compounds contain one or more bonding orbitals that are not restricted to two atoms, but rather they are spread out over three or more atoms. Such bonding is said to be *delocalized*.¹ In other words, the bonding electrons are dispersed over several atoms rather than localized on one atom. This Chapter 2 will discuss those compounds that must be represented in this way.

The two chief general methods of approximately solving the wave equation, discussed in Chapter 1, are also used for compounds containing delocalized bonds.² In the valence bond method, several possible Lewis structures (called *canonical forms*) are drawn, and the molecule is taken to be a weighted average of them. Each Ψ in Eq. (1–3), represents one of these structures. Therefore,

$$\Psi = c_1\psi_1 + c_2\psi_2 + \cdots$$

is the representation of a real structure as a weighted average of two or more canonical forms, which is called *resonance*. For benzene the canonical forms are drawn as **1** and **2**. Double-headed arrows (\longleftrightarrow) are used to indicate resonance. When the wave equation is solved, it is found that the energy value obtained by equal participation of **1** and **2** is lower than that for **1** or **2** alone. If **3–5** (called *Dewar structures*) are also considered, the value is lower still. According to this method, **1** and **2** contribute 39% each to the actual molecule and the others 7.3% each.³ The carbon–carbon bond order is 1.463 (not 1.5, which would be the case if only **1** and **2** contributed).



In the valence bond method, the *bond order* of a particular bond is the sum of the weights of those canonical forms in which the bond is double plus 1 for the single bond that

¹ See Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, **1955**.

² There are other methods. See Streitwieser, Jr., A. *Molecular Orbital Theory for Organic Chemists*, Wiley, NY, **1961**, pp. 27–29; Hirst, D.M.; Linnett, J.W. *J. Chem. Soc.* **1962**, 1035; Firestone, R.A. *J. Org. Chem.* **1969**, *34*, 2621.

³ Pullman, A. *Prog. Org. Chem.* **1958**, *4*, 31, p. 33.

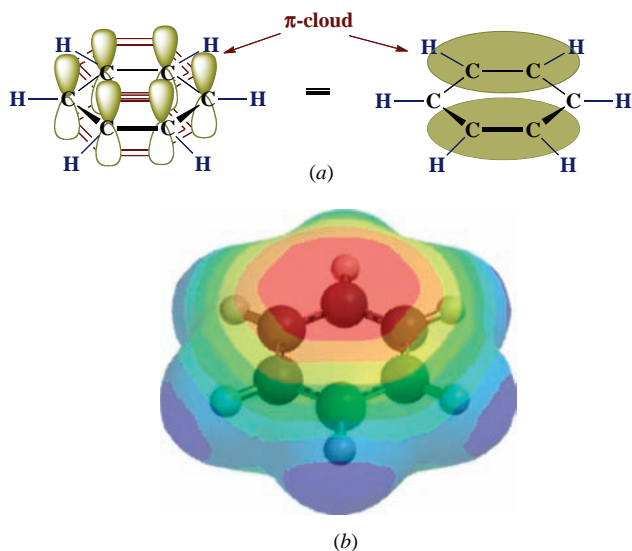


FIG. 2.1. (a) Traditional drawing of the overlapping p orbitals that comprise the π -cloud in benzene. (b) The electrostatic potential map of benzene, indicating the high concentration of electron density above and below the plane of the atoms, but in the center of the six-membered ring, consistent with the aromatic cloud.

is present in all of them.⁴ Thus, according to this picture, each C—C bond is not halfway between a single and a double bond but is somewhat less. The energy of the actual molecule is obviously less than that of any one Lewis structure, since otherwise it would have one of those structures. The difference in energy between the actual molecule and the Lewis structure of lowest energy is called the *resonance energy*. Of course, the Lewis structures are not real, and their energies can only be estimated. Resonance in benzene is possible by overlap of the p orbitals, orthogonal to the plane of carbon and hydrogen atoms. This resonance is associated with the aromatic π -cloud. Figure 2.1 shows the planar σ -bond framework of benzene, with the overlapping p -orbitals forming the aromatic π -cloud. Figure 2.1 also shows the electron potential map of benzene. Note the darker area above the middle of the ring that corresponds to high electron density, consistent with the high electron density of the aromatic π -cloud.

2.A. MOLECULAR ORBITALS

While the resonance picture is often used to describe the structure of molecules, as structures become more complicated (e.g., naphthalene and pyridine), quantitative valence bond calculations become much more difficult. Therefore, the MO method is used much more often for the solution of wave equations.⁵ Examination of benzene by this method (qualitatively) shows that each carbon atom, being connected to three other atoms, uses sp^2

⁴ See Clarkson, D.; Coulson, C.A.; Goodwin, T.H. *Tetrahedron* **1963**, *19*, 2153. See also, Herndon, W.C.; Párkányi, C. *J. Chem. Educ.* **1976**, *53*, 689.

⁵ See Dewar, M.J.S. *Mol. Struct. Energ.* **1988**, *5*, 1.

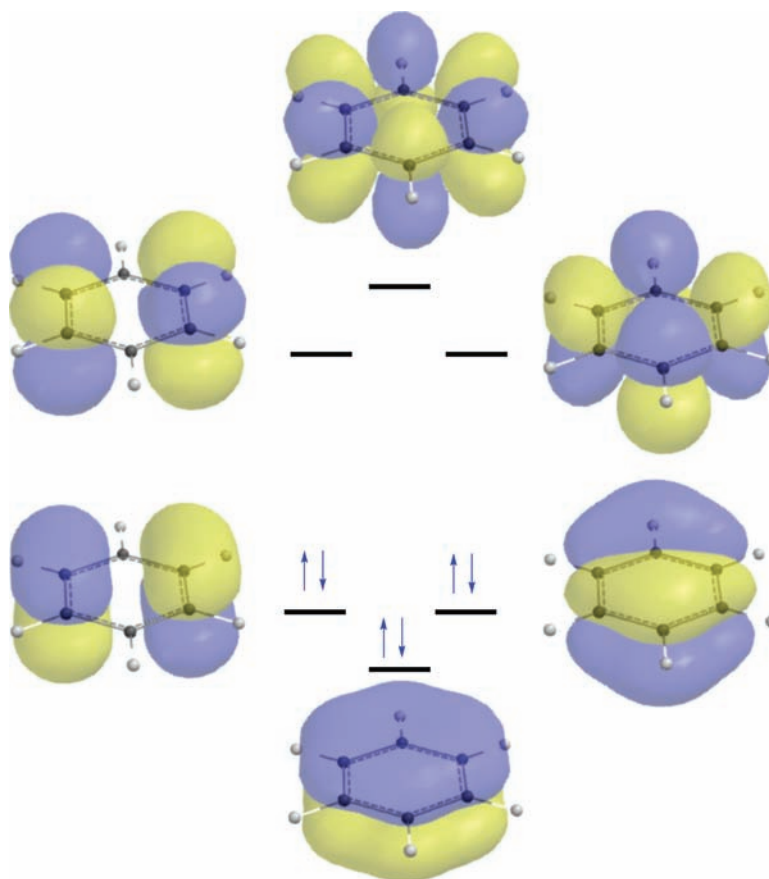


FIG. 2.2. The molecular orbitals of benzene, showing the three bonding orbitals, as generated by Spartan.10, v.1.0.1.

orbitals to form σ bonds, so that all 12 atoms are in one plane. This method shows that each carbon has a remaining p orbital that contains one electron, and each orbital can overlap equally with the two adjacent p orbitals. This overlap of six orbitals (see Fig. 2.2) produces six new orbitals, and the three lower energy orbitals are bonding. These three (called π orbitals) all occupy approximately the same space.⁶ One of the three is of lower energy than the other two, which are degenerate. They each have the plane of the ring as a node and so are in two parts, one above and one below the plane. The two orbitals of higher energy also have another node. The six electrons that occupy this torus-shaped cloud are called the *aromatic sextet*. A torus-shaped object is essentially a doughnut-shaped object. According to this explanation, the symmetrical hexagonal structure of benzene is caused by both the σ bonds and the (orbitals). Based on MO calculations, this symmetry is probably caused by the σ framework alone, and that the (π system would favor three localized double

⁶ Shaik, S.S.; Hiberty, P.C.; Lefour, J.; Ohanessian, G. *J. Am. Chem. Soc.* **1987**, *109*, 363; Stanger, A.; Vollhardt, K.P.C. *J. Org. Chem.* **1988**, *53*, 4889. See also, Jug, K.; Köster, A.M. *J. Am. Chem. Soc.* **1990**, *112*, 6772; Aihara, J. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1956.

bonds.⁶ The carbon–carbon bond order for benzene, calculated by the MO method, is 1.667.⁷

For planar unsaturated molecules that are aromatic, many *MO calculations* have been made by treating the σ and π electrons separately. It is assumed that the σ orbitals can be treated as localized bonds and the calculations involve only the π electrons. The first such calculations were made by Hückel, and such calculations are often called *Hückel molecular orbital (HMO) calculations*.⁸ Because electron–electron repulsions are either neglected or averaged out in the HMO method, another approach, the *self-consistent field (SCF)*, or *Hartree–Fock*, method, was devised.⁹ Although these methods give many useful results for planar unsaturated and aromatic molecules, they are often unsuccessful for other molecules. It would obviously be better if all electrons, both σ and π , could be included in the calculations. The development of modern computers has now made this possible.¹⁰ Many such calculations have been made¹¹ using a number of methods, among them an extension of the Hückel method¹² and the application of the SCF method to all valence electrons.¹³

One type of MO calculation that includes all electrons is called *ab initio*.¹⁴ Despite the name (which means “from first principles”) this type does involve some assumptions. Treatments that use certain simplifying assumptions (but still include all electrons) are called *semiempirical* methods.¹⁵ One of the first of these was called CNDO (Complete Neglect of Differential Overlap),¹⁶ but as computers have become more powerful, this has been superseded by more modern methods, including MINDO/3 (Modified Intermediate Neglect of Differential Overlap),¹⁷ MNDO (Modified Neglect of Diatomic Overlap),¹⁷ and AM1 (Austin Model 1), all of which were introduced by M.J. Dewar et al.¹⁸ There is also the PM3, or Parameterized Model number 3, which has the same formalism and equations as the AM1 method, but AM1 takes some of the parameter values from spectroscopic

⁷ See Pullman, A. *Prog. Org. Chem.* **1958**, *4*, 31, p. 36; Clarkson, D.; Coulson, C.A.; Goodwin, T.H. *Tetrahedron* **1963**, *19*, 2153. For a MO picture of aromaticity, see Pierrefix, S.C.A.H.; Bickelhaupt, F.M. *Chem. Eur. J.* **2007**, *13*, 6321.

⁸ See Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, **1978**; Coulson, C.A.; O’Leary, B.; Mallion, R.B. *Hückel Theory for Organic Chemists*, Academic Press, NY, **1978**; Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, **1987**, pp. 100–121.

⁹ Pople, J.A. *Trans. Faraday Soc.* **1953**, *49*, 1375; *J. Phys. Chem.* **1975**, *61*, 6; Dewar, M.J.S. *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, NY, **1969**; Dewar, M.J.S., in *Aromaticity*, Pub. no. 21, **1967**, pp. 177–215. See Merino, G.; Vela, A.; Heine, T. *Chem. Rev.* **2005**, *105*, 3812; Poater, J.; Duran, M.; Solà, M.; Silvi, B. *Chem. Rev.* **2005**, *105*, 3911.

¹⁰ See Ramsden, C.A. *Chem. Ber.* **1978**, *14*, 396; Hall, G.G. *Chem. Soc. Rev.* **1973**, *2*, 21.

¹¹ See Herndon, W.C. *Prog. Phys. Org. Chem.* **1972**, *9*, 99.

¹² Hoffmann, R. *J. Chem. Phys.* **1963**, *39*, 1397. See Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, **1978**, pp. 190–201.

¹³ Dewar, M.J.S. *The Molecular Orbital Theory of Chemistry*, McGraw-Hill, NY, **1969**; Jaffé, H.H. *Acc. Chem. Res.* **1969**, *2*, 136; Kutzelnigg, W.; Del Re, G.; Berthier, G. *Fortschr. Chem. Forsch.* **1971**, *22*, 1.

¹⁴ Hehre, W.J.; Radom, L.; Schleyer, P.v.R.; Pople, J.A. *Ab Initio Molecular Orbital Theory*, Wiley, NY, **1986**; Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, **1985**, pp. 233–317; Richards, W.G.; Cooper, D.L. *Ab Initio Molecular Orbital Calculations for Chemists*, 2nd ed., Oxford University Press, Oxford, **1983**.

¹⁵ For a review, see Thiel, W. *Tetrahedron* **1988**, *44*, 7393.

¹⁶ Pople, J.A.; Segal, G.A. *J. Chem. Phys.* **1965**, *43*, S136; **1966**, *44*, 3289; Pople, J.A.; Beveridge, D.L. *Approximate Molecular Orbital Theory*, McGraw-Hill, NY, **1970**.

¹⁷ For a discussion of MNDO and MINDO/3, and a list of systems for which these methods have been used, with references, see Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, **1985**, pp. 93–232. For a review of MINDO/3, see Lewis, D.F.V. *Chem. Rev.* **1986**, *86*, 1111.

¹⁸ See Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

measurements, whereas PM3 treats them as optimizable values.¹⁹ Semiempirical calculations are generally regarded as less accurate than *ab initio* methods,²⁰ but are much faster and cheaper.²¹ Note that modern computers are capable of completing >3 billion calculations per second, which makes MO calculations practical in modern organic chemistry.

Molecular orbital calculations, whether by *ab initio* or semiempirical methods, can be used to obtain structures (bond distances and angles), energies (e.g., heats of formation), dipole moments, ionization energies, and other properties of molecules, ions, and radicals: not only of stable ones, but also of those so unstable that these properties cannot be obtained from experimental measurements.²² Many of these calculations have been performed on transition states (Sec. 6.D). This is the only way to get this information, since transition states are not directly observable. Of course, it is not possible to check data obtained for unstable molecules and transition states against any experimental values, so that the reliability of the various MO methods for these cases is always a question. However, confidence in them increases when (1) different MO methods give similar results, and (2) a particular MO method works well for cases that can be checked against experimental methods.²³

Both the valence bond and MO methods show that there is delocalization in benzene. For example, each predicts that the six carbon–carbon bonds should have equal lengths, which is true. Since each method is useful for certain purposes, one or the other will be used as appropriate. Recent *ab initio*, SCF calculations confirm that the delocalization effect acts to strongly stabilize symmetric benzene, consistent with the concepts of classical resonance theory.²⁴ It is known that substituents influence the extent of resonance.²⁵

2.B. BOND ENERGIES AND DISTANCES IN COMPOUNDS CONTAINING DELOCALIZED BONDS

If the energies of all the bonds in benzene are added, taking the values from a source like Table 1.7, the value for the heat of atomization is less than the experimentally determined value (Fig. 2.3) of 1323 kcal mol⁻¹ (5535 kJ mol⁻¹). If *E* values for a C=C double bond obtained from cyclohexene (148.8 kcal mol⁻¹; 622.6 kJ mol⁻¹) are used, a C—C single bond from cyclohexane (81.8 kcal mol⁻¹, 342 kJ mol⁻¹), and C—H bonds from methane (99.5 kcal mol⁻¹, 416 kJ mol⁻¹), a value of 1289 kcal mol⁻¹ (5390 kJ mol⁻¹) is obtained for structure **1** or **2**. By this calculation, the resonance energy is 34 kcal mol⁻¹ (145 kJ mol⁻¹). Of course, this is an arbitrary calculation since, in addition to the fact that a heat of atomization is calculated for a nonexistent structure (**1**), *E* values must be used that do not have a firm basis in reality. The actual C—H bond energy for benzene has been measured to be 113.5 ± 0.5 kcal mol⁻¹ at 300 K and estimated to be 112.0 ± 0.6 kcal mol⁻¹ (469 kJ mol⁻¹) at 0 K.²⁶ The heat of atomization of a real molecule can be measured, but resonance

¹⁹ Stewart, J. J. P. *J. Comput. Chem.* **1989**, 10, 209, 221.

²⁰ See Dewar, M.J.S.; Storch, D.M. *J. Am. Chem. Soc.* **1985**, 107, 3898.

²¹ Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, **1985**, p. 141.

²² Another method of calculating such properties is molecular mechanics (Sec. 4.O).

²³ Dias, J.R. *Molecular Orbital Calculations Using Chemical Graph Theory*, Springer-Verlag, Berlin, **1993**.

²⁴ Glendening, E.D.; Faust, R.; Streitwieser, A.; Vollhardt, K.P.C.; Weinhold, F. *J. Am. Chem. Soc.* **1993**, 115, 10952.

²⁵ For an electrostatic scale of substituent resonance effects, see Sayyed, F.B.; Suresh, C.H. *Tetrahedron Lett.* **2009**, 50, 7351.

²⁶ Davico, G.E.; Bierbaum, V.M.; DePuy, C.H.; Ellison, G.B.; Squires, R.R. *J. Am. Chem. Soc.* **1995**, 117, 2590. See also, Pratt, D.A.; DiLabio, G.A.; Mulder, P.; Ingold, K.U. *Acc. Chem. Res.* **2004**, 37, 334.

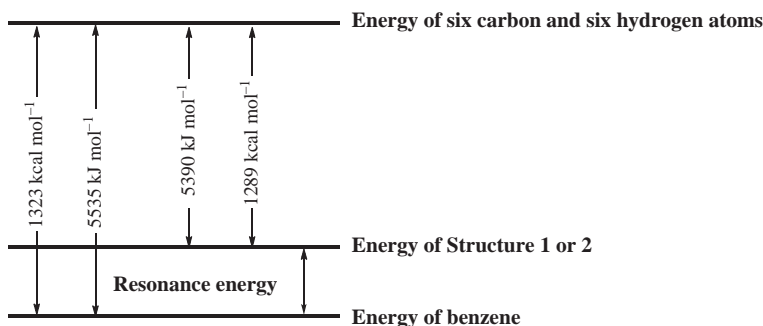


FIG. 2.3. Resonance energy in benzene.

energy can never be measured, only estimated, because only an intelligent guess can be made at that of the Lewis structure of lowest energy.

Another method frequently used for estimation of resonance energy involves measurements of heats of hydrogenation.²⁷ The heat of hydrogenation of cyclohexene is $28.6 \text{ kcal mol}^{-1}$ (120 kJ mol^{-1}), so a hypothetical **1** or **2** with three double bonds is expected to have a heat of hydrogenation of $\sim 85.8 \text{ kcal mol}^{-1}$ (360 kJ mol^{-1}). Benzene has a measured heat of hydrogenation of $49.8 \text{ kcal mol}^{-1}$ (208 kJ mol^{-1}), and the difference between the measured and expected value is the *resonance energy*, 36 kcal mol^{-1} (152 kJ mol^{-1}). By any calculation, the real molecule is more stable than a hypothetical **1** or **2**.

The energies of the six benzene orbitals can be calculated from HMO theory in terms of two quantities that are labeled α and β . Here α is the amount of energy possessed by an isolated $2p$ orbital before overlap, while β (called the *resonance integral*) is an energy unit expressing the degree of stabilization resulting from π -orbital overlap. A negative value of β corresponds to stabilization, and the energies of the six orbitals are (lowest to highest): $\alpha + 2\beta$, $\alpha + \beta$, $\alpha + \beta$, $\alpha - \beta$, $\alpha - \beta$, and $\alpha - 2\beta$.²⁸ The total energy of the three occupied orbitals is $6\alpha + 8\beta$, since there are two electrons in each orbital. The energy of an ordinary double bond is $\alpha + \beta$, so that structure **1** or **2** has an energy of $6\alpha + 6\beta$ and the resonance energy of benzene is 2β . Unfortunately, there is no convenient way to calculate the value of β from MO theory. Benzene is often given a value of β of $\sim 18 \text{ kcal mol}^{-1}$ (76 kJ mol^{-1}); this number is one-half of the resonance energy calculated from heats of combustion or hydrogenation. Using *ab initio* calculations, bond resonance energies for many aromatic hydrocarbons other than benzene have been reported.²⁹

Isodesmic and homodesmotic reactions are frequently used for the study of aromaticity from the energetic point of view.³⁰ However, the energy of the reactions used experimentally, or in calculations, may reflect only the relative aromaticity of benzene and not its absolute

²⁷ See Jensen, J.L. *Prog. Phys. Org. Chem.* **1976**, 12, 189.

²⁸ For the method for calculating these and similar results given in this chapter, see Higasi, K.; Baba, H.; Rembaum, A. *Quantum Organic Chemistry*, Interscience, NY, **1965**. For values of calculated orbital energies and bond orders for many conjugated molecules, see Coulson, C.A.; Streitwieser, Jr., A. *Dictionary of π Electron Calculations*, W.H. Freeman, San Francisco, **1965**.

²⁹ Aihara, J.-i. *J. Chem. Soc. Perkin Trans. 2* **1996**, 2185.

³⁰ George, P.; Trachtman, M.; Bock, C.W.; Brett, A.M. *J. Chem. Soc. Perkin Trans. 2* **1976**, 1222; George, P.; Trachtman, M.; Bock, C.W.; Brett, A.M. *Tetrahedron* **1976**, 32, 317; George, P.; Trachtman, M.; Brett, A.M.; Bock, C.W. *J. Chem. Soc. Perkin Trans. 2* **1977**, 1036.

aromaticity. New homodesmotic reactions based on radical systems predict an absolute aromaticity of $29.13 \text{ kcal mol}^{-1}$ ($121.9 \text{ kJ mol}^{-1}$) for benzene and an absolute antiaromaticity (Sec. 2.K.ii) of $40.28 \text{ kcal mol}^{-1}$ ($168.5 \text{ kJ mol}^{-1}$) for cyclobutadiene at the MP4 (SDQ)/6-31G-(d,p) level.³¹

Compounds that exhibit delocalization are expected to have bond distances that lie between the values given in Table 1.5. This is certainly the case for benzene, since the carbon–carbon bond distance is 1.40 \AA ,³² which is between the 1.48 \AA for an sp^2 – sp^2 C–C single bond and the 1.32 \AA of the sp^2 – sp^2 C=C double bond.³³

2.C. MOLECULES THAT HAVE DELOCALIZED BONDS

There are four main types of structure that exhibit delocalization:

1. *Double (or Triple) Bonds in Conjugation.*³⁴ The double bonds in benzene are conjugated, of course, but the conjugation exists in acyclic molecules (e.g., butadiene, **6**). In the MO picture (Fig. 2.4), the overlap of four orbitals gives

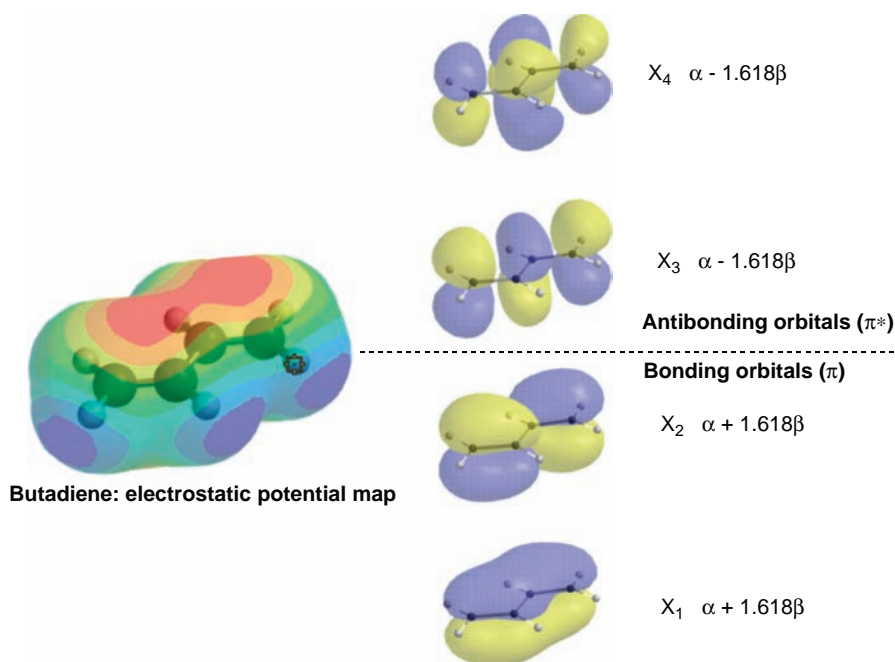


FIG. 2.4. The four π orbitals of butadiene, formed by overlap of four p orbitals.

³¹ Suresh, C.H.; Koga, N. *J. Org. Chem.* **2002**, 67, 1965. The heat of hydrogenation of phenylcyclobutadiene is reported to be $57.4 \pm 4.9 \text{ kcal mol}^{-1}$ ($240.3 \text{ kJ mol}^{-1}$): Fattahi, A.; Lis, L.; Kass, S.R. *J. Am. Chem. Soc.* **2005**, 127, 3065.

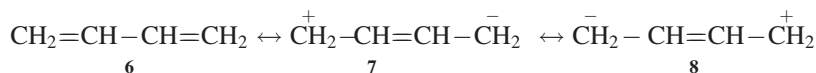
³² Tamagawa, K.; Iijima, T.; Kimura, M. *J. Mol. Struct.* **1976**, 30, 243.

³³ The average C–C bond distance in aromatic rings is 1.38 \AA : Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, p. S8.

³⁴ See Simmons, H.E. *Prog. Phys. Org. Chem.* 1970, 7, 1; Popov, E.M.; Kogan, G.A. *Russ. Chem. Rev.* 1968, 37, 119.

two bonding orbitals that contain four electrons and two vacant antibonding orbitals. It can be seen that each orbital has one more node than the one of next lower energy. The energies of the four orbitals are (lowest to highest): $\alpha + 1.618\beta$, $\alpha + 0.618\beta$, $\alpha - 0.618\beta$, and $\alpha - 1.618\beta$; hence the total energy of the two occupied orbitals is $4\alpha + 4.472\beta$. Since the energy of two isolated double bonds is $4\alpha + 4\beta$, the resonance energy by this calculation is 0.472β .

In the resonance picture, structures **7** and **8** are considered to contribute.



Despite the invocation of structures **7** and **8** in the resonance picture, butadiene and similar conjugated systems are *not* considered to be resonance stabilized in the ground state. The bond order of the central bond should be > 1 and that of the other carbon-carbon bonds < 2 , although neither predicts that the three bonds have equal electron density. Molecular orbital bond orders of 1.894 and 1.447 have been calculated.³⁵

The existence of delocalization in butadiene and similar molecules has been questioned. The bond lengths in butadiene are 1.34 Å for the double bonds and 1.48 Å for the single bond.³⁶ Since the typical single-bond distance of a bond that is not adjacent to an unsaturated group is 1.53 Å (Sec. 1.K), it has been argued that the shorter single bond in butadiene provides evidence for resonance. However, this shortening can also be explained by hybridization changes (See Sec. 1.K); and other explanations have also been offered.³⁷ Resonance energies for butadienes, calculated from heats of combustion or hydrogenation, are only $\sim 4 \text{ kcal mol}^{-1}$ (17 kJ mol^{-1}), and these values may not be entirely attributable to resonance.³⁸ Thus, a calculation from heat of atomization data gives a resonance energy of $4.6 \text{ kcal mol}^{-1}$ (19 kJ mol^{-1}) for *cis*-1,3-pentadiene, and $-0.2 \text{ kcal mol}^{-1}$ (-0.8 kJ mol^{-1}), for 1,4-pentadiene. These two compounds, each of which possesses two double bonds, two C—C single bonds, and eight C—H bonds, would seem to offer a direct comparison of a conjugated with a nonconjugated compound, but they are nevertheless not strictly comparable. The former has three sp^3 C—H and five sp^2 C—H bonds, while the latter has two and six, respectively. Also, the two single C—C bonds of the 1,4-diene are both sp^2 – sp^3 bonds, while in the 1,3-diene, one is sp^2 – sp^3 and the other is sp^2 – sp^2 . Therefore, it may be that some of the already small value of 4 kcal mol^{-1} (17 kJ mol^{-1}) is not resonance energy, but arises from differing energies of bonds of different hybridization.³⁹ As noted above, butadiene and related molecules are generally considered not to be resonance stabilized in the ground state.

³⁵ Coulson, C.A. *Proc. R. Soc. London, Ser. A* **1939**, 169, 413.

³⁶ Marais, D.J.; Sheppard, N.; Stoicheff, B.P. *Tetrahedron* **1962**, 17, 163.

³⁷ Politzer, P.; Harris, D.O. *Tetrahedron* **1971**, 27, 1567.

³⁸ For a discussion of so-called Y-aromaticity, and the relative stability of the butadienyl dication in relation to other dications, see Dworkin, A.; Naumann, R.; Seigfred, C.; Karty, J.M.; Mo, Y. *J. Org. Chem.* **2005**, 70, 7605.

³⁹ For negative views on delocalization in butadiene and similar molecules, see Dewar, M.J.S.; Gleicher, G.J. *J. Am. Chem. Soc.* **1965**, 87, 692; Mikhailov, B.M. *J. Gen. Chem. USSR* **1966**, 36, 379. For positive views, see Miyazaki, T.; Shigetani, T.; Shinoda, H. *Bull. Chem. Soc. Jpn.* **1971**, 44, 1491; Altmann, J.A.; Reynolds, W.F. *J. Mol. Struct.* **1977**, 36, 149. In general, the negative argument is that resonance involving excited structures, (e.g., **7** and **8**) is unimportant. (see rule 6 in Sec.2.E). See Popov, E.M.; Kogan, G.A. *Russ. Chem. Rev.* **1968**, 37, 119, pp. 119–124.

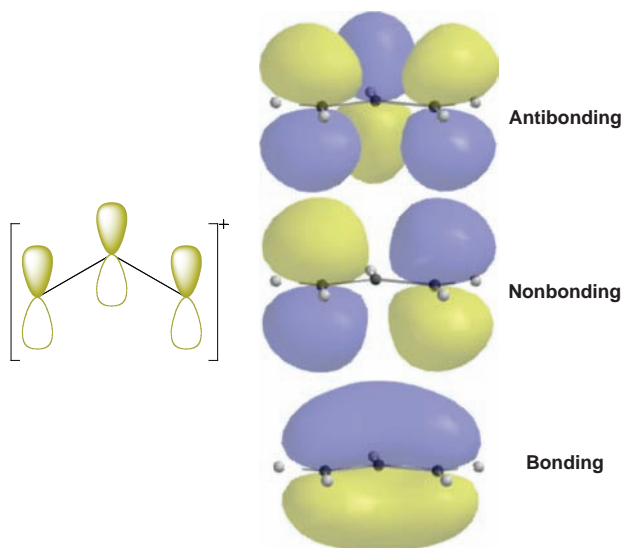
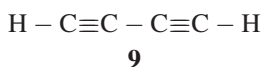


FIG. 2.5. Three orbitals of an allylic carbon, formed by overlap of three p orbitals.

Although bond distances fail to show it and the resonance energy is low, butadiene is planar.⁴⁰ This has been taken as an indication that there is some delocalization. Similar effects are found in other conjugated systems (e.g., $\text{C}=\text{C}-\text{C}=\text{O}$ ⁴¹ and $\text{C}=\text{C}-\text{C}=\text{N}$), in longer systems with three or more multiple bonds in conjugation, and where double or triple bonds are conjugated with aromatic rings. Diynes (e.g., 1,3-butadiyne, **9**) are also conjugated molecules. Based on calculations, Rogers et al.⁴² reported that the conjugation stabilization of 1,3-butadiyne is zero. Later calculations concluded that consideration of hyperconjugative interactions (Sec. 2.M) provides a more refined measure of conjugative stabilization.⁴³ When this measure is used, the conjugation energies of the isomerization and hydrogenation reactions considered agree with a conjugative stabilization of 9.3 (0.5 kcal mol⁻¹ for diynes and 8.2 0.1 kcal mol⁻¹ for dienes).



2. *Double (or Triple) Bonds in Conjugation with a p Orbital on an Adjacent Atom.*

When a p orbital is on an atom adjacent to a double bond, there are three parallel p orbitals that overlap. As previously noted, it is a general rule that the overlap of n atomic orbitals creates n molecular orbitals, so overlap of a p orbital with an adjacent double bond gives rise to three new orbitals, as shown in Fig. 2.5. The middle orbital is a *nonbonding orbital* of zero-bonding energy. The central carbon atom does not participate in the nonbonding orbital.

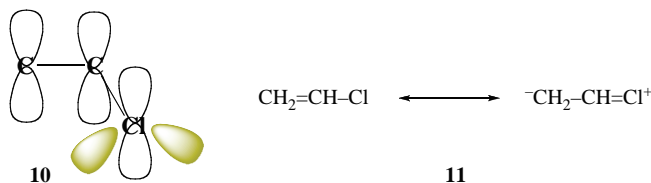
⁴⁰ Wiberg, K.B.; Rosenberg, R.E.; Rablen, P.R. *J. Am. Chem. Soc.* **1991**, 113, 2890.

⁴¹ See Patai, S.; Rappoport, Z. *The Chemistry of Enones*, two parts; Wiley, NY, **1989**.

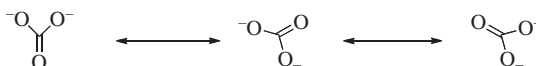
⁴² Rogers, D.W.; Matsunaga, N.; McLafferty, F.J.; Zavitsas, A.A.; Liebman, J.F. *J. Org. Chem.* **2004**, 69, 7143.

⁴³ Jarowski, P.D.; Wodrich, M.D.; Wannere, C.S.; Schleyer, P.v.R.; Houk, K.N. *J. Am. Chem. Soc.* **2004**, 126, 15036.

There are three cases: the original p orbital may have contained two, one, or no electrons. Since the original double bond contributes two electrons, the total number of electrons accommodated by the new orbitals is four, three, or two, respectively. A typical example of the first situation is vinyl chloride, ($\text{CH}_2=\text{CH}-\text{Cl}$). Although the p orbital of the chlorine atom is filled, it still overlaps with the double bond (See **10**). The four electrons occupy the two molecular orbitals of lowest energies, which is an example of resonance involving overlap between unfilled orbitals and a *filled* orbital. Canonical forms for vinyl chloride are shown in **11** (see Sec. 2.M).



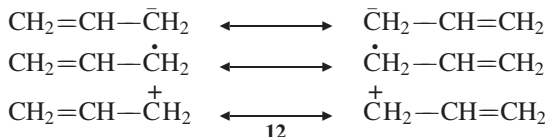
Any system that contains an atom that has an unshared pair and is directly attached to a multiple-bond atom can show this type of delocalization. Resonance delocalization is more important with charged species (e.g., the carbonate ion) and true resonance contributors can be drawn:



The resonance delocalization in allylic carbanions, (e.g., $\text{CH}_2=\text{CH}-\text{CH}_2^-$), is another example.

The other two cases have a p orbital that contains only one electron (radicals) or no electrons (cations). Allylic free radicals have one electron in the nonbonding orbital. In allylic cations, this orbital is vacant and only the bonding orbital is occupied. The orbital structures of the allylic carbanion, free radical, and cation differ from each other, only in that the nonbonding orbital is filled, half-filled, or empty. Since this is an orbital of zero bonding energy, it follows that the bonding π energies of the three species relative to electrons in the $2p$ orbitals of free atoms are the same. The electrons in the nonbonding orbital do not contribute to the bonding energy, positively or negatively.⁴⁴

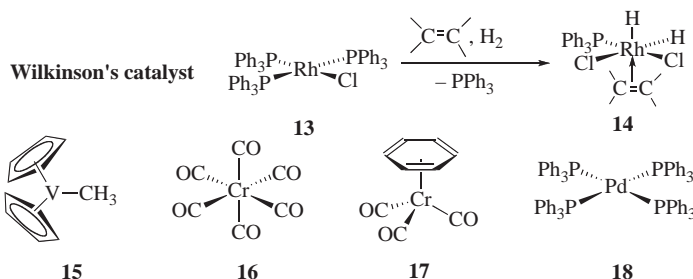
The resonance picture best describes three species that are charged or contain an unshared electron with double bonds in conjugation with, respectively, an unshared pair, an unpaired electron, and an empty orbital as in the allyl cation **12** (also see Chap 5).



⁴⁴ It has been argued that the geometry is forced upon allylic systems by the σ framework, and not the π system: Shaik, S.S.; Hiberty, P.C.; Ohanessian, G.; Lefour, J. *Nouv. J. Chim.*, **1985**, 9, 385. *ab initio* calculations suggest that the allyl cation has significant resonance stabilization, but the allyl anion has little stabilization: Wiberg, K.B.; Breneman, C.M.; LePage, T.J. *J. Am. Chem. Soc.* **1990**, 112, 61.

3. *π -Allyl and Other η -Complexes.* In the presence of transition metals, delocalized electrons in allylic cations may be donated to the metal, resulting in stabilization.⁴⁵ In a carbon–metal bond (e.g., $\text{H}_3\text{C}-\text{Fe}$), the carbon donates (shares) one electron with the metal, and is considered to be a one-electron donor. With a π bond (e.g., that found in ethylene), both electrons can be donated to the metal to form a complex (e.g., **14**) by reaction of Wilkinson's catalyst (**13**) with an alkene and hydrogen gas,⁴⁶ in addition, π bond is considered to be a two-electron donor. In these two cases, the electron donating ability of the group coordinated to the metal (the ligand) is indicated by terminology η^1 , η^2 , η^3 , and so on, for a one-, two-, and three-electron donor, respectively.

Ligands are categorized as η -ligands according to the ability to donate electrons to the metal. A hydrogen atom (as in **14**) or a halogen ligand (as in **13**) are η^1 ligands. An amine (NR_3), a phosphine (PR_3 , as in **13**, **14**, and **18**), CO (as in **16** or **17**), an ether (OR_2) or a thioether (SR_2) are η^2 ligands. Hydrocarbon ligands include alkyl (as the methyl in **15**) or aryl with a carbon–metal bond (η^1), alkenes or carbenes (η^2 , see Sec. 3.C.i), π -allyl (η^3), conjugated dienes (e.g., 1,3-butadiene) (η^4), cyclopentadienyl (η^5 , as in **15** and see Sec. 2.I.ii), and arenes or benzene (η^6).⁴⁷ Note that in the formation of **14** from **13**, the two-electron donor alkene displaces a two-electron donor phosphine. Other typical complexes include chromium hexacarbonyl ($\text{Cr}(\text{CO})_6$, **16**), with six η^2 CO ligands; $\eta^6\text{-C}_6\text{H}_6\text{Cr}(\text{CO})_3$ (**18**), and *tetrakis*-triphenylphosphinopalladium (0), (**17**), with four η^2 phosphine ligands.



In the context of this section, the electron-delocalized ligand π -allyl (**12**) is an η^3 donor and it is well known that allylic halides react with PdCl_2 to form a bis- η^3 -complex **19** (see **20**).⁴⁸ Complexes (e.g., **19**) react with nucleophiles to give the corresponding coupling product (**10–60**).⁴⁹ The reaction of allylic acetates or carbons and a catalytic amount of $\text{Pd}(0)$ compounds also lead to an η^3 -complex that can react with nucleophiles.⁵⁰

⁴⁵ Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, Wiley-Interscience, NY, **2005**; Hill, A.F. *Organotransition Metal Chemistry*, Wiley Interscience, Canberra, **2002**.

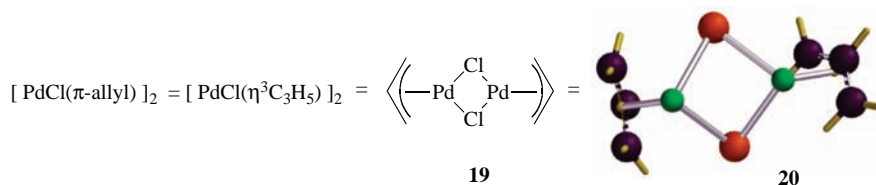
⁴⁶ Jardine, F.H., Osborn, J.A.; Wilkinson, G.; Young, G.F. *Chem. Ind. (London)* **1965**, 560; Imperial Chem. Ind. Ltd., *Neth. Appl.* 6,602,062 [*Chem. Abstr.*, 66: 10556y **1967**]; Bennett, M.A.; Longstaff, P.A. *Chem. Ind.* **1965**, 846.

⁴⁷ Davies, S.G. *Organotransition Metal Chemistry*, Pergamon, Oxford, **1982**, p. 4.

⁴⁸ Trost, B.M.; Strege, P.E.; Weber, L.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* **1978**, 100, 3407.

⁴⁹ Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* **1978**, 100, 3416.

⁵⁰ Melpolder, J.B.; Heck, R.F. *J. Org. Chem.* **1976**, 41, 265; Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.*, **1978**, 100, 3435; Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* **1980**, 102, 4730.

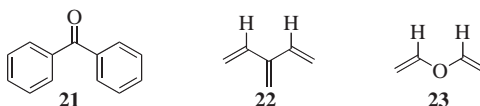


4. *Hyperconjugation*. The type of delocalization called *hyperconjugation* is discussed in Section 2.M.

Note that there are examples of delocalization that cannot be strictly classified as any of these types.

2.D. CROSS-CONJUGATION⁵¹

In a cross-conjugated compound, three groups are present, two of which are not conjugated with each other, although each is conjugated with the third. Some examples are benzophenone (**21**), triene (**22**),⁵² and divinyl ether (**23**). The MO method shows that the overlap of six *p* orbitals in **22** (a member of a family of compounds known as dendralenes)⁵² gives six molecular orbitals, and the three bonding orbitals are shown in Fig. 2.6, along with their energies. Note that two of the carbon atoms do not participate in the $\alpha + \beta$ orbital.



The total energy of the three occupied orbitals is $6\alpha + 6.900\beta$, so the resonance energy is 0.900β . Molecular orbital bond orders are 1.930 for the C-1–C-2 bond, 1.859 for the C-3–C-6 bond, and 1.363 for the C-2–C-3 bond.⁵¹ Comparing these values with those for butadiene (Sec. 2.C), the C-1–C-2 bond contains more and the C-3–C-6 bond less double-bond character than the double bonds in butadiene. The resonance picture supports

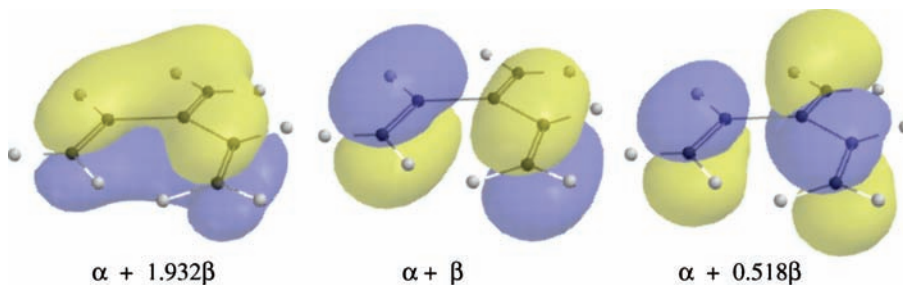


FIG. 2.6. The three bonding orbitals of the dendralene, 3-methylene-1,4-pentadiene (**22**).

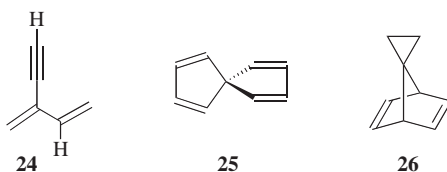
⁵¹ See Phelan, N.F.; Orchin, M. *J. Chem. Educ.* **1968**, 45, 633.

⁵² For a review of such compounds, see Hopf, H. *Angew. Chem. Int. Ed.* **1984**, 23, 948.

this conclusion, since each C-1–C-2 bond is double in three of the five canonical forms, while the C-3–C-6 bond is double in only one. In most cases, it is easier to treat cross-conjugated molecules by the MO method than by the valence bond method.

One consequence of this phenomenon is that the bond length of a cross-conjugated C=C unit is slightly longer than that of a non-cross-conjugated bond. In **24**, for example, the cross-conjugated bond is $\sim 0.01 \text{ \AA}$ longer.⁵³ The conjugative effect of a C=C or C \equiv C unit can be measured for a conjugated enone: $4.2 \text{ kcal mol}^{-1}$ (17.6 kJ mol^{-1}) for an ethenyl substituent, but $\sim 2.3 \text{ kcal mol}^{-1}$ (9.6 kJ mol^{-1}) for an ethynyl substituent, which is more variable.⁵⁴

The phenomenon of homoconjugation is related to cross-conjugation in that there are C=C units in close proximity, but not conjugated one to the other. Homoconjugation arises when the termini of two orthogonal π -systems are held in close proximity, as in compounds with a spiro-tetrahedral carbon atom.⁵⁵ Spiro[4.4]nonatetraene (**25**)⁵⁶ is an example and it is known that the HOMO (see Sec. 15.60) of **25** is raised relative to cyclopentadiene, whereas the LUMO is unaffected.⁵⁷ Another example is **26**, where there are bond length distortions caused by electronic interactions between the unsaturated bicyclic moiety and the cyclopropyl moiety.⁵⁸ It is assumed that cyclopropyl homoconjugation is responsible for this effect.



2.E. THE RULES OF RESONANCE

One way to express the actual structure of a molecule containing delocalized bonds is to draw several possible structures and to assume that the actual molecule is a hybrid of them. These structures are called canonical forms, but they are not real structures. In other words, the molecule does *not* rapidly shift between them and a given compound has a single actual structure. That structure is always the same all the time and is taken to be a weighted average of all the canonical forms. Drawing canonical forms and deriving the true structures from them is guided by certain rules, including the following:

1. All the canonical forms must be *bona fide* Lewis structures (Sec. 1.F). For example, none of them may have a carbon with five bonds.
2. The positions of the nuclei must be the same in all the structures. This means that when drawing the various canonical forms, the *electrons* are simply arranged in different ways. For this reason, shorthand ways of representing resonance are easy

⁵³ Trættemberg, M.; Hopf, H. *Acta Chem. Scand. B* **1994**, 48, 989.

⁵⁴ Trættemberg, M.; Liebman, J.F.; Hulce, M.; Bohn, A.A.; Rogers, D.W. *J. Chem. Soc. Perkin Trans. 2* **1997**, 1925.

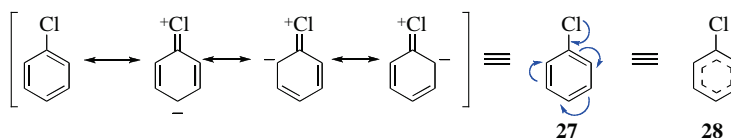
⁵⁵ See Durr, H.; Gleiter, R. *Angew. Chem. Int. Ed.* **1978**, 17, 559.

⁵⁶ For the synthesis of **25**, see Semmelhack, M.F.; Foos, J.S.; Katz, S. *J. Am. Chem. Soc.* **1973**, 95, 7325.

⁵⁷ Raman, J.V.; Nielsen, K.E.; Randall, L.H.; Burke, L.A.; Dmitrienko, G.I. *Tetrahedron Lett.* **1994**, 35, 5973.

⁵⁸ Haumann, T.; Benet-Buchholz, J.; Klärner, F.-G.; Boese, R. *Liebigs Ann. Chem.* **1997**, 1429.

to devise:



Invoking hyperconjugation (Sec. 2.M), resonance interaction of chlorine with the benzene ring can be represented as shown in **27** or **28** and both representations have been used in the literature to save space. However, the curved-arrow method of **27** will not be used since arrows in this book are used to express the actual movement of electrons in reactions. Representations like **28** will be used occasionally, but more often one or more of the canonical forms will be used. The convention used in dashed-line formulas like **28** is that bonds that are present in all canonical forms are drawn as solid lines, while bonds that are not present in all forms are drawn as dashed lines. A downside of this model is that electron transfer in reactions associated with benzene rings is difficult to track. For this reason, one of the canonical forms is most often used, as mentioned. In most resonance, σ bonds are not involved, and only the π or unshared electrons are utilized. This finding means that writing one canonical form for a molecule, allowed the others to be written by merely moving π and unshared electrons.

3. All atoms taking part in the resonance, (i.e., covered by delocalized electrons), must lie in a plane or nearly so (see Sec. 2.G). This, of course, does not apply to atoms that have the same bonding in all the canonical forms. Maximum overlap of the p orbitals leads to the planarity.
4. All canonical forms must have the same number of unpaired electrons. Thus the diradical structure $\bullet\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2\bullet$ is not a valid canonical form for butadiene.
5. The energy of the actual molecule is lower than that of any form, so delocalization is a stabilizing phenomenon.⁵⁹
6. All canonical forms do not contribute equally to the true molecule. Each form contributes in proportion to its stability, the most stable form contributing most. Thus, for ethylene, the form $^+\text{CH}_2-\text{CH}_2^-$ has such a high energy compared to $\text{CH}_2=\text{CH}_2$ that it essentially does not contribute at all. This argument was applied to butadiene.³⁹ Equivalent canonical forms, (e.g., **1** and **2**) contribute equally. The greater the number of significant structures that can be written and the more nearly equal they are, the greater the resonance energy, other things being equal.

It is not always easy to decide relative stabilities of imaginary structures; the chemist is often guided by intuition.⁶⁰ However, the following rules may be helpful:

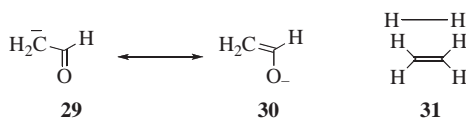
- (a) Structures with more covalent bonds are ordinarily more stable than those with fewer (cf. **6** and **7**).
- (b) Stability is decreased by an increase in charge separation. Structures with formal charges are less stable than uncharged structures. Structures with more than two

⁵⁹ It has been argued that resonance is not a stabilizing phenomenon in all systems, especially in acyclic ions: Wiberg, K.B. *Chemtracts. Org. Chem.* **1989**, 2, 85. See also, Siggel, M.R.; Streitwieser, Jr., A.; Thomas, T.D. *J. Am. Chem. Soc.* **1988**, 110, 8022; Thomas, T.D.; Carroll, T.X.; Siggel, M.R. *J. Org. Chem.* **1988**, 53, 1812.

⁶⁰ A quantitative method for weighting canonical forms was proposed by Gasteiger, J.; Saller, H. *Angew. Chem. Int. Ed.* **1985**, 24, 687.

formal charges usually contribute very little. An especially unfavorable type of structure is one with two like charges on adjacent atoms.

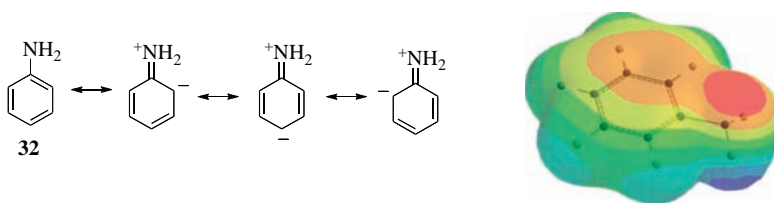
- (c) Structures that carry a negative charge on a more electronegative atom are more stable than those in which the charge is on a less electronegative atom. Thus, enolate anion **30** is more stable than canonical form **29**. Similarly, positive charges are best carried on atoms of low electronegativity.



- (d) Structures with distorted bond angles or lengths are unstable, (e.g., contributor **31** for ethane).

2.F. THE RESONANCE EFFECT

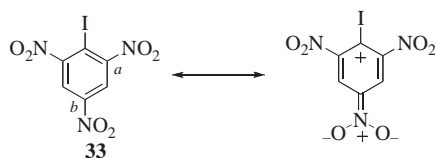
Resonance always results in a different distribution of electron density than would be the case if there were no resonance (i.e., the electrons are dispersed over several atoms rather than concentrated on one atom). For example, if **32** were the actual structure of aniline, the two unshared electrons of the nitrogen would reside entirely on that atom. The structure of **32** can be represented as a hybrid that includes contributions from the canonical forms shown, indicating that the electron density of the unshared pair does not reside entirely on the nitrogen, but is spread over the ring. However, as shown by the accompanying electron potential map for aniline, the charge distribution is such that most of the electron density resides on nitrogen. The decrease in electron density at one position (and corresponding increase elsewhere) means that the NH₂ contributes or donates electrons to the ring by a resonance effect (“electron releasing,” although no actual contribution takes place), and is called the *resonance* or *mesomeric effect*. To emphasize this point, the canonical forms associated with **32** indicate electron release from the nitrogen to the benzene ring (the mesomeric effect), and do not necessarily indicate that there are four canonical forms. In ammonia, where resonance is absent, the unshared pair *is* located on the nitrogen atom. As with the field effect (Sec. 1.I), a certain molecule (in this case ammonia) maybe thought of as a substrate and effects of substitution on the electron density may be studied. When one of the hydrogen atoms of the ammonia molecule is replaced by a benzene ring (to make aniline, **32**), the electrons are “withdrawn” from the ring by the resonance effect, just as when a methyl group replaces a hydrogen atom of benzene, electrons are “donated” by the field effect of the methyl. Note the increased electron density on the nitrogen in the model, as indicated by the darker area that is above the middle of the model as well and on the nitrogen (on the right side of the model) when compared to benzene in Fig. 2.1*b*. The idea of donation or withdrawal merely arises from the comparison of a compound with a closely related one or a real compound with a canonical form.



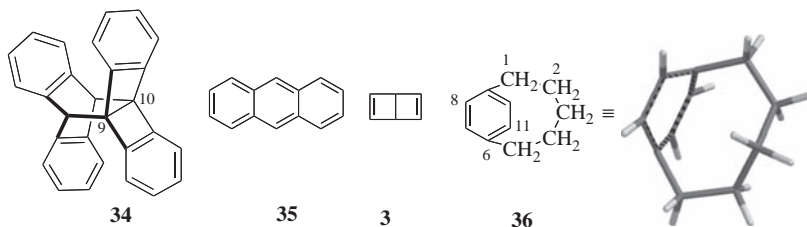
2.G. STERIC INHIBITION OF RESONANCE AND THE INFLUENCES OF STRAIN

Rule 3 above states that all the atoms covered by delocalized electrons must lie in a plane or nearly so. Many examples are known where resonance is diminished or prevented because the atoms are sterically forced out of planarity. It is known that if para substituents are able to interact via the through-resonance mechanism, π -electron delocalization due to the substituent effects leads to an increase of stability.⁶¹ If the substituents are both electron donating, there is a significant decrease in stability.

Bond lengths for the *o*- and *p*-nitro groups in picryl iodide (**33**) are quite different.⁶² Distance *a* in **33** is 1.45 Å, whereas *b* is 1.35 Å. This phenomenon can be explained if the oxygen atoms of the *p*-nitro group are in the plane of the ring and thus in resonance with it, so that *b* has partial double-bond character, while the oxygen atoms of the *o*-nitro groups are forced out of the plane by the large iodine atom. As discussed in Section 2.M, the difference in bond length is associated with hyperconjugative effects, represented by the canonical form.



Compound **34** is recognized as a Dewar-form of anthracene.⁶³ Dewar benzene forms (e.g., benzvalene) (**3**) are recognized as possible valence isomers of benzene.⁶⁴ Since **35** is the actual structure of anthracene, it is reasonable to ask if **34** is a canonical structure? The answer is no, because the 9,10 substituents prevent the system from being planar, so **34** is the actual structure of the molecule and it is not in resonance with forms like **35**. This finding is a consequence of rule 2 (Sec. 2.E). In order for a **35**-like structure to contribute to resonance in **34**, the nuclei would have to be in the same positions in both forms. In anthracene itself (**35**), Dewar structures are thought to contribute to the structure, however.



Even the benzene ring can be forced out of planarity.⁶⁵ In [5]-paracyclophane⁶⁶ (**36**) the presence of a short bridge (this is the shortest para bridge known for a benzene ring) forces

⁶¹ Krygowski, T.M.; Stepień, B.T. *Chem. Rev.* **2005**, *105*, 3482.

⁶² Wepster, B.M. *Prog. Stereochem.* **1958**, *2*, 99, p. 125. Also see Exner, O.; Folli, U.; Marcaccioli, S.; Vivarelli, P. *J. Chem. Soc. Perkin Trans. 2* **1983**, 757.

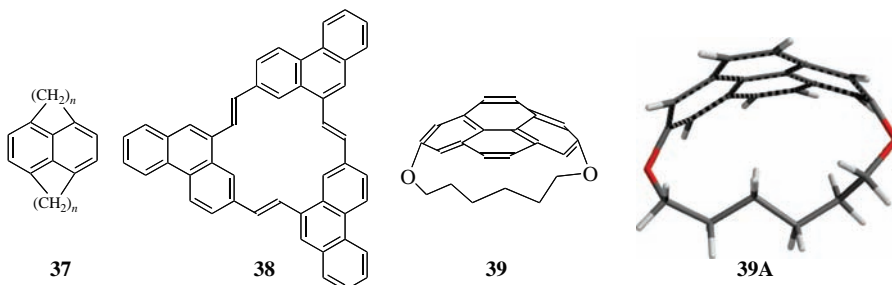
⁶³ Applequist, D.E.; Searle, R. *J. Am. Chem. Soc.* **1964**, *86*, 1389.

⁶⁴ Cardillo, M.J.; Bauer, S.H. *J. Am. Chem. Soc.* **1970**, *92*, 2399. See Hückel, E. *Elektrochem.* **1937**, *43*, 752; van Tamelen, E. *Angew. Chem. Int. Ed.* **1965**, *4*, 738; Viehe, H.G. *Angew. Chem. Int. Ed.* **1965**, *4*, 746.

⁶⁵ See Ferguson, G.; Robertson, J.M. *Adv. Phys. Org. Chem.* **1963**, *1*, 203.

⁶⁶ For a monograph, see Keehn, P.M.; Rosenfeld, S.M. *Cyclophanes*, 2 Vols., Academic Press, NY, **1983**. For reviews, see Bickelhaupt, F. *Pure Appl. Chem.* **1990**, *62*, 373; Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* **1971**, *4*, 204; Vögtle, F.; Neumann, P. Reviews in *Top. Curr. Chem.* **1985**, *115*, 1.

the benzene ring to become boat shaped. The distortion in the benzene ring is apparent in the molecular model of **36** that is provided. The parent **36** has so far not proven stable enough for isolation, but a UV spectrum was obtained and showed that the benzene ring was aromatic, despite the distortion.⁶⁷ The 8,11-dichloro analogue of **36** is a stable solid, and X-ray diffraction showed that benzene ring to be boat-shaped, with one end of the boat bending $\sim 27^\circ$ out of the plane, and the other $\sim 12^\circ$.⁶⁸ This compound too is aromatic, as shown by UV and NMR spectra. [6]-Paracyclophanes are also bent,⁶⁹ but in [7]-paracyclophanes the bridge is long enough so that the ring is only moderately distorted. Similarly, [*n,m*]paracyclophanes (**37**), where *n* and *m* are both 3 or less (the smallest yet prepared is [2.2]-paracyclophane),⁷⁰ have bent (boat-shaped) benzene rings. All these compounds have properties that depart significantly from those of ordinary benzene compounds. Strained paracyclophanes exhibit both π - and σ -strain, and the effect of the two types of strain on the geometry is approximately additive.⁷¹ In “belt” cyclophane (**38**),⁷² the molecule has a pyramidal structure with C_3 symmetry rather than the planar structure found in [18]annulene. 1,8-Dioxo[8](2,70-pyrenophane (**39**))⁷³ is another severely distorted aromatic hydrocarbon (see **39A**), in which the bridge undergoes rapid pseudorotation (Sec. 4.O.iv). A recent study showed that despite substantial changes in the hybridization of carbon atoms involving changes in the σ -electron structure of pyrenophane (e.g., **39**), the aromaticity of the system decreases slightly and regularly upon increasing the bend angle θ from 0° to 109.2° .⁷⁴ Heterocyclic paracyclophane analogues have been prepared, (e.g., the [2.*n*](2,5)pyridinophanes).⁷⁵



⁶⁷ Kostermans, G.B.M.; de Wolf, W.E.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, 27, 1095; van Zijl, P.C.M.; Jenneskens, L.W.; Bastiaan, E.W.; MacLean, C.; de Wolf, W.E.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1986**, 108, 1415; Rice, J.E.; Lee, T.J.; Remington, R.B.; Allen, W.D.; Clabo, Jr., D.A.; Schaefer, III, H.F. *J. Am. Chem. Soc.* **1987**, 109, 2902.

⁶⁸ Jenneskens, L.W.; Klamer, J.C.; de Boer, H.J.R.; de Wolf, W.H.; Bickelhaupt, F.; Stam, C.H. *Angew. Chem. Int. Ed.* **1984**, 23, 238.

⁶⁹ See Tobe, Y.; Ueda, K.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *Tetrahedron* **1986**, 42, 1851.

⁷⁰ For a computational study of [2.2]cyclophanes, see Caramori, G.F.; Galembeck, S.E.; Laali, K.K. *J. Org. Chem.* **2005**, 70, 3242.

⁷¹ Stanger, A.; Ben-Mergui, N.; Perl, S. *Eur. J. Org. Chem.* **2003**, 2709.

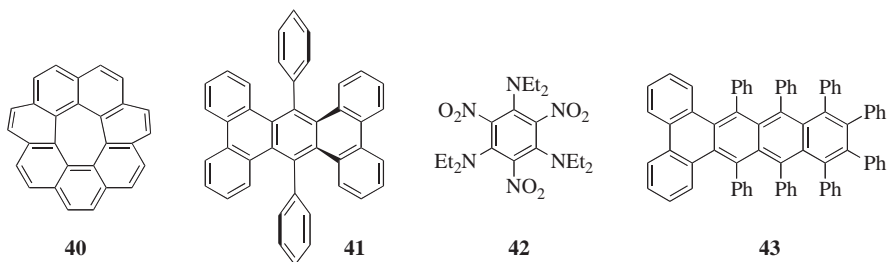
⁷² Meier, H.; Müller, K. *Angew. Chem. Int. Ed.*, **1995**, 34, 1437.

⁷³ Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem. Int. Ed.*, **1996**, 35, 1320.

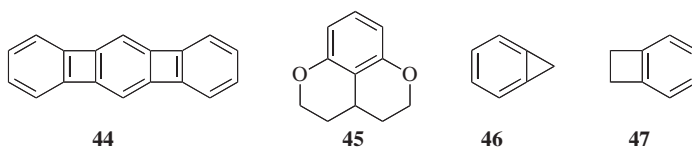
⁷⁴ Bodwell, G.J.; Bridson, J.N.; Cyrański, M.K.; Kennedy, J.W.J.; Krygowski, T.M.; Mannion, M.R.; Miller, D.O. *J. Org. Chem.* **2003**, 68, 2089; Bodwell, G.J.; Miller, D.O.; Vermeij, R.J. *Org. Lett.* **2001**, 3, 2093.

⁷⁵ Funaki, T.; Inokuma, S.; Ida, H.; Yonekura, T.; Nakamura, Y.; Nishimura, J. *Tetrahedron Lett.* **2004**, 45, 2393.

There are many examples of molecules in which benzene rings are forced out of planarity, including 7-circulene (**40**),⁷⁶ 9,8-diphenyltetrabenz[*a,c,h,j*]anthracene (**41**),⁷⁷ and **42**⁷⁸ (see also, Sec. 4.Q.iv). These have been called tormented aromatic systems.⁷⁹ The “record” for twisting an aromatic π -electron system appears to be 9,10,11,12,13,14,15,16-octaphenyldibenzo[*a,c*]naphthacene (**43**),⁸⁰ which has an end-to-end twist of 105°. This was 1.5 times greater than that observed in any previous polyaromatic hydrocarbon. Perchlorotriphenylene has been reported in the literature and said to show severe molecular twisting, however, recent work suggests this molecule was not actually isolated, with perchlorofluorene-9-spirocyclohexa-2',5'-diene being formed instead.⁸¹ The X-ray structure of the linear [3]phenylene (benzo[3,4]cyclobuta[1,2-*b*]biphenylene, **44**) has been obtained, and it shows a relatively large degree of bond alternation while the center distorts to a cyclic bis-(allyl) frame.⁸²



It is also possible to fuse strained rings on benzene, which induces great strain on the benzene ring. In **45**, the benzene ring is compressed by the saturated environment of the tetrahydropyran units and the strain leads to distortion of the benzene ring into a *boat* conformation.⁸³



The term strain-induced bond localization was introduced in 1930 by Mills and Nixon⁸⁴ and is commonly referred to as the *Mills–Nixon effect* (see Sec. 11.B.v). Ortho-fused aromatic compounds, (e.g., benzocyclopropene, **46**), are known as cycloproparenes⁸⁵ and are highly strained. Cyclopropabenzene (**46**) is a stable molecule with a strain energy of 68 kcal mol^{−1} (284.5 kJ mol^{−1}),⁸⁶ and the annellated bond is always the shortest, although

⁷⁶ Yamamoto, K.; Harada, T.; Okamoto, Y.; Chikamatsu, H.; Nakazaki, M.; Kai, Y.; Nakao, T.; Tanaka, M.; Harada, S.; Kasai, N. *J. Am. Chem. Soc.* **1988**, *110*, 3578.

⁷⁷ Pascal Jr., R.A.; McMillan, W.D.; Van Engen, D.; Eason, R.G. *J. Am. Chem. Soc.* **1987**, *109*, 4660.

⁷⁸ Chance, J.M.; Kahr, B.; Buda, A.B.; Siegel, J.S. *J. Am. Chem. Soc.* **1989**, *111*, 5940.

⁷⁹ Pascal Jr., R.A. *Pure Appl. Chem.* **1993**, *65*, 105.

⁸⁰ Qiao, X.; Ho, D.M.; Pascal Jr., R.A. *Angew. Chem. Int. Ed.*, **1997**, *36*, 1531.

⁸¹ Campbell, M.S.; Humphries, R.E.; Munn, N.M. *J. Org. Chem.* **1992**, *57*, 641.

⁸² Schleifenbaum, A.; Feeder, N.; Vollhardt, K.P.C. *Tetrahedron Lett.* **2001**, *42*, 7329.

⁸³ Hall, G.G. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1491.

⁸⁴ Mills, W. H.; Nixon, I. G. *J. Chem. Soc.* **1930**, 2510.

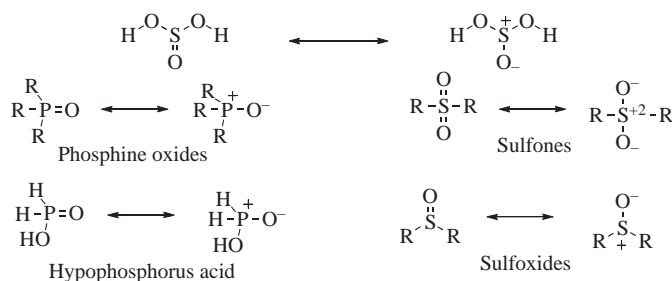
⁸⁵ See Halton, B. *Chem. Rev.* **2003**, *103*, 1327 and reviews cited therein.

⁸⁶ Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.* **1986**, *108*, 3241.

in benzocyclobutene (**47**) the adjacent bond is the shortest.⁸⁷ The bonds of annellation and those adjacent are strained. In cycloproparenes, there is the expectation of partial aromatic bond localization, with bond length alternation in the aromatic ring.⁸⁸ When the bridging units are saturated, the benzene ring current is essentially unchanged, but annellation with one or more cyclobutadieno units disrupts the benzene ring current.⁸⁹ The chemistry of the cycloproparenes is dominated by the influence of the high strain energy. When fused to a benzene ring, the bicyclo[1.1.0]butane unit also leads to strain-induced localization of aromatic π bonds.⁹⁰

2.H. $p\pi-d\pi$ BONDING. YLIDS

In Section 1.D, it was stated that, in general, atoms of the second row of the periodic table do not form stable double bonds of the type discussed in Chapter 1 (π bonds formed by overlap of parallel p orbitals). However, there is another type of double bond that is particularly common for the second-row atoms sulfur and phosphorus. Such a double bond is found in sulfurous acid, (H_2SO_3). While the $\text{S}=\text{O}$ double bond contains one s orbital, the second orbital is not a π orbital formed by overlap of half-filled p orbitals. Instead it is formed by overlap of a filled p orbital from the oxygen with an empty d orbital from the sulfur. It is called a $p\pi-d\pi$ orbital.⁹¹ Note that this molecule may be represented by two canonical forms, but the bond is nevertheless localized, despite the resonance that is inherent to this structure. Some other examples of $p\pi-d\pi$ bonding are the phosphine oxides, sulfones, hypophosphorus acid, and sulfoxides. Nitrogen analogues are known, but they are less stable than the phosphorus compounds because the resonance is lacking. For example, amine oxides, analogues of phosphine oxides, can only be written $\text{R}_3\text{N}^+-\text{O}^-$. The $p\pi-d\pi$ canonical form is impossible since nitrogen is limited to eight outer-shell electrons.



In all the examples given above, an oxygen atom donates the electron pair and, indeed, oxygen is the most common such atom. In another important class of compounds, called

⁸⁷ Boese, R.; Bläser, D.; Billups, W.E.; Haley, M.M.; Maulitz, A.H.; Mohler, D.L.; Vollhardt, K.P.C. *Angew. Chem. Int. Ed.*, **1994**, 33, 313.

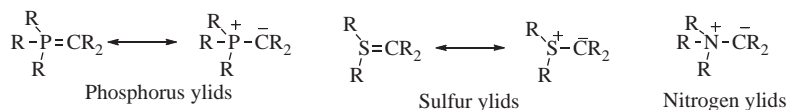
⁸⁸ Stanger, A. *J. Am. Chem. Soc.* **1998**, 120, 12034; Yáñez, O.M.O.; Eckert- Maksić, M.; Maksić, Z.B. *J. Org. Chem.* **1995**, 60, 1638; Eckert- Maksić, M.; Glasovac, Z.; Maksić, Z.B.; Zrinski, I. *J. Mol. Struct. (THEOCHEM)* **1996**, 366, 173; Baldrige, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* **1992**, 114, 9583.

⁸⁹ Soncini, A.; Havenith, R.W.A.; Fowler, P.W.; Jenneskens, L.W.; Steiner, E. *J. Org. Chem.* **2002**, 67, 4753

⁹⁰ Cohrs, C.; Reuchlein, H.; Musch, P.W.; Selinka, C.; Walfort, B.; Stalke, D.; Christl, M. *Eur. J. Org. Chem.* **2003**, 901.

⁹¹ For a monograph, see Kwart, H.; King, K. *d-Orbitals in the Chemistry of Silicon, Phosphorus, and Sulfur*, Springer, NY, **1977**.

ylids, this atom is carbon.⁹² There are three common types of ylids: P,⁹³ S,⁹⁴ and N ylids,⁹⁵ although As,⁹⁶ Se, and so on, ylids are also known. Ylids may be defined as compounds in which a positively charged atom from group 15 or 16 of the periodic table is connected to a carbon atom carrying an unshared pair of electrons (+ and – charges on adjacent atoms). Because of $p\pi-d\pi$ bonding, two canonical forms can be written for P and S, but there is only one for N ylids. Phosphorus ylids are much more stable than N ylids (see also **12–22**) which is one reason why N ylids tend to react more like carbanions (see **13–31** and **18–21**). While S ylids are generally less stable than P ylids, they are rather common.



In almost all compounds that have $p\pi-d\pi$ bonds, the central atom is connected to four or three atoms and an unshared pair, and the bonding is approximately tetrahedral. The $p\pi-d\pi$ bond, therefore, does not greatly change the geometry of the molecule in contrast to the normal π bond, which changes an atom from tetrahedral to trigonal. Calculations show that nonstabilized phosphonium ylids have nonplanar ylid carbon geometries whereas stabilized ylids have planar ylid carbons.⁹⁷

2.I. AROMATICITY⁹⁸

In the 19th century, it was recognized that aromatic compounds⁹⁹ differ greatly from unsaturated aliphatic compounds,¹⁰⁰ but for many years chemists were hard pressed to

⁹² See Johnson, A.W. *Ylid Chemistry*, Academic Press, NY, **1966**; Morris, D.G., *Surv. Prog. Chem.* **1983**, *10*, 189; Lowe, P.A. *Chem. Ind. (London)* **1970**, 1070. See Padwa, A.; Hornbuckle, S.F. *Chem. Rev.* **1991**, *91*, 263.

⁹³ Although the phosphorus ylid shown has three R groups on the phosphorus atom, other phosphorus ylids are known where other atoms, (e.g. oxygen), replace one or more of these R groups. When the three groups are all alkyl or aryl, the phosphorus ylid is also called a phosphorane.

⁹⁴ See Trost, B.M.; Melvin, Jr., L.S. *Sulfur Ylids*, Academic Press, NY, **1975**; Fava, A. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*; Elsevier, NY, **1985**, pp. 299–354; Belkin, Yu.V.; Polezhaeva, N.A. *Russ. Chem. Rev.* **1981**, *50*, 481; Block, E. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, p. 2, Wiley, NY, **1981**, pp. 680–702; Block, E. *Reactions of Organosulfur Compounds*; Academic Press, NY, **1978**, pp. 91–127.

⁹⁵ For a review of nitrogen ylids, see Musker, W.K. *Fortschr. Chem. Forsch.* **1970**, *14*, 295.

⁹⁶ For reviews of arsenic ylids, see Lloyd, D.; Gosney, I.; Ormiston, R.A. *Chem. Soc. Rev.* **1987**, *16*, 45; Yaozeng, H.; Yanchang, S. *Adv. Organomet. Chem.* **1982**, *20*, 115.

⁹⁷ Bachrach, S.M. *J. Org. Chem.* **1992**, *57*, 4367.

⁹⁸ Krygowski, T.M.; Cyrański, M.K. *Chem. Rev.* **2001**, *101*, 1385; Katritzky, A.R.; Jug, K.; Oniciu, D.C. *Chem. Rev.* **2001**, 1421; Fowler, P.W.; Lillington, M.; Olson, L.P. *Pure Appl. Chem.* **2007**, *79*, 969. See also, Cyrański, M. K.; Krygowski, T.M.; Katritzky, A.R.; Schleyer, P. R. *J. Org. Chem.* **2002**, *67*, 1333.

⁹⁹ See Lloyd, D. *The Chemistry of Conjugated Cyclic Compounds*, Wiley, NY, **1989**; *Non-Benzenoid Conjugated Carbocyclic Compounds*, Elsevier, NY, **1984**; Garratt, P.J. *Aromaticity*, Wiley, NY, **1986**; Balaban, A.T.; Banciu, M.; Ciorba, V. *Annulenes, Benzo-, Hetero-, Homo-Derivatives and their Valence Isomers*, 3 Vols., CRC Press, Boca Raton, FL, **1987**; Badger, G.M. *Aromatic Character and Aromaticity*, Cambridge University Press, Cambridge, **1969**; Snyder, J.P. *Nonbenzenoid Aromatics*, 2 Vols., Academic Press, NY, **1969–1971**; Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, **1971**. See Gorelik, M.V. *Russ. Chem. Rev.* **1990**, *59*, 116; Stevenson, G.R. *Mol. Struct. Energ.*, **1986**, *3*, 57; Figeys, H.P. *Top. Carbocyclic Chem.* **1969**, *1*, 269; Garratt, P.J.; Sargent, M.V. Papers in *Top. Curr. Chem.* **1990**, 153 and *Pure Appl. Chem.* **1980**, *52*, 1397.

¹⁰⁰ See Snyder, J.P., in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 1, Academic Press, NY, **1971**, pp. 1–31. See also, Balaban, A.T. *Pure Appl. Chem.* **1980**, *52*, 1409.

arrive at a mutually satisfactory definition of aromatic character.¹⁰¹ Qualitatively, there has never been real disagreement. Definitions include statements that aromatic compounds are characterized by a special stability and that they undergo substitution reactions more easily than addition reactions. These definitions are vague, however, and not easily applied to borderline cases. Definitions of aromaticity¹⁰² must encompass molecules ranging from polycyclic conjugated hydrocarbons,¹⁰³ to heterocyclic compounds¹⁰⁴ of various ring sizes, to reactive intermediates. In 1925, Armit and Robinson¹⁰⁵ recognized that the aromatic properties of the benzene ring are related to the presence of a closed loop of electrons, the aromatic sextet (aromatic compounds are thus the archetypal examples of delocalized bonding), but determining whether rings other than the benzene ring possessed such a loop remained difficult. With the advent of magnetic techniques, most notably NMR, it is possible to determine experimentally whether or not a compound has a closed ring of electrons. Aromaticity can now be defined as the ability to sustain an induced ring current. A compound with this ability is called *diatropic*. Although this definition also has its flaws,¹⁰⁶ it is the one most commonly accepted today. There are several methods of determining whether a compound can sustain a ring current, but the most important one is based on NMR chemical shifts.¹⁰⁷ Water-soluble calix[4]resorcarenes (see Sec. 3.C.ii) have been developed as an enantioselective NMR shift reagents for aromatic compounds.¹⁰⁸ In order to understand this, it is necessary to remember that, as a general rule, the value of the chemical shift of a proton in an NMR spectrum depends on the electron density of its bond; the greater the density of the electron cloud surrounding or partially surrounding a proton, the more upfield is its chemical shift (a lower value of δ). However, this rule has several exceptions; one is for protons in the vicinity of an aromatic ring. When an external magnetic field is imposed upon an aromatic ring (as in an NMR instrument), the closed loop of aromatic electrons circulates in a diamagnetic ring current, which generates a field of its own (ring current; known as magnetic anisotropy). As seen in Fig. 2.7, this induced field curves around and in the area of the proton is parallel to the external field, so the field “seen” by the aromatic protons is greater than it would have been in the absence of the diamagnetic ring current. The protons are moved downfield (to higher δ) compared to where they would be if electron density were the only factor. Thus ordinary alkene hydrogen atoms are found at $\sim 5\text{--}6\delta$, while the hydrogen atoms of benzene rings are located at $7\text{--}8\delta$. However, if there were protons located above or within the ring, they would be subjected to a *decreased* field and should appear at lower δ values than normal CH_2 groups (normal δ for CH_2 is $\sim 1\text{--}2$). The NMR spectrum of [10]paracyclophane (**48A**)

¹⁰¹ See Jones, A.J. *Pure Appl. Chem.* **1968**, *18*, 253. For methods of assigning Aromaticity, see Jug, K.; Köster, A. *M. J. Phys. Org. Chem.* **1991**, *4*, 163; Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* **1989**, *111*, 7371; Katritzky, A.R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* **1989**, *111*, 7. See also, Bird, C.W. *Tetrahedron* **1985**, *41*, 1409; **1986**, *42*, 89; **1987**, *43*, 4725.

¹⁰² For a critique of the concept of aromaticity, see Stanger, A. *Chem. Commun.* **2009**, 1939.

¹⁰³ Randic, M. *Chem. Rev.* **2003**, *103*, 3449.

¹⁰⁴ Balaban, A.T.; Oniciu, D.C.; Katritzky, A.R. *Chem. Rev.* **2004**, *104*, 2777.

¹⁰⁵ Armit, J.W.; Robinson, R. *J. Chem. Soc.* **1925**, 127, 1604.

¹⁰⁶ Jones, A.J. *Pure Appl. Chem.* **1968**, *18*, 253, pp. 266–274; Mallion, R.B. *Pure Appl. Chem.* **1980**, *52*, 1541. Also see, Schleyer, P.v.R.; Jiao, H. *Pure Appl. Chem.* **1996**, *68*, 209. For a discussion of the relationship between Pauling resonance energy and ring current, see Havenith, R.W.A. *J. Org. Chem.* **2006**, *71*, 3559.

¹⁰⁷ Geuenich, D.; Hess, K.; Felix Köhler, F.; Herges, R. *Chem. Rev.* **2005**, *105*, 3758; Haddon, R.C.; Haddon, V.R.; Jackman, L.M. *Fortschr. Chem. Forsch.* **1971**, *16*, 103; Dauben, Jr., H.J.; Wilson, J.D.; Laity, J.L. in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 2, Academic Press, NY, **1971**, pp. 167–206.

¹⁰⁸ Dignam, C.F.; Zopf, J.J.; Richards, C.J.; Wenzel, T.J. *J. Org. Chem.* **2005**, *70*, 8071.

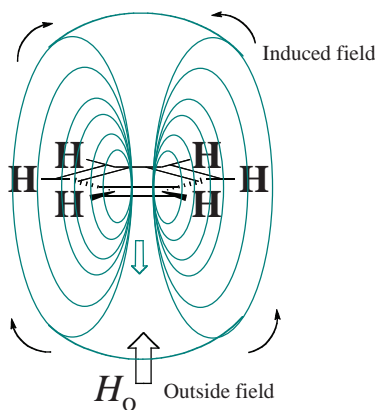
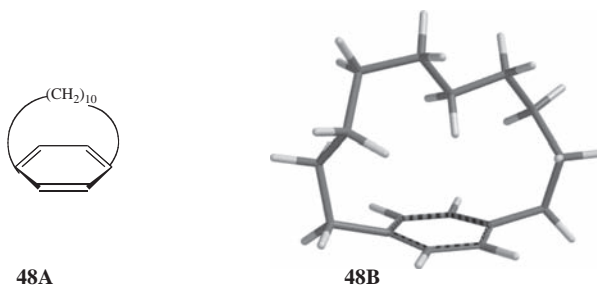


FIG. 2.7. Ring current in benzene.

showed that this was indeed the case,¹⁰⁹ and the CH₂ peaks were shifted to lower δ the closer they were to the middle of the chain. This fact that a portion of the methylene chain is positioned directly over the benzene ring is easier to see in the molecular model **48B**, and those protons are subject to the anisotropy shift.



It follows from this analysis that aromaticity can be determined from an NMR spectrum. If the protons attached to the ring are shifted downfield from the normal alkene region, it can be concluded that the molecule is diatropic and hence aromatic. In addition, if the compound has protons above or within the ring (see an example of the latter in Sec. 2.K.vi), then these will be shifted upfield if the compound is diatropic. However, local framework effects are important to aromaticity, and it has been argued that downfield chemical shifts of arene hydrogen atoms are not reliable indicators of aromaticity.¹¹⁰ One drawback to this method is that it cannot be applied to compounds that have no protons in either category (e.g, the dianion of squaric acid see Sec. 2.L). Unfortunately, ¹³C NMR is of no help here, since these spectra do not show ring currents.¹¹¹

¹⁰⁹ Waugh, J.S.; Fessenden, R.W. *J. Am. Chem. Soc.* **1957**, 79, 846. See also, Pascal, Jr., R.A.; Winans, C.G.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, 111, 3007.

¹¹⁰ Wannere, C.S.; Corminboeuf, C.; Allen, W.D.; Schaefer, III, H.F.; v. R. Schleyer, P. *Org. Lett.* **2005**, 7, 1457.

¹¹¹ See Günther, H.; Schmickler, H. *Pure Appl. Chem.* **1975**, 44, 807. See Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *Chem. Eur. J.* **2007**, 13, 6321; Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *J. Phys. Chem. A* **2008**, 112, 12816.

Bickelhaupt has argued that “double-bond delocalization” actually refers to bond-length equalization. The major effect is argued to be optimal sigma overlap, where the π electrons force the bonds to a somewhat shorter distance. For antiaromatic systems, the π electrons are said to have a stronger localizing drive.¹¹¹

It has been shown that when the nucleus independent chemical shifts for a set of aromatic and antiaromatic hydrocarbons are summed, there is a linear relationship with the magnetic susceptibility exaltation (the difference between the measured magnetic susceptibility of a compound and a calculated value based on group additivity tables) for neutral, cationic, and monoanionic species.¹¹² Aromatic and antiaromatic dianions show a similar relationship, but with a different slope.¹¹²

It appears that there are both energetic and magnetic criteria for aromaticity. The so-called *circuit resonance energy*¹¹³ is an important quantity that connects energetic and magnetic criteria of aromaticity. It is defined as a contribution of each cyclic path in a polycyclic π -system to the aromatic stabilization energy. The individual circuit contributions to aromaticity from the magnetic response of a polycyclic system have been determined, and named circuit resonance energies, with the same sign and essentially the same magnitude as the corresponding cyclic conjugation energy defined by Bosanac and by Gutman.¹¹⁴ Ring-current diamagnetism was taken as the tendency of a cyclic π system to retain aromatic stabilization energy of the individual circuits.

Antiaromatic systems exhibit a *paramagnetic* ring current,¹¹⁵ which causes protons on the outside of the ring to be shifted *upfield* while any inner protons are shifted *downfield*, in sharp contrast to a diamagnetic ring current, which causes shifts in the opposite directions (see above). Compounds that sustain a paramagnetic ring current are called *paratropic* and are prevalent in four and eight-electron systems. As with aromaticity, antiaromaticity should be at a maximum when the molecule is planar and when bond distances are equal. The diamagnetic and paramagnetic effects of the ring currents associated with aromatic and antiaromatic compounds (i.e., shielding and deshielding of nuclei) can be measured by a simple and efficient criterion known as nucleus independent chemical shift (NICS).¹¹⁶ The aromatic–antiaromatic ring currents reflect the extra π -effects that the molecules experience. The unique near zero value of NICS at the cyclobutadiene ring center is due to cancellation by large and opposite anisotropic components.¹¹⁷

Apart from the experimental NMR techniques, there are at least four theoretical models for aromaticity that have been compared and evaluated for predictive ability.¹¹⁸ The *Hess–Schaad model*¹¹⁹ is good for predicting aromatic stability of benzenoid hydrocarbons, but does not predict reactivity. The *Herndon model*¹²⁰ is also good for predicting aromatic stability, but is unreliable for benzenoidicity and does not predict reactivity. The *conjugated-circuit model*¹²¹

¹¹² Mills, N.S.; Llagostera, K.B. *J. Org. Chem.* **2007**, 72, 9163.

¹¹³ Aihara, J. *J. Am. Chem. Soc.* **2006**, 128, 2873.

¹¹⁴ Gutman, I. *Monatsh. Chem.* **2005**, 136, 1055.; Bosanac, S.; Gutman, I. *Z. Naturforsch.* **1977**, 32a, 10; Gutman, I.; Bosanac, S. *Tetrahedron* **1977**, 33, 1809.

¹¹⁵ Pople, J.A.; Untch, K.G. *J. Am. Chem. Soc.* **1966**, 88, 4811; Longuet-Higgins, H.C. in Garratt, P.J. *Aromaticity*, Wiley, NY, **1986**, pp. 109–111.

¹¹⁶ Schleyer, P.v.R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N.J.R.v.E. *J. Am. Chem. Soc.* **1996**, 118, 6317.

¹¹⁷ Schleyer, P.v.R.; Manoharan, M.; Wang, Z.-X.; Kiran, B.; Jiao, H.; Puchta, R.; Hommes, N.J.R.v.E. *Org. Lett.* **2001**, 3, 2465.

¹¹⁸ Playšić, D.; Babić, D.; Nikolić, S.; Trinajstić, N. *Gazz. Chim. Ital.*, **1993**, 123, 243.

¹¹⁹ Hess, Jr., B.A.; Schaad, L.J. *J. Am. Chem. Soc.* **1971**, 93, 305.

¹²⁰ Herndon, W.C. *Isr. J. Chem.* **1980**, 20, 270.

¹²¹ Randić, M. *Chem. Phys. Lett.* **1976**, 38, 68.

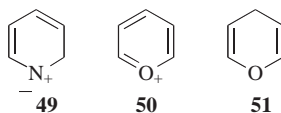
is very good for predicting aromatic stability but not reactivity, and the *hardness model*¹²² is best for predicting kinetic stability. Delocalization energy of π electrons has been used as an index for aromaticity in polycyclic aromatic hydrocarbons.¹²³ The claims for linear relationships between aromaticity and energetics, geometries, and magnetic criteria were said to be *invalid* for any representative set of heteroaromatics in which the number of heteroatoms varies.¹²⁴

It should be emphasized that the old and new definitions of aromaticity are not necessarily parallel. If a compound is diatropic, and therefore aromatic under the new definition, it is more stable than the canonical form of lowest energy, but this does not mean that it will be stable to air, light, or common reagents, since *this* stability is determined not by the resonance energy, but by the difference in free energy between the molecule and the transition states for the reactions involved. These differences may be quite small, even if the resonance energy is large. A unified theory has been developed that relates ring currents, resonance energies, and aromatic character.¹²⁵ Note that aromaticity varies in magnitude relatively and sometimes absolutely with the molecular environment, which includes the polarity of the medium.¹²⁶

The vast majority of aromatic compounds have a closed loop of six electrons in a ring (the aromatic sextet), and those compounds will be considered first.¹²⁷ Note that a “formula periodic table” for the benzenoid polyaromatic hydrocarbons has been developed.¹²⁸

2.1.i. Six-Membered Rings

Not only is the benzene ring aromatic, but so are many heterocyclic analogues in which one or more heteroatoms replace carbon in the ring.¹²⁹ When nitrogen is the heteroatom, there is a sextet and there is an unshared pair on the nitrogen that does not participate in the aromaticity. Therefore, derivatives (e.g., *N*-oxides or pyridinium ions) are still aromatic. There are more significant canonical forms (e.g., **49**) for nitrogen heterocycles than for benzene. Where oxygen or sulfur is the heteroatom, it must be present in its ionic form (**50**) in order to possess the valence of 3 demanded for participation in such a system. Thus, pyran (**51**) is not aromatic, but the pyrylium ion (**50**) is.¹³⁰



¹²² Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* **1989**, *111*, 7371; Zhou, Z.; Navangul, H.V. *J. Phys. Org. Chem.* **1990**, *3*, 784.

¹²³ See Cyrański, M.K. *Chem. Rev.* **2005**, *105*, 3773.

¹²⁴ Katritzky, A.R.; Karelson, M.; Sild, S.; Krygowski, T.M.; Jug, K. *J. Org. Chem.* **1998**, *63*, 5228.

¹²⁵ Haddon, R.C. *J. Am. Chem. Soc.* **1979**, *101*, 1722; Haddon, R.C.; Fukunaga, T. *Tetrahedron Lett.* **1980**, *21*, 1191.

¹²⁶ Katritzky, A.R.; Karelson, M.; Wells, A.P. *J. Org. Chem.* **1996**, *61*, 1619.

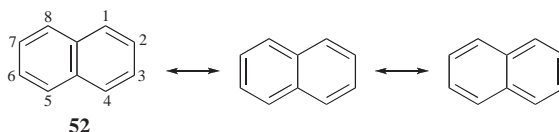
¹²⁷ Values of MO energies for many aromatic systems, calculated by the HMO method, are given in Coulson, C.A.; Streitwieser, Jr., A. *A Dictionary of π Electron Calculations*, W.H. Freeman, San Francisco, **1965**. Values calculated by a variation of the SCF method are given by Dewar, M.J.S.; Trinajstić, N. *Collect. Czech. Chem. Commun.* **1970**, *35*, 3136, 3484.

¹²⁸ Dias, J.R. *Chem. in Br.* **1994**, 384.

¹²⁹ See Katritzky, A.R.; Karelson, M.; Malhotra, N. *Heterocycles* **1991**, *32*, 127.

¹³⁰ See Balaban, A.T.; Schroth, W.; Fischer, G. *Adv. Heterocycl. Chem.* **1969**, *10*, 241.

In systems of fused six-membered aromatic rings,¹³¹ the principal canonical forms are usually not all equivalent. Naphthalene, (**52**) has a central double bond and is thus different from the other two canonical forms, which are equivalent to each other.¹³² For naphthalene, these are the only forms that can be drawn



without consideration of Dewar forms or those with charge separation.¹³³ If it is assumed that the three forms contribute equally, the 1,2-bond has more double-bond character than the 2,3-bond. Molecular orbital calculations show bond orders of 1.724 and 1.603, respectively (cf. benzene, 1.667). In agreement with these predictions, the 1,2 and 2,3 bond distances are 1.36 and 1.415 Å, respectively,¹³⁴ and ozone (**19–09** and **15–58**) preferentially attacks the 1,2-bond.¹³⁵ This nonequivalency of bonds, called *partial bond fixation*,¹³⁶ is found in nearly all fused aromatic systems. Note that a strained naphthalene derivative has been prepared in which one benzene ring is fused to two bicyclic systems. In this new naphthalene derivative, one six-membered ring has equalized bond lengths, but the other ring has alternating bond lengths.¹³⁷ The aromaticity of cation, anion, and ion-radical derivatives of naphthalene and other arenes has also been calculated.¹³⁸ A six-membered ring with a circle is often used to indicate an aromatic system, but Kekulé structures having the C=C units rather than a circle are used most often in this book. This statement is made here because one circle can be used for benzene, but it would be misleading to use two circles for naphthalene, for example, because that would imply 12 aromatic electrons, when naphthalene has only 10.¹³⁹

In phenanthrene, where the 9,10-bond is a single bond in only one of five canonical forms (**53**), bond fixation is significant and this bond is readily attacked by many reagents:¹⁴⁰ It has been observed that increased steric crowding leads to an increase in Dewar-benzene-type structures.¹⁴¹ In general, there is a good correlation between bond distances in fused aromatic compounds and bond orders. Another experimental quantity that correlates well with the bond order of a given bond in an aromatic system is the NMR

¹³¹ See Gutman, I.; Cyvin, S.J. *Introduction to the Theory of Benzenoid Hydrocarbons*, Springer, NY, **1989**; Dias, J.R. *Handbook of Polycyclic Hydrocarbons, Part A: Benzenoid Hydrocarbons*, Elsevier, NY, **1987**; Clar, E. *Polycyclic Hydrocarbons*, 2 Vols., Academic Press, NY, **1964**. For a “periodic table” that systematizes fused aromatic hydrocarbons, see Dias, J.R. *Acc. Chem. Res.* **1985**, 18, 241; *Top. Curr. Chem.* **1990**, 253, 123; *J. Phys. Org. Chem.* **1990**, 3, 765.

¹³² See Fuji, Z.; Xiaofeng, G.; Rongsi, C. *Top. Curr. Chem.* **1990**, 153, 181; Wenchen, H.; Wenjie, H. *Top. Curr. Chem.* **1990**, 153, 195; Sheng, R. *Top. Curr. Chem.* **1990**, 153, 211; Rongsi, C.; Cyvin, S.J.; Cyvin, B.N.; Brunvoll, J.; Klein, D.J. *Top. Curr. Chem.* **1990**, 153, 227, and references cited in these papers. For a monograph, see Cyvin, S.J.; Gutman, I. *Kekulé Structures in Benzenoid Hydrocarbons*, Springer, NY, **1988**.

¹³³ See Sironi, M.; Cooper, D.L.; Gerratt, J.; Raimondi, M. *J. Chem. Soc. Chem. Commun.* **1989**, 675.

¹³⁴ Cruickshank, D.W.J. *Tetrahedron* **1962**, 17, 155.

¹³⁵ Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas*, **1947**, 66, 201.

¹³⁶ For a review, see Efros, L.S. *Russ. Chem. Rev.* **1960**, 29, 66.

¹³⁷ Uto, T.; Nishinaga, T.; Matsuura, A.; Inoue, R.; Komatsu, K. *J. Am. Chem. Soc.* **2005**, 127, 10162.

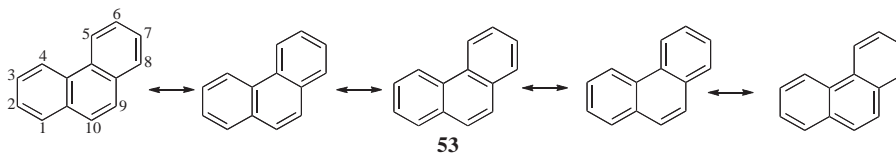
¹³⁸ Rosokha, S.V.; Kochi, J.K. *J. Org. Chem.* **2006**, 71, 9357.

¹³⁹ See Belloli, R. *J. Chem. Educ.* **1983**, 60, 190.

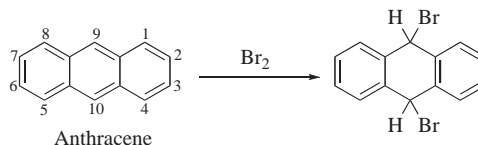
¹⁴⁰ See also, Lai, Y. *J. Am. Chem. Soc.* **1985**, 107, 6678.

¹⁴¹ Zhang, J.; Ho, D.M.; Pascal, Jr., R.A. *J. Am. Chem. Soc.* **2001**, 123, 10919.

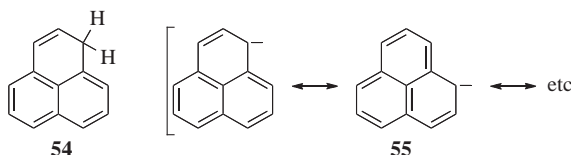
coupling constant for coupling between the hydrogen atoms on the two carbons of the bond.¹⁴²



The resonance energies of fused systems increase as the number of principal canonical forms increases, as predicted by rule 6 (Sec. 2.E).¹⁴³ Thus, for benzene, naphthalene, anthracene, and phenanthrene, for which can be drawn, respectively, two, three, four, and five principal canonical forms, the resonance energies are, respectively, 36, 61, 84, and 92 kcal mol⁻¹ (152, 255, 351, and 385 kJ mol⁻¹), calculated from heat of combustion data.¹⁴⁴ Note that when phenanthrene, which has a total resonance energy of 92 kcal mol⁻¹ (385 kJ mol⁻¹), loses the 9,10-bond by attack of a reagent (e.g., ozone or bromine), two complete benzene rings remain, each with 36 kcal mol⁻¹ (152 kJ mol⁻¹) that would be lost if those rings were similarly attacked. The fact that anthracene undergoes many reactions across the 9,10-positions can be explained in a similar manner. Resonance energies for fused systems can be estimated by counting canonical forms.¹⁴⁵ Calculations offer complementary evidence for the repulsive character of the H-H interactions in phenanthrene's bay region.¹⁴⁶



Not all fused systems can be fully aromatic. Thus for phenalene (**54**) there is no way to distribute double bonds so that each carbon has one single and one double bond.¹⁴⁷ However, phenalene is acidic and reacts with potassium methoxide to give the corresponding anion (**55**), which is completely aromatic. So are the corresponding radical and cation, in which the resonance energies are the same (see Sec. 2.I.iii).¹⁴⁸



¹⁴² Cooper, M.A.; Manatt, S.L. *J. Am. Chem. Soc.* **1969**, *91*, 6325.

¹⁴³ See Herndon, W.C.; Ellzey, Jr., M.L. *J. Am. Chem. Soc.* **1974**, *96*, 6631.

¹⁴⁴ Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, **1955**, p. 98.

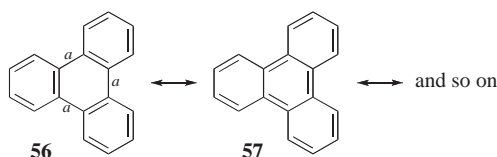
¹⁴⁵ Swinborne-Sheldrake, R.; Herndon, W.C. *Tetrahedron Lett.* **1975**, 755.

¹⁴⁶ Poater, J.; Visser, R.; Solà, M.; Bickelhaupt, F.M. *J. Org. Chem.* **2007**, *72*, 1134.

¹⁴⁷ For reviews of phenalenes, see Murata, I. *Top. Nonbenzenoid Aromat. Chem.* **1973**, *1*, 159; Reid, D.H. *Q. Rev. Chem. Soc.* **1965**, *19*, 274.

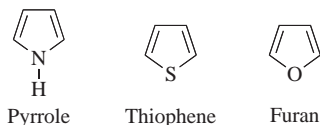
¹⁴⁸ Pettit, R. *J. Am. Chem. Soc.* **1960**, *82*, 1972.

Molecules that contain fused rings (e.g., phenanthrene or anthracene) are generally referred to as linear or angular polyacenes. **Acenes** are a class of organic compounds and polycyclic aromatic hydrocarbons made up of linearly fused benzene rings. In a fused system, with a focus on each individual ring, there are not six electrons for each ring.¹⁴⁹ In naphthalene, for example, if one ring is to have six, the other must have only four. The greater reactivity of the ring system of naphthalene compared with benzene has been explained by regarding one of the naphthalene rings as aromatic and the other as a butadiene system.¹⁵⁰ This effect can become extreme, as in the case of triphenylene.¹⁵¹ For this compound, there are eight canonical forms like **56**, in which none of the three bonds marked *a* is a double bond and only one form (**57**) in which at least one of them is double. Thus the molecule behaves as if the 18 electrons were distributed so as to give each of the outer rings a sextet, while the middle ring is “empty”. Since none of the outer rings need share any electrons with an adjacent ring, they are as stable as benzene. Triphenylene, unlike most fused aromatic hydrocarbons, does not dissolve in concentrated sulfuric acid and has a low reactivity.¹⁵² This phenomenon, whereby some rings in fused systems give up part of their aromaticity to adjacent rings, is called *annellation* and can be demonstrated by UV spectra,¹³¹ as well as chemical reactivity. In general, an increase of size of both linear and angular polyacenes is associated with a substantial decrease in their aromaticity, with a greater decrease for the linear polyacenes.¹⁵³ Note that molecular loops and belts can be made that involve acenes.¹⁵⁴



2.1.ii. Five, Seven, and Eight-Membered Rings

Aromatic sextets can also be present in five- and seven-membered rings. If a five-membered ring has two double bonds, and the fifth atom possesses an unshared pair of electrons, as in pyrrole, the ring has five *p* orbitals that can overlap to create five new orbitals: three bonding and two antibonding. There are six electrons for these orbitals: the four *p* orbitals of the double bonds each contribute one and the filled orbital contributes



the other two. The six electrons occupy the bonding orbitals and constitute an aromatic sextet, illustrated in Fig. 2.8. The electron potential map of pyrrole in Fig. 2.8 shows the aromatic cloud (dark area near the top of the model), indicative of significant electron

¹⁴⁹ See Glidewell, C.; Lloyd, D. *Tetrahedron* **1984**, 40, 4455, *J. Chem. Educ.* **1986**, 63, 306; Hosoya, H. *Top. Curr. Chem.* **1990**, 153, 255.

¹⁵⁰ Meredith, C.C.; Wright, G.F. *Can. J. Chem.* **1960**, 38, 1177.

¹⁵¹ For a review of triphenylenes, see Buess, C.M.; Lawson, D.D. *Chem. Rev.* **1960**, 60, 313.

¹⁵² Clar, E.; Zander, M. *J. Chem. Soc.* **1958**, 1861.

¹⁵³ Cyrański, M.K.; Słępień, B.T.; Krygowski, T.M. *Tetrahedron* **2000**, 56, 9663.

¹⁵⁴ Tahara, K.; Tobe, Y. *Chem. Rev.* **2006**, 106, 5274

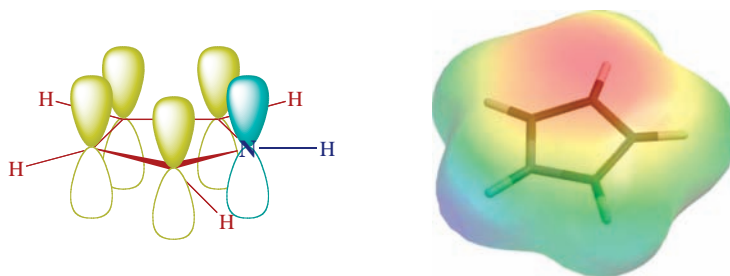
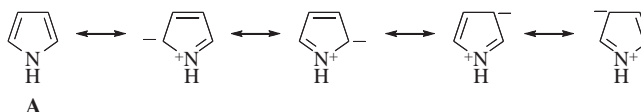


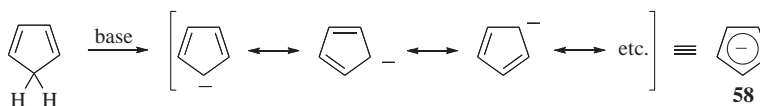
FIG. 2.8. Overlap of five p orbitals in pyrrole and the electron potential map of pyrrole.

density. The heterocyclic compounds pyrrole, thiophene, and furan are the most important examples of this kind of aromaticity, although furan has a lower degree of aromaticity when compared to the other two.¹⁵⁵ Resonance energies for these three compounds are, respectively, 21, 29, and 16 kcal mol⁻¹ (88, 121, and 67 kJ mol⁻¹).¹⁵⁶ The aromaticity can also be shown by canonical forms, (e.g., for pyrrole):



In contrast to pyridine, the unshared pair in canonical structure **A** in pyrrole is needed for the aromatic sextet. Since the electron pair is not available for donation, pyrrole is a much weaker base than pyridine.

The fifth atom may be carbon rather than a heteroatom, if carbon has an unshared pair (as in an anion). Cyclopentadiene is known to react with a suitable base, and loss of a proton to give a carbanion that is aromatic and therefore quite stable, although it is reactive to alkylating agents and electrophilic reagents. Due to formation of the stable cyclopentadienyl anion, cyclopentadiene ($pK_a \sim 16$) is approximately as strong an acid as water. The cyclopentadienide ion is sometimes represented as in **58**, although more commonly one of the canonical forms is used. Resonance in this ion is greater than in pyrrole, thiophene, and furan, since all five



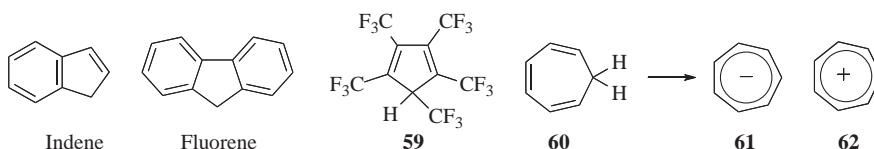
forms are equivalent, and the resonance energy for **58** has been estimated to be 24–27 kcal mol⁻¹ (100–113 kJ mol⁻¹).¹⁵⁷ All five carbons are equivalent, as demonstrated by labeling the starting compound with ¹⁴C and finding all positions equally labeled when

¹⁵⁵ The order of aromaticity of these compounds is benzene > thiophene > pyrrole > furan, as calculated by an aromaticity index based on bond distance measurements. This index has been calculated for five- and six-membered monocyclic and bicyclic heterocycles: Bird, C.W. *Tetrahedron* **1985**, 41, 1409; **1986**, 42, 89; **1987**, 43, 4725.

¹⁵⁶ Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, **1955**, p. 99. See also, Calderbank, K.E.; Calvert, R.L.; Lukins, P.B.; Ritchie, G.L.D. *Aust. J. Chem.* **1981**, 34, 1835.

¹⁵⁷ Bordwell, F.G.; Drucker, G.E.; Fried, H.E. *J. Org. Chem.* **1981**, 46, 632.

cyclopentadiene was regenerated.¹⁵⁸ As expected for an aromatic system, **58** is diatropic¹⁵⁹ and aromatic substitutions (see Chapters 11 and 13) on it have been successfully carried out.¹⁶⁰ Average bond order has been proposed as a parameter to evaluate the aromaticity of such rings, but there is poor correlation with nonaromatic and antiaromatic systems.¹⁶¹ A model that relies on calculating relative aromaticity from appropriate molecular fragments has also been developed.¹⁶² Bird¹⁶³ devised the aromatic index (I_A , or aromaticity index), which is a statistical evaluation of the extent of ring bond order, and has been used as a criterion of aromaticity. Another bond-order index was proposed by Pozharskii,¹⁶⁴ which builds on the work of Fringuelli et al.¹⁶⁵ Absolute hardness (see Sec. 8.E), calculated from molecular refractions for a range of aromatic and heteroaromatic compounds, shows good linear correlation with aromaticity.¹⁶⁶ Indene and fluorene are also acidic ($pK_a \sim 20$ and 23, respectively), but less so than cyclopentadiene, since annellation causes the electrons to be less available to the five-membered ring. On the other hand, the acidity of 1,2,3,4,5-pentakis(trifluoromethyl)cyclopentadiene (**59**) is greater than that of nitric acid,¹⁶⁷ because of the electron-withdrawing effects of the trifluoromethyl groups (see Sec. 8.F). Modifications of the Bird¹⁶³ and Pozharskii¹⁶⁴ systems have been introduced that are particularly useful for five-membered ring heterocycles.¹⁶⁸ Recent work introduced a new local aromaticity measure, defined as the mean of Bader's electron delocalization index (DI)¹⁶⁹ of para-related carbon atoms in six-membered rings.¹⁷⁰ Bond resonance energy has been used as an indicator of local aromaticity.¹⁷¹ The relative merits of several aromaticity indices has been discussed.¹⁷²



As seen above, relative acidity can be used to study the aromatic character of the resulting conjugate base of a given compound. In sharp contrast to cyclopentadiene (see Sec. 2.I.ii) is cycloheptatriene (**60**), which has no unusual acidity. This would be hard to explain without the aromatic sextet theory, since, on the basis of resonance forms or a simple consideration of orbital overlaps, **61** should be as stable as the cyclopentadienyl anion (**58**). This eight electron system is antiaromatic, however. While **61** has been

¹⁵⁸ Tkachuk, R.; Lee, C.C. *Can. J. Chem.* **1959**, *37*, 1644.

¹⁵⁹ Bradamante, S.; Marchesini, A.; Pagani, G. *Tetrahedron Lett.* **1971**, 4621.

¹⁶⁰ Webster, O.W. *J. Org. Chem.* **1967**, *32*, 39; Rybinskaya, M.I.; Korneva, L.M. *Russ. Chem. Rev.* **1971**, *40*, 247.

¹⁶¹ Jursic, B.S. *J. Heterocyclic Chem.* **1997**, *34*, 1387.

¹⁶² Hosmane, R.S.; Liebman, J.F. *Tetrahedron Lett.* **1992**, *33*, 2303.

¹⁶³ Bird, C.W. *Tetrahedron* **1996**, *52*, 9945; Hosoya, H. *Monat. Chemie* **2005**, *136*, 1037.

¹⁶⁴ Pozharskii, A.F. *Khimiya Geterotsikl Soedin* **1985**, 867.

¹⁶⁵ Fringuelli, F.; Marino, G.; Taticchi, A.; Grandolini, G. *J. Chem. Soc. Perkin Trans. 2* **1974**, 332.

¹⁶⁶ Bird, C.W. *Tetrahedron* **1997**, *53*, 3319; *Tetrahedron* **1998**, *54*, 4641.

¹⁶⁷ Laganis, E.D.; Lemal, D.M. *J. Am. Chem. Soc.* **1980**, *102*, 6633.

¹⁶⁸ Kotelevskii, S.I.; Prezhdo, O.V. *Tetrahedron* **2001**, *57*, 5715.

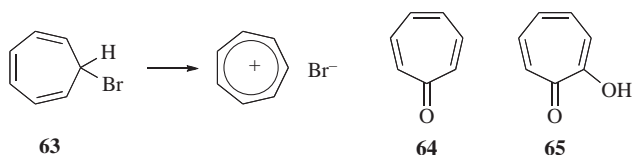
¹⁶⁹ See Bader, R.F.W. *Atoms in Molecules: A Quantum Theory*, Clarendon, Oxford, **1990**; Bader, R.F.W. *Acc. Chem. Res.* **1985**, *18*, 9; Bader, R.F.W. *Chem. Rev.* **1991**, *91*, 893.

¹⁷⁰ Poater, J.; Fradera, X.; Duran, M.; Solà, M. *Chem. Eur. J.* **2003**, *9*, 400; 1113.

¹⁷¹ Aihara, J.; Ishida, T.; Kanno, H. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1518.

¹⁷² Fallah-Bagher-Shaidaei, H.; Wannere, C.S.; Corminboeuf, C.; Puchta, R.; v.R. Schleyer, P. *Org. Lett.* **2006**, *8*, 863.

prepared in solution,¹⁷³ it is less stable than **58** and far less stable than **62**, in which **60** has lost not a proton but the equivalent of a hydride ion. The six double-bond electrons of **62** overlap with the empty orbital on the seventh carbon and there is a sextet of electrons covering seven carbon atoms. The cycloheptatrienyl cation (known as the *tropylium ion*, **62**) is quite stable,¹⁷⁴ but are generally formed from the corresponding halide rather than by loss of a hydride. Tropylium bromide (**63**), which could be completely covalent if the electrons of the bromine were sufficiently attracted to the ring, is actually better viewed as an ionic compound.¹⁷⁵ Many substituted tropylium ions have been prepared to probe the aromaticity, structure, and reactivity of such systems.¹⁷⁶ As with **58**, the equivalence of the carbon atoms in **62** has been demonstrated by isotopic labeling.¹⁷⁷ The aromatic cycloheptatrienyl cations $C_7Me_7^+$ and $C_7Ph_7^+$ are known,¹⁷⁸ although their coordination complexes with transition metals have been problematic, possibly because they assume a boat-like rather than a planar conformation¹⁷⁹



Tropone (**64**) is another seven-membered ring that shows some aromatic character. This molecule would have an aromatic sextet if the two C=O electrons stayed away from the ring and resided near the electronegative oxygen atom. In fact, tropones are stable compounds, and tropolones (**65**) are found in nature.¹⁸⁰ However, analyses of dipole moments, NMR spectra, and X-ray diffraction measurements show that tropones and tropolones display appreciable bond alternations.¹⁸¹ These molecules must be regarded as essentially non-aromatic, although some have aromatic character. Tropolones readily undergo aromatic substitution, emphasizing that the old and the new definitions of aromaticity are not always parallel. It is known that **65** is acidic ($pK_a \sim 6.7$),¹⁸² in large part because the resulting anion has aromatic character. Indeed, **65** is considered to be a vinylogous carboxylic acid. In sharp contrast to **64**, cyclopentadienone (**66**) has been isolated only in an Ar matrix < 38 K.¹⁸³ Above this temperature it dimerizes. Many earlier

¹⁷³ Dauben Jr., H.J.; Rifi, M.R. *J. Am. Chem. Soc.* **1963**, 85, 3041; also see, Breslow, R.; Chang, H.W. *J. Am. Chem. Soc.* **1965**, 87, 2200.

¹⁷⁴ See Pietra, F. *Chem. Rev.* **1973**, 73, 293; Bertelli, D.J. *Top. Nonbenzenoid Aromat. Chem.* **1973**, 1, 29; Kolomnikova, G.D.; Parnes, Z.N. *Russ. Chem. Rev.* **1967**, 36, 735; Harmon, K.H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4; Wiley, NY, 1973, pp. 1579–1641.

¹⁷⁵ Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* **1954**, 76, 3203.

¹⁷⁶ Pischel, U.; Abraham, W.; Schnabel, W.; Müller, U. *Chem. Commun.* **1997**, 1383. See Komatsu, K.; Nishinaga, T.; Maekawa, N.; Kagayama, A.; Takeuchi, K. *J. Org. Chem.* **1994**, 59, 7316 for a tropylium dication.

¹⁷⁷ Vol'pin, M.E.; Kursanov, D.N.; Shemyakin, M.M.; Maimind, V.I.; Neiman, L.A. *J. Gen. Chem. USSR* **1959**, 29, 3667.

¹⁷⁸ Takeuchi, K.; Yokomichi, Y.; Okamoto, K. *Chem. Lett.* **1977**, 1177; Battiste, M. A. *J. Am. Chem. Soc.* **1961**, 83, 4101.

¹⁷⁹ Tamm, M.; Dreßel, B.; Fröhlich, R. *J. Org. Chem.* **2000**, 65, 6795.

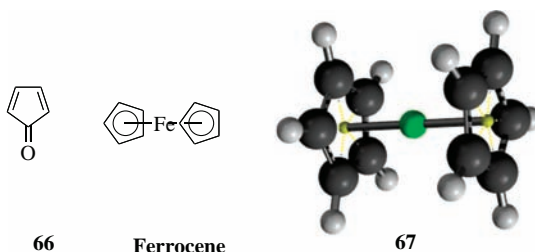
¹⁸⁰ Pietra, F. *Acc. Chem. Res.* **1979**, 12, 132; Nozoe, T. *Pure Appl. Chem.* **1971**, 28, 239.

¹⁸¹ Schaefer, J.P.; Reed, L.L. *J. Am. Chem. Soc.* **1971**, 93, 3902; Watkin, D.J.; Hamor, T.A. *J. Chem. Soc. B* **1971**, 2167; Barrow, M.J.; Mills, O.S.; Filippini, G. *J. Chem. Soc. Chem. Commun.* **1973**, 66.

¹⁸² von E. Doering, W.; Knox, L.H. *J. Am. Chem. Soc.* **1951**, 73, 828.

¹⁸³ Maier, G.; Franz, L.H.; Hartan, H.; Lanz, K.; Reisenauer, H.P. *Chem. Ber.* **1985**, 118, 3196.

attempts to prepare it were unsuccessful.¹⁸⁴ As in **64**, the electronegative oxygen atom draws electron density to itself, but in this case it leaves only four electrons and the molecule is unstable. Some derivatives of **66** have been prepared.¹⁴⁵



The *metallocenes* (also called *sandwich compounds*) constitute another type of five-membered aromatic compound in which two cyclopentadienide rings form a sandwich around a metal. The best known of these is ferrocene, where the η^5 -coordination of the two cyclopentadienyl rings to iron is apparent in the 3D model **67**. Other metallocenes have been prepared with Co, Ni, Cr, Ti, V, and many other metals.¹⁸⁵ As a reminder (see Sec. 2.C), the η terminology refers to π -donation of electrons to the metal (η^3 for π -allyl systems, η^6 for coordination to a benzene ring, etc.), and η^5 refers to donation of five π -electrons to the iron. Ferrocene is quite stable, subliming $>100^\circ\text{C}$ and unchanged at 400°C . The two rings rotate freely.¹⁸⁶ Many aromatic substitutions (Chapter 11) have been carried out on metallocenes.¹⁸⁷ Metallocenes containing two metal atoms and three cyclopentadienyl rings have also been prepared and are known as *triple-decker sandwiches*.¹⁸⁸ Even tetradecker, pentadecker, and hexadecker sandwiches have been reported.¹⁸⁹

The bonding in ferrocene may be looked upon in simplified MO terms as follows.¹⁹⁰ Each of the cyclopentadienide rings has five molecular orbitals: three filled bonding and two empty antibonding orbitals (Sec. 2.I.ii). The outer shell of the Fe atom possesses nine atomic orbitals, that is, one $4s$, three $4p$, and five $3d$ orbitals. The six filled orbitals of the two cyclopentadienide rings overlap with the s , three p , and two of the d orbitals of the Fe to form 12 new orbitals, six of which are bonding. These six orbitals make up two ring-metal triple bonds. In addition, further bonding results from the overlap of the empty antibonding orbitals of the rings with additional filled d orbitals of the iron. All told, there are 18 electrons (10 of which may be considered to come from the rings and 8 from iron in the

¹⁸⁴ See Ogliaruso, M.A.; Romanelli, M.G.; Becker, E.I. *Chem. Rev.* **1965**, 65, 261.

¹⁸⁵ See Rosenblum, M. *Chemistry of the Iron Group Metallocenes*, Wiley, NY, **1965**; Lukehart, C.M. *Fundamental Transition Metal Organometallic Chemistry*, Brooks/Cole, Monterey, CA, **1985**, pp. 85–118; Sikora, D.J.; Macomber, D.W.; Rausch, M.D. *Adv. Organomet. Chem.* **1986**, 25, 317; Pauson, P.L. *Pure Appl. Chem.* **1977**, 49, 839; Perevalova, E.G.; Nikitina, T.V. *Organomet. React.* **1972**, 4, 163; Bublit, D.E.; Rinehart, Jr., K.L. *Org. React.*, **1969**, 17, 1; Rausch, M.D. *Pure Appl. Chem.* **1972**, 30, 523; Bruce, M.I. *Adv. Organomet. Chem.* **1972**, 10, 273, 322–325.

¹⁸⁶ For a discussion of the molecular structure, see Haaland, A. *Acc. Chem. Res.* **1979**, 12, 415.

¹⁸⁷ See Plesske, K. *Angew. Chem. Int. Ed.* **1962**, 1, 312, 394.

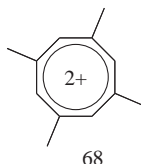
¹⁸⁸ For a review, see Werner, H. *Angew. Chem. Int. Ed.* **1977**, 16, 1.

¹⁸⁹ See, for example, Siebert, W. *Angew. Chem. Int. Ed.* **1985**, 24, 943.

¹⁹⁰ Rosenblum, M. *Chemistry of the Iron Group Metallocenes*, Wiley, NY, **1965**, pp. 13–28; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., Vol. 2, Methuen, London, **1968**, pp. 97–104; Grebenik, P.; Grinter, R.; Perutz, R.N. *Chem. Soc. Rev.* **1988**, 17, 453, 460.

zero oxidation state) in nine orbitals; six of these are strongly bonding and three weakly bonding or nonbonding.

The tropylium ion has an aromatic sextet spread over seven carbon atoms. An analogous ion, with the sextet spread over eight carbon atoms, is the 1,3,5,7-tetramethylcyclooctatetraene dication (**68**). This ion, which is stable in solution at -50°C , is diatropic and approximately planar. The dication **68** is not stable above about -30°C .¹⁹¹



2.1.iii. Other Systems Containing Aromatic Sextets

Simple resonance theory predicts that pentalene (**69**), azulene (**70**), and heptalene (**71**) should be aromatic, although no nonionic canonical form can have a double bond at the ring junction. Molecular orbital calculations show that azulene should be stable but not the other two. This finding is borne out by experiment. Heptalene has been prepared,¹⁹² but reacts readily with oxygen, acids, and bromine, is easily hydrogenated, and polymerizes on standing. Analysis of its NMR spectrum shows that it is not planar.¹⁹³ The 3,8-dibromo and 3,8-dicarbomethoxy derivatives of **71** are stable in air at room temperature, but are not diatropic.¹⁹⁴ A number of methylated heptalenes and dimethyl 1,2-heptalenedicarboxylates have also been prepared and are stable non-aromatic compounds.¹⁹⁵ Pentalene has not been prepared,¹⁹⁶ but the hexaphenyl¹⁹⁷ and 1,3,5-tri-*tert*-butyl derivatives¹⁹⁸ are known. The former is air sensitive in solution. The latter is stable, but X-ray diffraction and photoelectron spectral data show bond alternation.¹⁹⁹ Pentalene and its methyl and dimethyl derivatives have been formed in solution, but they dimerize before they can be isolated.²⁰⁰ Many other attempts to prepare these two systems have failed.

¹⁹¹ Olah, G.A.; Staral, J.S.; Liang, G.; Paquette, L.A.; Melega, W.P.; Carmody, M.J. *J. Am. Chem. Soc.* **1977**, *99*, 3349. See also, Radom, L.; Schaefer III, H.F. *J. Am. Chem. Soc.* **1977**, *99*, 7522; Olah, G.A.; Liang, G. *J. Am. Chem. Soc.* **1976**, *98*, 3033; Willner, I.; Rabinovitz, M. *Nouv. J. Chim.*, **1982**, *6*, 129.

¹⁹² Paquette, L.A.; Browne, A.R.; Chamot, E. *Angew. Chem. Int. Ed.* **1979**, *18*, 546. For a review of heptalenes, see Paquette, L.A. *Isr. J. Chem.* **1980**, *20*, 233.

¹⁹³ Bertelli, D.J., in Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, **1971**, p. 326. See also, Stegemann, J.; Lindner, H.J. *Tetrahedron Lett.* **1977**, 2515.

¹⁹⁴ Vogel, E.; Ippen, J. *Angew. Chem. Int. Ed.* **1974**, *13*, 734; Vogel, E.; Hogrefe, F. *Angew. Chem. Int. Ed.* **1974**, *13*, 735.

¹⁹⁵ Hafner, K.; Knaup, G.L.; Lindner, H.J. *Bull. Soc. Chem. Jpn.* **1988**, *61*, 155.

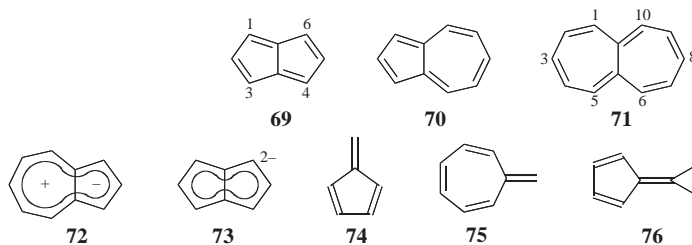
¹⁹⁶ See Knox, S.A.R.; Stone, F.G.A. *Acc. Chem. Res.* **1974**, *7*, 321.

¹⁹⁷ LeGoff, E. *J. Am. Chem. Soc.* **1962**, *84*, 3975. See also, Hartke, K.; Matusch, R. *Angew. Chem. Int. Ed.* **1972**, *11*, 50.

¹⁹⁸ Hafner, K.; Süß, H.U. *Angew. Chem. Int. Ed.* **1973**, *12*, 575. See also, Hafner, K.; Suda, M. *Angew. Chem. Int. Ed.* **1976**, *15*, 314.

¹⁹⁹ Bischof, P.; Gleiter, R.; Hafner, K.; Knauer, K.H.; Spanget-Larsen, J.; Süß, H.U. *Chem. Ber.* **1978**, *111*, 932.

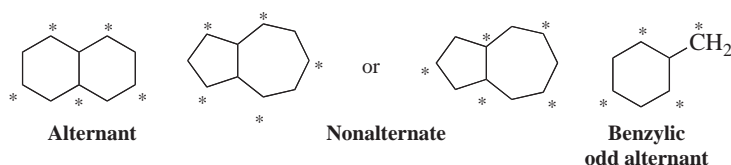
²⁰⁰ Hafner, K.; Dönges, R.; Goedecke, E.; Kaiser, R. *Angew. Chem. Int. Ed.* **1973**, *12*, 337.



In sharp contrast to **69** and **71**, azulene (**70**) is a blue solid, is quite stable, and many of its derivatives are known.²⁰¹ Azulene readily undergoes aromatic substitution. Azulene may be regarded as a combination of **58** and **62** and, indeed, possesses a dipole moment of $0.8 D$ (see **72**).²⁰² Interestingly, if two electrons are added to pentalene, a stable dianion (**73**) results.²⁰³ It can be concluded that an aromatic system of electrons will be spread over two rings only if 10 electrons (not 8 or 12) are available for aromaticity. $[n,m]$ -Fulvalenes ($n \neq m$, where fulvalene is **74**), as well as azulene are known to shift their π -electrons due to the influence of dipolar aromatic resonance structures.²⁰⁴ However, calculations showed that dipolar resonance structures contribute only 5% to the electronic structure of heptafulvalene (**75**), although 22–31% to calicene (**76**).²⁰⁵ Based on Baird's theory,²⁰⁶ these molecules are influenced by aromaticity in both the ground and excited states, therefore acting as aromatic "chameleons." This premise was confirmed in work by Ottosson and co-workers.²⁰⁴ Aromaticity indexes for various substituted fulvalene compounds has been reported.²⁰⁷

2.J. ALTERNANT AND NONALTERNANT HYDROCARBONS²⁰⁸

Aromatic hydrocarbons can be divided into alternant and nonalternant hydrocarbons. In alternant hydrocarbons, the conjugated carbon atoms can be divided into two sets such that no two atoms of the same set are directly linked. For convenience, one set may be starred. Naphthalene is an alternant and azulene a nonalternant hydrocarbon:



In alternant hydrocarbons, the bonding and antibonding orbitals occur in pairs; that is, for every bonding orbital with an energy $-E$ there is an antibonding one with energy $+E$

²⁰¹ For a review on azulene, see Mochalin, V.B.; Porshnev, Yu.N. *Russ. Chem. Rev.* **1977**, *46*, 530.

²⁰² Tobler, H.J.; Bauder, A.; Günthard, H.H. *J. Mol. Spectrosc.*, **1965**, *18*, 239.

²⁰³ Katz, T.J.; Rosenberger, M.; O'Hara, R.K. *J. Am. Chem. Soc.* **1964**, *86*, 249. See also, Willner, I.; Becker, J.Y.; Rabinovitz, M. *J. Am. Chem. Soc.* **1979**, *101*, 395.

²⁰⁴ Möllerstedt, H.; Piqueras, M.C.; Crespo, R.; Ottosson, H. *J. Am. Chem. Soc.* **2004**, *126*, 13938.

²⁰⁵ Scott, A.P.; Agranat, A.; Biedermann, P.U.; Riggs, N.V.; Radom, L. *J. Org. Chem.* **1997**, *62*, 2026.

²⁰⁶ Baird, N.C. *J. Am. Chem. Soc.* **1972**, *94*, 4941.

²⁰⁷ Stepien, B.T.; Krygowski, T.M.; Cyrański, M.K. *J. Org. Chem.* **2002**, *67*, 5987.

²⁰⁸ See Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, **1984**, pp. 122–129; Dewar, M.J.S. *Prog. Org. Chem.* **1953**, *2*, 1.

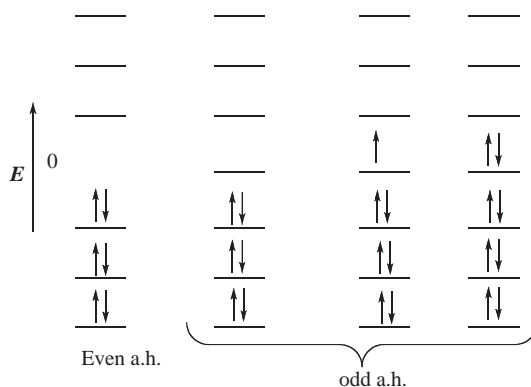


FIG. 2.9. Energy levels in odd- and even-alternant hydrocarbons.²⁰⁹ The arrows represent electrons. The orbitals are shown as having different energies, but some may be degenerate.

(Fig. 2.9²⁰⁹). Even-alternant hydrocarbons are those with an even number of conjugated atoms, that is, an equal number of starred and unstarred atoms. For these hydrocarbons all the bonding orbitals are filled and the π electrons are uniformly spread over the unsaturated atoms.

As with the allylic system, odd-alternant hydrocarbons (which must be carbocations, carbanions, or radicals) in addition to equal and opposite bonding and antibonding orbitals also have a nonbonding orbital of zero energy. When an odd number of orbitals overlap, an odd number is created. Since orbitals of alternant hydrocarbons occur in $-E$ and $+E$ pairs, one orbital can have no partner and must therefore have zero-bonding energy. For example, in the benzylic system the cation has an unoccupied nonbonding orbital, the free radical has one electron there and the carbanion has two (Fig. 2.10). As with the allylic system, all three species have the same bonding energy. The charge distribution (or unpaired-electron

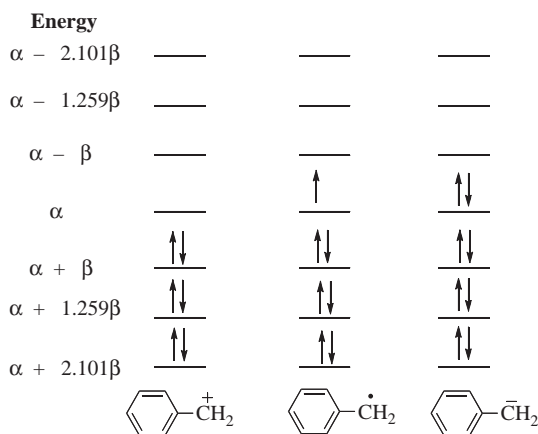


FIG. 2.10. Energy levels for the benzyl cation, free radical, and carbanion. Since α is the energy of a p orbital (Sec. 2.B), the nonbonding orbital has no bonding energy.

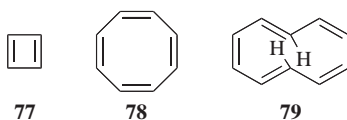
²⁰⁹ Taken from Dewar, M.J.S *Prog. Org. Chem.* **1953**, 2, 1, p. 8.

distribution) over the entire molecule is also the same for the three species and can be calculated by a relatively simple process.²⁰⁸

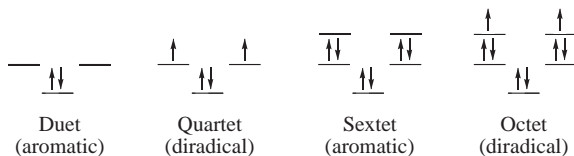
For nonalternant hydrocarbons, the energies of the bonding and antibonding orbitals are not equal and opposite and charge distributions are not the same in cations, anions, and radicals. Calculations are much more difficult, but have been carried out.²¹⁰ Theoretical approaches to calculate topological polarization and reactivity of these hydrocarbons have been reported.²¹¹

2.K. AROMATIC SYSTEMS WITH ELECTRON NUMBERS OTHER THAN SIX

The special stability of benzene is well recognized, and this stability is also associated with rings that are similar, but of different sizes, (e.g., cyclobutadiene (**77**), cyclooctatetraene (**78**), cyclodecapentaene (**79**))²¹²,



and so on. The general name *annulene* is given to these compounds,²¹³ benzene being [6]annulene, and **77–79** being called, respectively, [4], [8], and [10]annulene.²¹⁴ By a naïve consideration of resonance forms, these annulenes and higher ones should be as aromatic as benzene. Yet they proved remarkably elusive. The ubiquitous benzene ring is found in thousands of natural products, in coal and petroleum, and is formed by strong treatment of many noncyclic compounds. None of the other annulene ring systems has ever been found in nature and, except for cyclooctatetraene, their synthesis is not simple. Obviously, there is something special about the number six in a cyclic system of electrons.



Hückel's rule, based on MO calculations,²¹⁵ predicts that electron rings will constitute an aromatic system only if the number of electrons in the ring is of the form $4n + 2$, where n is zero or any position integer. Systems that contain $4n$ electrons are predicted to be nonaromatic.

²¹⁰ Brown, R.D.; Burden, F.R.; Williams, G.R. *Aust. J. Chem.* **1968**, *21*, 1939. For reviews, see Zahradnik, R., in Snyder, J.P. *Nonbenzenoid Aromatics* Vol. 2, Academic Press, NY, **1971**, pp. 1–80; Zahradnik, R. *Angew. Chem. Int. Ed.* **1965**, *4*, 1039.

²¹¹ Langler, R.F. *Aust. J. Chem.* **2000**, *53*, 471; Frederiksen, M.U.; Langler, R.F.; Staples, M.A.; Verma, S.D. *Aust. J. Chem.* **2000**, *53*, 481.

²¹² For other stereoisomers, see Section 2.K.iv.

²¹³ Spitler, E.L.; Johnson, II, C.A.; Haley, M.M. *Chem. Rev.* **2006**, *106*, 5344; for a discussion of annulenylenes, annulynes, and annulenes, see Stevenson, C.D. *Acc. Chem. Res.* **2007**, *40*, 703.

²¹⁴ For a discussion of bond shifting and automerization in [10]annulene, see Castro, C.; Karney, W.L.; McShane, C.M.; Pemberton, R.P. *J. Org. Chem.* **2006**, *71*, 3001.

²¹⁵ See Nakajima, T. *Pure Appl. Chem.* **1971**, *28*, 219; *Fortschr. Chem. Forsch.* **1972**, *32*, 1.

The rule predicts that rings of 2, 6, 10, 14, and so on, electrons will be aromatic, while rings of 4, 8, 12, and so on, will not be. This is actually a consequence of *Hund's rule*. The first pair of electrons in an annulene goes into the π orbital of lowest energy. After that the bonding orbitals are degenerate and occur in pairs of equal energy. When there is a total of four electrons, Hund's rule predicts that two will be in the lowest orbital, but the other two will be unpaired, so that the system will exist as a diradical rather than as two pairs. The degeneracy can be removed if the molecule is distorted from maximum molecular symmetry to a structure of lesser symmetry. For example, if **77** assumes a rectangular rather than a square shape, one of the previously degenerate orbitals has a lower energy than the other and will be occupied by two electrons. In this case, of course, the double bonds are essentially separate and the molecule is still not aromatic. Distortions of symmetry can also occur when one or more carbons are replaced by heteroatoms or in other ways.²¹⁶ The enthalpy of formation of cyclobutadiene was reported by Kass and co-workers.²¹⁷ There is a brief discussion of the importance of cyclobutadiene with respect to antiaromaticity.²¹⁸ A word of caution is in order for MO calculations in these systems. It is known that *ab initio* computations on benzene at electron-correlated MP2, MP3, CISD, and CCSD levels using a number of popular basis sets²¹⁹ give anomalous, nonplanar equilibrium structures.²²⁰ The origin of these anomalies has been addressed.²²⁰

In the following sections, systems with various numbers of electrons are discussed. Any probe of aromaticity must include (1) the presence of a diamagnetic ring current; (2) equal or approximately equal bond distances, except when the symmetry of the system is disturbed by a heteroatom or in some other way; (3) planarity; (4) chemical stability; (5) the ability to undergo aromatic substitution.

2.K.i Systems of Two Electrons²²¹

Obviously, there can be no ring of two carbon atoms (a double bond may be regarded as a degenerate case). However, by analogy to the tropylium ion, a three-membered ring with a double bond and a positive charge on the third atom (the *cyclopropenyl cation*) is a $4n + 2$ system and expected to show aromaticity. Unsubstituted **80** has been prepared,²²² as well as several derivatives, (e.g., the trichloro, diphenyl, and dipropyl derivatives), and they are stable despite bond angles of only 60°. Tripropylcyclopropenyl,²²³ tricyclopropylcyclopropenyl,²²⁴ chlorodipropylcyclopropenyl,²²⁵ and chloro-bis-dialkylaminocyclopropenyl²²⁶ cations are among the most stable carbocations known, being stable even in

²¹⁶ See Hoffmann, R. *Chem. Commun.* **1969**, 240.

²¹⁷ Fattahi, A.; Liz, L.; Tian, Z.; Kass, S.R. *Angew. Chem.* **2006**, *118*, 5106.

²¹⁸ Bally, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6616–6619.

²¹⁹ Hehre, W. J.; Radom, L.; Pople, J. A.; Schleyer, P. v. R. *Ab Initio Molecular Orbital Theory*, John Wiley & Sons: New York, **1986**; v.R. Schleyer, P.; Allinger, N.L.; Clark, T.; Gasteiger, J.; Kollman, P.A.; Schaefer, III, H.F.; Schreiner, P.R. (Eds.) *The Encyclopedia of Computational Chemistry*, John Wiley & Sons, Ltd., Chichester, **1998**.

²²⁰ Moran, D.; Simmonett, A.C.; Leach, III, F.E.; Allen, W.D.; v. R. Schleyer, P.; Schaefer, III, H.F. *J. Am. Chem. Soc.* **2006**, *128*, 9342.

²²¹ See Billups, W.E.; Moorehead, A.W., in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, **1987**, pp. 1533–1574; Potts, K.T.; Baum, J.S. *Chem. Rev.* **1974**, *74*, 189; Closs, G.L. *Adv. Alicyclic Chem.* **1966**, *1*, 53, 102–126; Krebs, A.W. *Angew. Chem. Int. Ed.* **1965**, *4*, 10.

²²² Breslow, R.; Groves, J.T. *J. Am. Chem. Soc.* **1970**, *92*, 984.

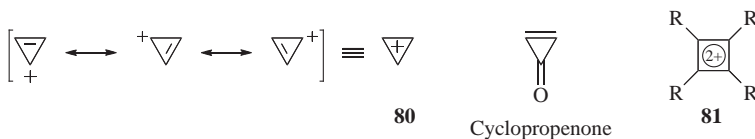
²²³ Breslow, R.; Höver, H.; Chang, H.W. *J. Am. Chem. Soc.* **1962**, *84*, 3168.

²²⁴ Moss, R.A.; Shen, S.; Krogh-Jespersen, K.; Potenza, J.A.; Schugar, H.J.; Munjal, R.C. *J. Am. Chem. Soc.* **1986**, *108*, 134.

²²⁵ Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* **1992**, *33*, 3773.

²²⁶ Taylor, M.J.; Surman, P.W.J.; Clark, G.R. *J. Chem. Soc. Chem. Commun.* **1994**, 2517.

water solution. The tri-*tert*-butylcyclopropenyl cation is also very stable.²²⁷ In addition, cyclopropenone and several of its derivatives are stable compounds,²²⁸ in accord with the corresponding stability of the tropones.²²⁹ The ring system **80** is nonalternant and the corresponding radical and anion, which do not have an aromatic duet, have electrons in antibonding orbitals, so that their energies are much higher. As with **58** and **62**, the equivalence of the three carbon atoms in the triphenylcyclopropenyl cation has been demonstrated by ¹⁴C labeling experiments.²³⁰ The interesting dications **81** (R = Me or Ph) have been prepared,²³¹ and they too should represent aromatic systems of two electrons.²³²



2.K.ii. Systems of Four Electrons: Antiaromaticity

The most obvious compound in which to look for a closed loop of four electrons is cyclobutadiene (**77**).²³³ *Hückel's rule* predicts no aromatic character since 4 is not a number generated from $4n + 2$. There is a long history of attempts to prepare this compound and its simple derivatives, and those experiments fully bear out *Hückel's* prediction. Cyclobutadienes display none of the characteristics that would lead us to call them aromatic, and there is evidence that a closed loop of four electrons is actually *antiaromatic*.²³⁴ If such compounds simply lacked aromaticity, we would expect them to be about as stable as similar nonaromatic compounds, but both theory and experiment show that they are *much less stable*.²³⁵ An antiaromatic compound may be defined as a compound that is destabilized by a closed loop of electrons.

Cyclobutadiene was first prepared by Pettit and co-workers.²³⁶ It is now clear that **77** and its simple derivatives are extremely unstable compounds with very short lifetimes (they dimerize by a *Diels–Alder reaction*; see **15–60**) unless they are stabilized in some fashion,

²²⁷ Ciabattoni, J.; Nathan, III, E.C. *J. Am. Chem. Soc.* **1968**, 90, 4495.

²²⁸ See Breslow, R.; Oda, M. *J. Am. Chem. Soc.* **1972**, 94, 4787; Yoshida, Z.; Konishi, H.; Tawara, Y.; Ogoishi, H. *J. Am. Chem. Soc.* **1973**, 95, 3043.

²²⁹ See Eicher, T.; Weber, J.L. *Top. Curr. Chem. Soc.* **1975**, 57, 1; Tobey, S.W., in Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, **1971**, pp. 351–362; Greenberg, A.; Tomkins, R.P.T.; Dobrovolny, M.; Liebman, J.F. *J. Am. Chem. Soc.* **1983**, 105, 6855.

²³⁰ D'yakonov, I.A.; Kostikov, R.R.; Molchanov, A.P. *J. Org. Chem. USSR* **1969**, 5, 171; **1970**, 6, 304.

²³¹ Olah, G.A.; Staral, J.S. *J. Am. Chem. Soc.* **1976**, 98, 6290. See also, Lambert, J.B.; Holcomb, A.G. *J. Am. Chem. Soc.* **1971**, 93, 2994; Seitz, G.; Schmiedel, R.; Mann, K. *Synthesis*, **1974**, 578.

²³² See Pittman Jr., C.U.; Kress, A.; Kispert, L.D. *J. Org. Chem.* **1974**, 39, 378. See, however, Krogh-Jespersen, K.; Schleyer, P.v.R.; Pople, J.A.; Cremer, D. *J. Am. Chem. Soc.* **1978**, 100, 4301.

²³³ For a monograph, see Cava, M.P.; Mitchell, M.J. *Cyclobutadiene and Related Compounds*, Academic Press, NY, **1967**. For reviews, see Maier, G. *Angew. Chem. Int. Ed.* **1988**, 27, 309; **1974**, 13, 425–438; Bally, T.; Masamune, S. *Tetrahedron* **1980**, 36, 343; Vollhardt, K.P.C. *Top. Curr. Chem.* **1975**, 59, 113.

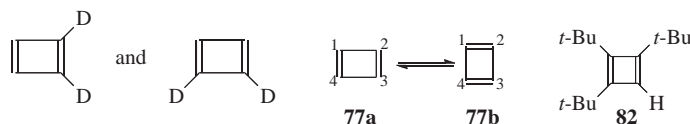
²³⁴ See Glukhovtsev, M.N.; Simkin, B.Ya.; Minkin, V.I. *Russ. Chem. Rev.* **1985**, 54, 54; Breslow, R. *Pure Appl. Chem.* **1971**, 28, 111; *Acc. Chem. Res.* **1973**, 6, 393.

²³⁵ See Bauld, N.L.; Welsher, T.L.; Cessac, J.; Holloway, R.L. *J. Am. Chem. Soc.* **1978**, 100, 6920.

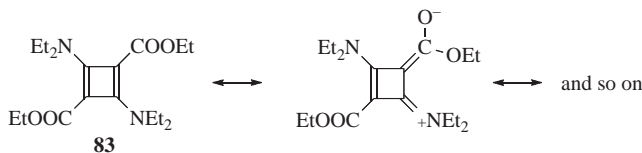
²³⁶ Watts, L.; Fitzpatrick, J.D.; Pettit, R. *J. Am. Chem. Soc.* **1965**, 87, 3253, **1966**, 88, 623. See also, Cookson, R. C.; Jones, D.W. *J. Chem. Soc.* **1965**, 1881.

either at ordinary temperatures embedded in the cavity of a hemicarcerand²³⁷ (see the structure of a carcerand in Sec. 3.C.iii), or in matrices at very low temperatures (generally < 35 K). In either of these cases, the cyclobutadiene molecules are forced to remain apart from each other, and other molecules cannot get in. The structures of **77** and some of its derivatives have been studied a number of times using the low-temperature matrix technique.²³⁸ The ground-state structure of **77** is a rectangular diene (not a diradical), as shown by the (Ir) spectra of **77** and deuterated **77** trapped in matrices,²³⁹ as well as by a photoelectron spectrum.²⁴⁰ Molecular orbital calculations agree.²⁴¹ The same conclusion was also reached in an elegant experiment in which 1,2-dideuterocyclobutadiene was generated. If **77** is a rectangular diene, the dideutero compound should exist as two isomers, as shown.

The compound was generated (as an intermediate that was not isolated) and two isomers were indeed found.²⁴² The cyclobutadiene molecule is not static, even in the matrices. There are two forms (**77a** and **77b**) that rapidly interconvert.²⁴³ Note that there is experimental evidence that the aromatic and antiaromatic characters of neutral and dianionic systems are measurably increased via deuteration.²⁴⁴



There are some simple cyclobutadienes that are stable at room temperature for varying periods of time. These either have bulky substituents or carry certain other stabilizing substituents, such as seen in tri-*tert*-butylcyclobutadiene (**83**).²⁴⁵ Such compounds are relatively stable because dimerization is sterically hindered. Examination of the NMR spectrum of **82** showed that the ring proton ($\delta = 5.38$) was shifted *upfield*, compared with the position expected for a nonaromatic proton, (e.g., cyclopentadiene). As will be seen in Section. 2.K.vi, this indicates that the compound is antiaromatic.



²³⁷ Cram, D.J.; Tanner, M.E.; Thomas, R. *Angew. Chem. Int. Ed.* **1991**, 30, 1024.

²³⁸ See Chapman, O.L.; McIntosh, C.L.; Pacansky, J. *J. Am. Chem. Soc.* **1973**, 95, 614; Maier, G.; Mende, U. *Tetrahedron Lett.* **1969**, 3155. For a review, see Sheridan, R.S. *Org. Photochem.* **1987**, 8, 159; pp. 167–181.

²³⁹ Masamune, S.; Souto-Bachiller, F.A.; Machiguchi, T.; Bertie, J.E. *J. Am. Chem. Soc.* **1978**, 100, 4889.

²⁴⁰ Kreile, J.; Münzel, N.; Schweig, A.; Specht, H. *Chem. Phys. Lett.* **1986**, 124, 140.

²⁴¹ See Ermer, O.; Heilbronner, E. *Angew. Chem. Int. Ed.* **1983**, 22, 402; Voter, A.F.; Goddard, III, W.A. *J. Am. Chem. Soc.* **1986**, 108, 2830.

²⁴² Whitman, D.W.; Carpenter, B.K. *J. Am. Chem. Soc.* **1980**, 102, 4272. See also, Whitman, D.W.; Carpenter, B. *K. J. Am. Chem. Soc.* **1982**, 104, 6473.

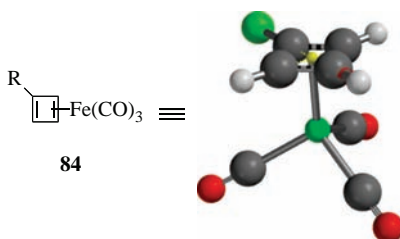
²⁴³ Orendt, A.M.; Arnold, B.R.; Radziszewski, J.G.; Facelli, J.C.; Malsch, K.D.; Strub, H.; Grant, D.M.; Michl, J. *J. Am. Chem. Soc.* **1988**, 110, 2648. See, however, Arnold, B.R.; Radziszewski, J.G.; Campion, A.; Perry, S.S.; Michl, J. *J. Am. Chem. Soc.* **1991**, 113, 692.

²⁴⁴ For experiments with [16]annulene (see Sec. 2.K.v), see Stevenson, C. D.; Kurth, T. L. *J. Am. Chem. Soc.* **1999**, 121, 1623.

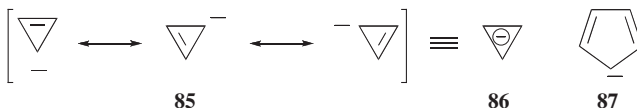
²⁴⁵ Masamune, S.; Nakamura, N.; Suda, M.; Ona, H. *J. Am. Chem. Soc.* **1973**, 95, 8481; Maier, G.; Alzérreca, A. *Angew. Chem. Int. Ed.* **1973**, 12, 1015; Masamune, S. *Pure Appl. Chem.* **1975**, 44, 861.

The other type of stable cyclobutadiene has two electron-donating and two electron-withdrawing groups,²⁴⁶ and is stable in the absence of water.²⁴⁷ An example is **83**. The stability of these compounds is generally attributed to the resonance shown, a type of resonance stabilization called the *push–pull or captodative effect*,²⁴⁸ although it has been concluded from a PES that second-order bond fixation is more important.²⁴⁹ An X-ray crystallographic study of **83** has shown²⁵⁰ the ring to be a distorted square with bond lengths of 1.46 Å and angles of 87° and 93°.

It is clear that simple cyclobutadienes, which could easily adopt a square planar shape if that would result in aromatic stabilization, do not in fact do so and are not aromatic. The high reactivity of these compounds is not caused merely by steric strain, since the strain should be no greater than that of simple cyclopropenes, which are known compounds. It is probably caused by antiaromaticity.²⁵¹



The cyclobutadiene system can be stabilized as a η^4 -complex with metals,²⁵² as with the iron complex **84** (see Chap 3), but in these cases electron density is withdrawn from the ring by the metal and there is no aromatic quartet. In fact, these cyclobutadiene–metal complexes can be looked upon as systems containing an aromatic duet. The ring is square planar,²⁵³ the compounds undergo aromatic substitution,²⁵⁴ and NMR spectra of mono-substituted derivatives show that the C-2 and C-4 protons are equivalent.²²⁹



Other systems that have been studied as possible aromatic or antiaromatic four-electron systems include the cyclopropenyl anion (**86**) and the cyclopentadienyl cation (**87**).²⁵⁵ With respect to **86**, HMO theory predicts that an unconjugated **85** (i.e., a single canonical

²⁴⁶ See Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* **1988**, 27, 1437.

²⁴⁷ Gompper, R.; Kroner, J.; Seybold, G.; Wagner, H. *Tetrahedron* **1976**, 32, 629.

²⁴⁸ Hess, Jr., B.A.; Schaad, L.J. *J. Org. Chem.* **1976**, 41, 3058.

²⁴⁹ Gompper, R.; Holsboer, F.; Schmidt, W.; Seybold, G. *J. Am. Chem. Soc.* **1973**, 95, 8479.

²⁵⁰ Lindner, H.J.; von Ross, B. *Chem. Ber.* **1974**, 107, 598.

²⁵¹ For evidence, see Breslow, R.; Murayama, D.R.; Murahashi, S.; Grubbs, R. *J. Am. Chem. Soc.* **1973**, 95, 6688; Herr, M.L. *Tetrahedron* **1976**, 32, 2835.

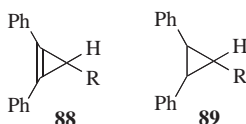
²⁵² Efraty, A. *Chem. Rev.* **1977**, 77, 691; Pettit, R. *Pure Appl. Chem.* **1968**, 17, 253; Maitlis, P.M. *Adv. Organomet. Chem.* **1966**, 4, 95; Maitlis, P.M.; Eberius, K.W., in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 2, Academic Press, NY, **1971**, pp. 359–409.

²⁵³ See Yannoni, C.S.; Ceasar, G.P.; Dailey, B.P. *J. Am. Chem. Soc.* **1967**, 89, 2833.

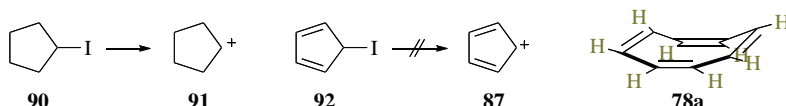
²⁵⁴ Fitzpatrick, J.D.; Watts, L.; Emerson, G.F.; Pettit, R. *J. Am. Chem. Soc.* **1965**, 87, 3255. For a discussion, see Pettit, R. *J. Organomet. Chem.* **1975**, 100, 205.

²⁵⁵ See Breslow, R. *Top. Nonbenzenoid Aromat. Chem.* **1973**, 1, 81.

form) is more stable than a conjugated **86**,²⁵⁶ so that **85** would actually lose stability by forming a closed loop of four electrons. The HMO theory is supported by experiment. Among other evidence, it has been shown that **88** ($R = \text{COPh}$) loses its proton in hydrogen-exchange reactions ~ 6000 times more slowly than **89** ($R = \text{COPh}$).²⁵⁷ Where $R = \text{CN}$, the ratio is $\sim 10,000$.²⁵⁸ This indicates that **88** are much more reluctant to form carbanions (which would have to be cyclopropenyl carbanions) than **89**, which form ordinary carbanions. Thus the carbanions of **88** are less stable than corresponding ordinary carbanions. Although derivatives of cyclopropenyl anion have been prepared as fleeting intermediates (as in the exchange reactions mentioned above), all attempts to prepare the ion or any of its derivatives as relatively stable species have so far met with failure.²⁵⁹



In the case of **87**, the ion has been prepared and shown to be a diradical in the ground state,²⁶⁰ as predicted by the discussion in Section 2.K.ii.²⁶¹ Evidence that **87** is not only nonaromatic, but is antiaromatic comes from studies on **90** and **92**.²⁶² When **90** is treated with silver perchlorate in propionic acid, the molecule is rapidly solvolyzed (a reaction in which the intermediate **91** is formed; see Chapters 5 and 10). Under the same conditions, **92** undergoes no solvolysis at all; that is, **87** does not form. If **87** were merely nonaromatic, it should be about as stable as **91** (which of course has no resonance stabilization at all). The fact that it is so much more reluctant to form indicates that **87** is much less stable than **91**. Note that under certain conditions, **91** can be generated solvolytically.²⁶³



The fact that **86** and **87** are not aromatic while the cyclopropenyl cation (**80**) and the cyclopentadienyl anion (**58**) is strong evidence for *Hückel's rule* since simple resonance theory predicts no difference between **86** and **80** or **87** and **58** (the same number of equivalent canonical forms can be drawn for **86** as for **80** and for **87** as for **58**).

²⁵⁶ Breslow, R. *Pure Appl. Chem.* **1971**, 28, 111; *Acc. Chem. Res.* **1973**, 6, 393.

²⁵⁷ Breslow, R.; Brown, J.; Gajewski, J.J. *J. Am. Chem. Soc.* **1967**, 89, 4383.

²⁵⁸ Breslow, R.; Douek, M. *J. Am. Chem. Soc.* **1968**, 90, 2698.

²⁵⁹ See Breslow, R.; Cortés, D.A.; Juan, B.; Mitchell, R.D. *Tetrahedron Lett.* **1982**, 23, 795. See Bartmess, J.E.; Kester, J.; Borden, W.T.; Köser, H.G. *Tetrahedron Lett.* **1986**, 27, 5931.

²⁶⁰ Saunders, M.; Berger, R.; Jaffe, A.; McBride, J.M.; O'Neill, J.; Breslow, R.; Hoffman, Jr., J.M.; Perchonock, C.; Wasserman, E.; Hutton, R.S.; Kuck, V.J. *J. Am. Chem. Soc.* **1973**, 95, 3017.

²⁶¹ See Breslow, R.; Chang, H.W.; Hill, R.; Wasserman, E. *J. Am. Chem. Soc.* **1967**, 89, 1112; Gompper, R.; Glöckner, H. *Angew. Chem. Int. Ed.* **1984**, 23, 53.

²⁶² Breslow, R.; Mazur, S. *J. Am. Chem. Soc.* **1973**, 95, 584. See Lossing, F.P.; Treager, J.C. *J. Am. Chem. Soc.* **1975**, 97, 1579. See also, Breslow, R.; Canary, J.W. *J. Am. Chem. Soc.* **1991**, 113, 3950.

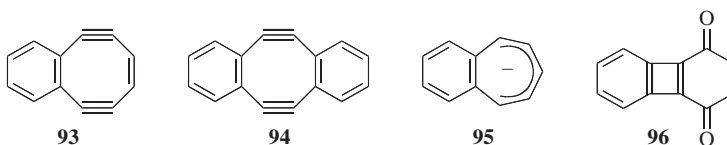
²⁶³ Allen, A.D.; Sumonja, M.; Tidwell, T.T. *J. Am. Chem. Soc.* **1997**, 119, 2371.

2.K.iii. Systems of Eight Electrons

Cyclooctatetraene²⁶⁴ ([8]annulene, **78a**) is not planar, but tub shaped,²⁶⁵ so it is neither aromatic nor antiaromatic, since both these conditions require overlap of parallel *p* orbitals. The reason for the lack of planarity is that a regular octagon has angles of 135°, while sp² angles are most stable at 120°. To avoid the strain, the molecule assumes a nonplanar shape, in which orbital overlap is greatly diminished.²⁶⁶ Single- and double-bond distances in **78** are, respectively, 1.46 and 1.33 Å, which is expected for a compound made up of four individual double bonds.²⁶⁵ The *Jahn–Teller effect* has been invoked to explain the instability of such antiaromatic compounds.²⁶⁷ The Jahn–Teller effect arises from molecular distortions due to an electronically degenerate ground state.²⁶⁸

The reactivity is also what would be expected for a linear polyene. Reactive intermediates can be formed in solution. Dehydrohalogenation of bromocyclooctatetraene at –100 °C has been reported, for example, and trapping by immediate electron transfer gave a stable solution of the [8]annulyne anion radical.²⁶⁹

The cyclooctadiendiynes **93** and **94** are planar conjugated eight-electron systems (the four extra triple-bond electrons do not participate), which NMR evidence show to be antiaromatic.²⁷⁰ There is evidence that part of the reason for the lack of planarity in **78** itself is that a planar molecule would have to be antiaromatic.²⁷¹ The cycloheptatrienyl anion (**61**) also has eight electrons, but does not behave like an aromatic system.¹⁶⁷ The bond lengths for a series of molecules containing the cycloheptatrienide anion have recently been published.²⁷² The NMR spectrum of the benzocycloheptatrienyl anion (**95**) shows that, like **82**, **93**, and **94**, this compound is antiaromatic.²⁷³ A new antiaromatic compound 1,4-biphenylene quinone (**96**) was prepared, but it rapidly dimerizes due to instability.²⁷⁴



²⁶⁴ See Fray, G.I.; Saxton, R.G. *The Chemistry of Cyclooctatetraene and its Derivatives*, Cambridge University Press, Cambridge, **1978**; Paquette, L.A. *Tetrahedron* **1975**, 31, 2855. For reviews of heterocyclic 8 π systems, see Kaim, W. *Rev. Chem. Intermed.* **1987**, 8, 247; Schmidt, R.R. *Angew. Chem. Int. Ed.* **1975**, 14, 581.

²⁶⁵ Bastiansen, O.; Hedberg, K.; Hedberg, L. *J. Chem. Phys.* **1957**, 27, 1311. See Havenith, R.W.A.; Fowler, P.W.; Jenneskens, L.W. *Org. Lett.* **2006**, 8, 1255.

²⁶⁶ See Einstein, F.W.B.; Willis, A.C.; Cullen, W.R.; Soulen, R.L. *J. Chem. Soc. Chem. Commun.* **1981**, 526. See also, Paquette, L.A.; Wang, T.; Cottrell, C.E. *J. Am. Chem. Soc.* **1987**, 109, 3730.

²⁶⁷ Frank-Gerrit Klärner, F.-G. *Angew. Chem. Int. Ed.* **2001**, 40, 3977.

²⁶⁸ *The Jahn–Teller Effect* Bersuker, I.B. Cambridge University Press, **2006**; Ceulemans, A.; Lijnen, E. *Bull. Chem. Soc. Jpn.* **2007**, 80, 1229.

²⁶⁹ Peters, S.J.; Turk, M.R.; Kiesewetter, M.K.; Stevenson, C.D. *J. Am. Chem. Soc.* **2003**, 125, 11264.

²⁷⁰ Huang, N.Z.; Sondheimer, F. *Acc. Chem. Res.* **1982**, 15, 96. See also, Chan, T.; Mak, T.C.W.; Poon, C.; Wong, H.N.C.; Jia, J.H.; Wang, L.L. *Tetrahedron* **1986**, 42, 655.

²⁷¹ Figeys, H.P.; Dralants, A. *Tetrahedron Lett.* **1971**, 3901; Buchanan, G.W. *Tetrahedron Lett.* **1972**, 665.

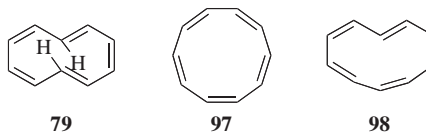
²⁷² Dietz, F.; Rabinowitz, M.; Tadjer, A.; Tyutyulkov, N. *J. Chem. Soc. Perkin Trans. 2* **1995**, 735.

²⁷³ Staley, S.W.; Orvedal, A.W. *J. Am. Chem. Soc.* **1973**, 95, 3382.

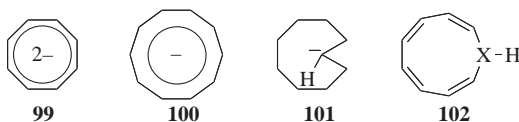
²⁷⁴ Kiliç, H.; Balci, M. *J. Org. Chem.* **1997**, 62, 3434.

2.K.iv. Systems of Ten Electrons²⁷⁵

There are three possible geometrical isomers of [10]annulene: the all-*cis* (**97**), the mono-*trans* (**98**), and the *cis-trans-cis-cis-trans* (**79**). If Hückel's rule applies, they should be planar. But it is far from obvious that the



molecules would adopt a planar shape, since they must overcome considerable strain to do so. For a regular decagon (**97**) the angles would have to be 144° , considerably larger than the 120° required for sp^2 angles. Some of this strain would also be present in **98**, but this kind of strain is eliminated in **79** since all the angles are 120° . However, it was pointed out by Mislow²⁷⁶ that the hydrogen atoms in the 1 and 6 positions should interfere with each other and force the molecule out of planarity. Such configurational changes are not necessarily without cost energetically. It has been determined that configurational changes in [14]annulene, for example, requires Möbius antiaromatic bond shifting.²⁷⁷



Compounds **97** and **98** have been prepared²⁷⁸ as crystalline solids at -80°C . The NMR spectra show that all the hydrogen atoms lie in the alkene region, and it was concluded that neither compound is aromatic. Calculations on **98** suggest that it may indeed be aromatic, although the other isomers are not.²⁷⁹ It is known that the Hartree-Fock (HF) method incorrectly favors bond-length-alternating structures for [10]annulene, and aromatic structures are incorrectly favored by density functional theory. Improved calculations predict that the twist conformation is lowest in energy, and the naphthalene-like and heart-shaped conformations lie higher than the twist by 1.40 and 4.24 kcal mol⁻¹ (5.86 and 17.75 kJ mol⁻¹), respectively.²⁸⁰ Analysis of ¹³C and ¹H NMR spectra suggest that neither is planar. However, the preparation of several compounds that have large angles, but that are definitely planar 10-electron aromatic systems, clearly demonstrate that the angle strain is not insurmountable. Among these are the dianion **99**, the anions **100** and **101**, and the

²⁷⁵ See Kemp-Jones, A.V.; Masamune, S. *Top. Nonbenzenoid Aromat. Chem.* **1973**, *1*, 121; Masamune, S.; Darby, N. *Acc. Chem. Res.* **1972**, *5*, 272; Burkoth, T.L.; van Tamelen, E.E. in Snyder, J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, **1969**, pp. 63–116; Vogel, E., in Garratt, P.J. *Aromaticity*, Wiley, NY, **1986**, pp. 113–147.

²⁷⁶ Mislow, K. *J. Chem. Phys.* **1952**, *20*, 1489.

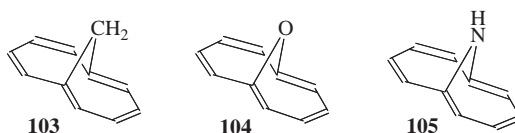
²⁷⁷ Moll, J.F.; Pemberton, R.P.; Gertrude Gutierrez, M.; Castro, C.; Karney, W.L. *J. Am. Chem. Soc.* **2007**, *129*, 274.

²⁷⁸ Masamune, S.; Hojo, K.; Bigam, G.; Rabenstein, D.L. *J. Am. Chem. Soc.* **1971**, *93*, 4966; van Tamelen, E.E.; Burkoth, T.L.; Greeley, R.H. *J. Am. Chem. Soc.* **1971**, *93*, 6120.

²⁷⁹ Sulzbach, H.M.; Schleyer, P.v.R.; Jiao, H.; Xie, Y.; Schaefer, III, H.F. *J. Am. Chem. Soc.* **1995**, *117*, 1369; Sulzbach, H.M.; Schaefer, III, H.F.; Kloppe, W.; Lüthi, H.P. *J. Am. Chem. Soc.* **1996**, *118*, 3519.

²⁸⁰ King, R.A.; Crawford, T.D.; Stanton, J.F.; Schaefer, III, H.F. *J. Am. Chem. Soc.* **1999**, *121*, 10788.

azonine **102**.²⁸¹ Compound **99**²⁸² has angles of $\sim -135^\circ$, while **100**²⁸³ and **101**²⁸⁴ have angles of $\sim 140^\circ$, which are not very far from 144° . The inner proton in **101**²⁸⁵ which is the mono-trans isomer of the all-*cis* **100** is found far upfield in the NMR (-3.5δ). For **97** and **98**, the cost in strain energy to achieve planarity apparently outweighs the extra stability that would come from an aromatic ring. Further emphasizing the delicate balance between these factors, it is known that the oxygen analogue of **102** ($X=O$, oxonin) and the *N*-carbethoxy derivative of **102** ($X=CH$) are nonaromatic and nonplanar, while **102** ($X=N$) is aromatic and planar.²⁸⁶ Other azaannulenes are known, including Vogel's 2,7-methanoazaannulene,²⁸⁷ as well as 3,8-methanoaza[10]annulene,²⁸⁸ and the alkoxy derivative of both.²⁸⁹ Calculations for aza[10]annulene concluded that the best olefinic twist isomer is 2.1 kcal mol^{-1} (8.8 kJ mol^{-1}) more stable than the aromatic form,²⁹⁰ and is probably the more stable form.



So far, **79** from above has not been prepared despite many attempts. However, there are various ways of avoiding the interference between the two inner protons. The approach that has been most successful involves bridging the 1 and 6 positions.²⁹¹ Thus, 1,6-methano[10]annulene (**103**)²⁹² and its oxygen and nitrogen analogues **104**²⁹³ and **105**²⁹⁴ have been prepared, and they are stable compounds, are diatropic, and undergo aromatic substitution.²⁹⁵ For example, the perimeter protons of **103** are found at $6.9\text{--}7.3\delta$, while the bridge protons are at -0.5δ . The crystal structure of **103** shows that the perimeter is nonplanar,

²⁸¹ See Anastassiou, A.G. *Acc. Chem. Res.* **1972**, 5, 281, *Top. Nonbenzenoid Aromat. Chem.* **1973**, 1, 1, *Pure Appl. Chem.* **1975**, 44, 691. For a review of heteroannulenes in general, see Anastassiou, A.G.; Kasmai, H.S. *Adv. Heterocycl. Chem.* **1978**, 23, 55.

²⁸² Evans, W.J.; Wink, D.J.; Wayda, A.L.; Little, D.A. *J. Org. Chem.* **1981**, 46, 3925; Heinz, W.; Langensee, P.; Müllen, K. *J. Chem. Soc. Chem. Commun.* **1986**, 947.

²⁸³ Paquette, L.A.; Ley, S.V.; Meisinger, R.H.; Russell, R.K.; Oku, M. *J. Am. Chem. Soc.* **1974**, 96, 5806; Radlick, P.; Rosen, W. *J. Am. Chem. Soc.* **1966**, 88, 3461.

²⁸⁴ Anastassiou, A.G.; Gebrian, J.H. *Tetrahedron Lett.* **1970**, 825.

²⁸⁵ Boche, G.; Weber, H.; Martens, D.; Bieberbach, A. *Chem. Ber.* **1978**, 111, 2480. See also, Anastassiou, A.G.; Reichmanis, E. *Angew. Chem. Int. Ed.* **1974**, 13, 728.

²⁸⁶ Chiang, C.C.; Paul, I.C.; Anastassiou, A.G.; Eachus, S.W. *J. Am. Chem. Soc.* **1974**, 96, 1636.

²⁸⁷ Shani, A.; Sondheimer, F. *J. Am. Chem. Soc.* **1967**, 89, 6310; Bailey, N.A.; Mason, R. *J. Chem. Soc. Chem. Commun.* **1967**, 1039.

²⁸⁸ Destro, R.; Simonetta, M.; Vogel, E. *J. Am. Chem. Soc.* **1981**, 103, 2863.

²⁸⁹ Schleyer, P.v.R.; Jiao, H.; Sulzbach, H.M.; Schaefer, III, H.F. *J. Am. Chem. Soc.* **1996**, 118, 2093.

²⁹⁰ Bettinger, H.F.; Sulzbach, H.M.; Schleyer, P.v.R.; Schaefer, III, H.F. *J. Org. Chem.* **1999**, 64, 3278.

²⁹¹ See Vogel, E. *Pure Appl. Chem.* **1982**, 54, 1015; *Isr. J. Chem.* **1980**, 20, 215; *Chimia*, **1968**, 22, 21; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* **1967**, 6, 385.

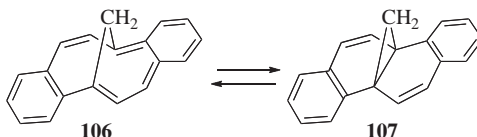
²⁹² Vogel, E.; Roth, H.D. *Angew. Chem. Int. Ed.* **1964**, 3, 228; Vogel, E.; Böll, W.A. *Angew. Chem. Int. Ed.* **1964**, 3, 642; Vogel, E.; Böll, W.A.; Biskup, M. *Tetrahedron Lett.* **1966**, 1569.

²⁹³ Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W.A. *Angew. Chem. Int. Ed.* **1964**, 3, 642; Shani, A.; Sondheimer, F. *J. Am. Chem. Soc.* **1967**, 89, 6310; Bailey, N.A.; Mason, R. *Chem. Commun.* **1967**, 1039.

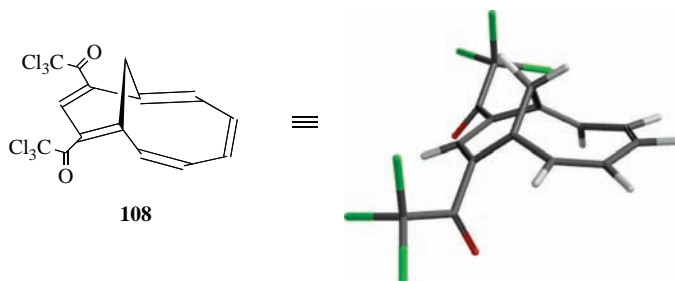
²⁹⁴ Vogel, E.; Pretzer, W.; Böll, W.A. *Tetrahedron Lett.* **1965**, 3613. See also, Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W.A. *Angew. Chem. Int. Ed.* **1964**, 3, 642.

²⁹⁵ Also see McCague, R.; Moody, C.J.; Rees, C.W. *J. Chem. Soc. Perkin Trans. 1* **1984**, 165, 175; Gibbard, H.C.; Moody, C.J.; Rees, C.W. *J. Chem. Soc. Perkin Trans. 1* **1985**, 731, 735.

but the bond distances are in the range 1.37–1.42 Å.²⁹⁶ It has therefore been amply demonstrated that a closed loop of 10 electrons is an aromatic system, although some molecules that could conceivably have such a system are too distorted from planarity to be aromatic. A small distortion from planarity (as in **103**) does not prevent aromaticity, at least in part because the σ orbitals so distort themselves as to maximize the favorable (parallel) overlap of p orbitals to form the aromatic 10-electron loop.²⁹⁷



In **106**, where **103** is fused to two benzene rings in such a way that no canonical form can be written in which both benzene rings have six electrons, the aromaticity is diminished by annellation, as shown by the fact that the molecule rapidly converts to the more stable **107**, in which both benzene rings can be fully aromatic²⁹⁸ (this is similar to the cycloheptatriene–norcaradiene conversions discussed in **18–32**).



Molecules can sustain significant distortion from planarity and retain their aromatic character. 1,3-Bis(trichloroacetyl)homoazulene (**108**) qualifies as aromatic using the geometric criterion that there is only a small average deviation from the C—C bond length in the [10]annulene perimeter.²⁹⁹ The X-ray crystal structure shows that the 1,5-bridge distorts the [10]annulene π -system away from planarity (see the 3D model) with torsion angles as large as 42.2° at the bridgehead position, but **108** does not lose its aromaticity.

2.K.v. Systems of More Than Ten Electrons: $4n + 2$ Electrons³⁰⁰

Extrapolating from the discussion of [10]annulene, larger $4n + 2$ systems are expected to be aromatic if they are planar. Mislow²⁷⁶ predicted that [14]annulene (**109**) would possess

²⁹⁶ Bianchi, R.; Pilati, T.; Simonetta, M. *Acta Crystallogr. Sect. B*, **1980**, 36, 3146. See also, Dobler, M.; Dunitz, J. D. *Helv. Chim. Acta* **1965**, 48, 1429.

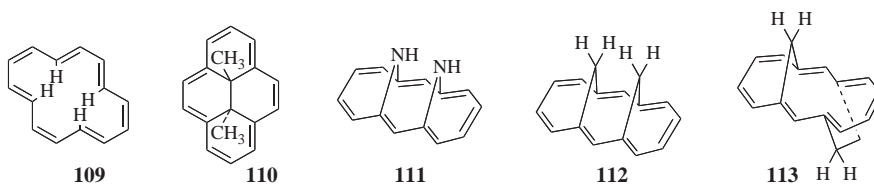
²⁹⁷ For a discussion, see Haddon, R.C. *Acc. Chem. Res.* **1988**, 21, 243.

²⁹⁸ Hill, R.K.; Giberson, C.B.; Silvertown, J.V. *J. Am. Chem. Soc.* **1988**, 110, 497. See also, McCague, R.; Moody, C.J.; Rees, C.W.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* **1984**, 909.

²⁹⁹ Scott, L.T.; Sumpter, C.A.; Gantzel, P.K.; Maverick, E.; Trueblood, K.N. *Tetrahedron* **2001**, 57, 3795.

³⁰⁰ See Sondheimer, F. *Acc. Chem. Res.* **1972**, 5, 81–91; *Pure Appl. Chem.* **1971**, 28, 331; *Proc. R. Soc. London. Ser. A*, **1967**, 297, 173; Sondheimer, F.; Calder, I.C.; Elix, J.A.; Gaoni, Y.; Garratt, P.J.; Grohmann, K.; di Maio, G.; Mayer, J.; Sargent, M.V.; Wolovsky, R. in Garratt, P.G. *Aromaticity*, Wiley, NY, **1986**, pp. 75–107; Nakagawa, M. *Angew. Chem. Int. Ed.* **1979**, 18, 202; Müllen, K. *Chem. Rev.* **1984**, 84, 603; Rabinovitz, M. *Top. Curr. Chem.* **1988**, 146, 99. Also see, Cyvin, S.J.; Brunvoll, J.; Chen, R.S.; Cyvin, B.N.; Zhang, F.J. *Theory of Coronoid Hydrocarbons II*, Springer-Verlag, Berlin, **1994**.

the same type of interference as **79**, although to a lesser degree. This is borne out by experiment. Compound **109** is aromatic (it is diatropic; inner protons at 0.00 δ , outer protons at 7.6 δ),³⁰¹ but is highly reactive and is completely destroyed by light and air in 1 day. X-ray analysis shows that although there are no alternating single and double bonds (the molecule is not planar).³⁰² A number of stable bridged [14]annulenes have been prepared³⁰³ [e.g., *trans*-15,16-dimethyldihydropyrene (**110**),³⁰⁴ *syn*-1,6:8,13-diimino[14]annulene (**111**),³⁰⁵ and *syn*- and *anti*-1,6:8,13-bismethano[14]annulene (**112** and **113**)].³⁰⁶ The dihydropyrene (**110**, and its diethyl and dipropyl homologues) is undoubtedly aromatic: The π perimeter is approximately planar,³⁰⁷ the bond distances are all 1.39–1.40 Å, and the molecule undergoes aromatic substitution³⁰⁴ as well as being diatropic.³⁰⁸ The outer protons are found at 8.14–8.67 δ , while the CH₃ protons are at –4.25 δ . Other nonplanar aromatic dihydropyrenes are known.³⁰⁹ Annulenes **111** and **112** are also diatropic,³¹⁰ although X-ray crystallography indicates that the π periphery in **111** is not quite planar.³¹¹ In **113**, the geometry of the molecule greatly reduces the overlap of the *p* orbitals at the bridgehead positions with adjacent *p* orbitals, and it is definitely not aromatic,³¹² as shown by NMR spectra³⁰⁶ and X-ray crystallography, from which bond distances of 1.33–1.36 Å for the double bonds and 1.44–1.49 Å for the single bonds have been obtained.³¹³ In contrast, all the bond distances in **111** are \sim 1.38–1.40 Å.³¹¹



Another way of eliminating the hydrogen interferences of [14]annulene is to introduce one or more triple bonds into the system, as in dehydro[14]annulene

³⁰¹ Gaoni, Y.; Melera, A.; Sondheimer, F.; Wolovsky, R. *Proc. Chem. Soc.* **1964**, 397.

³⁰² Chiang, C.C.; Paul, I.C. *J. Am. Chem. Soc.* **1972**, 94, 4741; Oth, J.F.M.; Schröder, G. *J. Chem. Soc. B*, **1971**, 904. See also, Oth, J.F.M.; Müllen, K.; Königshofen, H.; Mann, M.; Sakata, Y.; Vogel, E. *Angew. Chem. Int. Ed.* **1974**, 13, 284; Wife, R.L.; Sondheimer, F. *J. Am. Chem. Soc.* **1975**, 97, 640; Willner, I.; Gutman, A.L.; Rabinovitz, M. *J. Am. Chem. Soc.* **1977**, 99, 4167; Röttle, H.; Schröder, G. *Chem. Ber.* **1982**, 115, 248.

³⁰³ For a review, see Vogel, E. *Pure Appl. Chem.* **1971**, 28, 355.

³⁰⁴ Boekelheide, V.; Phillips, J.B. *J. Am. Chem. Soc.* **1967**, 89, 1695; Boekelheide, V.; Miyasaka, T. *J. Am. Chem. Soc.* **1967**, 89, 1709. For reviews of dihydropyrenes, see Mitchell, R.H. *Adv. Theor. Interesting Mol.* **1989**, 1, 135; Boekelheide, V. *Top. Nonbenzoid Arom. Chem.* **1973**, 1, 47; *Pure Appl. Chem.* **1975**, 44, 807.

³⁰⁵ Destro, R.; Pilati, T.; Simonetta, M.; Vogel, E. *J. Am. Chem. Soc.* **1985**, 107, 3185, 3192. For the di-*O*-analogue of **102**, see Vogel, A.; Biskup, M.; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* **1966**, 5, 734.

³⁰⁶ Vogel, E.; Sombroek, J.; Wagemann, W. *Angew. Chem. Int. Ed.* **1975**, 14, 564.

³⁰⁷ Hanson, A.W. *Acta Crystallogr.* **1965**, 18, 599, 1967, 23, 476.

³⁰⁸ See Mitchell, R.H.; Williams, R.V.; Mahadevan, R.; Lai, Y.H.; Dingle, T.W. *J. Am. Chem. Soc.* **1982**, 104, 2571 and other papers in this series.

³⁰⁹ Bodwell, G. J.; Bridson, J. N.; Chen, S.-L.; Poirier, R. A. *J. Am. Chem. Soc.* **2001**, 123, 4704; Bodwell, G.J.; Fleming, J.J.; Miller, D.O. *Tetrahedron* **2001**, 57, 3577.

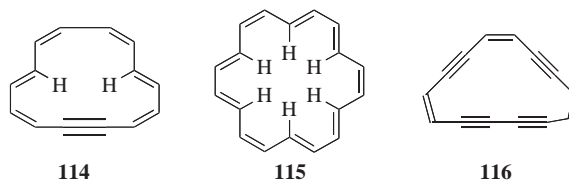
³¹⁰ See Vogel, E.; Wieland, H.; Schmalstieg, L.; Lex, J. *Angew. Chem. Int. Ed.* **1984**, 23, 717; Neumann, G.; Müllen, K. *J. Am. Chem. Soc.* **1986**, 108, 4105.

³¹¹ Ganis, P.; Dunitz, J.D. *Helv. Chim. Acta*, **1967**, 50, 2369.

³¹² See Vogel, E.; Nitsche, R.; Krieg, H. *Angew. Chem. Int. Ed.* **1981**, 20, 811. See also, Vogel, E.; Schieb, T.; Schulz, W.H.; Schmidt, K.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* **1986**, 25, 723.

³¹³ Gramaccioli, C.M.; Mimun, A.; Mugnoli, A.; Simonetta, M. *Chem. Commun.* **1971**, 796. See also, Destro, R.; Simonetta, M. *Tetrahedron* **1982**, 38, 1443.

(**114**).³¹⁴ All five known dehydro[14]annulenes are diatropic, and **87** can be nitrated or sulfonated.³¹⁵ The extra electrons of the triple bond do not form part of the



aromatic system, but it simply exists as a localized bond. There has been a debate concerning the extent of delocalization in dehydrobenzoannulenes,³¹⁶ but there is evidence for a weak, but discernible ring current.³¹⁷ 3,4,7,8,9,10,13,14-Octahydro[14]annulene (**116**) has been prepared, for example, and the evidence supported its aromaticity.³¹⁸ This study suggested that increasing benzoannulation of the parent **116** led to a step-down in aromaticity, a result of competing ring currents in the annulenic system. Note that [12]annulyne has been prepared.³¹⁹

[18]Annulene (**115**) is diatropic:³²⁰ the 12 outer protons are found at $\sim \delta = 9$ and the 6 inner protons at $\sim \delta = -3$. X-ray crystallography³²¹ shows that it is nearly planar, so that interference of the inner hydrogen atoms is not important in annulenes this large. Compound **115** is reasonably stable, being distillable at reduced pressures, and undergoes aromatic substitutions³²² (Chapter 11). The C—C bond distances are not equal, but they do not alternate. There are 12 inner bonds of $\sim 1.38 \text{ \AA}$ and 6 outer bonds of $\sim 1.42 \text{ \AA}$.³²¹ Compound **115** has been estimated to have a resonance energy of $\sim 37 \text{ kcal mol}^{-1}$ (155 kJ mol^{-1}), similar to that of benzene.³²³

The known bridged [18]annulenes are also diatropic,³²⁴ as are most of the known dehydro[18]annulenes.³²⁵ The dianions of open and bridged [16]annulenes³²⁶ are also 18-electron aromatic systems,³²⁷ and there are dibenzo[18]annulenes.³²⁸

³¹⁴ For a review of dehydroannulenes, see, Nakagawa, M. *Top. Nonbenzenoid Aromat. Chem.* **1973**, 1, 191.

³¹⁵ Gaoni, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1964**, 86, 521.

³¹⁶ Balaban, A.T.; Banciu, M.; Ciorba, V. *Annulenes, Benzo-, Hetero-, Homo- Derivatives and their Valence Isomers*, Vols. 1–3, CRC Press, Boca Raton, FL, **1987**; Garratt, P.J. *Aromaticity*, Wiley, NY, **1986**; Minkin, V.I.; Glukhovtsev, M.N.; Simkin, B.Ya. *Aromaticity and Antiaromaticity*, Wiley, NY, **1994**.

³¹⁷ Bell, M.L.; Chiechi, R.C.; Johnson, C.A.; Kimball, D.B.; Matzger, A.J.; Wan, W.B.; Weakley, T.J.R.; Haley, M.M. *Tetrahedron* **2001**, 57, 3507; Wan, W.B.; Chiechi, R.C.; Weakley, T.J.R.; Haley, M.M. *Eur. J. Org. Chem.* **2001**, 3485.

³¹⁸ Boydston, A.J.; Haley, M.M.; Williams, R.V.; Armantrout, J.R. *J. Org. Chem.* **2002**, 67, 8812.

³¹⁹ Gard, M.N.; Kiesewetter, M.K.; Reiter, R.C.; Stevenson, C.D. *J. Am. Chem. Soc.* **2005**, 127, 16143.

³²⁰ Gilles, J.; Oth, J.F.M.; Sondheimer, F.; Woo, E.P. *J. Chem. Soc. B*, **1971**, 2177. For a thorough discussion, see Baumann, H.; Oth, J.F.M. *Helv. Chim. Acta*, **1982**, 65, 1885.

³²¹ Bregman, J.; Hirshfeld, F.L.; Rabinovich, D.; Schmidt, G.M.J. *Acta Crystallogr.* **1965**, 19, 227; Hirshfeld, F. L.; Rabinovich, D. *Acta Crystallogr.* **1965**, 19, 235.

³²² Sondheimer, F. *Tetrahedron* **1970**, 26, 3933.

³²³ Oth, J.F.M.; Bünzli, J.; de Julien de Zélicourt, Y. *Helv. Chim. Acta*, **1974**, 57, 2276.

³²⁴ Ogawa, H.; Sadakari, N.; Imoto, T.; Miyamoto, I.; Kato, H.; Taniguchi, Y. *Angew. Chem. Int. Ed.* **1983**, 22, 417; Vogel, E.; Sicken, M.; Röhrig, P.; Schmickler, H.; Lex, J.; Ermer, O. *Angew. Chem. Int. Ed.* **1988**, 27, 411.

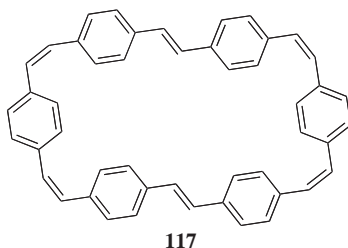
³²⁵ Sondheimer, F. *Acc. Chem. Res.* **1972**, 5, 81. For two that are not, see Endo, K.; Sakata, Y.; Misumi, S. *Bull. Chem. Soc. Jpn.* **1971**, 44, 2465.

³²⁶ See Rabinovitz, M.; Willner, I.; Minsky, A. *Acc. Chem. Res.* **1983**, 16, 298.

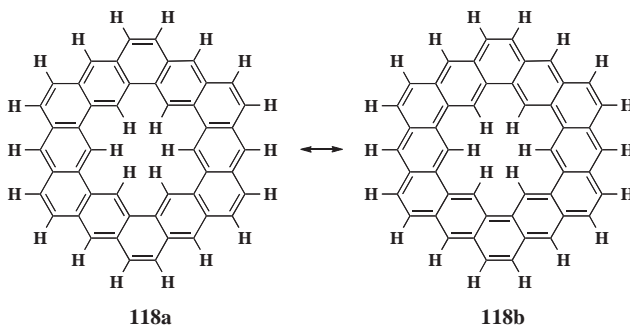
³²⁷ Oth, J.F.M.; Baumann, H.; Gilles, J.; Schröder, G. *J. Am. Chem. Soc.* **1972**, 94, 3948. See also, Brown, J.M.; Sondheimer, F. *Angew. Chem. Int. Ed.* **1974**, 13, 337; Rabinovitz, M.; Minsky, A. *Pure Appl. Chem.* **1982**, 54, 1005.

³²⁸ Michels, H.P.; Nieger, M.; Vögtle, F. *Chem. Ber.* **1994**, 127, 1167.

[22]Annulene³²⁹ and dehydro[22]annulene³³⁰ are also diatropic. A dehydrobenzo[22]annulene has been prepared that has eight $\text{C}\equiv\text{C}$ units, is planar, and possesses a weak induced ring current.³³¹ In the latter compound, there are 13 outer protons at 6.25–8.45 δ and 7 inner protons at 0.70–3.45 δ . Some aromatic bridged [22]annulenes are known.³³² [26]Annulene has not yet been prepared, but several dehydro[26]annulenes are aromatic.³³³ Furthermore, the dianion of 1,3,7,9,13,15,19,21-octadehydro[24]annulene is another 26-electron system that is aromatic.³³⁴ Ojima and et al.³³⁵ prepared bridged dehydro derivatives of [26], [30], and [34]annulenes. All are diatropic. The same workers prepared a bridged tetrahydro[38]annulene,³³⁵ which showed no ring current. On the other hand, the dianion of the cyclophane, (**117**) also has 38 perimeter electrons, and this species is diatropic.³³⁶



There is now no doubt that $4n + 2$ systems are aromatic if they can be planar, although **97** and **113** among others, demonstrate that not all such systems are in fact planar enough for aromaticity. Both **109** and **111** prove that absolute planarity is not required for aromaticity, but that aromaticity decreases with decreasing planarity.



³²⁹ McQuilkin, R.M.; Metcalf, B.W.; Sondheimer, F. *Chem. Commun.* **1971**, 338.

³³⁰ Iyoda, M.; Nakagawa, M. *J. Chem. Soc. Chem. Commun.* **1972**, 1003. See also, Akiyama, S.; Nomoto, T.; Iyoda, M.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* **1976**, 49, 2579.

³³¹ Wan, W.B.; Kimball, D.B.; Haley, M.M. *Tetrahedron Lett.* **1998**, 39, 6795.

³³² See Ojima, J.; Ejiri, E.; Kato, T.; Nakamura, M.; Kuroda, S.; Hirooka, S.; Shibutani, M. *J. Chem. Soc. Perkin Trans. 1* **1987**, 831; Yamamoto, K.; Kuroda, S.; Shibutani, M.; Yoneyama, Y.; Ojima, J.; Fujita, S.; Ejiri, E.; Yanagihara, K. *J. Chem. Soc. Perkin Trans. 1* **1988**, 395.

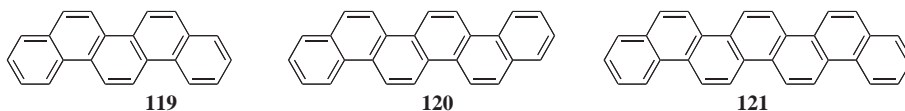
³³³ Ojima, J.; Fujita, S.; Matsumoto, M.; Ejiri, E.; Kato, T.; Kuroda, S.; Nozawa, Y.; Hirooka, S.; Yoneyama, Y.; Tatemitsu, H. *J. Chem. Soc. Perkin Trans. 1* **1988**, 385.

³³⁴ McQuilkin, R.M.; Garratt, P.J.; Sondheimer, F. *J. Am. Chem. Soc.* **1970**, 92, 6682. See also, Huber, W.; Müllen, K.; Wennerström, O. *Angew. Chem. Int. Ed.* **1980**, 19, 624.

³³⁵ Ojima, J.; Fujita, S.; Matsumoto, M.; Ejiri, E.; Kato, T.; Kuroda, S.; Nozawa, Y.; Hirooka, S.; Yoneyama, Y.; Tatemitsu, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 385.

³³⁶ Müllen, K.; Unterberg, H.; Huber, W.; Wennerström, O.; Norinder, U.; Tanner, D.; Thulin, B. *J. Am. Chem. Soc.* **1984**, 106, 7514.

The ^1H NMR spectrum of **118** (called kekulene) showed that in a case where electrons can form either aromatic sextets or larger systems, the sextets are preferred.³³⁷ There was initial speculation that kekulene might be *superaromatic*, that is, it would show enhanced aromatic stabilization. Calculations suggest that there is no enhanced stabilization.³³⁸ The 48 π electrons of **118** might, in theory, prefer structure **118a**, where each ring is a fused benzene ring, or **118b**, which has a [30]annulene on the outside and an [18]annulene on the inside. The ^1H NMR spectrum of this compound shows three peaks at $\delta = 7.94$, 8.37, and 10.45 in a ratio of 2:1:1. Examination of the structure shows that **118** contains three groups of protons. The peak at 7.94 δ is attributed to the 12 ortho protons and the peak at 8.37 δ to the six external para protons. The remaining peak comes from the six inner protons. If the molecule preferred **118b**, this peak should be upfield, probably with a negative δ , as in the case of **115**. The fact that this peak is far downfield indicates that the electrons prefer to be in benzenoid rings. Note that in the case of the dianion of **117**, the opposite situation prevails. In this ion, the 38-electron system is preferred even though 24 of these must come from the six benzene rings, which therefore cannot have aromatic sextets.



Phenacenes are a family of “graphite ribbons,” where benzene rings are fused together in an alternating pattern. Phenanthrene is the simplest member of this family and other members include the 22 electron system picene (**119**), the 26 electron system fulminene (**120**) and the larger member of this family, the 30 electron [7]phenacene, with seven rings (**121**).³³⁹ In the series benzene to heptacene, reactivity increases although acene resonance energies per π electron are nearly constant. The inner rings of the “acenes” are more reactive, and calculations showed that those rings are more aromatic than the outer rings, and are even more aromatic than benzene itself.³⁴⁰ *N*-Heteroacenes are also known.³⁴¹

A super-ring molecule is formed by rolling a polyacene molecule into one ring with one edge benzene ring folding into the other. These are called cyclopolyacenes or cyclacenes.³⁴² Although the *zigzag* cyclohexacenes (**122**) are highly aromatic (this example is a 22 electron system), the linear cyclohexacenes (e.g., the 24 electron **123**) are much less aromatic.³⁴³ It is possible to deform an acene by attaching bulky substituents to its periphery by single covalent bonds. The presence of these substituents, which often leads to twisting of torsion angles, is usually easier than distortion of bond angles or C-C bond lengths. Such compounds are called twisted acenes.³⁴⁴

³³⁷ Staab, H.A.; Diederich, F. *Chem. Ber.* **1983**, *116*, 3487; Staab, H.A.; Diederich, F.; Krieger, C.; Schweitzer, D. *Chem. Ber.* **1983**, *116*, 3504; Funhoff, D.J.H.; Staab, H.A. *Angew. Chem. Int. Ed.* **1986**, *25*, 742.

³³⁸ Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.*, **1996**, *35*, 2383.

³³⁹ Mallory, F.B.; Butler, K.E.; Evans, A.C.; Mallory, C.W. *Tetrahedron Lett.* **1996**, *37*, 7173.

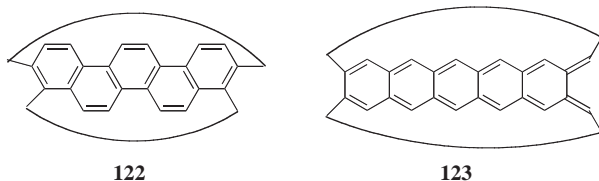
³⁴⁰ Schleyer, P.v.R.; Manoharan, M.; Jiao, H.; Stahl, F. *Org. Lett.* **2001**, *3*, 3643. For a discussion of local aromaticity, see Portella, G.; Poater, J.; Bofill, J.M.; Alemany, P.; Solà, M. *J. Org. Chem.* **2005**, *70*, 2509.

³⁴¹ Bunz, U.H.F. *Chemistry: Eur. J.* **2009**, *15*, 6780.

³⁴² Ashton, P.R.; Girreser, U.; Giuffrida, D.; Kohnke, F.H.; Mathias, J.P.; Raymo, F.M.; Slawin, A.M.Z.; Stoddart, J.F.; Williams, D.J. *J. Am. Chem. Soc.* **1993**, *115*, 5422.

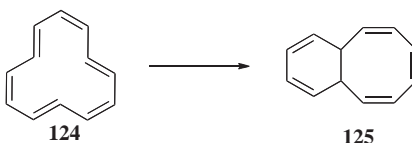
³⁴³ Aihara, J-i. *J. Chem. Soc. Perkin Trans. 2* **1994**, 971. For a discussion of hexacene stability, see Mondal, R.; Adhikari, R.M.; Shah, B.K.; Neckers, D.C. *Org. Lett.* **2007**, *9*, 2505.

³⁴⁴ Pascal, Jr., R.A. *Chem. Rev.* **2006**, *106*, 4809. See also, Chauvin, R.; Lepetit, C.; Maraval, V.; Leroyer, L. *Pure Appl. Chem.* **2010**, *82*, 769.



2.K.vi. Systems of More Than 10 Electrons: $4n$ Electrons²⁴⁹

As seen in Section 2.K.ii, these systems are expected to be not only nonaromatic, but also antiaromatic. The [12]annulene (**124**) has been prepared.³⁴⁵ In solution, **124** exhibits rapid conformational mobility (as do many other annulenes),³⁴⁶ and above -150°C in this particular case, all protons are magnetically equivalent. However, at -170°C the mobility is greatly slowed and the three inner protons are found at $\sim 8\delta$ while the nine



outer protons are at $\sim 6\delta$. Interaction of the ‘internal’ hydrogen atoms in annulene (**124**) leads to nonplanarity. Above -50°C , **124** is unstable and rearranges to **125**. Several bridged and dehydro[12]annulenes are known, for example, 5-bromo-1,9-didehydro[12]annulene (**126**),³⁴⁷ cycl[3.3.3]azine (**127**),³⁴⁸ *s*-indacene (**128**),³⁴⁹ and 1,7-methano[12]annulene (**129**).³⁵⁰ *s*-Indacene is a planar, conjugated system perturbed by two cross links, and studies showed that the low-energy structure has *localized* double bonds. In these compounds, both hydrogen interference and conformational mobility are prevented. In **127–129**, the bridge prevents conformational changes, while in **126** the bromine atom is too large to be found inside the ring. The NMR spectra show that all four compounds are paratropic, the inner proton of **126** being found at 16.4δ . The dication of **112**³⁵¹ and the dianion of **103**³⁵² are also 12-electron paratropic species. An interesting 12-electron [13]annulenone has recently been reported, 5,10-dimethyl[13]annulenone (**130**). This annulenone is the first monocyclic annulene larger than tropene,³⁵³ and a linearly-fused benzodehydro[12]annulene system has been reported.³⁵⁴

³⁴⁵ Oth, J.F.M.; Röttele, H.; Schröder, G. *Tetrahedron Lett.* **1970**, 61; Oth, J.F.M.; Gilles, J.; Schröder, G. *Tetrahedron Lett.* **1970**, 67. See Braten, M.N.; Castro, C.; Herges, R.; Köhler, F.; Karney, W.L. *J. Org. Chem.* **2008**, 73, 1532.

³⁴⁶ For a review of conformational mobility in annulenes, see Oth, J.F.M. *Pure Appl. Chem.* **1971**, 25, 573.

³⁴⁷ Untch, K.G.; Wysocki, D.C. *J. Am. Chem. Soc.* **1967**, 89, 6386.

³⁴⁸ Farquhar, D.; Leaver, D. *Chem. Commun.* **1969**, 24. For a review, see Matsuda, Y.; Gotou, H. *Heterocycles* **1987**, 26, 2757.

³⁴⁹ Hertwig, R.H.; Holthausen, M.C.; Koch, W.; Maksić, Z.B. *Angew. Chem. Int. Ed.* **1994**, 33, 1192.

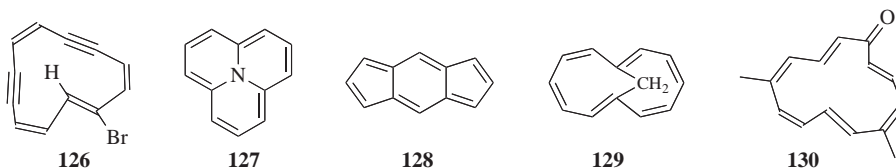
³⁵⁰ Scott, L.T.; Kirms, M.A.; Günther, H.; von Puttkamer, H. *J. Am. Chem. Soc.* **1983**, 105, 1372; Destro, R.; Ortoleva, E.; Simonetta, M.; Todeschini, R. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1227.

³⁵¹ Müllen, K.; Meul, T.; Schade, P.; Schmickler, H.; Vogel, E. *J. Am. Chem. Soc.* **1987**, 109, 4992. See also, Hafner, K.; Thiele, G.F. *Tetrahedron Lett.* **1984**, 25, 1445.

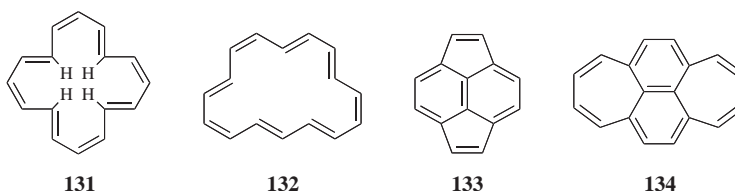
³⁵² Schmalz, D.; Günther, H. *Angew. Chem. Int. Ed.* **1988**, 27, 1692.

³⁵³ Higuchi, H.; Hiraiwa, N.; Kondo, S.; Ojima, J.; Yamamoto, G. *Tetrahedron Lett.* **1996**, 37, 2601.

³⁵⁴ Gallagher, M.E.; Anthony, J.E. *Tetrahedron Lett.* **2001**, 42, 7533.



The results for [16]annulene are similar. The compound was synthesized in two different ways,³⁵⁵ both of which gave **131**, which in solution is in equilibrium with **132**. Above -50°C there is conformational mobility, resulting in the magnetic equivalence of all protons, but at -130°C the compound is clearly paratropic: There are 4 protons at 10.56 δ and 12 at 5.35 δ . In the solid state, where the compound exists entirely as **131**, X-ray crystallography³⁵⁶ shows that the molecules are nonplanar with almost complete bond alternation: The single bonds are 1.44–1.47 Å and the double bonds are 1.31–1.35 Å. A number of dehydro and bridged [16]annulenes are also paratropic,³⁵⁷ as are [20]annulene,³⁵⁸ and [24]annulene.³⁵⁹ However, a bridged tetradehydro[32]annulene was atropic.³³³



Both pyracylene (**133**),³⁶⁰ which because of strain is stable only in solution, and dipoleadiene (**134**)³⁶¹ are paratropic, as shown by NMR spectra. These molecules might have been expected to behave like naphthalenes with outer bridges, but the outer π frameworks (12 and 16 electrons, respectively) constitute antiaromatic systems with an extra central double bond. With respect to **133**, the $4n+2$ rule predicts pyracylene to be “aromatic” if it is regarded as a 10- π -electron naphthalene unit connected to two 2- π -electron etheno systems, but “antiaromatic” if it is viewed as a 12- π -electron cyclo-dodecahexaene periphery perturbed by an internal cross-linked etheno unit.³⁶² Recent studies have concluded on energetic grounds that **133** is a “borderline” case, in terms of aromaticity–antiaromaticity character.³⁶⁰ Dipoleadiene appears to be antiaromatic.³⁶¹

The fact that many $4n$ systems are paratropic even though they may be nonplanar and have unequal bond distances indicates that if planarity were enforced, the ring currents

³⁵⁵ Gilles, J. *Tetrahedron Lett.* **1968**, 6259; Calder, I.C.; Gaoni, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1968**, *90*, 4946. See Schröder, G.; Kirsch, G.; Oth, J.F.M. *Chem. Ber.* **1974**, *107*, 460.

³⁵⁶ Johnson, S.M.; Paul, I.C.; King, G.S.D. *J. Chem. Soc. B* **1970**, 643.

³⁵⁷ See Ogawa, H.; Kubo, M.; Tabushi, I. *Tetrahedron Lett.* **1973**, 361; Nakatsuji, S.; Morigaki, M.; Akiyama, S.; Nakagawa, M. *Tetrahedron Lett.* **1975**, 1233; Vogel, E.; Kürshner, U.; Schmickler, H.; Lex, J.; Wennerström, O.; Tanner, D.; Norinder, U.; Krüger, C. *Tetrahedron Lett.* **1985**, *26*, 3087.

³⁵⁸ Metcalf, B.W.; Sondheimer, F. *J. Am. Chem. Soc.* **1971**, *93*, 6675. See also, Wilcox, Jr., C.F.; Farley, E.N. *J. Am. Chem. Soc.* **1984**, *106*, 7195.

³⁵⁹ Calder, I.C.; Sondheimer, F. *Chem. Commun.* **1966**, 904. See also, Yamamoto, K.; Kuroda, S.; Shibutani, M.; Yoneyama, Y.; Ojima, J.; Fujita, S.; Ejiri, E.; Yanagihara, K. *J. Chem. Soc. Perkin Trans. 1* **1988**, 395.

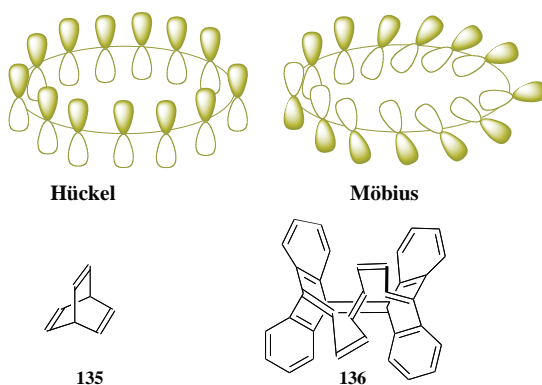
³⁶⁰ Trost, B.M.; Herdle, W.B. *J. Am. Chem. Soc.* **1976**, *98*, 4080.

³⁶¹ Vogel, E.; Neumann, B.; Klug, W.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* **1985**, *24*, 1046.

³⁶² Diogo, H. P.; Kiyobayashi, T.; Minas da Piedade, M. E.; Burlak, N.; Rogers, D. W.; McMasters, D.; Persy, G.; Wirz, J.; Liebman, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 2065.

might be even greater. The NMR spectrum of the dianion of **110**³⁶³ (and its diethyl and dipropyl homologues)³⁶⁴ effectively illustrate this point. Recall that in **110**, the outer protons were found at 8.14–8.67 δ with the methyl protons at -4.25 δ . For the dianion, however, which is forced to have approximately the same planar geometry, but now has 16 electrons, the outer protons are shifted to about -3 δ while the methyl protons are found at ~ 21 δ , a shift of ~ 25 δ ! A converse shift was made when [16]annulenes that were antiaromatic were converted to 18-electron dianions that were aromatic.²⁸² In these cases, the changes in NMR chemical shifts were almost as dramatic. Heat-of-combustion measures also show that [16]annulene is much less stable than its dianion.³⁶⁵ It has also been reported that the fluorenyl cation shows substantial destabilization, suggesting that it is an antiaromatic species.³⁶⁶

It seems clear that $4n$ systems will be at a maximum where a molecule is constrained to be planar (as in **86** or the dianion of **110**) but, where possible, the molecule will distort itself from planarity and avoid equal bond distances in order to reduce. In some cases (e.g., cyclo-octatetraene), the distortion and bond alternation are great enough to be completely avoided. In other cases, (e.g., **124** or **131**), it is apparently not possible for the molecules to avoid at least some p orbital overlap. Such molecules show evidence of paramagnetic ring currents, although the degree of is not as great as in molecules (e.g., **86** or the dianion of **110**).



The concept of “Möbius aromaticity” was conceived by Helbronner in 1964,³⁶⁷ when he suggested that large cyclic $[4n]$ annulenes might be stabilized if the π orbitals were twisted gradually around a Möbius strip. This concept is illustrated by the diagrams labeled Hückel, which is a destabilized $[4n]$ system, in contrast to the Möbius model, which is a stabilized $[4n]$ system.³⁶⁸ Zimmerman generalized this idea and applied the “Hückel–Möbius concept” to the analysis of ground-state systems [e.g., barrelene (**135**)].³⁶⁹ In 1998, a computational reinterpretation of existing experimental evidence for $(\text{CH})_9^+$ as a Möbius aromatic cyclic annulene with $4n$ π -electrons was reported.³⁷⁰ This reversal of

³⁶³ For a review of polycyclic dianions, see Rabinovitz, M.; Cohen, Y. *Tetrahedron* **1988**, *44*, 6957.

³⁶⁴ Mitchell, R.H.; Klopfenstein, C.E.; Boekelheide, V. *J. Am. Chem. Soc.* **1969**, *91*, 4931. For another example, see Deger, H.M.; Müllen, K.; Vogel, E. *Angew. Chem. Int. Ed.* **1978**, *17*, 957.

³⁶⁵ Stevenson, G.R.; Forch, B.E. *J. Am. Chem. Soc.* **1980**, *102*, 5985.

³⁶⁶ Herndon, W.C.; Mills, N.S. *J. Org. Chem.* **2005**, *70*, 8492.

³⁶⁷ Helbronner, E. *Tetrahedron Lett.* **1964**, 1923.

³⁶⁸ Kawase, T.; Oda, M. *Angew. Chem. Int. Ed.*, **2004**, *43*, 4396.

³⁶⁹ Zimmerman, H. E. *J. Am. Chem. Soc.* **1966**, *88*, 1564; Zimmerman, H. E. *Acc. Chem. Res.* **1972**, *4*, 272.

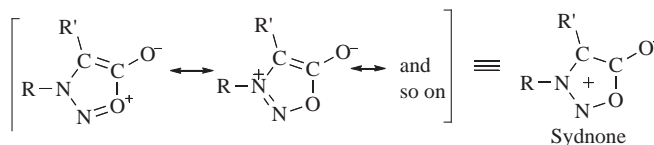
³⁷⁰ Mauksch, M.; Gogonea, V.; Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* **1998**, *37*, 2395.

[4*n*]annulene antiaromaticity has been demonstrated by stacking rings into a superphane.³⁷¹ A superphane is a sixfold bridged cyclophane with all arene positions in the corresponding dimer taken up by ethylene spacers.³⁷² A recent computational study predicted several Möbius local minima for [12], [16], and [20]annulenes.³⁷³ A twisted [16]annulene has been prepared and calculations suggested it should show Möbius aromaticity.³⁷⁴ High-performance liquid chromatography (HPLC) separation of isomers gave **136**, and the authors concluded it is Möbius aromatic. The synthesis and study of molecules that demonstrate Möbius aromaticity continues to be an area of interest.³⁷⁵

2.L. OTHER AROMATIC COMPOUNDS

Three additional types of aromatic compounds must be noted.

1. *Mesoionic Compounds*:³⁷⁶ These compounds cannot be satisfactorily represented by Lewis structures not involving charge separation. Most of them contain five-membered rings. The most common are the *sydnones*, stable aromatic compounds that undergo aromatic substitution when R' is hydrogen.



2. *The Dianion of Squaric Acid*.³⁷⁷ The stability of this system is illustrated by the fact that the pK_1 of squaric acid³⁷⁸ is ~ 1.5 and the pK_2 is ~ 3.5 ,³⁷⁹ which means that even the second proton is given up much more readily than the proton of acetic acid.³⁸⁰ The analogous three-,³⁸¹ five-, and six-membered ring compounds are also known.³⁸²

³⁷¹ Bean, D.E.; Fowler, P.W. *Org. Lett.* **2008**, *10*, 5573.

³⁷² For a discussion of superphanes and beltenes, see Gleiter, R.; Hellbach, B.; Gath, S.; Schaller, R.J. *Pure Appl. Chem.* **2006**, *78*, 699.

³⁷³ Castro, C.; Isborn, C. M.; Karney, W. L.; Mauksch, M.; Schleyer, P.v.R. *Org. Lett.* **2002**, *4*, 3431.

³⁷⁴ Ajami, D.; Oeckler, O.; Simon, A.; Herges, R. *Nature (London)* **2003**, *426*, 819; Rappaport, S.M.; Rzepa, H.S. *J. Am. Chem. Soc.* **2008**, *130*, 7613.

³⁷⁵ Rzepa, H.S. *Chem. Rev.* **2005**, *105*, 3697; Herges, R. *Chem. Rev.* **2006**, *106*, 4820. For monocyclic [11]annulenium cations see Warner, P.M. *J. Org. Chem.* **2006**, *71*, 9271. For lemniscular hexaphyrins see Rzepa, H.S. *Org. Lett.* **2008**, *10*, 949.

³⁷⁶ For reviews, see Newton, C.G.; Ramsden, C.A. *Tetrahedron* **1982**, *38*, 2965; Ollis, W.D.; Ramsden, C.A. *Adv. Heterocycl. Chem.* **1976**, *19*, 1; Yashunskii, V.G.; Kholodov, L.E. *Russ. Chem. Rev.* **1980**, *49*, 28; Ohta, M.; Kato, H., in Snyder, J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, **1969**, pp. 117–248.

³⁷⁷ West, R.; Powell, D.L. *J. Am. Chem. Soc.* **1963**, *85*, 2577; Ito, M.; West, R. *J. Am. Chem. Soc.* **1963**, *85*, 2580.

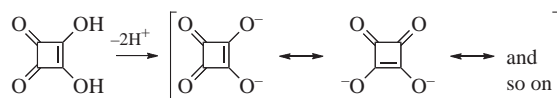
³⁷⁸ See Wong, H.N.C.; Chan, T.; Luh, T. in Patai, S.; Rappaport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, **1988**, pp. 1501–1563.

³⁷⁹ MacDonald, D.J. *J. Org. Chem.* **1968**, *33*, 4559.

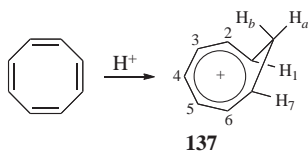
³⁸⁰ There has been a controversy as to whether this dianion is in fact aromatic. See Aihara, J. *J. Am. Chem. Soc.* **1981**, *103*, 1633.

³⁸¹ Eggerding, D.; West, R. *J. Am. Chem. Soc.* **1976**, *98*, 3641; Pericás, M.A.; Serratos, F. *Tetrahedron Lett.* **1977**, 4437; Semmingsen, D.; Groth, P. *J. Am. Chem. Soc.* **1987**, *109*, 7238.

³⁸² See West, R. *Oxocarbons*, Academic Press, NY, **1980**; Serratos, F. *Acc. Chem. Res.* **1983**, *16*, 170; Schmidt, A.H. *Synthesis* **1980**, 961; West, R. *Isr. J. Chem.* **1980**, *20*, 300; West, R.; Niu, J., in Snyder, J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, **1969**, pp. 311–345; Maahs, G.; Hegenberg, P. *Angew. Chem. Int. Ed.* **1966**, *5*, 888.



3. *Homoaromatic Compounds*. When cyclooctatetraene is dissolved in concentrated H_2SO_4 , a proton adds to one of the double bonds to form the homotropylium ion (**137**).³⁸³ In this species, an aromatic sextet is spread over seven carbons, as in the tropylium ion. The eighth carbon is an sp^3 carbon and so cannot take part in the aromaticity. The NMR spectra show the presence of a diatropic ring current: H_b is found at $\delta = -0.3$; H_a at 5.1 δ ; H_1 and H_7 at 6.4 δ ; H_2 – H_6 at 8.5 δ . This ion is an example of a *homoaromatic* compound, generally defined as a compound that contains one or more³⁸⁴ sp^3 -hybridized carbon atoms in an otherwise conjugated cycle.³⁸⁵



In order for the orbitals to overlap most effectively so as to close a loop, the sp^3 atoms are forced to lie almost vertically above the plane of the aromatic atoms.³⁸⁶ In **137**, H_b is directly above the aromatic sextet, and so is shifted far upfield in the NMR. Virtually all homoaromatic compounds so far discovered are ions, and the existence of homoaromatic character in uncharged systems³⁸⁷ has been questioned.³⁸⁸ However, neutral homoaromaticity in some heterocyclic compounds has been observed by replacing CH_2 at C-2 in bicyclo[3.2.1]octa-3,6-diene with $\text{X} = \text{BH}$, AlH , Be , Mg , O , S , PH , NH (antihomoaromatic for $\text{X} = \text{BH}$, AlH , and Be ; nonhomoaromatic for $\text{X} = \text{O}$, S , NH , PH); replacement of CH at C-3 in bicyclo[3.2.1]octa-3,6-dien-2-yl anion with PH , S , NH , O (homoaromatic for $\text{X} = \text{S}$, PH , NH , O); and replacement at C-2 and C-3 with N and O (homoaromatic).³⁸⁹ Homoaromatic ions of 2 and 10 electrons are also known.

³⁸³ Haddon, R.C. *J. Am. Chem. Soc.* **1988**, *110*, 1108. See also, Childs, R.F.; Mulholland, D.L.; Varadarajan, A.; Yeroushalmi, S. *J. Org. Chem.* **1983**, *48*, 1431. See also, Alkorta, I.; Elguero, J.; Eckert-Maksić, M.; Maksić, Z.B. *Tetrahedron* **2004**, *60*, 2259.

³⁸⁴ If a compound contains two such atoms it is bishomoaromatic; if three, trishomoaromatic, and so on. For examples see Paquette, L.A. *Angew. Chem. Int. Ed.* **1978**, *17*, 106.

³⁸⁵ See Childs, R.F. *Acc. Chem. Res.* **1984**, *17*, 347; Paquette, L.A. *Angew. Chem. Int. Ed.* **1978**, *17*, 106; Garratt, P.J. *Aromaticity*, Wiley, NY, **1986**, pp. 5–45; and in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Wiley, NY, Vol. 3, **1972**, the reviews by Story, P.R.; Clark Jr., B.C. 1007–1098, pp. 1073–1093.

³⁸⁶ Calculations show that only $\sim 60\%$ of the chemical shift difference between H_a and H_b is the result of the aromatic ring current, and that even H_a is shielded; it would appear at $\delta \sim 5.5$ without the ring current: Childs, R.F.; McGlinchey, M.J.; Varadarajan, A. *J. Am. Chem. Soc.* **1984**, *106*, 5974.

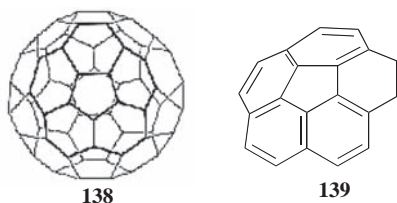
³⁸⁷ Examples of uncharged homoantiaromatic compounds have been claimed: See Scott, L.T.; Cooney, M.J.; Rogers, D.W.; Dejoongruang, K. *J. Am. Chem. Soc.* **1988**, *110*, 7244.

³⁸⁸ Houk, K.N.; Gandour, R.W.; Strozier, R.W.; Rondan, N.G.; Paquette, L.A. *J. Am. Chem. Soc.* **1979**, *101*, 6797; Paquette, L.A.; Snow, R.A.; Muthard, J.L.; Cynkowski, T. *J. Am. Chem. Soc.* **1979**, *101*, 6991. See, however, Liebman, J.F.; Paquette, L.A.; Peterson, J.R.; Rogers, D.W. *J. Am. Chem. Soc.* **1986**, *108*, 8267.

³⁸⁹ Freeman, P.K. *J. Org. Chem.* **2005**, *70*, 1998. See the discussion for methano[10]annulenes, Caramori, G.F.; de Oliveira, K.T.; Galembeck, S.E.; Bultinck, P.; Constantino, M.G. *J. Org. Chem.* **2007**, *72*, 76.

New conceptual applications to 3D homoaromatic systems with cubane, dodecahedrane, and adamantane frameworks have been presented.³⁹⁰ This concept includes families of spherical homoaromatics with both two and eight mobile electrons. Each set has complete *spherical homoaromaticity*, that is, all the sp^2 carbon atoms in a highly symmetrical framework are separated by one or two sp^3 -hybridized atoms.

4. *Fullerenes*. Fullerenes are a family of aromatic hydrocarbons³⁹¹ based on the parent buckminsterfullerene (**138**; C_{60})³⁹² that have a variety of very interesting properties.³⁹³ Derivatives of **138** are sometimes called buckyballs. Molecular orbital calculations show that “fullerene aromaticity lies within 2 kcal mol^{-1} (8.4 kJ mol^{-1}) per carbon of a hypothetical ball of rolled up graphite.”³⁹⁴ Fullerenes may exhibit what is known as spherical aromaticity (3D aromaticity),³⁹⁵ and the *Hückel rule* cannot be used for spherical systems (e.g., fullerenes). The $2(n + 1)^2$ rule was proposed by Hirsch et al.,³⁹⁶ as the 3D analogue of the $4n + 2$ rule for planar systems proposed by Hückel.³⁹⁷ Heterofullerenes are also known.³⁹⁸



Buckybowls constitute another class of polynuclear aromatic hydrocarbons, and they are essentially fragments of **138**. Corannulene (**139**)³⁹⁹ (also called 5-circulene), for example, is the simplest curved-surface hydrocarbon possessing a carbon framework that be identified with the buckminsterfullerene surface. It has been synthesized by Scott, et al.³⁹⁹ and several other groups.⁴⁰⁰ Corannulene is a flexible molecule, with a bowl–bowl inversion barrier of $\sim 10\text{--}11 \text{ kcal mol}^{-1}$

³⁹⁰ Chen, Z.; Jiao, H.; Hirsch, A.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.*, **2002**, *41*, 4309

³⁹¹ Thilgen, C.; François Diederich, F. *Chem. Rev.* **2006**, *106*, 5049.

³⁹² Billups, W. E.; Ciufolini, M.A. *Buckminsterfullerenes*, VCH, NY, **1993**; Taylor, R. *The Chemistry of Fullerenes*, World Scientific, River Edge, NJ, Singapore, **1995**; Aldersey-Williams, H. *The Most Beautiful Molecule: The Discovery of the Buckyball*, Wiley, NY, **1995**; Baggott, J.E. *Perfect Symmetry: the Accidental Discovery of Buckminsterfullerene*, Oxford University Press, Oxford, NY, **1994**. Also see, Kroto, H.W.; Heath, J.R.; O'Brien, S.C.; Curl, R.F.; Smalley, R.E. *Nature (London)* **1985**, *318*, 162.

³⁹³ Smalley, R.E. *Acc. Chem. Res.* **1992**, *25*, 98; Diederich, F.; Whetten, R.L. *Acc. Chem. Res.* **1992**, *25*, 119; Hawkins, J. M. *Acc. Chem. Res.* **1992**, *25*, 150; Wudl, F. *Acc. Chem. Res.* **1992**, *25*, 157; McElvany, S.W.; Ross, M.M.; Callahan, J.H. *Acc. Chem. Res.* **1992**, *25*, 162; Johnson, R.D.; Bethune, D.S.; Yannoni, C.S. *Acc. Chem. Res.* **1992**, *25*, 169.

³⁹⁴ Warner, P.M. *Tetrahedron Lett.* **1994**, *35*, 7173.

³⁹⁵ Chen, Z.; King, R.B. *Chem. Rev.* **2005**, *105*, 3613; Bühl, M.; Hirsch, A. *Chem. Rev.* **2001**, *101*, 1153.

³⁹⁶ Hirsch, A.; Chen, Z.; Jiao, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 3915.

³⁹⁷ Hückel, E. *Z. Phys.* **1931**, *70*, 204; Hückel, E. *Z. Phys.* **1931**, *72*, 310; Hückel, E. *Z. Phys.* **1932**, *76*, 628.

³⁹⁸ Vostrowsky, O.; Hirsch, A. *Chem. Rev.* **2006**, *106*, 5191

³⁹⁹ Scott, L.T.; Hashemi, M.M.; Meyer, D.T.; Warren, H.B. *J. Am. Chem. Soc.* **1991**, *113*, 7082.

⁴⁰⁰ Liu, C.Z.; Rabideau, P.W. *Tetrahedron Lett.* **1996**, *37*, 3437.

(41.8–46.0 kJ mol⁻¹).⁴⁰¹ Benzocorannulenes are known,⁴⁰² and other bowl-shaped hydrocarbons include acenaphtho[3,2,1,8-*ijklm*]diindeno[4,3,2,1-*cdef*-1',2',3',4'*pqra*]triphenylene.⁴⁰³ The inversion barrier to buckybowl inversion has been lowered by such benzannulation of the rim.⁴⁰⁴ Other semibuckminsterfullerenes include C_{2v}-C₃₀H₁₂ and C₃-C₃₀H₁₂.³⁹⁹ Larger fullerenes include C₆₀, C₈₀, C₈₄, and fullerenes are known that contain an endohedral metal (e.g., scandium or even Sc₃N).⁴⁰⁵ Synthetic methods often generate mixtures of fullerenes that must be separated, as in the report of new methods for separating C₈₄-fullerenes.⁴⁰⁶ A homofullerene has been prepared,⁴⁰⁷ and the azaaceptanidenide anion, which is a bowl-shaped heterocycle, has been prepared.⁴⁰⁸

2.M. HYPERCONJUGATION

Conjugation in molecules (e.g., 1,3-butadiene and benzene) was well known to organic chemists in the 19th century. For example, it became understood that one could view 1,3-butadiene as two ethylene units. The overlap of the end *p* orbitals of the two ethylenes that are to be attached leads to conjugation, which in turn leads to a lowering of the energy of the system, a change in geometry in several respects, and most obviously, to changes in chemical and physical properties of the molecule. In this case, two *p* orbitals overlap. Mulliken suggested that if one has a sigma orbital overlapping with a *p* orbital, then one has “hyperconjugation.” Qualitatively hyperconjugation is similar to conjugation, but smaller. When a methyl group is attached to ethylene, for example, there is a shift of the UV absorption spectrum to longer wavelength, an increase in the reactivity of the molecule, and a lowering of energy, similar to the changes that occur in the ethylene to butadiene case, but to a lesser extent. Hyperconjugation shows the same effects, but to a lesser amount, because the sigma orbital lies at a lower energy than the π orbital. Hence the electrons delocalize out of the sigma orbital in hyperconjugation to a lesser extent than from a π orbital in conjugation. The term hyperconjugation therefore arises from the hyperconjugative forms that make small but definite contributions to the ground state of a molecule.⁴⁰⁹

⁴⁰¹ Biedermann, P.U.; Pogodin, S.; Agranat, I. *J. Org. Chem.* **1999**, *64*, 3655; Rabideau, P.W.; Sygula, A. *Acc. Chem. Res.* **1996**, *29*, 235; Hagan, S.; Bratcher, M.S.; Erickson, M.S.; Zimmermann, G.; Scott, L.T. *Angew. Chem. Int. Ed.* **1997**, *36*, 406. See also, Dinadayalane, T.C.; Sastry, G.N. *Tetrahedron* **2003**, *59*, 8347.

⁴⁰² Dinadayalane, T.C.; Sastry, G.N. *J. Org. Chem.* **2002**, *67*, 4605.

⁴⁰³ Marcinow, Z.; Grove, D.I.; Rabideau, P.W. *J. Org. Chem.* **2002**, *67*, 3537. Multiethynyl corannulenes have been prepared: Wu, Y.-T.; Bandera, D.; Maag, R.; Linden, A.; Baldrige, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* **2008**, *130*, 10729.

⁴⁰⁴ Marcinow, Z.; Sygula, A.; Ellern, D.A.; Rabideau, P.W. *Org. Lett.* **2001**, *3*, 3527.

⁴⁰⁵ Stevenson, S.; Rice, G.; Glass, T.; Harich, K.; Cromer, F.; Jordan, M.R.; Craft, J.; Hadju, E.; Bible, R.; Olmstead, M.M.; Maitra, K.; Fisher, A.J.; Balch, A.L.; Dorn, H.C. *Nature (London)* **1999**, *401*, 55.

⁴⁰⁶ Wang, G.-W.; Saunders, M.; Khong, A.; Cross, R.J. *J. Am. Chem. Soc.* **2000**, *122*, 3216.

⁴⁰⁷ Kiely, A.F.; Haddon, R.C.; Meier, M.S.; Selegue, J.P.; Brock, C.P.; Patrick, B.O.; Wang, G.-W.; Chen, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7971.

⁴⁰⁸ Mascal, M.; Bertran, J.C. *J. Am. Chem. Soc.* **2005**, *127*, 1352.

⁴⁰⁹ Pauling, L.; Springall, H. D.; Palmer, K. J. *J. Am. Chem. Soc.* **1939**, *61*, 927; Wheland, G.W. *J. Chem. Phys.* **1934**, *2*, 474.

Another delocalization phenomenon has been discussed that involves σ electrons.⁴¹⁰ Baker and Nathan⁴¹¹ observed that the rates of reaction of p-substituted benzyl bromides with pyridine (see Reaction **10-31**) were opposite from the results expected from electron release. That is, the methyl-substituted compound reacted fastest and the tert-butyl substituted compound reacted slowest. This appeared to be an anomalous electron-release pattern for alkyl groups because the field effect predicted the order of electron release for simple alkyl groups connected to an unsaturated system should be tert-butyl > isopropyl > ethyl > methyl. At least one hydrogen atom should be attached to the α -carbon that is connected to the sp^2 carbon for the Baker–Nathan effect. The Baker–Nathan effect has clouded the issue because some interpreted that it indicates hyperconjugation occurs with hydrogen and a double bond, but either did not occur or occurred to a very small amount with carbon. In the 1930s, Baker and Nathan did not have the tools to experimentally or theoretically understand hyperconjugation to any great extent. Those chemists looked for lowering of energy that could be detected, but these experiments do not necessarily help to explain hyperconjugation. Indeed, it is now known that the Baker–Nathan effect is a result of changes in solvation energy⁴¹² and has very little to do with hyperconjugation. It was recently reported that hyperconjugation is an important factor determining alkane C—H bond dissociation energies.⁴¹³ In certain instances where the Baker–Nathan effect was found to apply in solution, the order was completely reversed in the gas phase.⁴¹⁴ Since the molecular structures are unchanged in going from the gas phase into solution, it appears that each alkyl group is solvated to a different extent.⁴¹⁵ However, this only demonstrates that the Baker–Nathan effect is not the same as hyperconjugation. The structural changes that occur upon hyperconjugation can be determined from quantum mechanics and from experiment. Such changes can be qualitatively predicted by looking at the resonance structures involved.

Hyperconjugation is probably important for carbocations, as well as for free radicals⁴¹⁶ and for excited states of molecules.⁴¹⁷ In free radicals and carbocations, the canonical forms display no more charge separation than the main form. Muller and Mulliken call this *isovalent hyperconjugation*.

Apart from contributions to aromaticity, hyperconjugation has been used to explain the stability of intermediates (e.g., carbocations, see Chapter 5 for an introduction to carbocations). It was stated that C—C hyperconjugation is most important in stabilizing carbocations when the C—C bond(s) involved have more than 75% *p* character.⁴¹⁸ This effect can be illustrated by a typical case (e.g., carbocation **140**), where hyperconjugation is invoked to explain the relative stability of the ion as attached groups are varied. If the

⁴¹⁰ For monographs, see Baker, J.W. *Hyperconjugation*, Oxford University Press, Oxford, **1952**; Dewar, M.J.S. *Hyperconjugation*, Ronald Press, NY, **1962**. For a review, see de la Mare, P.B.D. *Pure Appl. Chem.* **1984**, *56*, 1755.

⁴¹¹ Baker, J.W.; Nathan, W.S. *J. Chem. Soc.* **1935**, 1840, 1844.

⁴¹² This idea was first suggested by Schubert, W.M.; Sweeney, W.A. *J. Org. Chem.* **1956**, *21*, 119.

⁴¹³ Ingold, K.U.; DiLabio, G.A. *Org. Lett.* **2006**, *8*, 5923.

⁴¹⁴ Hehre, W.J.; McIver, Jr., R.T.; Pople, J.A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1974**, *96*, 7162; Arnett, E.M.; Abboud, J.M. *J. Am. Chem. Soc.* **1975**, *97*, 3865; Glyde, E.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1977**, 678. See also, Taylor, R. *J. Chem. Res. (S)*, **1985**, 318.

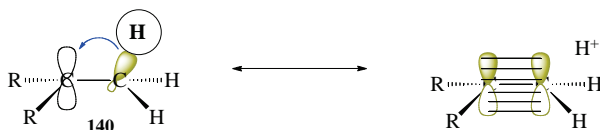
⁴¹⁵ For an opposing view, see Cooney, B.T.; Happer, D.A.R. *Aust. J. Chem.* **1987**, *40*, 1537.

⁴¹⁶ Symons, M.C.R. *Tetrahedron* **1962**, *18*, 333.

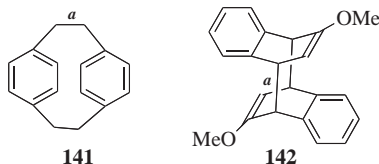
⁴¹⁷ Rao, C.N.R.; Goldman, G.K.; Balasubramanian, A. *Can. J. Chem.* **1960**, *38*, 2508.

⁴¹⁸ Jensen, F.R.; Smart, B.E. *J. Am. Chem. Soc.* **1969**, *91*, 5686.

orbitals of an adjacent C—H bond align with the empty orbital of the positive center; a canonical form can be



drawn by electron donation to C^+ to form a canonical form that is formally an alkene and H^+ . Note that the H in **140** could be any atom and C could be any sp^2 -hybridized atom and hyperconjugation would still occur. The key part is that a σ -bond overlaps a π -bond. For **140**, an alkene and a closely bound proton constitute a canonical form that helps stabilize the carbocation. Each of the three methyl hydrogen atoms in **140** can contribute to the hyperconjugative stabilization. In other words, resonance contributors involving the C—H bonds represent the bond elongation due to hyperconjugation, and provide stabilization of a carbocation.⁴¹⁹ To determine whether hyperconjugation is important in a given situation using molecular modeling, one must ask if the localized model is adequate for that situation at the particular level of precision, or whether the model must be corrected by including some delocalization.⁴²⁰ To a first approximation, delocalization can be neglected, but it is needed for better approximations. The effect of the alkene canonical form on **140** is that the electrons in the C—H bond are closer to the carbon than if hyperconjugation did not contribute at all.



In neutral molecules, the structural elements noted above should be present for hyperconjugation. There is usually at least one sp^2 -hybridized atom, usually carbon, but for hyperconjugation in general, all that is needed is a σ -bond. Resonating structures due to hyperconjugation may be written involving “no bonds” between the alpha carbon and hydrogen atoms, as shown below for propene.

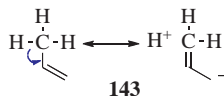
Contributions of this type are seen by a comparison of the X-ray data for **141** and **142** with the calculated data (MM40). The bond length for bond *a* in **141** is 1.571 Å by analysis of the X-ray data, but analysis by MM40 calculations gave a value of 1.565 Å.⁴²¹ Similar analysis of bond *a* in **142** gave an experimental value of 1.627 Å, but MM40 calculations gave a value of 1.589 Å. The calculated values are shorter than the actual values. When hyperconjugation was included in the MM4 calculations, the calculated values were 1.574 Å for **141** and 1.623 Å for **142**.⁴²¹ The hyperconjugative stretching effect was calculated to be 0.009 Å for **141** and 0.034 Å for **142**. This work suggests that hyperconjugation is actually a bond stretching effect,⁴²¹ and it has been represented as resonance contributors several times in this

⁴¹⁹ See Radom, L.; Poppinger, D.; Haddon, R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5; Wiley, NY, **1976**, pp. 2303–2426.

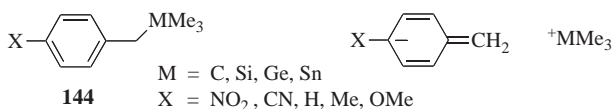
⁴²⁰ Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd Ed., Harper Collins, NY, **1987**, p. 68.

⁴²¹ Allinger, N.L. *J. Comput. Aided Mol. Des.* **2011**, 25, 295.

chapter. If the bond elongation found in propene, due to hyperconjugation, is represented as the canonical forms shown for **143**, the charge separation illustrates bond elongation. In a different example using toluene, there is evidence that the main interaction between methyl groups and the ring system in the positive ions of aromatic hydrocarbons is due to hyperconjugation rather than an inductive effect.⁴²²



There is evidence that bond length effects were the result of the *s* character of the saturated carbon rather than of neutral hyperconjugation.⁴²³ These experimental results seem to follow from hyperconjugation in the ground states of neutral molecules, and there is evidence in favor of hyperconjugation.⁴²⁴ Indeed, hyperconjugation appears to operate for both carbon and hydrogen in various systems (supported by quantum mechanics).⁴²⁵ These works tie together experimental and computational results into a unified picture that supports hyperconjugation.^{424,425} A study of the one-bond coupling constants for the aromatic system **144**



appears to provide structural evidence for hyperconjugation in a neutral ground state.⁴²⁶ Hyperconjugation in the ground state of neutral molecules has been called *sacrificial hyperconjugation* by Muller and Mulliken.⁴²⁷

Another way to view this phenomenon is to say that electron release is permitted by a mechanism that is essentially a type of tautomeric effect (Sec. 2.N). Dewar suggested that the delocalization of electrons of single bonds (hyperconjugation) and of p or π electrons (conjugation) should be included as part of the electronic description only if the localized bond picture fails.⁴²⁸ This result is a good first approximation, but modern molecular mechanics allows a much better analysis.

Hyperconjugation has been invoked to explain various aspects of aromaticity, as utilized early in this chapter. It is known that 5,5-disubstituted cyclopentadienes, where the substituents are electropositive groups, show enhanced cyclic conjugation in comparison with cyclopentadiene itself.⁴²⁹ 5,5-Distannylcyclopentadiene, for example, was found to be nearly as aromatic as furan. This is explained by hyperconjugative electron donation by the substituents, resulting in a partially anionic ring.⁴²⁴ Another effect is the so-called C*-aromaticity, which is a

⁴²² Bolton, J.R.; Carrington, A.; McLachlan, A.D. *Mol. Phys.* **1962**, 5, 31

⁴²³ Dewar, M.J.S.; Schmeising, H.N. *Tetrahedron* **1959**, 5, 166; Dewar, M.J.S. *Hyperconjugation*, Ronald Press, New York, **1962**; Alden, R. A.; Kraut, J.; Traylor, T. G. *J. Am. Chem. Soc.* **1968**, 90, 74. Also see Lambert, J.B.; Shawl, C.E.; Basso, E. *Can. J. Chem.* **2000**, 78, 1441.

⁴²⁴ See Laube, T.; Ha, T. *J. Am. Chem. Soc.* **1988**, 110, 5511.

⁴²⁵ Allinger, N.L. *Molecular Structure: Understanding Steric and Electronic Effect from Molecular Mechanics* Wiley, Hoboken, NJ, **2010**.

⁴²⁶ Lambert, J.B.; Singer, R.A. *J. Am. Chem. Soc.* **1992**, 114, 10246.

⁴²⁷ Muller, N.; Mulliken, R.S. *J. Am. Chem. Soc.* **1958**, 80, 3489.

⁴²⁸ Dewar, M.J.S. *Hyperconjugation* Ronald Press Co., New York, **1962**.

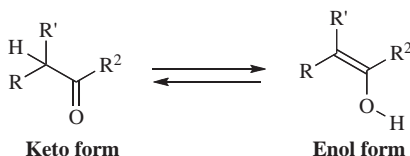
⁴²⁹ Nyulászi, L.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1999**, 121, 6872.

hyperconjugative effect found in small disubstituted rings that leads to lowering of ring-strain energies for the unsaturated rings, particularly when electronegative substituents are attached.⁴³⁰

2.N. TAUTOMERISM⁴³¹

There is another topic that is important for an understanding of chemical bonding in organic compounds. For most compounds, all the molecules are represented by a single structure. But for many compounds, there is a mixture of two or more structurally distinct compounds that are in rapid equilibrium. When this phenomenon, called *tautomerism*,⁴³² exists, there is a rapid shift back and forth among the molecules. In most cases, it is a proton that shifts from one atom of a molecule to another. Mass spectrometry was used to study tautomerism,⁴³³ which takes several forms.

2.N.i Keto–Enol Tautomerism^{434–444}



A very common form of tautomerism is that between a carbonyl compound containing an α hydrogen and its enol form.⁴⁴⁵ Such equilibria are pH dependent, as in the case of 2-acetylcyclohexanone.⁴⁴⁶ In simple cases ($\text{R}^2 = \text{H}$, alkyl, OR, etc.), the equilibrium lies well to the left (Table 2.1). Examining the bond energies in Table 1.7 leads to an explanation for this fact. The keto form differs from the enol form by the presence of a C—H, a C—C, and a

⁴³⁰ Goller, A.; Clark, T.J. *J. Mol. Model.* **2000**, *6*, 133.

⁴³¹ Baker, J.W. *Tautomerism*, D. Van Nostrand Company, Inc., New York, **1934**; Minkin, V.I.; Olekhovich, L.P.; Zhdanov, Y.A. *Molecular Design of Tautomeric Compounds*, D. Reidel Publishing Co.: Dordrecht, Holland, **1988**.

⁴³² Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1; Kolsov, A.I.; Kheifets, G.M. *Russ. Chem. Rev.* **1971**, *40*, 773; **1972**, *41*, 452–467; Forsén, S.; Nilsson, M., in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, **1970**, pp. 157–240.

⁴³³ Furlong, J.J.P.; Schiavoni, M.M.; Castro, E.A.; Allegretti, P.E. *Russ. J. Org. Chem.* **2008**, *44*, 1725.

⁴³⁴ The mechanism for conversion of one tautomer to another is discussed in Chapter 12 (Reaction **12-3**).

⁴³⁵ Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460. See also, Dubois, J.E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* **1981**, *103*, 5393; Toullec, J. *Tetrahedron Lett.* **1984**, *25*, 4401; Chiang, Y.; Kresge, A.J.; Schepp, N.P. *J. Am. Chem. Soc.* **1989**, *111*, 3977.

⁴³⁶ Keffe, J.R.; Kresge, A.R.; Toullec, J. *Can. J. Chem.* **1986**, *64*, 1224.

⁴³⁷ Keffe, J.R.; Kresge, A.J.; Schepp, N.P. *J. Am. Chem. Soc.* **1990**, *112*, 4862; Iglesias, E. *J. Chem. Soc. Perkin Trans. 2* **1997**, 431. See these papers for values for other simple compounds.

⁴³⁸ Chiang, Y.; Hojatti, M.; Keffe, J.R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000.

⁴³⁹ Bohne, C.; MacDonald, I.D.; Dunford, H.B. *J. Am. Chem. Soc.* **1986**, *108*, 7867.

⁴⁴⁰ Chiang, Y.; Kresge, A.J.; Walsh, P.A. *J. Am. Chem. Soc.* **1986**, *108*, 6314.

⁴⁴¹ Chiang, Y.; Kresge, A.J.; Krogh, E.T. *J. Am. Chem. Soc.* **1988**, *110*, 2600.

⁴⁴² Moriyasu, M.; Kato, A.; Hashimoto, Y. *J. Chem. Soc. Perkin Trans. 2* **1986**, 515. For enolization of β -ketoamides, see Hynes, M.J.; Clarke, E.M. *J. Chem. Soc. Perkin Trans. 2* **1994**, 901.

⁴⁴³ Jefferson, E.A.; Keffe, J.R.; Kresge, A.J. *J. Chem. Soc. Perkin Trans. 2* **1995**, 2041.

⁴⁴⁴ Williams, D.L.H.; Xia, L. *J. Chem. Soc. Chem. Commun.* **1992**, 985.

⁴⁴⁵ Capponi, M.; Gut, I.G.; Hellrung, B.; Persy, G.; Wirz, J. *Can. J. Chem.* **1999**, *77*, 605. For a treatise, see Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, **1990**.

⁴⁴⁶ Iglesias, E. *J. Org. Chem.* **2003**, *68*, 2680.

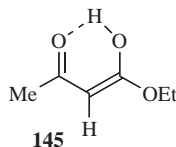
TABLE 2.1 The Enol Content of Some Carbonyl Compounds

Compound	Enol Content (%)	Reference
Acetone	6×10^{-7}	435
PhCOCH ₃	1.1×10^{-6}	436
Cyclopentanone	1×10^{-6}	437
CH ₃ CHO	6×10^{-5}	438
Cyclohexanone	4×10^{-5}	437
Butanal	5.5×10^{-4}	439
(CH ₃) ₂ CHCHO	1.4×10^{-2}	439,440
Ph ₂ CHCHO	9.1	441
CH ₃ COOEt	No enol found ^a	437
CH ₃ COCH ₂ COOEt	8.4	442
CH ₃ COCH ₂ COCH ₃	80	353
PhCOCH ₂ COCH ₃	89.2	437
EtOOCCH ₂ COOEt	7.7×10^{-3}	437
N≡CCH ₂ COOEt	2.5×10^{-1}	437
Indane-1-one	3.3×10^{-8}	443
Malonamide	No enol found	444

^aLess than 1 part in 10 million.

C=O bond, whereas the enol has a C=C, a C—O, and an O—H bond. The approximate sum of the first three is 359 kcal mol⁻¹ (1500 kJ mol⁻¹) and of the second three is 347 kcal mol⁻¹ (1452 kJ mol⁻¹). The keto form is thermodynamically more stable by ~12 kcal mol⁻¹ (48 kJ mol⁻¹), and in most cases the enol forms cannot normally be isolated.⁴⁴⁷ In certain cases, however, a larger amount of the enol form is present, and it can even be the predominant form.⁴⁴⁸ There are three main types of the more stable enols:⁴⁴⁹

1. Molecules in which the enolic double bond is in conjugation with another double bond. Some of these are shown in Table 2.1. Carboxylic esters have a much smaller enol content than ketones, for example. In molecules like acetoacetic ester (**145**), the enol is also stabilized by internal hydrogen bonding, which is unavailable to the keto form:



Analysis of acetoacetamide by gas electron diffraction shows that it exists as a mixture of 63% enol tautomer and 37% diketo form at 74°C.⁴⁵⁰ There is a discussion of electron delocalization with respect to amides.⁴⁵¹

⁴⁴⁷ For reviews on the generation of unstable enols, see Kresge, A.J. *Pure Appl. Chem.* **1991**, 63, 213; Capon, B. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, **1990**, pp. 307–322.

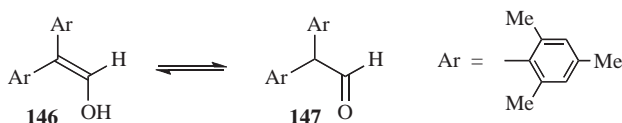
⁴⁴⁸ For reviews of stable enols, see Kresge, A.J. *Acc. Chem. Res.* **1990**, 23, 43; Hart, H.; Rappoport, Z.; Biali, S.E. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, **1990**, pp. 481–589; Hart, H. *Chem. Rev.* **1979**, 79, 515; Hart, H.; Sasaoka, M. *J. Chem. Educ.* **1980**, 57, 685.

⁴⁴⁹ For some examples of other types, see Pratt, D.V.; Hopkins, P.B. *J. Am. Chem. Soc.* **1987**, 109, 5553; Nadler, E. B.; Rappoport, Z.; Arad, D.; Apeloig, Y. *J. Am. Chem. Soc.* **1987**, 109, 7873.

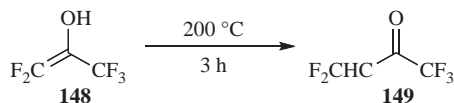
⁴⁵⁰ Belova, N.V.; Girichev, G.V.; Shlykov, S.A.; Oberhammer, H. *J. Org. Chem.* **2006**, 71, 5298.

⁴⁵¹ Mujika, J.I.; Matxain, J.M.; Eriksson, L.A.; Lopez, X. *Chem. Eur. J.* **2006**, 12, 7215; Kemnitz, C.R.; Loewen, M.J. *J. Am. Chem. Soc.* **2007**, 129, 2521.

2. Molecules that contain two or three bulky aryl groups.⁴⁵² An example is 2,2-dimesitylethenol (**146**), where the keto content at equilibrium is only 5%.⁴⁵³ In cases such as this, steric hindrance (Sec. 4.Q.iv) destabilizes the keto form. In **146**, the two aryl groups are $\sim 120^\circ$ apart, but in **147** they must move closer together ($\sim 109.5^\circ$). Such compounds are often called *Fuson-type enols*.⁴⁵⁴ There is one example of an amide with a bulky aryl group [*N*-methyl bis(2,4,6-triisopropylphenyl)acetamide] that has a measurable enol content, in sharp contrast to most amides.⁴⁵⁵



3. Highly fluorinated enols (e.g., **148**).⁴⁵⁶



In this case, the enol form is not more stable than the keto form (**149**). The enol form is less stable, and converts to the keto form upon prolonged heating. It can, however, be kept at room temperature for long periods of time because the tautomerization Reaction (12-3) is very slow, owing to the electron-withdrawing power of the fluorines.

Frequently, when the enol content is high, both forms can be isolated. The pure keto form of acetoacetic ester melts at -39°C , while the enol is a liquid even at -78°C . Each can be kept at room temperature for days if catalysts, (e.g., acids or bases) are rigorously excluded.⁴⁵⁷ Even the simplest enol, vinyl alcohol ($\text{CH}_2=\text{CHOH}$), has been prepared in the gas phase at room temperature, where it has a half-life of ~ 30 min.⁴⁵⁸ The enol $\text{Me}_2\text{C}=\text{CCHOH}$ is indefinitely stable in the solid state at -78°C and has a half-life of ~ 24 h in the liquid state at 25°C .⁴⁵⁹ When both forms cannot be isolated, the extent of enolization is often measured by NMR.⁴⁶⁰

⁴⁵² For a review, see Rappoport, Z.; Biali, S.E. *Acc. Chem. Res.* **1988**, *21*, 442. For a discussion of their structures, see Kaftory, M.; Nugiel, D.A.; Biali, D.A.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 8181.

⁴⁵³ Nugiel, D.A.; Nadler, E.B.; Rappoport, Z. *J. Am. Chem. Soc.* **1987**, *109*, 2112; O'Neill, P.; Hegarty, A.F. *J. Chem. Soc. Chem. Commun.* **1987**, 744; Becker, H.; Andersson, K. *Tetrahedron Lett.* **1987**, *28*, 1323.

⁴⁵⁴ See Fuson, R.C.; Southwick, P.L.; Rowland, S.P. *J. Am. Chem. Soc.* **1944**, *66*, 1109.

⁴⁵⁵ Frey, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3994.

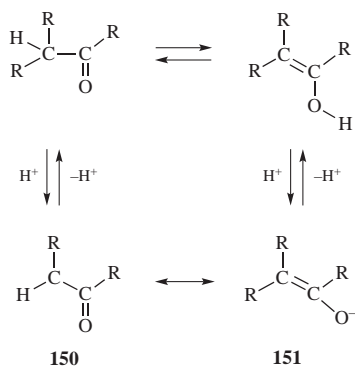
⁴⁵⁶ For a review, see Bekker, R.A.; Knunyants, I.L. *Sov. Sci. Rev. Sect. B* **1984**, *5*, 145.

⁴⁵⁷ For an example of particularly stable enol and keto forms, which could be kept in the solid state for more than a year without significant interconversion, see Schulenberg, J.W. *J. Am. Chem. Soc.* **1968**, *90*, 7008.

⁴⁵⁸ Saito, S. *Chem. Phys. Lett.* **1976**, *42*, 399. See also, Rodler, M.; Blom, C.E.; Bauder, A. *J. Am. Chem. Soc.* **1984**, *106*, 4029; Capon, B.; Guo, B.; Kwok, F.C.; Siddhanta, A.K.; Zucco, C. *Acc. Chem. Res.* **1988**, *21*, 135.

⁴⁵⁹ Chin, C.S.; Lee, S.Y.; Park, J.; Kim, S. *J. Am. Chem. Soc.* **1988**, *110*, 8244.

⁴⁶⁰ Cravero, R.M.; González-Sierra, M.; Olivieri, A.C. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1067.



The extent of enolization⁴⁶¹ is greatly affected by solvent,⁴⁶² concentration, and temperature. Lactone enols, for example, have been shown to be stable in the gas phase, but unstable in solution.⁴⁶³ Another example is acetoacetic ester, which has an enol content of 0.4% in water and 19.8% in toluene.⁴⁶⁴ In this case, water reduces the enol concentration by hydrogen bonding with the carbonyl, making this group less available for internal hydrogen bonding. The effect of temperature is clear from the enol content of pentan-2,4-dione ($\text{CH}_3\text{COCH}_2\text{COCH}_3$), which was found to be 95, 68, and 44%, respectively, at 22, 180, and 275 °C.⁴⁶⁵ When a strong base is present, both the enol and the keto form can lose a proton. The resulting anion (the *enolate ion*) is the same in both cases. Since **150** and **151** differ only in placement of electrons, *they are not tautomers, but canonical forms*. The true structure of the enolate ion is a hybrid of **150** and **151** although **151** contributes more, since in this form the negative charge is on the more electronegative atom.

2.N.ii Other Proton-Shift Tautomerism

The valence tautomerism is discussed of a proton from either tautomer is the same because of resonance. Some examples follows:⁴⁶⁶

⁴⁶¹ See Toullec, J. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, **1990**, pp. 323–398.

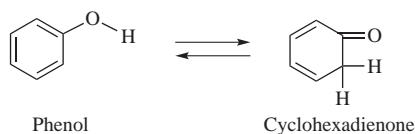
⁴⁶² For an extensive study, see Mills, S.G.; Beak, P. *J. Org. Chem.* **1985**, *50*, 1216. for keto–enol tautomerism in aqueous alcohol solutions, see Blokzijl, W.; Engberts, J.B.F.N.; Blandamer, M.J. *J. Chem. Soc. Perkin Trans. 2* **1994**, 455; For theoretical calculations of keto-enol tautomerism in aqueous solutions, see Karelson, M.; Maran, U.; Katritzky, A.R. *Tetrahedron* **1996**, *52*, 11325.

⁴⁶³ Tureček, F.; Vivekananda, S.; Sadílek, M.; Polášek, M. *J. Am. Chem. Soc.*, **2002**, *124*, 13282.

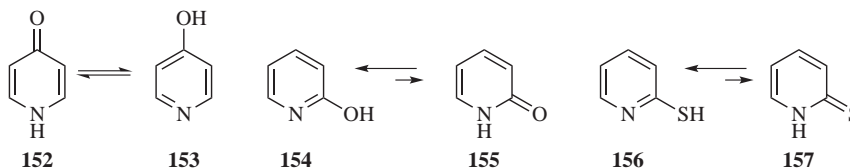
⁴⁶⁴ Meyer, K.H. *Leibigs Ann. Chem.* **1911**, 380, 212. See also, Moriyasu, M.; Kato, A.; Hashimoto, Y. *J. Chem. Soc. Perkin Trans. 2* **1986**, 515.

⁴⁶⁵ Hush, N.S.; Livett, M.K.; Peel, J.B.; Willett, G.D. *Aust. J. Chem.* **1987**, *40*, 599.

⁴⁶⁶ For a review of the use of X-ray crystallography to determine tautomeric forms, see Furmanova, N.G. *Russ. Chem. Rev.* **1981**, *50*, 775.

1. Phenol–Keto Tautomerism.⁴⁶⁷

For most simple phenols, this equilibrium lies well to the side of the phenol, which is aromatic. For phenol itself, there is no evidence for the existence of the keto form.⁴⁶⁸ However, the keto form becomes important and may predominate: (1) where certain groups, (e.g., a second OH group or an N=O group), are present;⁴⁶⁹ (2) in systems of fused aromatic rings⁴⁷⁰; (3) in heterocyclic systems. In many heterocyclic compounds in the liquid phase or in solution, the keto form is more stable,⁴⁷¹ although in the vapor phase the positions of many of these equilibria are reversed.⁴⁷² For example, **152** is the only form detectable in ethanolic solution in the equilibrium between 4-pyridone (**152**) and 4-hydroxypyridine (**153**), while **153** predominates in the vapor phase.⁴⁷² In other heterocycles, the hydroxy-form predominates. 2-Hydroxypyridone (**154**) and pyridone-2-thiol (**156**)⁴⁷³ are in equilibrium with their tautomers, 2-pyridone (**155**) and pyridine-2-thione (**157**), respectively. In both cases, the most stable form is the hydroxy or thiol tautomer, **154** and **156**.⁴⁷⁴



2. Nitroso–Oxime Tautomerism.



The equilibrium shown for formaldehyde oxime and nitrosomethane illustrates this process.⁴⁷⁵ In molecules where the products are stable, the equilibrium lies far to the right, and as a rule nitroso compounds are stable only when there is not a hydrogen.

⁴⁶⁷ For reviews, see Ershov, V.V.; Nikiforov, G.A. *Russ. Chem. Rev.* **1966**, 35, 817; Forsén, S.; Nilsson, M., in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, **1970**, pp. 168–198.

⁴⁶⁸ See Lasne, M.; Ripoll, J.; Denis, J. *Tetrahedron Lett.* **1980**, 21, 463. See also, Capponi, M.; Gut, I.; Wirz, J. *Angew. Chem. Int. Ed.* **1986**, 25, 344.

⁴⁶⁹ Ershov, V.V.; Nikiforov, G.A. *Russ. Chem. Rev.* **1966**, 35, 817. See also, Highet, R.J.; Chou, F.E. *J. Am. Chem. Soc.* **1977**, 99, 3538.

⁴⁷⁰ See, for example, Majerski, Z.; Trinajstić, N. *Bull. Chem. Soc. Jpn.* **1970**, 43, 2648.

⁴⁷¹ See Elguero, J.; Marzin, C.; Katritzky, A.R.; Linda, P. *The Tautomerism of Heterocycles*, Academic Press, NY, **1976**. For reviews, see Katritzky, A.R.; Karelson, M.; Harris, P.A. *Heterocycles* **1991**, 32, 329; Beak, P. *Acc. Chem. Res.* **1977**, 10, 186; Katritzky, A.R. *Chimia*, **1970**, 24, 134.

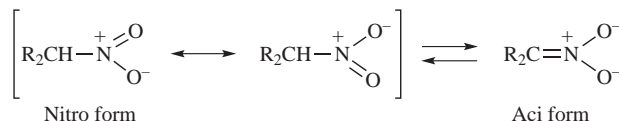
⁴⁷² Beak, P.; Fry, Jr., F.S.; Lee, J.; Steele, F. *J. Am. Chem. Soc.* **1976**, 98, 171.

⁴⁷³ Moran, D.; Sukcharoenphon, K.; Puchta, R.; Schaefer, III, H.F.; Schleyer, P.v.R.; Hoff, C.D. *J. Org. Chem.* **2002**, 67, 9061.

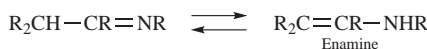
⁴⁷⁴ Parchment, O.G.; Burton, N.A.; Hillier, I.H.; Vincent, M.A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 861.

⁴⁷⁵ Long, J.A.; Harris, N.J.; Lammertsma, K. *J. Org. Chem.* **2001**, 66, 6762.

3. Aliphatic Nitro Compounds Are in Equilibrium with Aci Forms.



The nitro form is much more stable than the aci form, in sharp contrast to the parallel case of nitroso-oxime tautomerism, undoubtedly because the nitro form has resonance not found in the nitroso case. Aci forms of nitro compounds are also called nitronic acids and azinic acids.

4. Imine–Enamine Tautomerism.⁴⁷⁶

Enamines are normally stable only when no hydrogen is attached to the nitrogen ($\text{R}_2\text{C}=\text{CR}-\text{NR}_2$). Otherwise, the imine form predominates.⁴⁷⁷ The energy of various imine–enamine tautomers has been calculated.⁴⁷⁸ In the case of 6-amino-fulvene-1-aldimines, tautomerism was observed in the solid state, as well as in solution.⁴⁷⁹ Porphyrins and porphycenes also undergo this type of tautomerism, and the two tautomers may be imaged using single-molecule spectroscopy.⁴⁸⁰

5. Ring–Chain Tautomerism. Ring–chain tautomerism⁴⁸¹ occurs in sugars (aldehyde vs the pyranose or furanose structures), and in γ -oxocarboxylic acids.⁴⁸² In benzamide carbaldehyde, (**159**), whose ring-chain tautomer is **158**, the equilibrium favors the cyclic form (**159**).⁴⁸³ Similarly, benzoic acid 2-carbaldehyde (**160**) exists largely as the cyclic form (**161**).⁴⁸⁴ In these latter cases, and in many others, this tautomerism influences chemical reactivity. Conversion of **160** to an ester, for example, is difficult since most standard methods lead to the OR derivative of **161** rather than the ester of **160**. Ring–chain tautomerism also occurs in spirooxathianes,⁴⁸⁵ in decahydroquinazolines (e.g. **162** and **163**),⁴⁸⁶ in other 1,3-heterocycles,⁴⁸⁷ and in 2-ferrocenyl-2,4-dihydro-1H-3,1-benzoxazine derivatives.⁴⁸⁸

⁴⁷⁶ See Shainyan, B.A.; Mirskova, A.N. *Russ. Chem. Rev.* **1979**, *48*, 107; Mamaev, V.P.; Lapachev, V.V. *Sov. Sci. Rev. Sect. B.* **1985**, *7*, 1.

⁴⁷⁷ For examples of the isolation of primary and secondary enamines, see Shin, C.; Masaki, M.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1657; de Jeso, B.; Pommier, J. *J. Chem. Soc. Chem. Commun.* **1977**, 565.

⁴⁷⁸ Lammertsma, K.; Prasad, B.V. *J. Am. Chem. Soc.* **1994**, *116*, 642.

⁴⁷⁹ Sanz, D.; Perez-Torralba, M.; Alarcon, S.H.; Claramunt, R.M.; Foces-Foces, C.; Elguero, J. *J. Org. Chem.* **2002**, *67*, 1462.

⁴⁸⁰ Piwoński, H.; Stupperich, C.; Hartschuh, A.; Sepiol, J.; Meixner, A.; Waluk, J. *J. Am. Chem. Soc.* **2005**, *127*, 5302.

⁴⁸¹ Valters, R.E.; Flitsch, W. *Ring-Chain Tautomerism*, Plenum, NY, **1985**. For reviews, see Valters, R.E. *Russ. Chem. Rev.* **1973**, *42*, 464; **1974**, *43*, 665; Escalé, R.; Verducci, J. *Bull. Soc. Chim. Fr.*, **1974**, 1203.

⁴⁸² Fabian, W.M.F.; Bowden, K. *Eur. J. Org. Chem.* **2001**, 303.

⁴⁸³ Bowden, K.; Hiscocks, S.P.; Perjéssy, A. *J. Chem. Soc. Perkin Trans. 2* **1998**, 291.

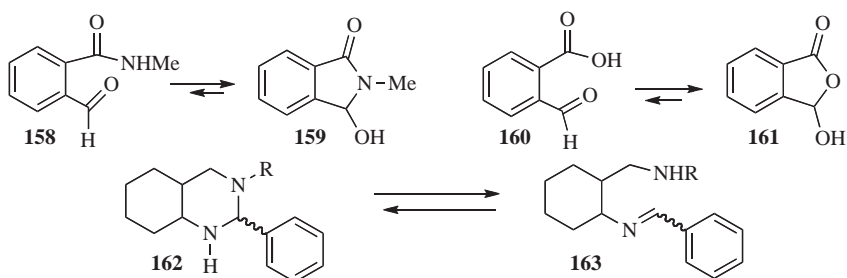
⁴⁸⁴ Ring chain tautomer of benzoic acid 2-carboxaldehyde.

⁴⁸⁵ Terec, A.; Grosu, I.; Muntean, L.; Toupet, L.; Plé, G.; Socaci, C.; Mager, S. *Tetrahedron* **2001**, *57*, 8751; Muntean, L.; Grosu, I.; Mager, S.; Plé, G.; Balog, M. *Tetrahedron Lett.* **2000**, *41*, 1967.

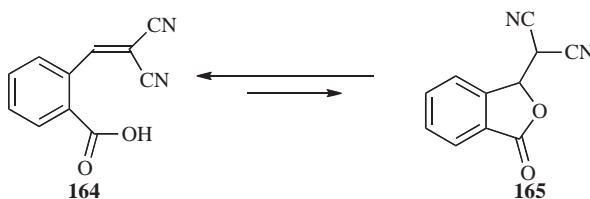
⁴⁸⁶ Lazar, L.; Goblyos, A.; Martinek, T. A.; Fulop, F. *J. Org. Chem.* **2002**, *67*, 4734.

⁴⁸⁷ Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* **2003**, 3025.

⁴⁸⁸ Pérez, S.; López, C.; Caubet, A.; Roig, A.; Molins, E. *J. Org. Chem.* **2005**, *70*, 4857.



There are many other highly specialized cases of proton-shift tautomerism, including an internal *Michael reaction* (see **15-24**) in which 2-(2,2-dicyano-1-methylethenyl)benzoic acid (**164**) exists largely in the open-chain form rather than its tautomer (**162**) in the solid state, but in solution there is an increasing amount of **165** as the solvent becomes more polar.⁴⁸⁹



⁴⁸⁹ Kolsaker, P.; Arukwe, J.; Barc oczy, J.; Wiberg, A.; Fagerli, A.K. *Acta Chem. Scand. B* **1998**, 52, 490.

Bonding Weaker Than Covalent

The discussions in Chapters 1 and 2 focused on the structure of molecules as an aggregate of atoms in a distinct 3D arrangement, held together by bonds with energies on the order of 50–100 kcal mol⁻¹ (200–400 kJ mol⁻¹). There are also very weak attractive forces *between* molecules, on the order of a few tenths of a kilocalorie per mole. These forces, called *van der Waals forces*,¹ are caused by electrostatic attractions, such as those between dipole and dipole, or induced dipole and induced dipole, and are responsible for liquefaction of gases at sufficiently low temperatures. The bonding discussed in this chapter has energies on the order of 2–10 kcal mol⁻¹ (9–40 kJ/mol⁻¹), which is intermediate between the bond orders given above, and produces clusters of molecules. Compounds will also be discussed in which portions of molecules are held together without any attractive forces at all.

3.A. HYDROGEN BONDING²

A *hydrogen bond* is less than a covalent bond, but it is an attractive force between a functional group A—H and an atom or group of atoms B in the same or a different molecule.³ With exceptions to be noted later, hydrogen bonds are *assumed to form only when A is oxygen, nitrogen, or fluorine and when B is oxygen, nitrogen, or fluorine*.⁴ The ability of functional groups to act as hydrogen-bond acids and bases can be obtained from either equilibrium constants for 1:1 hydrogen bonding or overall hydrogen-bond constants.⁴ There are so-called unconventional hydrogen bonds, particularly with organometallic complexes

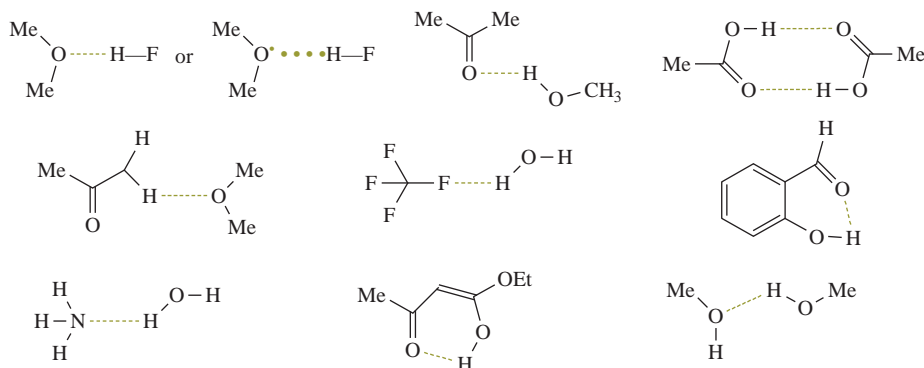
¹ For a theoretical treatment, see Becke, A.A.A.; Kannemann, F.O. *Can. J. Chem.* **2010**, 88, 1057.

² For a discussion of hydrogen bonding in organic synthesis, *Hydrogen Bonding in Organic Synthesis*, see Pihko, M. (Ed.), Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim, **2009**.

³ See Schuster, P.; Zundel, G.; Sandorfy, C. *The Hydrogen Bond*, 3 Vols., North Holland Publishing Co., Amsterdam, The Netherlands, **1976**. For a monograph, see Joesten, M.D.; Schaad, L.J. *Hydrogen Bonding*, Marcel Dekker, NY, **1974**. For reviews, see Meot-Ner, M. *Mol. Struct. Energ.* **1987**, 4, 71; Joesten, M.D. *J. Chem. Educ.* **1982**, 59, 362; Gur'yanova, E.N.; Gol'dshtein, I.P.; Perepelkova, T.I. *Russ. Chem. Rev.* **1976**, 45, 792; Kollman, P.A.; Allen, L.C. *Chem. Rev.* **1972**, 72, 283; Huggins, M.L. *Angew. Chem. Int. Ed.* **1971**, 10, 147; Rochester, C.H. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, pp. 327–392. See also, Hamilton, W.C.; Ibers, J.A. *Hydrogen Bonding in Solids*, W.A. Benjamin, NY, **1968**. Also see, Chen, J.; McAllister, M.A.; Lee, J. K.; Houk, K.N. *J. Org. Chem.* **1998**, 63, 4611.

⁴ See Abraham, M.H.; Platts, J.A. *J. Org. Chem.* **2001**, 66, 3484.

and transition metal or main group hydrides.⁵ This chapter will largely ignore such compounds. In normal hydrogen bonds, to oxygen or nitrogen, oxygen may be singly or doubly bonded and the nitrogen singly, doubly, or triply bonded. In structures, hydrogen bonds are usually represented by dotted or dashed lines, as shown in the following examples:



Hydrogen bonds can exist in solid⁶ and liquid phases, and in solution.⁷ The efficacy of many organic reactions that will be discussed in later chapters is due to the use of an aqueous media,⁸ which is due in part, to the hydrogen-bonding nature of such media.⁹ Even in the gas phase, compounds that form particularly strong hydrogen bonds may remain associated.¹⁰ Acetic acid, for example, exists in the gas phase as a dimer, except at very low pressures.¹¹ In the liquid phase and in solution, hydrogen bonds rapidly form and break. The mean lifetime of the $\text{NH}_3 \cdots \text{H}_2\text{O}$ bond is 2×10^{-12} s, for example.¹² Except for a few very strong hydrogen bonds¹³ (e.g., the $\text{FH} \cdots \text{F}^-$ bond) which has an energy of $\sim 50 \text{ kcal mol}^{-1}$ or 210 kJ mol^{-1} , the strongest hydrogen bonds are those connecting one carboxylic acid with another. The energies of these bonds are in the range of $6\text{--}8 \text{ kcal mol}^{-1}$ or $25\text{--}30 \text{ kJ mol}^{-1}$ (for carboxylic acids, this refers to the energy of each bond). In general, short contact hydrogen bonds between fluorine and HO or NH are rare.¹⁴ Other $\text{OH} \cdots \text{O}$ and $\text{NH} \cdots \text{N}$ bonds¹⁵ have energies of $3\text{--}6 \text{ kcal mol}^{-1}$ ($12\text{--}25 \text{ kJ mol}^{-1}$). The intramolecular $\text{O}=\text{H} \cdots \text{N}$ hydrogen bond in hydroxy-amines is also rather strong.¹⁶

⁵ Belkova, N.V.; Shubina, E.S.; Epstein, L.M. *Acc. Chem. Res.* **2005**, *38*, 624. For a review of hydrogen bonding in cluster ions, see Meot-Ner (Mautner), M. *Chem. Rev.* **2005**, *105*, 213.

⁶ Steiner, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 48. See also, Damodharan, L.; Pattabhi, V. *Tetrahedron Lett.* **2004**, *45*, 9427.

⁷ See Nakahara, M.; Wakai, C. *Chem. Lett.* **1992**, 809.

⁸ Li, C.-J.; Chen, T.-H. *Organic Reactions in Aqueous Media*, Wiley, NY, **1997**.

⁹ Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023.

¹⁰ See Curtiss, L.A.; Blander, M. *Chem. Rev.* **1988**, *88*, 827.

¹¹ For a review of hydrogen bonding in carboxylic acids and acid derivatives, see Hadži, D.; Detoni, S. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, **1979**, pp. 213–266.

¹² Emerson, M.T.; Grunwald, E.; Kaplan, M.L.; Kromhout, R.A. *J. Am. Chem. Soc.* **1960**, *82*, 6307.

¹³ For a review of very strong hydrogen bonding, see Emsley, J. *Chem. Soc. Rev.* **1980**, *9*, 91.

¹⁴ Howard, J.A.K.; Hoy, V.J.; O'Hagan, D.; Smith, G.T. *Tetrahedron* **1996**, *52*, 12613. For a discussion of the strength of such hydrogen bonds, see Perrin, C.L. *Acc. Chem. Res.* **2010**, *43*, 1550.

¹⁵ See Sorensen, J.B.; Lewin, A.H.; Bowen, J.P. *J. Org. Chem.* **2001**, *66*, 4105. Also see Ohshima, Y.; Sato, K.; Sumiyoshi, Y.; Endo, Y. *J. Am. Chem. Soc.* **2005**, *127*, 1108.

¹⁶ Grech, E.; Nowicka-Scheibe, J.; Olejnik, Z.; Lis, T.; Pawęka, Z.; Malarski, Z.; Sobczyk, L. *J. Chem. Soc., Perkin Trans. 2* **1996**, 343. See Steiner, T. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1315.

To a first approximation, the strength of a hydrogen bond will increase with increasing acidity of $A-H$ ¹⁷ and basicity of B , but the parallel is far from exact.¹⁸ A quantitative measure of the strengths of hydrogen bonds has been established, involving the use of an α scale to represent hydrogen-bond donor acidities and a β scale for hydrogen-bond acceptor basicities.¹⁹ The use of the β scale, along with another parameter (ξ), allows hydrogen-bond basicities to be related to proton-transfer basicities (pK values).²⁰ A database has been developed to locate all possible occurrences of bimolecular cyclic hydrogen-bond motifs in the Cambridge Structural Database,²¹ and donor–acceptor, as well as polarity parameters, have been calculated for hydrogen-bonding solvents.²² Bickelhaupt and co-workers²² has stated that hydrogen bonds ($X-H \cdots Y$) have significant covalent interactions that stem from donor–acceptor orbital interactions between the lone-pair electrons of Y and the empty σ^* acceptor orbital of $X-H$, so they are not predominantly electrostatic phenomena.

When two compounds whose molecules form hydrogen bonds with each other are both dissolved in water, the hydrogen bond between the two molecules is usually greatly weakened or completely removed.²³ This finding means that the molecules generally form hydrogen bonds with the water molecules (intermolecular) rather than with each other (intramolecular), presumably because the water molecules are present in such great numbers. In amides, the oxygen atom is the preferred site of protonation or complexation with water.²⁴ In the case of dicarboxylic acids, arguments have been presented that there is little or no evidence for strong hydrogen bonding in aqueous solution,²⁵ although other studies concluded that strong, intramolecular hydrogen bonding can exist in aqueous acetone solutions (0.31 mole-fraction water) of hydrogen maleate and hydrogen *cis*-cyclohexane-1,2-dicarboxylate.²⁶

Many studies have been made of the geometry of hydrogen bonds,²⁷ and in most (though not all) cases the evidence shows that the hydrogen is on or near the straight line

¹⁷ For a comparison of the relative strengths of $OH \cdots Cl$ versus $OH \cdots F$ hydrogen bonds, see Caminati, W.; Melandri, S.; Maris, A.; Paolo Ottaviani, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2438.

¹⁸ For reviews of the relationship between hydrogen bond strength and acid-base properties, see Pogorelyi, V.K.; Vishnyakova, T.B. *Russ. Chem. Rev.* **1984**, *53*, 1154; Epshtein, L.M. *Russ. Chem. Rev.* **1979**, *48*, 854.

¹⁹ See Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Taft, R.W. *Chem. Br.* **1986**, 551; Kamlet, M.J.; Abboud, J.M.; Abraham, M.H.; Taft, R.W. *J. Org. Chem.* **1983**, *48*, 2877. For a criticism of the β scale, see Laurence, C.; Nicolet, P.; Helbert, M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1081. See also, Roussel, C.; Gentric, E.; Sraidi, K.; Lauransan, J.; Guihéneuf, G.; Kamlet, M.J.; Taft, R.W. *J. Org. Chem.* **1988**, *53*, 1545; Abraham, M.H.; Grellier, P.L.; Prior, D.V.; Morris, J.J.; Taylor, P.J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 521. Deuterium exchange has been used as an indicator of hydrogen-bond donors and acceptors: see Strobel, T.A.; Hester, K.C.; Sloan Jr., E.D.; Koh, C.A. *J. Am. Chem. Soc.* **2007**, *129*, 9544.

²⁰ Kamlet, M.J.; Gal, J.; Maria, P.; Taft, R.W. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1583.

²¹ Allen, F.H.; Raithby, P.R.; Shields, G.P.; Taylor, R. *Chem. Commun.* **1998**, 1043.

²² Joerg, S.; Drago, R.S.; Adams, J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2431. See Guerra, C.F.; van der Wijst, T.; Bickelhaupt, F.M. *Chem. Eur. J.* **2006**, *12*, 3032; Guerra, C.F.; Zijlstra, H.; Paragi, G.T.; Bickelhaupt, F.M. *Chem. Eur. J.* **2011**, *17*, 12612.

²³ Stahl, N.; Jencks, W.P. *J. Am. Chem. Soc.* **1986**, *108*, 4196.

²⁴ Scheiner, S.; Wang, L. *J. Am. Chem. Soc.* **1993**, *115*, 1958.

²⁵ Perrin, C. L. *Annu. Rev. Phys. Org. Chem.* **1997**, *48*, 511.

²⁶ Lin, J.; Frey, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 11258.

²⁷ Etter, M.C. *Acc. Chem. Res.* **1990**, *23*, 120; Taylor, R.; Kennard, O. *Acc. Chem. Res.* **1984**, *17*, 320.

formed by A and B.²⁸ This is true both in the solid state (where X-ray crystallography and neutron diffraction have been used to determine structures),²⁹ and in solution.³⁰ It is significant that the vast majority of intramolecular hydrogen bonding occurs where *six-membered rings* (counting the hydrogen as one of the six) can be formed, in which linearity of the hydrogen bond is geometrically favorable. Intramolecular hydrogen bonding is much rarer in five-membered rings, where linearity is usually not favored (although it is known). A novel nine-membered intramolecular hydrogen bond has been reported.³¹

In certain cases X-ray crystallography has shown that a single H—A can form simultaneous hydrogen bonds with two B atoms (*bifurcated* or *three-center hydrogen bonds*). An example is an adduct (**1**) formed from pentane-2,4-dione in its enol form (Sec. 2.N.i) and diethylamine. In **1**, the O—H hydrogen simultaneously bonds³² to an O and an N, where the N—H hydrogen forms a hydrogen bond with the O of another pentane-2,4-dione molecule.³³ On the other hand, the B atom (in this case oxygen) forms simultaneous hydrogen bonds with two A···H hydrogens in the adduct (**2**) formed from 1,8-biphenylenediol and hexamethylphosphoramide (HMPA),³⁴ Another such case is found in methyl hydrazine carboxylate (**3**).³⁵ Except for the special case of FH···F[−] bonds (see above), the hydrogen is not equidistant between A and B. For example, the O—H distance in ice is 0.97 Å, while the H···O distance is 1.79 Å.³⁶ A theoretical study of the vinyl alcohol–vinyl alcoholate system (i.e., an enol–enolate anion system) concluded the hydrogen bonding is strong but asymmetric.³⁷ The hydrogen bond in the enol of malonaldehyde, in organic solvents, is asymmetric with the hydrogen atom closer to the basic oxygen atom.³⁸ There is evidence, however, that symmetrical hydrogen bonds to carboxylates should be regarded as two-center rather than three-center hydrogen bonds since the criteria traditionally used to infer three-center hydrogen bonding are inadequate for carboxylates.³⁹ There is also an example of cooperative hydrogen bonding [O—H···C≡C—H···Ph] in crystalline 2-ethynyl-6,8-diphenyl-7*H*-benzocyclohepten-7-ol (**4**).⁴⁰ Related to this discussion is the work that showed the hydrogen bond radii for OH, NH, and acidic CH groups to be 0.60 ± 0.15 , 0.76 ± 0.15 , and 1.10 ± 0.20 Å, respectively.⁴¹

²⁸ Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, **1985**, pp. 148–153.

²⁹ A statistical analysis of X-ray crystallographic data has shown that most hydrogen bonds in crystals are nonlinear by ~ 10 – 15° : Kroon, J.; Kanters, J.A.; van Duijneveldt-van de Rijdt, J.G.C.M.; van Duijneveldt, F.B.; Vliegthart, J.A. *J. Mol. Struct.* **1975**, *24*, 109. See also, Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761; **1984**, *106*, 244.

³⁰ For a discussion of the symmetry of hydrogen bonds in solution, see Perrin, C.L. *Pure Appl. Chem.* **2009**, *81*, 571. For reviews of a different aspect of hydrogen bond geometry, see Legon, A.C.; Millen, D.J. *Chem. Soc. Rev.* **1987**, *16*, 467, *Acc. Chem. Res.* **1987**, *20*, 39.

³¹ Yoshimi, Y.; Maeda, H.; Sugimoto, A.; Mizuno, K. *Tetrahedron Lett.* **2001**, *42*, 2341.

³² Emsley, J.; Freeman, N.J.; Parker, R.J.; Dawes, H.M.; Hursthouse, M.B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 471.

³³ For some other three-center hydrogen bonds, see Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1984**, *106*, 244; Jeffrey, G.A.; Mitra, J. *J. Am. Chem. Soc.* **1984**, *106*, 5546; Staab, H.A.; Elbl, K.; Krieger, C. *Tetrahedron Lett.* **1986**, *27*, 5719.

³⁴ Hine, J.; Hahn, S.; Miles, D.E. *J. Org. Chem.* **1986**, *51*, 577.

³⁵ Caminati, W.; Fantoni, A.C.; Schäfer, L.; Siam, K.; Van Alsenoy, C. *J. Am. Chem. Soc.* **1986**, *108*, 4364.

³⁶ Pimentel, G.C.; McClellan, A.L. *The Hydrogen Bond*, W.H. Freeman, San Francisco, **1960**, p. 260.

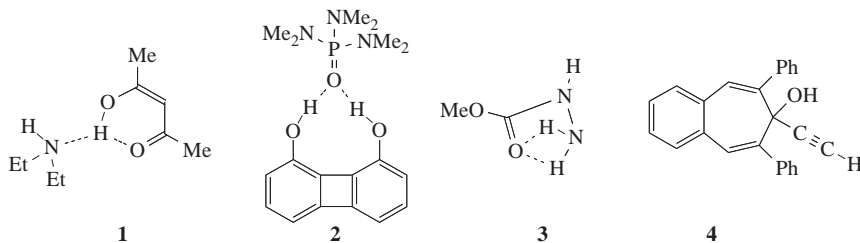
³⁷ Chandra, A.K.; Zeegers-Huyskens, T. *J. Org. Chem.* **2003**, *68*, 3618.

³⁸ Perrin, C.L.; Kim, Y.-J. *J. Am. Chem. Soc.* **1998**, *120*, 12641.

³⁹ Görbitz, C.H.; Etter, M.C. *J. Chem. Soc., Perkin Trans. 2* **1992**, 131.

⁴⁰ Steiner, T.; Tamm, M.; Lutz, B.; van der Maas, J. *Chem. Commun.* **1996**, 1127.

⁴¹ Lakshmi, B.; Samuelson, A.G.; Jovan Jose, K.V.; Gadre, S.R.; Arunan, E. *New J. Chem.* **2005**, *29*, 371.



Hydrogen bonding has been detected in many ways, including measurements of dipole moments, solubility behavior, freezing-point lowering, and heats of mixing, but one important way is by the effect of the hydrogen bond on IR spectroscopy.⁴² The IR frequencies of functional groups (e.g., O—H or C=O) are shifted when the group is hydrogen bonded. Hydrogen bonding always moves the peak toward lower frequencies, for both the A—H and the B groups, though the shift is greater for the former. For example, a free OH group of an alcohol or phenol absorbs at $\sim 3590\text{--}3650\text{ cm}^{-1}$, and a hydrogen-bonded OH group is found $\sim 50\text{--}100\text{ cm}^{-1}$ lower.⁴³ In many cases, in dilute solution, there is partial hydrogen bonding, that is, some OH groups are free and some are hydrogen bonded. In such cases, two peaks appear.

Infrared spectroscopy can also distinguish between inter- and intramolecular hydrogen bonding, since intermolecular peaks are intensified by an increase in concentration while intramolecular peaks are unaffected. Other types of spectra that have been used for the detection of hydrogen bonding include Raman, electronic,⁴⁴ and NMR.⁴⁵ Since hydrogen bonding involves a rapid movement of protons from one atom to another, NMR records an average value that is often broadened. Hydrogen bonding can be detected because it usually produces a chemical shift to a lower field. For example, carboxylic acid–carboxylate systems arising from either mono- or diacids generally exhibit a downfield resonance (16–22 ppm), which indicates “strong” hydrogen bonding in anhydrous, aprotic solvents.⁴⁶ Hydrogen bonding changes with temperature and concentration, and comparison of spectra taken under different conditions also serves to detect and measure it. As with IR spectra, intramolecular hydrogen bonding in the NMR can be distinguished from intermolecular by its constancy when the concentration is varied. The spin–spin coupling constant across a hydrogen bond, obtained by NMR studies, has been shown to provide a “fingerprint” for hydrogen-bond type.⁴⁷ Indeed, the determination of $^1J_{\text{CH}}$ correlates with the strength of the hydrogen bonds formed by an alcohol.⁴⁸

⁴² See Symons, M.C.R. *Chem. Soc. Rev.* **1983**, 12, 1; Egorochkin, A.N.; Skobeleva, S.E. *Russ. Chem. Rev.* **1979**, 48, 1198; Aaron, H.S. *Top. Stereochem.* **1979**, 11, 1. For a review of the use of rotational spectra to study hydrogen bonding, see Legon, A.C. *Chem. Soc. Rev.* **1990**, 19, 197.

⁴³ Tichy, M. *Adv. Org. Chem.* **1965**, 5, 115 contains a lengthy table of free and intramolecularly hydrogen-bonding peaks. For a discussion of the role of methyl groups in the formation of hydrogen bonds in dimethyl sulfide (DMS)–methanol mixtures, see Li, Q.; Wu, G.; Yu, Z. *J. Am. Chem. Soc.* **2006**, 128, 1438.

⁴⁴ See Lees, W.A.; Burawoy, A. *Tetrahedron* **1963**, 19, 419.

⁴⁵ See Davis, Jr., J.C.; Deb, K.K. *Adv. Magn. Reson.* **1970**, 4, 201. Also see, Kumar, G.A.; McAllister, M.A. *J. Org. Chem.* **1998**, 63, 6968.

⁴⁶ Bruck, A.; McCoy, L.L.; Kilway, K.V. *Org. Lett.* **2000**, 2, 2007. For a discussion of the effect of solvents on hydrogen bonding, see Cook, J.L.; Hunter, C.A.; Low, C.M.R.; Perez-Velasco, A.; Vinter, J.G. *Angew. Chem. Int. Ed.* **2007**, 46, 3706.

⁴⁷ Del Bene, J.E.; Perera, S.A.; Bartlett, R.J. *J. Am. Chem. Soc.* **2000**, 122, 3560.

⁴⁸ Maiti, N.C.; Zhu, Y.; Carmichael, I.; Serianni, A.S.; Anderson, V.E. *J. Org. Chem.* **2006**, 71, 2878.

Hydrogen bonds are important because of the effects they have on the properties of compounds, among them:

1. Intermolecular hydrogen bonding raises boiling points and frequently melting points.
2. If hydrogen bonding is possible between solute and solvent, this greatly increases solubility and often results in large or even infinite solubility where none would otherwise be expected.
3. Hydrogen bonding causes lack of ideality in gas and solution laws.
4. As previously mentioned, hydrogen bonding changes spectral absorption positions.
5. Hydrogen bonding, especially the intramolecular variety, changes many chemical properties. For example, it is responsible for the large amount of enol present in certain tautomeric equilibria (see Sec. 2.N). Also, by influencing the conformation of molecules (see Chapter 4), it often plays a significant role in determining reaction rates.⁴⁹ Hydrogen bonding is also important in maintaining the 3D structures of protein and nucleic acid molecules.

Besides oxygen, nitrogen, and fluorine, there is evidence that weaker hydrogen bonding exists in other systems.⁵⁰ Although many searches have been made for hydrogen bonding where A is carbon,⁵¹ only three types of C—H bonds have been found that are acidic enough to form weak hydrogen bonds.⁵² These are found in terminal alkynes ($\text{RC}\equiv\text{CH}$),⁵³ chloroform and some other halogenated alkanes, and HCN. Sterically unhindered C—H groups (CHCl_3 , CH_2Cl_2 , $\text{RC}\equiv\text{CH}$) form short contact hydrogen bonds with carbonyl acceptors, where there is a significant preference for coordination with the conventional carbonyl lone-pair direction.⁵⁴ Weak hydrogen bonds are formed by compounds containing S—H bonds.⁵⁵ There has been much speculation regarding other possibilities for B. There is evidence that Cl can form weak hydrogen bonds,⁵⁶ but Br and I form very weak bonds if at all.⁵⁷ However, the *ions* Cl^- , Br^- , and I^- form hydrogen bonds that are much stronger than those of the covalently bonded atoms.⁵⁸ As noted above, the $\text{FH}\cdots\text{F}^-$ bond is especially strong. In this case, the

⁴⁹ For reviews of the effect of hydrogen bonding on reactivity, see Hibbert, F.; Emsley, J. *Adv. Phys. Org. Chem.* **1990**, 26, 255; Sadekov, I.D.; Minkin, V.I.; Lutsikii, A.E. *Russ. Chem. Rev.* **1970**, 39, 179.

⁵⁰ For a review, see Pogorelyi, V.K. *Russ. Chem. Rev.* **1977**, 46, 316.

⁵¹ See Green, R.D. *Hydrogen Bonding by C—H Groups*, Wiley, NY, **1974**. See also, Nakai, Y.; Inoue, K.; Yamamoto, G.; Ōki, M. *Bull. Chem. Soc. Jpn.* **1989**, 62, 2923; Seiler, P.; Dunitz, J.D. *Helv. Chim. Acta* **1989**, 72, 1125.

⁵² For a theoretical study of weak hydrogen-bonds, see Calhorda, M.J. *Chem. Commun.* **2000**, 801.

⁵³ For a review, see Hopkinson, A.C., in Patai, S. *The Chemistry of the Carbon—Carbon Triple Bond*, pt. 1, Wiley, NY, **1978**, pp. 75–136. See also, DeLaat, A.M.; Ault, B.S. *J. Am. Chem. Soc.* **1987**, 109, 4232.

⁵⁴ Streiner, T.; Kanters, J.A.; Kroon, J. *Chem. Commun.* **1996**, 1277.

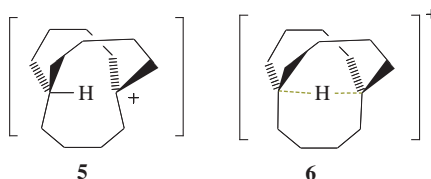
⁵⁵ See Zuika, I.V.; Bankovskii, Yu.A. *Russ. Chem. Rev.* **1973**, 42, 22; Crampton, M.R. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, 1974, pp. 379–396; Pogorelyi, V.K. *Russ. Chem. Rev.* **1977**, 46, 316.

⁵⁶ See Smith, J.W. in Patai, S. *The Chemistry of the Carbon—Halogen Bond*, pt. 1; Wiley, NY, **1973**, pp. 265–300. See also, Bastiansen, O.; Fernholt, L.; Hedberg, K.; Seip, R. *J. Am. Chem. Soc.* **1985**, 107, 7836.

⁵⁷ Fujimoto, E.; Takeoka, Y.; Kozima, K. *Bull. Chem. Soc. Jpn.* **1970**, 43, 991; Azrak, R.G.; Wilson, E.B. *J. Chem. Phys.* **1970**, 52, 5299.

⁵⁸ Fujiwara, F.Y.; Martin, J.S. *J. Am. Chem. Soc.* **1974**, 96, 7625; French, M.A.; Ikuta, S.; Kebarle, P. *Can. J. Chem.* **1982**, 60, 1907.

hydrogen is equidistant from the fluorine atoms.⁵⁹ Similarly, a sulfur atom⁵⁵ can be the B component ($A \cdots B$) in weak hydrogen bonds,⁶⁰ but the ^-SH ion forms much stronger bonds.⁶¹ There are theoretical studies of weak hydrogen bonding.⁶² Hydrogen bonding has been directly observed (by NMR and IR) between a negatively charged carbon (see carbanions in Chapter 5) and an OH group in the same molecule.⁶³ Isocyanides ($R-N \equiv C^-$) constitute another type of molecule in which carbon is the B component that forms a rather strong hydrogen bond.⁶⁴ There is evidence that double and triple bonds, aromatic rings,⁶⁵ and even cyclopropane rings⁶⁶ may be the B component of hydrogen bonds, but these bonds are very weak. An interesting case is that of the *in*-bicyclo[4.4.4]-1-tetradecyl cation **5** (see out-in isomerism, Sec. 4.L The NMR and IR spectra show that the actual structure of this ion is **6**, in which both the A and the B component of the hydrogen bond is a carbon.⁶⁷ These are sometimes called 3-center-2-electron $C-H-C$ bonds.⁶⁸ A technique called generalized population analysis has been developed to study this type of multicenter bonding.⁶⁹



A weak ($\sim 1.5 \text{ kcal mol}^{-1}$, 6.3 kJ mol^{-1}) and rare $C-H \cdots O=C$ hydrogen bond has been reported in a class of compounds known as a [6]semirubin (a dipyrinone).⁷⁰ There is also evidence for a $C-H \cdots N/CH \cdots OH$ bond in the crystal structures of α,β -unsaturated ketones carrying a terminal pyridine subunit,⁷¹ and for $R_3N^+-C-H \cdots O=C$ hydrogen bonding.⁷²

Deuterium also forms hydrogen bonds; in some systems these seem to be stronger than the corresponding hydrogen bonds; in others, weaker.⁷³ Weak hydrogen bonds can be formed between a π bond (from both alkenes and aromatic compounds) and an appropriate hydrogen. For example, IR data in dilute dichloromethane suggests that the predominant

⁵⁹ In a few cases, the presence of an unsymmetrical cation causes the hydrogen to be closer to one fluorine than to the other: Williams, J.M.; Schneemeyer, L.F. *J. Am. Chem. Soc.* **1973**, 95, 5780.

⁶⁰ Schaefer, T.; McKinnon, D.M.; Sebastian, R.; Peeling, J.; Penner, G.H.; Veregin, R.P. *Can. J. Chem.* **1987**, 65, 908; Marstokk, K.; Møllendal, H.; Uggerud, E. *Acta Chem. Scand.* **1989**, 43, 26.

⁶¹ McDaniel, D.H.; Evans, W.G. *Inorg. Chem.* **1966**, 5, 2180; Sabin, J.R. *J. Chem. Phys.* **1971**, 54, 4675.

⁶² Calhorda, M.J. *Chem. Commun.* **2000**, 801.

⁶³ Ahlberg, P.; Davidsson, O.; Johnsson, B.; McEwen, I.; Rönnqvist, M. *Bull. Soc. Chim. Fr.* **1988**, 177.

⁶⁴ Allerhand, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1963**, 85, 866.

⁶⁵ For example, see Bakke, J.M.; Chadwick, D.J. *Acta Chem. Scand. Ser. B* **1988**, 42, 223; Atwood, J.L.; Hamada, F.; Robinson, K.D.; Orr, G.W.; Vincent, R.L. *Nature* **1991**, 349, 683.

⁶⁶ Yoshida, Z.; Ishibe, N.; Kusumoto, H. *J. Am. Chem. Soc.* **1969**, 91, 2279.

⁶⁷ McMurphy, J.E.; Lectka, T.; Hodge, C.N. *J. Am. Chem. Soc.* **1989**, 111, 8867. See also, Sorensen, T.S.; Whitworth, S.M. *J. Am. Chem. Soc.* **1990**, 112, 8135.

⁶⁸ McMurphy, J.E.; Lectka, T. *Accts. Chem. Res.* **1992**, 25, 47.

⁶⁹ Ponec, R.; Yuzhakov, G.; Tantillo, D. J. *J. Org. Chem.* **2004**, 69, 2992.

⁷⁰ Huggins, M.T.; Lightner, D.A. *J. Org. Chem.* **2001**, 66, 8402.

⁷¹ Mazik, M.; Bläser, D.; Boese, R. *Tetrahedron* **2001**, 57, 5791.

⁷² Cannizzaro, C.E.; Houk, K.N. *J. Am. Chem. Soc.* **2002**, 124, 7163.

⁷³ Cummings, D.L.; Wood, J.L. *J. Mol. Struct.* **1974**, 23, 103.

bonds.⁷⁶

3.B. π - π INTERACTIONS

and exchange-repulsion contributions are all significant to the overall binding energies.⁸⁰



⁷⁴ Gallo, E.A.; Gelman, S.H. *Tetrahedron Lett.* **1992**, 33, 7485.

⁷⁵ Adams, H.; Harris, K.D.M.; Hembury, G.A.; Hunter, C.A.; Livingstone, D.; McCabe, J.F. *Chem. Commun.* **1996**, 2531. See Steiner, T.; Starikov, E.B.; Tamm, M. *J. Chem. Soc., Perkin Trans. 2* **1996**.

⁷⁶ Allen, F.H.; Howard, J.A.K.; Hoy, V.J.; Desiraju, G.R.; Reddy, D.S.; Wilson, C.C. *J. Am. Chem. Soc.* **1996**, *118*, 4081.

⁷⁷ Tsuzuki, S.; Lüthi, H.P. *J. Chem. Phys.* **2001**, *114*, 3949; Arunan, E.; Gutowsky, H.S. *J. Chem. Phys.* **1993**, *98*, 4294; Felker, P.M.; Maxton, P.M.; Schaeffer, M.W. *Chem. Rev.* **1994**, *94*, 1787; Venturo, V.A.; Felker, P.M. *J. Chem. Phys.* **1993**, *99*, 748; Tsuzuki, S.; Honda, K.; Uchimar, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104; Hobza, P.; Jureceka, P. *J. Am. Chem. Soc.* **2003**, *125*, 15608.

⁷⁸ Meyer, E.A.; Castellano, R.K.; Diederich, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1210.

⁷⁹ Sinnokrot, M.O.; Valeev, E.F.; Sherrill, C.D. *J. Am. Chem. Soc.* **2002**, *124*, 10887.

⁸⁰ Sinnokrot, M.O.; Sherrill, C.D. *J. Am. Chem. Soc.* **2004**, *126*, 7690.

The π electrons of aromatic rings can interact with charged species, yielding strong cation– π interactions that are dominated by electrostatic and polarization effects.⁸¹ An interaction with CH units is also possible. For CH– π interactions in both alkyl- and aryl-based model systems, dispersion effects dominate the interaction, but the electrostatics term is also relevant for aryl CH– π interactions.⁸²

Detection of π – π interactions has largely relied on NMR based techniques (e.g., chemical shifts variations),⁸³ and Nuclear Overhauser Effect Spectroscopy (NOESY) or Rotating-Frame NOE Spectroscopy (ROESY).⁸⁴ Diffusion-ordered NMR spectroscopy (DOSY) has also been used to detect π – π stacked complexes.⁸⁵

3.C. ADDITION COMPOUNDS

When the reaction of two compounds results in a product that contains all the mass of the two compounds, the product is called an *addition compound*. There are several kinds. The remainder of this chapter will discuss addition compounds in which the molecules of the starting materials remain more or less intact and weak bonds hold two or more molecules together. There are four broad classes: electron donor–acceptor complexes, complexes formed by crown ethers and similar compounds, inclusion compounds, and catenanes.

3.C.i. Electron Donor–Acceptor Complexes⁸⁶

In *electron donor–acceptor (EDA) complexes*,⁸⁷ there is always a donor and an acceptor molecule. The donor may donate an unshared pair (an n donor) or a pair of electrons in a π orbital of a double bond or aromatic system (a π donor). The electronic spectrum constitutes a good test for the presence of an EDA complex. These complexes generally exhibit a spectrum (called a *charge-transfer spectrum*) that is not the same as the sum of the spectra of the two individual molecules.⁸⁸ Because the first excited state of the

⁸¹ Lindeman, S.V.; Kosynkin, D.; Kochi, J.K. *J. Am. Chem. Soc.* **1998**, *120*, 13268; Ma, J.C.; Dougherty, D.A. *Chem. Rev.* **1997**, *97*, 1303; Dougherty, D.A. *Science* **1996**, *271*, 163; Cubero, E.; Luque, F.J.; Orozco, M. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 5976.

⁸² Ribas, J.; Cubero, E.; Luque, F.J.; Orozco, M. *J. Org. Chem.* **2002**, *67*, 7057.

⁸³ Petersen, S.B.; Led, J.J.; Johnston, E.R.; Grant, D.M. *J. Am. Chem. Soc.* **1982**, *104*, 5007.

⁸⁴ Wakita, M.; Kuroda, Y.; Fujiwara, Y.; Nakagawa, T. *Chem. Phys. Lipids* **1992**, *62*, 45.

⁸⁵ Viel, S.; Mannina, L.; Segre, A. *Tetrahedron Lett.* **2002**, *43*, 2515. See also, Ribas, J.; Cubero, E.; Luque, F.J.; Orozco, M. *J. Org. Chem.* **2002**, *67*, 7057. For a discussion of substituent effects on aromatic stacking interactions, see Cockcroft, S.L.; Perkins, J.; Zonta, C.; Adams, H.; Spey, S.E.; Low, C.M.R.; Vinter, J.G.; Lawson, K.R.; Urch, C.J.; Hunter, C.A. *Org. Biomol. Chem.* **2007**, *5*, 1062.

⁸⁶ Foster, R. *Organic Charge-Transfer Complexes*, Academic Press, NY, **1969**; Mulliken, R.S.; Person, W.B. *Molecular Complexes*, Wiley, NY, **1969**; Rose, J. *Molecular Complexes*, Pergamon, Elmsford, NY, **1967**; Poleshchuk, O.Kh.; Maksyutin, Yu.K. *Russ. Chem. Rev.* **1976**, *45*, 1077; Banthorpe, D.V. *Chem. Rev.* **1970**, *70*, 295; Kosower, E.M. *Prog. Phys. Org. Chem.* **1965**, *3*, 81; Foster, R. *Chem. Br.* **1976**, *12*, 18.

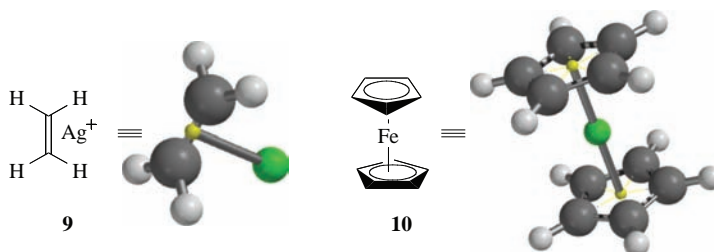
⁸⁷ These have often been called *charge-transfer complexes*, but this term implies that the bonding involves charge transfer, which is not always the case, so that the more neutral name EDA complex is preferable. See Mulliken, R.S.; Person, W.B. *J. Am. Chem. Soc.* **1969**, *91*, 3409.

⁸⁸ Also see Bentley, M.D.; Dewar, M.J.S. *Tetrahedron Lett.* **1967**, 5043.

complex is relatively close in energy to the ground state, there is usually a peak in the visible or near-UV region, and EDA complexes are often colored. Many EDA complexes are unstable and exist only in solutions in equilibrium with their components, but others are stable solids. In most EDA complexes, the donor and acceptor molecules are present in an integral ratio, most often 1:1, but complexes with nonintegral ratios are also known. There are several types of acceptor molecules; complexes formed by two of them will be discussed.

1. *Complexes in which the Acceptor is a Metal Ion and the Donor is an Alkene or an Aromatic Ring.*

The n donors do not give EDA complexes with metal ions, but form covalent bonds instead).⁸⁹ Many metal ions form complexes with alkenes, dienes (usually conjugated, but not always), alkynes, and aromatic rings that are often stable solids. The donor (or ligand) molecules in these complexes are classified by the prefix *hapto*⁹⁰ and/or the descriptor η^n (the Greek letter *eta*), where n indicates how many atoms the ligand uses to bond with the metal.⁹¹



The generally accepted picture of the bonding in these complexes,⁹² first proposed by Dewar,⁹³ can be illustrated by the ethylene complex with silver (**9**), in which the alkene unit forms an η^2 -complex with the silver ion (the alkene functions as a 2-electron donating ligand to the metal). There is evidence of π -complexation of Na^+ by $\text{C}=\text{C}$.⁹⁴ In the case of the silver complex, the bond is not from one atom of the $\text{C}=\text{C}$ unit to the silver ion, but from the π center (two electrons are transferred from the alkene to the metal ion). Ethene has two π -electrons and is a dihapto or η^2 ligand, as are other simple alkenes. Similarly, benzene has six π electrons and is a hexahapto or η^6 ligand. Ferrocene (**10**) is an

⁸⁹ See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed, University Science Books, Mill Valley, CA, **1987**; Alper, H. *Transition Metal Organometallics in Organic Synthesis*, 2 Vols., Academic Press, NY, **1976**, **1978**. For general reviews, see Churchill, M.R.; Mason, R. *Adv. Organomet. Chem.* **1967**, 5, 93; Cais, M. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, **1964**, pp. 335–385; Nakamura, A. *J. Organomet. Chem.* **1990**, 400, 35; Bennett, M.A.; Schwemlein, H.P. *Angew. Chem. Int. Ed.* **1989**, 28, 1296; metals-pentadienyl ions, Powell, P. *Adv. Organomet. Chem.* **1986**, 26, 125; complexes of main group metals. For a list of review articles on this subject, see Bruce, M.I. *Adv. Organomet. Chem.* **1972**, 10, 273, pp. 317–321.

⁹⁰ For a discussion of how this system originated, see Cotton, F.A. *J. Organomet. Chem.* **1975**, 100, 29.

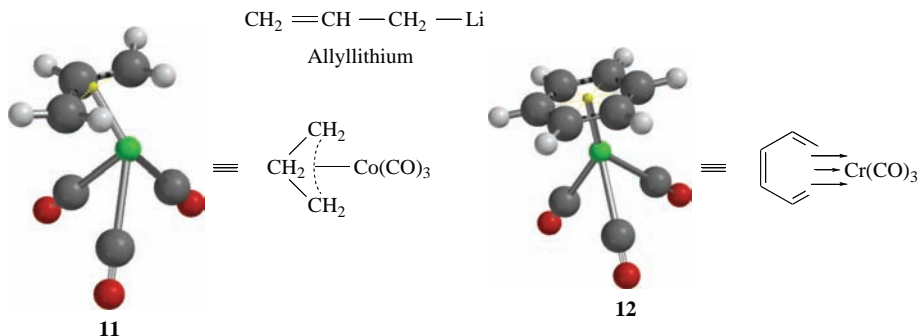
⁹¹ Another prefix used for complexes is μ (mu), which indicates that the ligand bridges two metal atoms.

⁹² See Pearson, A.J. *Metallo-organic Chemistry* Wiley, NY, **1985**; Ittel, S.D.; Ibers, J.A. *Adv. Organomet. Chem.* **1976**, 14, 33; Hartley, F.R. *Chem. Rev.* **1973**, 73, 163; *Angew. Chem. Int. Ed.* **1972**, 11, 596.

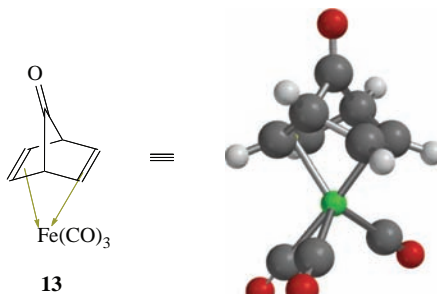
⁹³ Dewar, M.J.S. *Bull. Soc. Chim. Fr.* **1951**, 18, C79.

⁹⁴ Hu, J.; Gokel, G.W.; Barbour, L.J. *Chem. Commun.* **2001**, 1858.

example of a *metallocene*, with two cyclopentadienyl ligands (each is a five-electron donor or an η^5 ligand), and ferrocene is properly called bis(η^5 -cyclopentadienyl)iron(II). This system can be extended to compounds in which only a single σ bond connects the organic group to the metal, (e.g., $\text{C}_6\text{H}_5\text{—Li}$ a monohapto or η^1 ligand), and to complexes in which the organic group is an ion, (π -allyl complexes, e.g., **11**), in which the allyl ligand is trihapto or η^3 . Note that in a compound such as allyllithium, where a σ bond connects the carbon to the metal, the allyl group is referred to as monohapto or η^1 .



As mentioned, benzene is an η^6 ligand that forms complexes with silver and other metals.⁹⁵ When the metal involved has a coordination number > 1 , more than one donor molecule (ligand) participates. The CO group is a common ligand (a two-electron donating or η^2 ligand), and in metal complexes the CO group is classified as a metal carbonyl. Benzenechromium tricarbonyl (**12**) is a stable compound⁹⁶ that illustrates both benzene and carbonyl ligands. Three arrows are shown to represent the six-electron donation (an η^6 ligand), but the accompanying model gives a clearer picture of the bonding. Cyclooctatetraene is an eight-electron donating or η^8 ligand that also forms complexes with metals. Metallocenes (e.g., **10**) may be considered a special case of this type of complex, although the bonding in metallocenes is much stronger.



⁹⁵ See Zeiss, H.; Wheatley, P.J.; Winkler, H.J.S. *Benzenoid Metal Complexes*, Ronald Press, NY, **1966**.

⁹⁶ Nicholls, B.; Whiting, M.C. *J. Chem. Soc.* **1959**, 551. For reviews of arene-transition metal complexes, see Uemura, M. *Adv. Met.-Org. Chem.* **1991**, 2, 195; Silverthorn, W.E. *Adv. Organomet. Chem.* **1975**, 13, 47.

In a number of cases, alkenes that are too unstable to be isolated as discrete molecules have been isolated in the form of their metal complexes. An example is norbornadienone, which was isolated as its iron–tricarbonyl complex (**13**),⁹⁷ where the norbornadiene unit is an η^4 ligand, and each of the carbonyl units are η^2 ligands. The free dienone spontaneously decomposes to carbon monoxide and benzene (see Reaction 17–28).

2. Complexes in Which the Acceptor Is an Organic Molecule.

Picric acid (2,4,6-trinitrophenol) and similar polynitro compounds are the most important of these.⁹⁸ Picric acid forms addition compounds with many aromatic hydrocarbons, aromatic amines, aliphatic amines, alkenes, and other compounds. These addition compounds are usually solids that have definite melting points and have been used as derivatives of the compounds in question. They are called picrates, and are addition compounds and not salts of picric acids. Unfortunately, the actual salts of picric acid are also called picrates. Similar complexes are formed between phenols and quinones (quinhydrone).⁹⁹ Alkenes that contain electron-withdrawing substituents also act as acceptor molecules, as do carbon tetrahalides¹⁰⁰ and certain anhydrides.¹⁰¹ A particularly strong alkene acceptor is tetracyanoethylene.¹⁰²

The bonding in these cases is more difficult to explain than in the previous case, and indeed no truly satisfactory explanation is available.¹⁰³ The difficulty is that the donor has a pair of electrons to contribute (both n donors and π donors are found here), but the acceptor does not have a vacant orbital. Simple attraction of the dipole–induced-dipole type accounts for some of the bonding,¹⁰⁴ but is too weak to explain the bonding in all cases.¹⁰⁵ Nitromethane, with about the same dipole moment as nitrobenzene, is an example of a molecule that forms much weaker complexes. Some other type of bonding clearly must also be present in many EDA complexes. The exact nature of this bonding, called *charge-transfer bonding*, is not well understood, but it presumably involves some kind of donor–acceptor interaction.

⁹⁷ Landesberg, J.M.; Sieczkowski, J. *J. Am. Chem. Soc.* **1971**, 93, 972.

⁹⁸ See Parini, V.P. *Russ. Chem. Rev.* **1962**, 31, 408; for a review of complexes in which the acceptor is an organic cation, see Kampar, V.E. *Russ. Chem. Rev.* **1982**, 51, 107; also see, Ref. 86.

⁹⁹ For a review of quinone complexes, see Foster, R.; Foreman, M.I. in Patai, S. *The Chemistry of the Quinonoid Compounds*, pt. 1, Wiley, NY, **1974**, pp. 257–333.

¹⁰⁰ See Blackstock, S.C.; Lorand, J.P.; Kochi, J.K. *J. Org. Chem.* **1987**, 52, 1451.

¹⁰¹ See Foster, R. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, **1979**, pp. 175–212.

¹⁰² See Melby, L.R. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 639–669. See also, Fatiadi, A.J. *Synthesis* **1987**, 959.

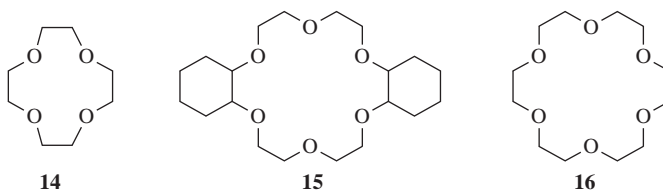
¹⁰³ For reviews, see Bender, C.J. *Chem. Soc. Rev.* **1986**, 15, 475; Kampar, E.; Neilands, O. *Russ. Chem. Rev.* **1986**, 55, 334; Bent, H.A. *Chem. Rev.* **1968**, 68, 587.

¹⁰⁴ See, for example, Le Fevre, R.J.W.; Radford, D.V.; Stiles, P.J. *J. Chem. Soc. B* **1968**, 1297.

¹⁰⁵ Mulliken, R.S.; Person, W.B. *J. Am. Chem. Soc.* **1969**, 91, 3409.

3.C.ii Crown Ether Complexes and Cryptates¹⁰⁶

Crown ethers are large-ring compounds that contain several oxygen atoms, usually in a regular pattern. Examples are 12-crown-4 (**14**; where 12 is the size of the ring and 4 represents the number of coordinating atoms, here oxygen),¹⁰⁷ dicyclohexano-18-crown-6 (**15**), and 15-crown-5 (**16**). These compounds have the property¹⁰⁸ of forming complexes with positive ions, generally metallic ions (though not usually ions of transition metals) or ammonium and substituted ammonium ions.¹⁰⁹ The crown ether is called the *host* and the ion is the *guest*. In most cases, the ions are held tightly in the center of the cavity.¹¹⁰ Each crown ether binds different ions, depending on the size of the cavity. For example, **14** binds Li^{+111} , but not K^{+} ,¹¹² while **15** binds K^{+} but not Li^{+} .¹¹³ Similarly, **15** binds Hg^{2+} , but not Cd^{2+} or Zn^{2+} , and Sr^{2+} but not Ca^{2+} .¹¹⁴ 18-Crown-5 binds alkali and ammonium cations >1000 times weaker than 18-crown-6, presumably because the larger 18-crown-6 cavity involves more hydrogen bonds.¹¹⁵ The complexes can frequently be prepared as well-defined sharp-melting solids.



¹⁰⁶ See Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, 3 Vols., Academic Press, NY, **1984**; Vögtle, F. *Host Guest Complex Chemistry I, II, and III* (Top. Curr. Chem. **1998**, 101, 121), Springer, Berlin, **1981**, **1982**, **1984**; Vögtle, F.; Weber, E. *Host Guest Complex Chemistry/Macrocycles*, Springer, Berlin, **1985**; Izatt, R. M.; Christensen, J.J. *Synthetic Multidentate Macrocyclic Compounds*, Academic Press, NY, **1978**. For reviews, see McDaniel, C.W.; Bradshaw, J.S.; Izatt, R.M. *Heterocycles*, **1990**, 30, 665; Sutherland, I.O. *Chem. Soc. Rev.* **1986**, 15, 63; Franke, J.; Vögtle, F. *Top. Curr. Chem.* **1986**, 132, 135; Cram, D.J. *Angew. Chem. Int. Ed.* **1986**, 25, 1039; Gutsche, C.D. *Acc. Chem. Res.* **1983**, 16, 161; Tabushi, I.; Yamamura, K. *Top. Curr. Chem.* **1983**, 113, 145; Stoddart, J.F. *Prog. Macrocyclic Chem.* **1981**, 2, 173; Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* **1978**, 11, 8; *Science*, **1974**, 183, 803; Gokel, G.W.; Durst, H.D. *Synthesis* **1976**, 168; *Aldrichim. Acta* **1976**, 9, 3; Lehn, J.M. *Struct. Bonding (Berlin)* **1973**, 16, 1; Christensen, J.J.; Eatough, D.J.; Izatt, R.M. *Chem. Rev.* **1974**, 74, 351; Pedersen, C.J.; Frensdorff, H.K. *Angew. Chem. Int. Ed.* **1972**, 11, 16. For reviews of acyclic molecules with similar properties, see Vögtle, E. *Chimia* **1979**, 33, 239; Vögtle, E.; Weber, E. *Angew. Chem. Int. Ed.* **1979**, 18, 753. See *Angew. Chem. Int. Ed.* **1988**, 27, pp. 1021, 1009, 89; and *Chem. Scr.*, **1988**, 28, pp. 229, 263, 237. See also, the series *Advances in Supramolecular Chemistry*.

¹⁰⁷ Cook, F.L.; Caruso, T.C.; Byrne, M.P.; Bowers, C.W.; Speck, D.H.; Liotta, C. *Tetrahedron Lett.* **1974**, 4029.

¹⁰⁸ Discovered by Pedersen, C.J. *J. Am. Chem. Soc.* **1967**, 89, 2495, 7017. For an account of the discovery, see Schroeder, H.E.; Petersen, C.J. *Pure Appl. Chem.* **1988**, 60, 445.

¹⁰⁹ See Inoue, Y.; Gokel, G.W. *Cation Binding by Macrocycles*, Marcel Dekker, NY, **1990**.

¹¹⁰ See Izatt, R.M.; Bradshaw, J.S.; Nielsen, S.A.; Lamb, J.D.; Christensen, J.J.; Sen, D. *Chem. Rev.* **1985**, 85, 271; Parsonage, N.G.; Staveley, L.A.K. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, **1984**, pp. 1–36.

¹¹¹ Anet, F.A.L.; Krane, J.; Dale, J.; Daasvatn, K.; Kristiansen, P.O. *Acta Chem. Scand.* **1973**, 27, 3395.

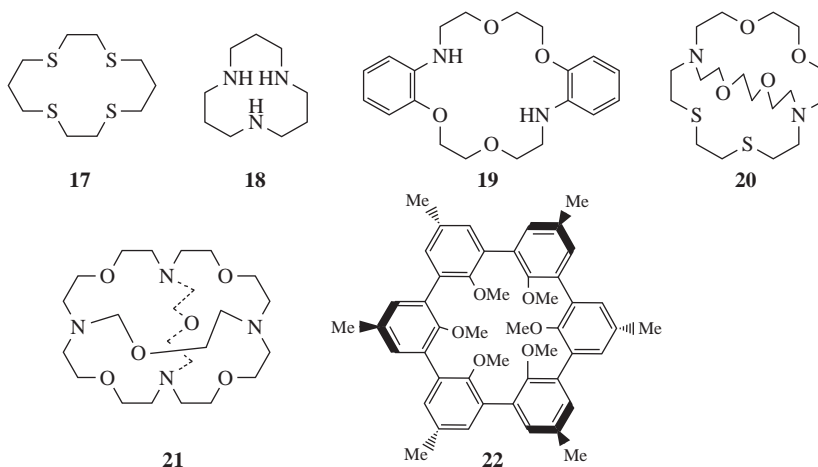
¹¹² See Dale, J.; Eggestad, J.; Fredriksen, S.B.; Groth, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1391; Dale, J.; Fredriksen, S.B. *Pure Appl. Chem.* **1989**, 61, 1587.

¹¹³ Izatt, R.M.; Nelson, D.P.; Rytting, J.H.; Haymore, B.L.; Christensen, J.J. *J. Am. Chem. Soc.* **1971**, 93, 1619.

¹¹⁴ Kimura, Y.; Iwashima, K.; Ishimori, T.; Hamaguchi, H. *Chem. Lett.* **1977**, 563.

¹¹⁵ Raevsky, O.A.; Solov'ev, V.P.; Solotnov, A.F.; Schneider, H.-J.; Rüdiger, V. *J. Org. Chem.* **1996**, 61, 8113.

Apart from their obvious utility in separating mixtures of cations,¹¹⁶ crown ethers are widely used in organic synthesis (see the discussion on Sec. 10.G.v). Chiral crown ethers have been used for the resolution of racemic mixtures (Sec. 4.A). Although crown ethers are most frequently used to complex cations, amines, phenols, and other neutral molecules have also been complexed¹¹⁷ (see Sec. 4.L for the complexing of anions).¹¹⁸ Macrocycles containing nitrogen (azacrown ethers) or sulfur atoms (thiacrown ethers)¹¹⁹ (e.g., **17** and **18**),¹²⁰ have complexing properties similar to other crown ethers, as do mixed-heteroatom crown ethers (e.g., **19**,¹²¹ **20**,¹²² or **21**¹²³).



Bicyclic molecules (e.g., **20**) can surround the enclosed ion in 3D, binding it even more tightly than the monocyclic crown ethers. Bicyclics and cycles of higher order¹²⁴ are called *cryptands* and the complexes formed are called *cryptates* (monocyclic compounds are sometimes called cryptands). When the molecule contains a cavity that can accommodate a guest molecule, usually through hydrogen-bonding interactions,

¹¹⁶ Crown ethers have been used to separate isotopes of cations, (e.g., ⁴⁴Ca from ⁴⁰Ca). For a review, see Heumann, K.G. *Top. Curr. Chem.* **1985**, 127, 77.

¹¹⁷ For reviews, see Vögtle, F.; Müller, W.M.; Watson, W.H. *Top. Curr. Chem.* **1984**, 125, 131; Weber, E. *Prog. Macrocycl. Chem.* **1987**, 3, 337; Diederich, F. *Angew. Chem. Int. Ed.* **1988**, 27, 362.

¹¹⁸ See van Staveren, C.J.; van Eerden, J.; van Veggel, F.C.J.M.; Harkema, S.; Reinhoudt, D.N. *J. Am. Chem. Soc.* **1988**, 110, 4994. See also, Rodrigue, A.; Bovenkamp, J.W.; Murchie, M.P.; Buchanan, G.W.; Fortier, S. *Can. J. Chem.* **1987**, 65, 2551; Fraser, M.E.; Fortier, S.; Markiewicz, M.K.; Rodrigue, A.; Bovenkamp, J.W. *Can. J. Chem.* **1987**, 65, 2558.

¹¹⁹ Voronkov, M.G.; Knutov, V.I. *Sulfur Rep.* **1986**, 6, 137, *Russ. Chem. Rev.* **1982**, 51, 856; Reid, G.; Schröder, M. *Chem. Soc. Rev.* **1990**, 19, 239.

¹²⁰ For a review of **17** and its derivatives, see Chaudhuri, P.; Wieghardt, K. *Prog. Inorg. Chem.* **1987**, 35, 329. *N*-Aryl-azacrown ethers are known, see Zhang, X.-X.; Buchwald, S.L. *J. Org. Chem.* **2000**, 65, 8027.

¹²¹ Gersch, B.; Lehn, J.-M.; Grell, E. *Tetrahedron Lett.* **1996**, 37, 2213.

¹²² Newcomb, M.; Gokel, G.W.; Cram, D.J. *J. Am. Chem. Soc.* **1974**, 96, 6810.

¹²³ Ragunathan, K.G.; Shukla, R.; Mishra, S.; Bharadwaj, P.K. *Tetrahedron Lett.* **1993**, 34, 5631.

¹²⁴ See Potvin, P.G.; Lehn, J.M. *Prog. Macrocycl. Chem.* **1987**, 3, 167; Kiggen, W.; Vögtle, F. *Prog. Macrocycl. Chem.* **1987**, 3, 309; Dietrich, B. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, **1984**, pp. 337–405; Parker, D. *Adv. Inorg. Radichem.* **1983**, 27, 1; Lehn, J.M. *Acc. Chem. Res.* **1978**, 11, 49, *Pure Appl. Chem.* **1977**, 49, 857.

it is sometimes called a *cavitand*.¹²⁵ The tricyclic cryptand **21** has 10 binding sites and a spherical cavity.⁹⁸ Another molecule with a spherical cavity (though not a cryptand) is **22**, which complexes Li^+ and Na^+ (preferentially Na^+), but not K^+ , Mg^{2+} , or Ca^{2+} .¹²⁶ Molecules such as these, whose cavities can be occupied only by spherical entities, have been called *spherands*.⁸³ Other types are *calixarenes*¹²⁷ (e.g., **23**).¹²⁸ Spherand-type calixarenes are known.¹²⁹ There is significant hydrogen bonding involving the phenolic OH units in [4]calixarenes, but this diminishes as the size of the cavity increases in larger ring calixarenes.¹³⁰ There are also calix[6]arenes¹³¹ that have been shown to have conformational isomers (Sec. 4.O) in equilibrium (cone vs alternate) that can sometimes be isolated:¹³² calix[8]arenes,¹³³ azacalixarenes,¹³⁴ homooxacalixarenes,¹³⁵ and calix[9–20]arenes.¹³⁶ Note that substitution of the unoccupied “meta” positions immobilizes calix[4]arenes and the conformational mobility (Sec. 4.O.iv) in calix[8]arenes is substantially diminished.¹³⁷ Amide-bridged calix[4]arenes¹³⁸ calix[4]azulene,¹³⁹ and quinone-bridged calix[6]arenes.¹⁴⁰ are known, and diammoniumcalix[4]arene has been prepared.¹⁴¹ Enantiopure calix[4]resorcinarene derivatives are known,¹⁴² and water-soluble calix[4]arenes have been prepared.¹⁴³ There are also a variety of calix [*n*]crown ethers,¹⁴⁴ some of which are cryptands¹⁴⁵ and there is evidence for formation of a calix[4]arene-proton complex.¹⁴⁶

¹²⁵ Shivanyuk, A.; Spaniol, T.P.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Angew. Chem. Int. Ed.* **2000**, *39*, 3497.

¹²⁶ Bryany, J.A.; Ho, S.P.; Knobler, C.B.; Cram, D.J. *J. Am. Chem. Soc.* **1990**, *112*, 5837.

¹²⁷ Shinkai, S. *Tetrahedron* **1993**, *49*, 8933.

¹²⁸ See Vicens, J.; Böhmer, V. *Calixarenes: A Versatile Class of Macrocyclic Compounds*, Kluwer: Dordrecht, **1991**; Gutsche, C.D. *Calixarenes*; Royal Society of Chemistry, Cambridge, **1989**; Gutsche, C.D. *Prog. Macrocycl. Chem.* **1987**, *3*, 93. Also see, Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1995**, *36*, 5429; Zhong, Z.-L.; Chen, Y.-Y.; Lu, X.-R. *Tetrahedron Lett.* **1995**, *36*, 6735; No, K.; Kim, J.E.; Kwon, K.M. *Tetrahedron Lett.* **1995**, *36*, 8453.

¹²⁹ Agbaria, K.; Aleksiuik, O.; Biali, S.E.; Böhmer, V.; Frings, M.; Thondorf, I. *J. Org. Chem.* **2001**, *66*, 2891. See Agbaria, K.; Biali, S.E.; Böhmer, V.; Brenn, J.; Cohen, S.; Frings, M.; Grynszpan, F.; Harrowfield, J.Mc B.; Sobolev, A.N.; Thondorf, I. *J. Org. Chem.* **2001**, *66*, 2900.

¹³⁰ Cerioni, G.; Biali, S.E.; Rappoport, Z. *Tetrahedron Lett.* **1996**, *37*, 5797; Molard, Y.; Bureau, C.; Parrot-Lopez, H.; Lamartine, R.; Regnourf-de-Vains, J.-B. *Tetrahedron Lett.* **1999**, *40*, 6383.

¹³¹ Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1995**, *60*, 4862.

¹³² Kanamathareddy, S.; Gutsche, C.D. *J. Org. Chem.* **1994**, *59*, 3871.

¹³³ Cunsolo, F.; Consoli, G.M.L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, *37*, 715.

¹³⁴ Miyazaki, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2002**, *43*, 7945; Khan, I.U.; Takemura, H.; Suenaga, M.; Shinmyozu, T.; Inazu, T. *J. Org. Chem.* **1993**, *58*, 3158.

¹³⁵ Masci, B. *J. Org. Chem.* **2001**, *66*, 1497; Seri, N.; Thondorf, I.; Biali, S.E. *J. Org. Chem.* **2004**, *69*, 4774; Tsubaki, K.; Morimoto, T.; Otsubo, T.; Kinoshita, T.; Fujii, K. *J. Org. Chem.* **2001**, *66*, 4083.

¹³⁶ Stewart, D.R.; Gutsche, C.D. *J. Am. Chem. Soc.* **1999**, *121*, 4136.

¹³⁷ Mascal, M.; Naven, R.T.; Warmuth, R. *Tetrahedron Lett.* **1995**, *36*, 9361.

¹³⁸ Wu, Y.; Shen, X.-P.; Duan, C.-y.; Liu, Y.-i.; Xu, Z. *Tetrahedron Lett.* **1999**, *40*, 5749.

¹³⁹ Colby, D.A.; Lash, T.D. *J. Org. Chem.* **2002**, *67*, 1031.

¹⁴⁰ Akine, S.; Goto, K.; Kawashima, T. *Tetrahedron Lett.* **2000**, *41*, 897.

¹⁴¹ Aeunghmaîtrepirom, W.; Hagège, A.; Asfari, Z.; Bennouna, L.; Vicens, J.; Leroy, M. *Tetrahedron Lett.* **1999**, *40*, 6389.

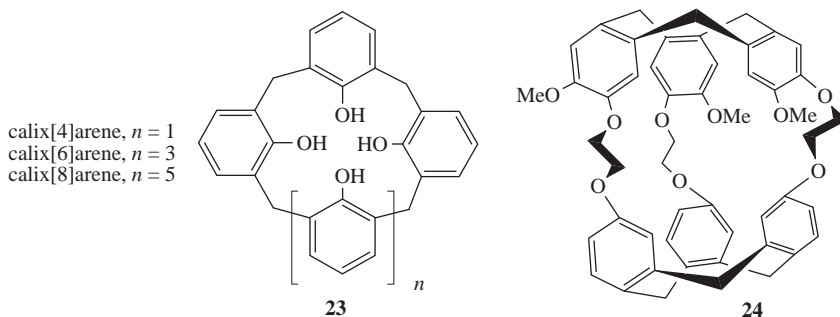
¹⁴² Shirakawa, S.; Moriyama, A.; Shimizu, S. *Eur. J. Org. Chem.* **2008**, 5957.

¹⁴³ Shimizu, S.; Shirakawa, S.; Sasaki, Y.; Hirai, C. *Angew. Chem. Int. Ed.* **2000**, *39*, 1256.

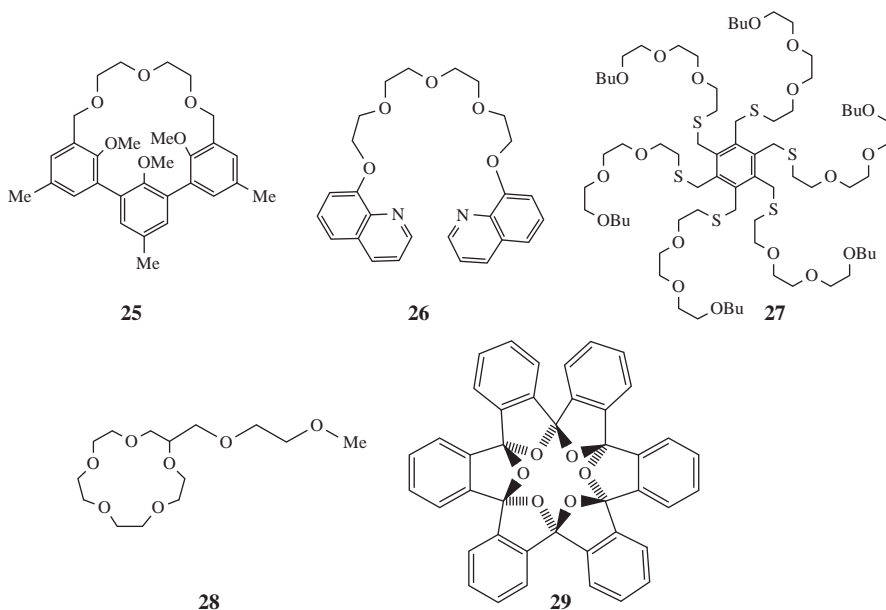
¹⁴⁴ Stephan, H.; Gloe, K.; Paulus, E.F.; Saadioui, M.; Böhmer, V. *Org. Lett.* **2000**, *2*, 839; Asfari, Z.; Thuéry, P.; Nierlich, M.; Vicens, J. *Tetrahedron Lett.* **1999**, *40*, 499; Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, *37*, 3899; Pappalardo, S.; Petringa, A.; Parisi, M.F.; Ferguson, G. *Tetrahedron Lett.* **1996**, *37*, 3907.

¹⁴⁵ Pulpoka, B.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1996**, *37*, 6315.

¹⁴⁶ Makrlík, E.; Vaňura, P. *Monat. Chemie* **2006**, *137*, 1185-.



Other molecules include *cryptophanes* (e.g., **24**),¹⁴⁷ *hemispherands* (an example is **25**¹⁴⁸), and *podands*.¹⁴⁹ The last-named are host compounds in which two or more arms come out of a central structure. Examples are **26**¹⁵⁰ and **27**¹⁵¹ and the latter molecule binds simple cations (e.g., Na^+ , K^+ , and Ca^{2+}). *Lariat ethers*¹⁵² are compounds containing a crown ether ring with one or more side chains that can also serve as ligands, (e.g., **28**).¹⁵³ There is also a class of ortho cyclophanes that are crown ethers (see **29**) and have been given the name *starands*.¹⁵⁴



¹⁴⁷ See Collet, A. *Tetrahedron* **1987**, 43, 5725, in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 1, Academic Press, NY, **1984**, pp. 97–121.

¹⁴⁸ Lein, G.M.; Cram, D.J. *J. Am. Chem. Soc.* **1985**, 107, 448.

¹⁴⁹ Fo Kron, T.E.; Tsvetkov, E.N. *Russ. Chem. Rev.* **1990**, 59, 283; Menger, F.M. *Top. Curr. Chem.* **1986**, 136, 1.

¹⁵⁰ Tümmmler, B.; Maass, G.; Weber, E.; Wehner, W.; Vögtle, F. *J. Am. Chem. Soc.* **1977**, 99, 4683.

¹⁵¹ Vögtle, F.; Weber, E. *Angew. Chem. Int. Ed.* **1974**, 13, 814.

¹⁵² For the synthesis of *N*-pivot lariat ethers, see Elwahy, A.H.M.; Abbas, A.A. *J. Het. Chem.* **2008**, 45, 1.

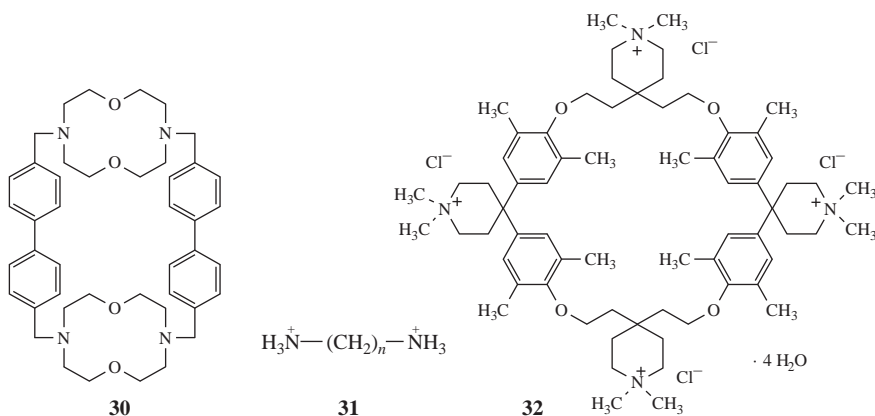
¹⁵³ Gatto, V.J.; Gokel, G.W. *J. Am. Chem. Soc.* **1984**, 106, 8240; Nakatsuji, Y.; Nakamura, T.; Yonetani, M.; Yuya, H.; Okahara, M. *J. Am. Chem. Soc.* **1988**, 110, 531.

¹⁵⁴ Lee, W.Y.; Park, C.H. *J. Org. Chem.* **1993**, 58, 7149.

The bonding in these complexes is the result of ion-dipole attractions between the heteroatoms and the positive ions. The parameters of the host-guest interactions can sometimes be measured by NMR.¹⁵⁵

It has been implied that the ability of these host molecules to bind guests is often very specific, often linked to the hydrogen-bonding ability of the host,¹⁵⁶ enabling the host to pull just one molecule or ion out of a mixture. This is called *molecular recognition*.¹⁵⁷ In general, cryptands, with their well-defined 3D cavities, are better for this than monocyclic crown ethers or ether derivatives. An example is the host (**30**), which selectively binds the dication **31** ($n = 5$) rather than **31** ($n = 4$), and **31** ($n = 6$) rather than **31** ($n = 7$).¹⁵⁸ The host **32**, which is water-soluble, forms 1:1 complexes with neutral aromatic hydrocarbons (e.g., pyrene and fluoranthene), and even (though more weakly) with biphenyl and naphthalene, I is also capable of transporting them through an aqueous phase.¹⁵⁹

Of course, it has long been known that molecular recognition is very important in biochemistry. The action of enzymes and various other biological molecules is extremely specific because these molecules also have host cavities that are able to recognize only one or a few particular types of guest molecules. Now, organic chemists can synthesize non-natural hosts that can also perform crude (compared to biological molecules) molecular recognition. The macrocycle **33** has been used as a catalyst, for the hydrolysis of acetyl phosphate and the synthesis of pyrophosphate.¹⁶⁰



No matter what type of host, the strongest attractions occur when combination with the guest causes the smallest amount of distortion of the host.¹⁶¹ That is, a fully preorganized

¹⁵⁵ Wang, T.; Bradshaw, J.S.; Izatt, R.M. *J. Heterocyclic Chem.* **1994**, 31, 1097.

¹⁵⁶ Fujimoto, T.; Yanagihara, R.; Kobayashi, K.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* **1995**, 68, 2113.

¹⁵⁷ For reviews, see Rebek, Jr., *J. Angew. Chem. Int. Ed.* **1990**, 29, 245; *Acc. Chem. Res.* **1990**, 23, 399; *Top. Curr. Chem.* **1988**, 149, 189; Diederich, F. *J. Chem. Educ.* **1990**, 67, 813; Hamilton, A.D. *J. Chem. Educ.* **1990**, 67, 821; Raevskii, O.A. *Russ. Chem. Rev.* **1990**, 59, 219.

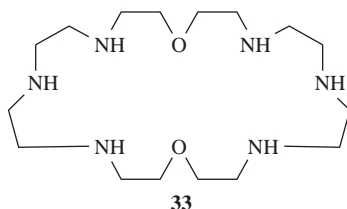
¹⁵⁸ Mageswaran, R.; Mageswaran, S.; Sutherland, I.O. *J. Chem. Soc., Chem. Commun.* **1979**, 722.

¹⁵⁹ Diederich, F.; Dick, K. *J. Am. Chem. Soc.* **1984**, 106, 8024; Diederich, F.; Griebel, D. *J. Am. Chem. Soc.* **1984**, 106, 8037. See also, Vögtle, F.; Müller, W.M.; Werner, U.; Losensky, H. *Angew. Chem. Int. Ed.* **1987**, 26, 901.

¹⁶⁰ Hosseini, M.W.; Lehn, J.M. *J. Am. Chem. Soc.* **1987**, 109, 7047. For a discussion, see Mertes, M.P.; Mertes, K. *B. Acc. Chem. Res.* **1990**, 23, 413.

¹⁶¹ See Cram, D.J. *Angew. Chem. Int. Ed.* **1986**, 25, 1039.

host will bind better than a host whose molecular shape must change in order to accommodate the guest.



3.C.iii Inclusion Compounds

This type of addition compound is different from either the EDA complexes or the crown ether type of complexes previously discussed. Here, the host forms a crystal lattice that has spaces large enough for the guest to fit into. *van der Waals forces* constitute the only bonding between the host and the guest. There are two main types, depending on the shape of the space.¹⁶² The spaces in *inclusion compounds*, are in the shape of long tunnels or channels, while the other type, often called *clathrate*,¹⁶³ or *cage compounds*, have spaces that are completely enclosed. In both types, the guest molecule must fit into the space and potential guests that are too large or too small will not go into the lattice, so that the addition compound will not form. Such structures need not be restricted to large molecules. Indeed, the structure and stability of the hydrogen clathrate hydrate with cyclohexanone is known.¹⁶⁴

Several important host molecules are known, and inclusion compounds include small molecules (e.g., urea).¹⁶⁵ Hydrogen sulfide forms hexagonal clathrate hydrate cages, and a guest molecule (e.g., pinacolone), may be present, as shown in Fig. 3.1.¹⁶⁶ Commonly, *van der Waals forces* between the host and the guest, while small, are essential to the stability of the structure. Which molecules can be a guest is usually dependent on their shapes and sizes and not necessarily on any electronic or chemical effects. For example, octane and 1-bromooctane are suitable guests for urea, but 2-bromooctane, 2-methylheptane, and 2-methyloctane are not. Also, both dibutyl maleate and dibutyl fumarate are guests; neither diethyl maleate nor diethyl fumarate is a guest, but dipropyl fumarate is a guest and dipropyl maleate is not.¹⁶⁷ In these complexes, there is usually no integral molar ratio (though by chance there may be). For example, the octane/urea ratio is 1:6.73.¹⁶⁸ A deuterium quadrupole echo spectroscopy study of a urea complex showed that the urea molecules do not remain rigid, but undergo 180° flips about the C=O axis at the rate of $>10^6 \text{ s}^{-1}$ at 30 °C.¹⁶⁹

¹⁶² See Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vols. 1–3, Academic Press, NY, **1984**; Weber, E. *Top. Curr. Chem.* **1987**, 140, 1; Gerdil, R. *Top. Curr. Chem.* **1987**, 140, 71; Mak, T.C.W.; Wong, H.N.C. *Top. Curr. Chem.* **1987**, 140, 141; Bishop, R.; Dance, I.G. *Top. Curr. Chem.* **1988**, 149, 137.

¹⁶³ For reviews, see Goldberg, I. *Top. Curr. Chem.* **1988**, 149, 1; Weber, E.; Czugler, M. *Top. Curr. Chem.* **1988**, 149, 45; MacNicol, D.D.; McKendrick, J.J.; Wilson, D.R. *Chem. Soc. Rev.* **1978**, 7, 65.

¹⁶⁴ Strobel, T.A.; Hester, K.C.; Sloan Jr., E.D.; Koh, C.A. *J. Am. Chem. Soc.* **2007**, 129, 9544.

¹⁶⁵ For a review of urea and thiourea inclusion compounds, see Takemoto, K.; Sonoda, N. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, **1984**, pp. 47–67.

¹⁶⁶ Taken from Alavi, S.; Udachin, K.; Ripmeester, J.A. *Chem. Eur. J.* **2010**, 16, 1017.

¹⁶⁷ Radell, J.; Connolly, J.W.; Cosgrove, Jr., W.R. *J. Org. Chem.* **1961**, 26, 2960.

¹⁶⁸ Redlich, O.; Gable, C.M.; Dunlop, A.K.; Millar, R.W. *J. Am. Chem. Soc.* **1950**, 72, 4153.

¹⁶⁹ Heaton, N.J.; Vold, R.L.; Vold, R.R. *J. Am. Chem. Soc.* **1989**, 111, 3211.

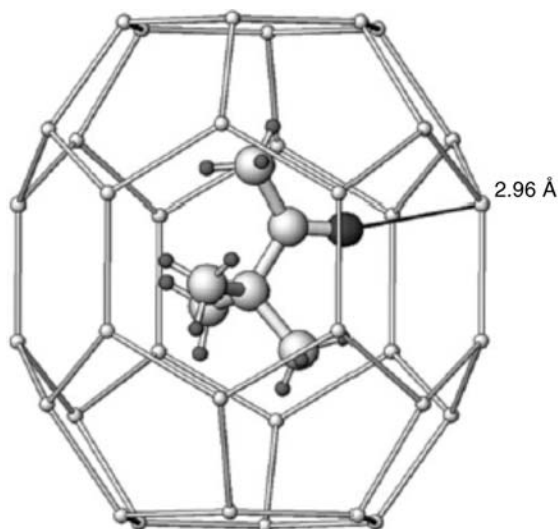


FIG. 3.1. X-ray structure of pinacolone in a H_2S hexagonal clathrate hydrate cage molecule at 100 K.¹⁶⁶ [Reprinted with permission from Alavi, S.; Udachin, K.; Ripmeester, J.A. *Chem. Eur. J.* **2010**, *16*, 1017, Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © 2010 by Wiley–VCH Verlag.]

The complexes are solids, but are not useful as derivatives, since they melt, with decomposition of the complex at the melting point of urea. They are useful, however, in separating isomers that would be quite difficult to separate otherwise. Thiourea also forms inclusion compounds though with channels of larger diameter, so that *n*-alkanes cannot be guests but, (e.g., 2-bromooctane, cyclohexane, and chloroform readily fit).

Hydroquinone is a useful host for clathrates.¹⁷⁰ Three molecules, held together by hydrogen bonding, make a cage in which fits one molecule of guest. Typical guests are methanol (but not ethanol), sulfur dioxide, carbon dioxide, and argon (but not neon). One important use is the isolation of anhydrous hydrazine as complex.¹⁷¹ Anhydrous hydrazine is highly explosive, so preparation by distillation of aq hydrazine solutions is both difficult and dangerous. The inclusion complex can be readily isolated and reactions done in the solid state (e.g., the reaction with esters to give hydrazides, Reaction 16–75).¹⁷² In contrast to the inclusion compounds, the crystal lattices here can exist partially empty. Another host is water. Usually six molecules of water form the cage and many guest molecules, among them Cl_2 , propane, and methyl iodide, can fit. The water clathrates (see Fig. 3.1), which are solids, can normally be kept only at low temperatures; at room temperature, they decompose.¹⁷¹ Methane hydrate, which is a promising energy source that exists in vast quantities at the seabed of various oceans,¹⁷³ is an example of this type of

¹⁷⁰ For a review, see MacNicol, D.D. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, **1984**, pp. 1–45.

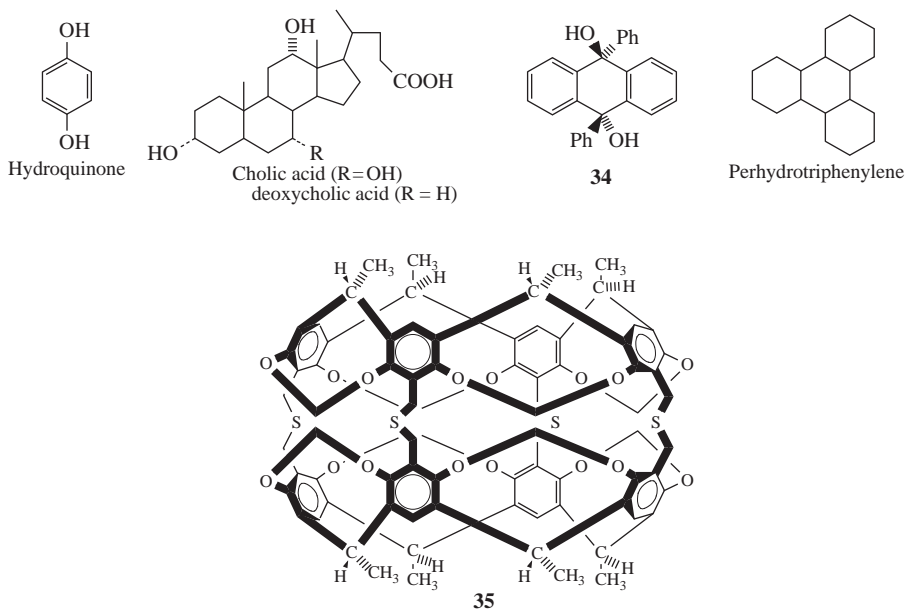
¹⁷¹ Toda, F.; Hyoda, S.; Okada, K.; Hirotsu, K. *J. Chem. Soc., Chem. Commun.* **1995**, 1531.

¹⁷² For a monograph on water clathrates, see Berecz, E.; Balla-Achs, M. *Gas Hydrates*; Elsevier, NY, **1983**. For reviews, see Jeffrey, G.A. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 1, Academic Press, NY, **1984**, pp. 135–190; Cady, G.H. *J. Chem. Educ.* **1983**, *60*, 915.

¹⁷³ Sloan, E.D. *Clathrate Hydrate of Natural Gases*, Marcel Dekker, Inc., **1998**.

clathrate. Another inorganic host is sodium chloride (and some other alkali halides), which can encapsulate organic molecules (e.g., benzene, naphthalene, and diphenylmethane).¹⁷⁴

Among other hosts¹⁷⁵ for inclusion and/or clathrate compounds are deoxycholic acid,¹⁷⁶ cholic acid,¹⁷⁷ anthracene compounds, (e.g., **34**),¹⁷⁸ dibenzo-24-crown-8,¹⁷⁹ and the compound **35**, which has been called a *carcerand*.¹⁸⁰ When carcerand-type molecules trap ions or other molecules (called guests), the resulting complex is called a carciplex.¹⁸¹ It has been shown that in some cases, the motion of the guest within the carciplex is restricted.¹⁸²



¹⁷⁴ Kirkor, E.; Gebicki, J.; Phillips, D.R.; Michl, J. *J. Am. Chem. Soc.* **1986**, 108, 7106.

¹⁷⁵ See also, Toda, F. *Pure App. Chem.* **1990**, 62, 417, *Top. Curr. Chem.* **1988**, 149, 211; **1987**, 140, 43; Davies, J. E.; Finocchiaro, P.; Herbstein, F.H. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, **1984**, pp. 407–453.

¹⁷⁶ For a review, see Giglio, E. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, **1984**, pp. 207–229.

¹⁷⁷ See Miki, K.; Masui, A.; Kasei, N.; Miyata, M.; Shibakami, M.; Takemoto, K. *J. Am. Chem. Soc.* **1988**, 110, 6594.

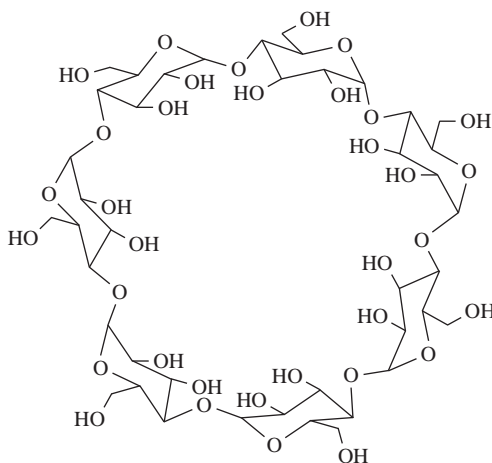
¹⁷⁸ Barbour, L.J.; Caira, M.R.; Nassimbeni, L.R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2321. Also see, Barbour, L. J.; Caira, M.R.; Nassimbeni, L.R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1413.

¹⁷⁹ Lämsä, M.; Suorsa, T.; Pursiainen, J.; Huuskonen, J.; Rissanen, K. *Chem. Commun.* **1996**, 1443.

¹⁸⁰ Sherman, J.C.; Knobler, C.B.; Cram, D.J. *J. Am. Chem. Soc.* **1991**, 113, 2194.

¹⁸¹ van Wageningen, A.M.A.; Timmerman, P.; van Duynhoven, J.P.M.; Verboom, W.; van Veggel, F.C.J.M.; Reinhoudt, D.N. *Chem. Eur. J.* **1997**, 3, 639; Fraser, J.R.; Borecka, B.; Trotter, J.; Sherman, J.C. *J. Org. Chem.* **1995**, 60, 1207; Place, D.; Brown, J.; Deshayes, K. *Tetrahedron Lett.* **1998**, 39, 5915. See also: Jasat, A.; Sherman, J.C. *Chem. Rev.* **1999**, 99, 931.

¹⁸² Chapman, R.G.; Sherman, J.C. *J. Org. Chem.* **2000**, 65, 513.

FIG. 3.2. β -Cyclodextrin.

3.C.iv Cyclodextrins

There is one type of host that can form both channel and cage complexes. This type is called *cyclodextrins* or *cycloamyloses*.¹⁸³ The host molecules are made up of six, seven, or eight glucose units connected in a large ring, called, respectively, α -, β -, or γ -cyclodextrin (Fig. 3.2 shows the β or seven-membered ring compound). The three molecules are in the shape of hollow truncated cones (Fig. 3.3) with primary OH groups projecting from the narrow side of the cones and secondary OH group from the wide side. As expected for carbohydrate molecules, all of them are soluble in water and the cavities normally fill with water molecules held in place by hydrogen bonds (6, 12, and 17 H_2O molecules for the α , β , and γ forms, respectively), but the insides of the cones are less polar than the outsides, so that nonpolar organic molecules readily displace the water. The polarity of such cavities has been probed by a chemical reaction: the solvolysis of benzoyl halides Reaction (16–57).¹⁸⁴ Thus the cyclodextrins form 1:1 cage complexes with many guests, ranging in size from the noble gases to large organic molecules. A guest molecule must not be too large or it will not fit, though many stable complexes are known in which one end of the guest molecule protrudes from the cavity (Fig. 3.4). On the other hand, if the guest is too small, it may go through the bottom hole (though some small polar molecules, e.g., methanol, do form complexes in which the cavity also contains some water molecules). Since the cavities of the three cyclodextrins are of different sizes (Fig. 3.3), a large variety of guests can be accommodated. Since

¹⁸³ See Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*, Springer, NY, **1978**. For reviews, see in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Academic Press, NY, **1984**, the reviews, by Saenger, W. Vol. 2, pp. 231–259; Bergeron, R.J. Vol. 3, pp. 391–443; Tabushi, I. Vol. 3, pp. 445–471; Breslow, R. Vol. 3, pp. 473–508; Croft, A.P.; Bartsch, R.A. *Tetrahedron* **1983**, 39, 1417; Tabushi, I.; Kuroda, Y. *Adv. Catal.*, **1983**, 32, 417; Tabushi, I. *Acc. Chem. Res.* **1982**, 15, 66; Saenger, W. *Angew. Chem. Int. Ed.* **1980**, 19, 344; Bergeron, R. *J. Chem. Ed.* **1977**, 54, 204; Griffiths, D.W.; Bender, M.L. *Adv. Catal.* **1973**, 23, 209.

¹⁸⁴ García-Río, L.; Hall, R.W.; Mejuto, J.C.; Rodríguez-Dafonte, P. *Tetrahedron* **2007**, 63, 2208.

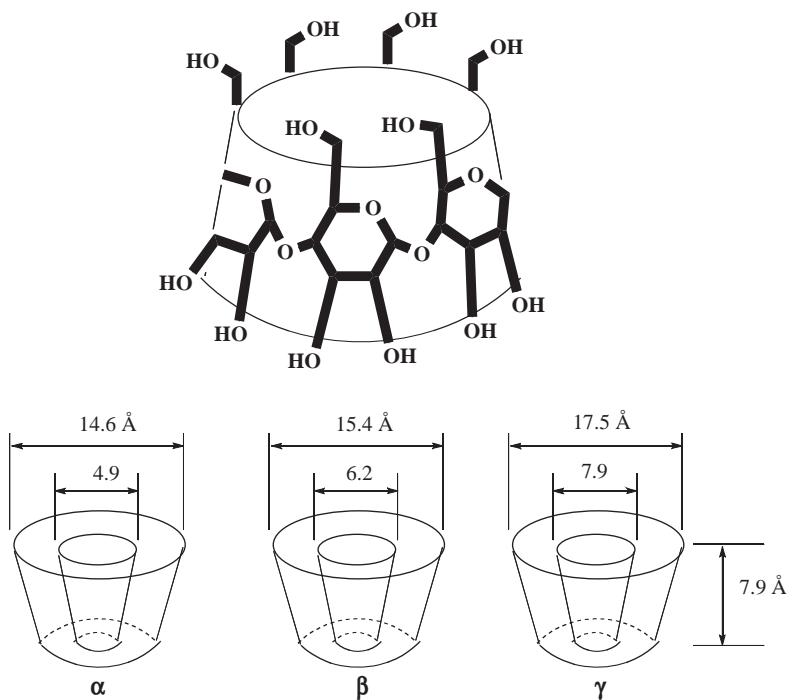


FIG. 3.3. Shape and dimensions of the α -, β -, and γ -cyclodextrin molecules.¹⁸⁵

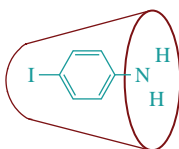


FIG. 3.4. Schematic drawing of the complex of α -cyclodextrin and *p*-iodoaniline.¹⁸⁶

cyclodextrins are nontoxic (they are actually small starch molecules), they are now used industrially to encapsulate foods and drugs.¹⁸⁷

The cyclodextrins also form channel-type complexes, in which the host molecules are stacked on top of each other, like coins in a row.¹⁸⁸ For example, α -cyclodextrin (cyclohexaamylose) forms cage complexes with acetic, propionic, and butyric acids, but channel complexes with valeric and higher acids. Capped cyclodextrins are known.¹⁸⁹

¹⁸⁵ Szejtli, J. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, **1984**, p. 332; Nickon, A.; Silversmith, E.F. *The Name Game*, Pergamon, Elmsford, NY, p. 235.

¹⁸⁶ Modified from Saenger, W.; Beyer, K.; Manor, P.C. *Acta Crystallogr. Sect. B*, **1976**, 32, 120.

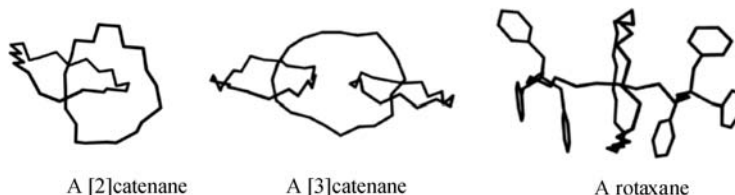
¹⁸⁷ For reviews, see Pagington, J.S. *Chem. Br.*, **1987**, 23, 455; Szejtli, J. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, **1984**, pp. 331–390.

¹⁸⁸ See Saenger, W. *Angew. Chem. Int. Ed.* **1980**, 19, 344.

¹⁸⁹ Engeldinger, E.; Armspach, D.; Matt, D. *Chem. Rev.* **2003**, 103, 4147.

3.D. CATENANES AND ROTAXANES¹⁹⁰

These compounds contain two or more independent portions that are not bonded to each other by any valence forces, but nevertheless must remain linked. [*n*]-*Catenanes* (where *n* corresponds to the number of



linked rings) are made up of two or more rings held together as links in a chain, while in *rotaxanes* a linear portion is threaded through a ring and cannot get away because of bulky end groups. Among several types of bulky molecular units, porphyrin units have been used to cap rotaxanes¹⁹¹ as have C₆₀ fullerenes.¹⁹² [2]Rotaxanes and [2]catenanes are quite common, and [3]catenanes are known having rather robust amide linkages.¹⁹³ More intricate variants [e.g., oligocatenanes,¹⁹⁴ molecular necklaces (a cyclic oligorotaxane in which a number of small rings are threaded onto a large ring),¹⁹⁵ and cyclic daisy chains (an interwoven chain in which each monomer unit acts as a donor and an acceptor for a threading interaction)]¹⁹⁶ are known. Ring-in-ring complexes have also been reported.¹⁹⁷ Molecular thread, ribbon, and belt assemblies have been synthesized.¹⁹⁸ Rotaxanes have been used as the basis for molecular switches,¹⁹⁹ and a rotaxane eciplex has been generated that may have applications to molecular-scale photonic devices.²⁰⁰

Transitional isomers are possible in [2]rotaxanes.²⁰¹ Catenanes and rotaxanes can be prepared by statistical methods or directed syntheses.²⁰² Catenanes can contain heteroatoms and heterocyclic units. In some cases, the catenane exists in equilibrium with the cyclic-non-catenane structures and in some cases this exchange is thought to proceed by

¹⁹⁰ For a monograph, see Schill, G. *Catenanes, Rotaxanes, and Knots*, Academic Press, NY, **1971**. For a review, see Schill, G. in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, **1971**, pp. 229–239.

¹⁹¹ Solladié, N.; Chambron, J.-C.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1999**, *121*, 3684.

¹⁹² Sasabe, H.; Kihara, N.; Furusho, Y.; Mizuno, K.; Ogawa, A.; Takata, T. *Org. Lett.* **2004**, *6*, 3957.

¹⁹³ Safarowsky, O.; Vogel, E.; Vögtle, F. *Eur. J. Org. Chem.* **2000**, 499.

¹⁹⁴ Amabilino, D.B.; Ashton, P.R.; Balzani, V.; Boyd, S.E.; Credi, A.; Lee, J.Y.; Menzer, S.; Stoddart, J.F.; Venturi, M.; Williams, D.J. *J. Am. Chem. Soc.* **1998**, *120*, 4295.

¹⁹⁵ Chiu, S.-H.; Rowan, S.J.; Cantrill, S.J.; Ridvan, L.; Ashton, R.P.; Garrell, R.L.; Stoddart, J.-F. *Tetrahedron* **2002**, *58*, 807; Roh, S.-G.; Park, K.-M.; Park, G.-J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 638.

¹⁹⁶ See Onagi, H.; Easton, C.J.; Lincoln, S.F. *Org. Lett.* **2001**, *3*, 1041; Cantrill, S.J.; Youn, G.J.; Stoddart, J.F.; Williams, D.J. *J. Org. Chem.* **2001**, *66*, 6857.

¹⁹⁷ Chiu, S.-H.; Pease, A.R.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Angew. Chem. Int. Ed.* **2002**, *41*, 270.

¹⁹⁸ Schwierz, H.; Vögtle, F. *Synthesis* **1999**, 295.

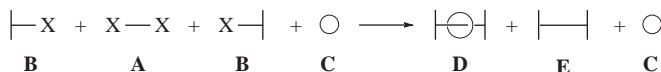
¹⁹⁹ Elizarov, A.M.; Chiu, S.-H.; Stoddart, J.-F. *J. Org. Chem.* **2002**, *67*, 9175.

²⁰⁰ MacLachlan, M. J.; Rose, A.; Swager, T. M. *J. Am. Chem. Soc.* **2001**, *123*, 9180.

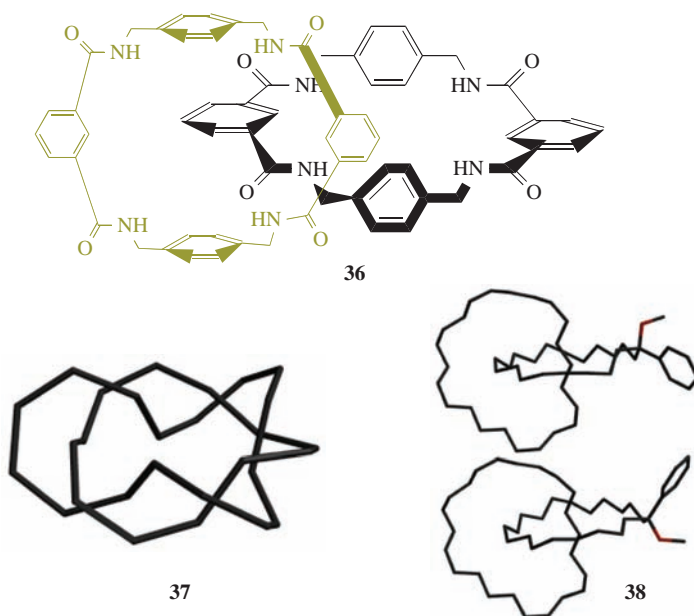
²⁰¹ Amabilino, D.B.; Ashton, P.R.; Boyd, S.E.; Gómez-López, M.; Hayes, W.; Stoddart, J.F. *J. Org. Chem.* **1997**, *62*, 3062.

²⁰² For discussions, see Schill, G. *Catenanes, Rotaxanes, and Knots*, Academic Press, NY, **1971**. For a review, see Schill, G. in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, **1971**, pp. 229–239; Walba, D.M. *Tetrahedron* **1985**, *41*, 3161.

ligand exchange and a Möbius strip mechanism.²⁰³ An example of a statistical synthesis of a rotaxane is a reaction where a compound **A** is bonded at two positions to another compound **B** in the presence of a large ring **C**. It is hoped that some **A** molecules would by chance be threaded through **C** before combining with the two **B** molecules, so that some rotaxane (**D**) would be formed along with the normal product **E**.²⁰⁴ In a directed synthesis,²⁰⁵ the separate parts of the molecule are held together by other bonds that are later cleaved.



Rotation of one unit through the other catenanes is complex, often driven by making and breaking key hydrogen bonds or π - π interactions. In the case of the isophthaloyl [2]catenane (**36**), the rate-determining steps do not necessarily correspond to the passage of the bulkiest groups.²⁰⁶



Singly and doubly interlocked [2]catenanes²⁰⁷ can exist as *topological stereoisomers*²⁰⁸ (see Sec. 4.G for a discussion of diastereomers). Catenanes **37** and **38** are such stereoisomers, and would be expected to have identical mass spectra. Analysis showed that

²⁰³ Fujita, M.; Ibukuro, F.; Seki, H.; Kamo, O.; Imanari, M.; Ogura, K. *J. Am. Chem. Soc.* **1996**, *118*, 899.

²⁰⁴ Harrison, I.T.; Harrison, S. *J. Am. Chem. Soc.* **1967**, *89*, 5723; Ogino, H. *J. Am. Chem. Soc.* **1981**, *103*, 1303; Harrison, I.T. *J. Chem. Soc., Perkin Trans. 1* **1974**, 301; Schill, G.; Beckmann, W.; Schweikert, N.; Fritz, H. *Chem. Ber.* **1986**, *119*, 2647. See also, Agam, G.; Graiver, D.; Zilkha, A. *J. Am. Chem. Soc.* **1976**, *98*, 5206.

²⁰⁵ For a directed synthesis of a rotaxane, see Schill, G.; Zürcher, C.; Vetter, W. *Chem. Ber.* **1973**, *106*, 228.

²⁰⁶ Deleuze, M. S.; Leigh, D. A.; Zerbetto, F. *J. Am. Chem. Soc.* **1999**, *121*, 2364.

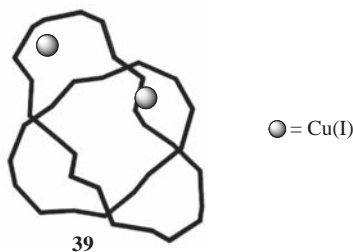
²⁰⁷ For the synthesis of a doubly interlocking [2]catenane, see Ibukuro, F.; Fujita, M.; Yamaguchi, K.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1999**, *121*, 11014.

²⁰⁸ See Lukin, O.; Godt, A.; Vögtle, F. *Chem. Eur. J.*, **2004**, *10*, 1879.

37 is more constrained and cannot readily accommodate an excess of energy during the mass spectrometry ionization process and, hence, breaks more easily.

Catenanes, molecular knots, and other molecules in these structural categories can exist as enantiomers. In other words, stereoisomers can be generated in some cases. This phenomenon was first predicted by Frisch and Wassermann,²⁰⁹ and the first stereoisomeric catenanes and molecular knots were synthesized by Sauvage and Dietrich-Buchecker.²¹⁰ Enantiomeric resolution has been achieved.²¹¹ A chiral [3]rotaxane containing two achiral wheels, mechanically bonded has been reported,²¹² generating a cyclodiastereomeric compound, and the enantiomers were separated using chiral HPLC. The terms cyclo-enantiomerism and cyclodiastereomerism were introduced by Prelog et. al.²¹³ This type of stereoisomerism occurs in cyclic arrangements of several centrally chiral elements in combination with an orientation of the macrocycle.²¹²

A rotaxane can also be an inclusion compound.²¹⁴ The molecule contains bulky end groups (or “stoppers,” e.g., triisopropylsilyl groups, $i\text{Pr}_3\text{Si}-$) and a chain that consists of a series of $-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-$ groups, but also contains two benzene rings. Cyclodextrins have been threaded onto axle molecules.²¹⁵ The ring (or bead) around the chain is a macrocycle containing two benzene rings and four pyridine rings. It is preferentially attracted to one of the benzene rings in the chain. The benzene moiety serves as a “station” for the “bead.” However, symmetry of the chain can make the two “stations” equivalent, so that the “bead” is equally attracted to them, and the “bead” actually moves back and forth rapidly between the two “stations,” as shown by the temperature dependence of the NMR spectrum.²¹⁶ This molecule has been called a *molecular shuttle*. A copper(I) complexed rotaxane has been prepared with two fullerene (see Sec. 2.L) stoppers.²¹⁷



²⁰⁹ Frisch, H.L.; Wasserman, E. *J. Am. Chem. Soc.* **1961**, *83*, 3789.

²¹⁰ *Molecular Catenanes, Rotaxanes and Knots* (Eds., Sauvage, J.-P.; Dietrich-Buchecker, C.O.) Wiley-VCH, Weinheim, **1999**; Ashton, P.R.; Bravo, J.A.; Raymo, F.M.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Eur. J. Org. Chem.* **1999**, 899; Mitchell, D.K.; Sauvage, J.-P. *Angew. Chem. Int. Ed.* **1988**, *27*, 930; Nierengarten, J.-F.; Dietrich-Buchecker, C.O.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1994**, *116*, 375; Chen, C.-T.; Gantzel, P.; Siegel, J.S.; Baldrige, K.K.; English, R.B.; Ho, D.M. *Angew. Chem. Int. Ed.* **1995**, *34*, 2657.

²¹¹ Kaida, T.; Okamoto, Y.; Chambron, J.-C.; Mitchell, D.K.; Sauvage, J.-P. *Tetrahedron Lett.* **1993**, *34*, 1019.

²¹² Schmieder, R.; Hübner, G.; Seel, C.; Vögtle, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 3528.

²¹³ Prelog, V.; Gerlach, H. *Helv. Chim. Acta* **1964**, *47*, 2288; Gerlach, H.; Owtischinnkow, J.A.; Prelog, V. *Helv. Chim. Acta* **1964**, *47*, 2294; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**, pp. 1176–1181; Chorev, M.; Goodman, M. *Acc. Chem. Res.* **1993**, *26*, 266; Mislow, K. *Chimia*, **1986**, *40*, 395.

²¹⁴ For an example, see Anelli, P.L.; Spencer, N.; Stoddart, J.F. *J. Am. Chem. Soc.* **1991**, *113*, 5131.

²¹⁵ Oshikiri, T.; Takashima, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* **2005**, *127*, 12186.

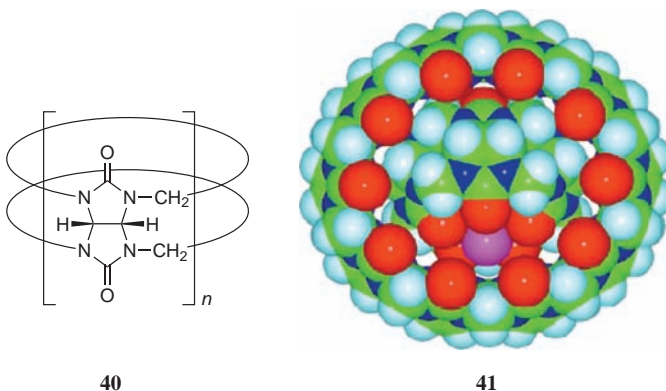
²¹⁶ Anelli, P.L.; Spencer, N.; Stoddart, J.F. *J. Am. Chem. Soc.* **1991**, *113*, 5131. For a review of the synthesis and properties of molecules of this type, see Philp, D.; Stoddart, J.F. *Synlett* **1991**, 445.

²¹⁷ Diederich, F.; Dietrich-Buchecker, C.O.; Nierengarten, S.-F.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* **1995**, 781.

Another variation of these molecules is called molecular knots (e.g., **39**), where the \bigcirc represents a metal [in this case, Cu(I)].²¹⁸ This is particularly interesting since knotted forms of deoxyribonucleic acid (DNA) have been reported.²¹⁹ There are mechanically interlocked molecules, and one example is known as suit[2]ane.²²⁰

3.E. CUCURBIT[M]URIL-BASED GYROSCANE

A new molecule known as gyroscane has been prepared, and proposed as a new supramolecular form.²²¹ The class of compounds known as cucurbit[*n*]urils, abbreviated Q_n (**40**),²²² are condensation products of glycoluril and formaldehyde. These macrocycles can act as molecular hosts. The new “supramolecular form is one in which a smaller macrocycle (Q5) is located inside a larger macrocycle (Q10), with facile rotation of one relative to the other in solution (see **41**).²²¹ The image of a ring rotating independently inside another ring, which resembles a gyroscope, suggests the name gyroscane for this new class of supramolecular system.”²²²



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²¹⁸ Dietrich-Buchecker, C.O.; Nierengarten, J.-F.; Sauvage, J.-P. *Tetrahedron Lett.* **1992**, 33, 3625. See Dietrich-Buchecker, C.O.; Guilhem, J.; Pascard, C.; Sauvage, J.-P. *Angew. Chem. Int. Ed.* **1990**, 29, 1154.

²¹⁹ Liu, L.F.; Depew, R.E.; Wang, J.C. *J. Mol. Biol.* **1976**, 106, 439.

²²⁰ Williams, A.R.; Northrop, B.N.; Chang, T.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Angew. Chem. Int. Ed.* **2006**, 45, 6665.

²²¹ Day, A.I.; Blanch, R.J.; Arnold, A.P.; Lorenzo, S.; Lewis, G.R.; Dance, I. *Angew. Chem. Int. Ed.* **2002**, 41, 275.

²²² Mock, W.L. *Top. Curr. Chem.* **1995**, 175, 1; Mock, W.L. in *Comprehensive Supramolecular Chemistry*, Vol. 2 (Eds.: Atwood, J.L.; Davies, J.E.D.; MacNicol, D.D.; Vogtle, F.), Pergamon, Oxford, **1996**, pp. 477–493; Day, A.; Arnold, A.P.; Blanch, R.J.; Snushall, B. *J. Org. Chem.* **2001**, 66, 8094. For cucurbit[10]uril, see Liu, S.; Zavalij, P.Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, 127, 16798.

Stereochemistry and Conformation

The discussions in Chapters 1–3 focused on electron distribution in organic molecules. In this chapter, the focus will be on the 3D structure of organic compounds.¹ The structure may be such that *stereoisomerism*² is possible. Stereoisomers are compounds made up of the same atoms bonded by the same sequence of bonds, but having different 3D structures that are not interchangeable. These structures are called *configurations*.

4.A. OPTICAL ACTIVITY AND CHIRALITY³

Any material that rotates the plane of polarized light is said to be *optically active*. If a pure compound is optically active, the molecule is nonsuperimposable on its mirror image. If a molecule is superimposable on its mirror image, the two structures constitute the same compound and the compound does not rotate the plane of polarized light; it is *optically inactive*. The property of nonsuperimposability of an object on its mirror image is called *chirality*. If a molecule is not superimposable on its mirror image, it is *chiral*. If it is superimposable on its mirror image, it is *achiral*. The relationship between optical activity and chirality is absolute. No exceptions are known, and many thousands of cases have been found in accord with it (however, see Sec. 4.C). The ultimate criterion, then, for optical activity is chirality (nonsuperimposability on the mirror image). This finding is both a necessary and a sufficient condition.⁴ This fact has been used as evidence for the structure determination of many compounds, and historically the tetrahedral nature of carbon was deduced from the hypothesis that the relationship might be true. Note that parity violation

¹ See Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**; Sokolov, V.I. *Introduction to Theoretical Stereochemistry*, Gordon and Breach, NY, **1991**; Nógrádi, M. *Stereochemistry*, Pergamon, Elmsford, NY, **1981**; Kagan, H. *Organic Stereochemistry*, Wiley, NY, **1979**; Testa, B. *Principles of Organic Stereochemistry*, Marcel Dekker, NY, **1979**; Izumi, Y.; Tai, A. *Stereo-Differentiating Reactions*, Academic Press, NY, Kodansha Ltd., Tokyo, **1977**; Natta, G.; Farina, M. *Stereochemistry*, Harper and Row, NY, **1972**; Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, **1969**; Mislow, K. *Introduction to Stereochemistry*, W.A. Benjamin, NY, **1965**. For a historical treatment, see Ramsay, O.B. *Stereochemistry*, Heyden & Son, Ltd., London, **1981**.

² See *Pure Appl. Chem.* **1976**, *45*, 13 and in *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, **1979** (the Blue Book).

³ See Cintas, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 4016.

⁴ For a discussion of the conditions for optical activity in liquids and crystals, see O'Loane, J.K. *Chem. Rev.* **1980**, *80*, 41. For a discussion of chirality as applied to molecules, see Quack, M. *Angew. Chem. Int. Ed.* **1989**, *28*, 571.

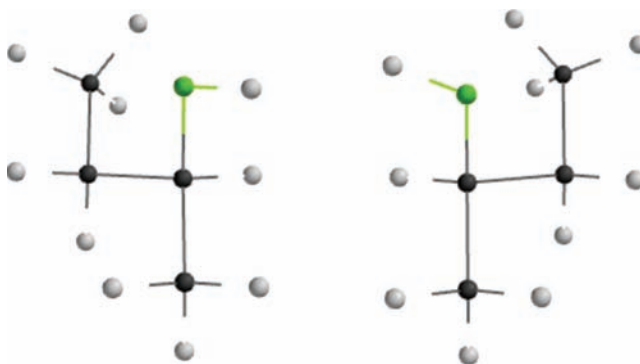


FIG. 4.1. Enantiomers of 2-butanol.

represents an essential property of particle and atomic handedness, and has been related to chirality.⁵

If a molecule is nonsuperimposable on its mirror image, the mirror image must be a different molecule, since superimposability is the same as identity. In each case of optical activity of a pure compound there are two and only two isomers, called *enantiomers* (sometimes *enantiomorphs*), which differ in structure only in the left- and right-handedness of their orientations (see the enantiomers for 2-butanol in Fig. 4.1). Enantiomers have identical⁶ physical and chemical properties except in two important respects:

1. They rotate the plane of polarized light in opposite directions, although in equal amounts. The isomer that rotates the plane to the left (counterclockwise) is called the *levo isomer* and is designated (–), while the one that rotates the plane to the right (clockwise) is called the *dextro isomer* and is designated (+). Because they differ in this property they are often called *optical antipodes*.
2. They may react at different rates with other chiral compounds. These rates may be so close together that the distinction is practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate while the other does not react at all. This finding is the reason that many compounds are biologically active while their enantiomers are not. Enantiomers react at the same rate with achiral compounds.⁷

In general, it may be said that enantiomers have identical properties in a symmetrical environment, but their properties may differ in an unsymmetrical environment.⁸ Besides the important differences previously noted, enantiomers may react at different rates with achiral molecules if an optically active *catalyst* is present; they may have different

⁵ Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J.L.; Palacios, J.C. *Tetrahedron Asymm.* **2000**, *11*, 2845.

⁶ Interactions among electrons, nucleons, and certain components of nucleons (e.g., bosons), called *weak interactions*, violate parity; that is, mirror image interactions do not have the same energy. It has been contended that interactions of this sort cause one of a pair of enantiomers to be (slightly) more stable than the other. See Tranter, G.E. *J. Chem. Soc. Chem. Commun.* **1986**, 60, and references cited therein. See also, Barron, L.D. *Chem. Soc. Rev.* **1986**, *15*, 189.

⁷ For a reported exception, see Hata, N. *Chem. Lett.* **1991**, 155.

⁸ See Craig, D.P.; Mellor, D.P. *Top. Curr. Chem.* **1976**, *63*, 1.

solubilities in an optically active *solvent*; they may have different indexes of refraction or absorption spectra *when examined with circularly polarized light*, and so on. In most cases, these differences are too small to be useful and are often too small to be measured.

Although pure compounds are always optically active if they are composed of chiral molecules, mixtures of equal amounts of enantiomers are optically inactive since the equal and opposite rotations cancel. Such mixtures are called *racemic mixtures*⁹ or *racemates*.¹⁰ Their properties are not always the same as those of the individual enantiomers. The properties in the gaseous or liquid state or in solution usually are the same, since such a mixture is nearly ideal, but properties involving the solid state¹¹ (e.g., melting points, solubilities, and heats of fusion), are often different. Thus racemic tartaric acid has a melting point of 204–206 °C and a solubility in water at 20 °C of 206 g L⁻¹ while for the (+) or the (–) enantiomer, the corresponding figures are 170 °C and 1390 g L⁻¹. The separation of a racemic mixture into its two optically active components is called *resolution*. The presence of optical activity always proves that a given compound is chiral, but its absence does not prove that the compound is achiral. A compound that is optically inactive may be achiral, or it may be a racemic mixture (see also, Sec. 4.C).

4.A.i. Dependence of Rotation on Conditions of Measurement

The *amount* of rotation α is not a constant for a given enantiomer; it depends on the length of the sample vessel, the temperature, the solvent¹² and concentration (for solutions), the pressure (for gases), and the wavelength of light.¹³ Of course, rotations determined for the same compound under the same conditions are identical. The length of the vessel and the concentration or pressure determine the number of molecules in the path of the beam, and α is linear with this. To make it possible for one value of α for a pure compound to be compared with another α for that compound taken under different circumstances, a physical property is defined, called the *specific rotation* $[\alpha]$, which is

$$[\alpha] = \frac{\alpha}{lc} \text{ for solutions} \quad [\alpha] = \frac{\alpha}{ld} \text{ for pure compounds}$$

where α is the observed rotation, l is the cell length in decimeters, c is the concentration in grams per milliliter, and d is the density in the same units. The specific rotation is usually given along with the temperature and wavelength of light used for the measurement, in this manner: $[\alpha]_{546}^{25}$. These conditions must be duplicated for comparison of rotations, since there is no way to put them into a simple formula. The expression $[\alpha]_D$ means that the rotation was measured with sodium D light; that is, $\lambda = 589 \text{ nm}$. The *molar rotation* $[M]_{\lambda}^t$ is the specific rotation times the molecular weight divided by 100.

It must be emphasized that the value of α changes with conditions, but the molecular structure is unchanged. This finding is true even when the changes in conditions are

⁹ Strictly speaking, the term *racemic mixture* applies only when the mixture of molecules is present as separate solid phases, but in this book this expression refers to any equimolar mixture of enantiomeric molecules, liquid, solid, gaseous, or in solution.

¹⁰ See Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, and Resolutions*, Wiley, NY, **1981**.

¹¹ See Wynberg, H.; Lorand, J.P. *J. Org. Chem.* **1981**, *46*, 2538 and references cited therein.

¹² A good example is found in Kumata, Y.; Furukawa, J.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3920.

¹³ For a review of polarimetry see Lyle, G.G.; Lyle, R.E. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, **1983**, pp. 13–27.

sufficient to change not only the amount of rotation, but even the direction. Thus one of the enantiomers of aspartic acid, when dissolved in water, has $[\alpha]_D$ equal to $+4.36^\circ$ at 20°C and -1.86° at 90°C , although the molecular structure is unchanged. A consequence of such cases is that there is a temperature at which there is *no* rotation (in this case 75°C). Of course, the other enantiomer exhibits opposite behavior.

Other cases are known in which the direction of rotation is reversed by changes in wavelength, solvent, and even concentration.¹⁴ In theory, there should be no change in $[\alpha]$ with concentration, since this is taken into account in the formula, but associations, dissociations, and solute–solvent interactions often cause nonlinear behavior. For example, $[\alpha]_D^{24}$ for (–)-2-ethyl-2-methylsuccinic acid in CHCl_3 is -5.0° at $c = 16.5 \text{ g } 100 \text{ mL}^{-1}$ (0.165 g mL^{-1}), -0.7° at $c = 10.6$, $+1.7^\circ$ at $c = 8.5$, and $+18.9^\circ$ at $c = 2.2$.¹⁵ Note that the concentration is sometimes reported in $\text{g } 100 \text{ mL}^{-1}$ (as shown) or as g dL^{-1} (decaliters) rather than the standard g mL^{-1} . One should always check the concentration term to be certain. Note that calculation of the optical rotation of (*R*)-(–)-3-chloro-1-butene found a remarkably large dependence on the $\text{C}=\text{C}-\text{C}-\text{C}$ torsional angle.¹⁶ However, the observed rotations are a factor of 2.6 smaller than the calculated values, independent of both conformation and wavelength from 589 to 365 nm.

4.B. WHAT KINDS OF MOLECULES DISPLAY OPTICAL ACTIVITY?

Although the ultimate criterion is, of course, nonsuperimposability on the mirror image (chirality), other tests may be used that are simpler to apply, but not always accurate. One such test is the presence of a *plane of symmetry*.¹⁷ A plane of symmetry¹⁸ (also called a *mirror plane*) is a plane passing through an object such that the part on one side of the plane is the exact reflection of the part on the other side (the plane acting as a mirror). *Compounds possessing such a plane are always optically inactive*, but there are a few cases known in which compounds lack a plane of symmetry and are nevertheless inactive. Such compounds possess a *center of symmetry* (e.g., in α -truxillic acid), or an *alternating axis of symmetry* as in **1**.¹⁹ A center of symmetry¹⁸ is a point within an object such that a straight line drawn from any part or element of the object to the center and extended an equal distance on the other side encounters an equal part or element. An alternating axis of symmetry¹⁸ of order n is an axis such that when an object containing such an axis is rotated by $360^\circ/n$ about the axis and then reflection is effected across a plane at right angles to the axis, a new object is obtained that is indistinguishable from the original one. Compounds that lack an alternating axis of symmetry are always chiral.

¹⁴ For examples, see Shriner, R.L.; Adams, R.; Marvel, C.S. in Gilman, H. *Advanced Organic Chemistry*, Vol. 1, 2nd ed. Wiley, NY, **1943**, pp. 291–301.

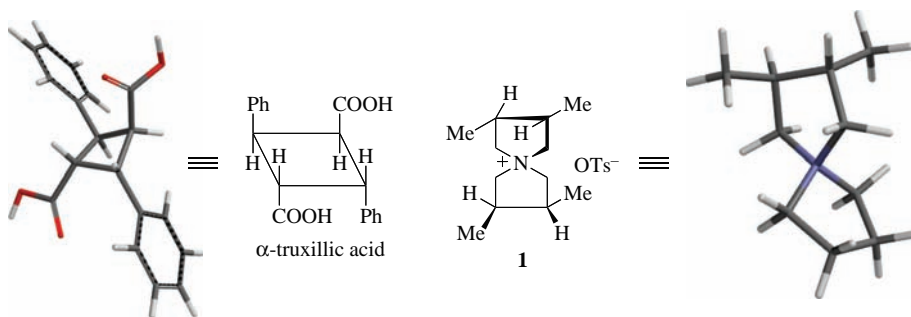
¹⁵ Krow, G.; Hill, R.K. *Chem. Commun.* **1968**, 430.

¹⁶ Wiberg, K. B.; Vaccaro, P. H.; Cheeseman, J.R. *J. Am. Chem. Soc.* **2003**, *125*, 1888.

¹⁷ See Barron L.D. *Chem. Soc. Rev.* **1986**, *15*, 189.

¹⁸ The definitions of plane, center, and alternating axis of symmetry are taken from Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, **1969**, pp. 6,7. See also, Lemièrre, G.L.; Alderweireldt, F.C. *J. Org. Chem.* **1980**, *45*, 4175.

¹⁹ McCasland, G.E.; Proskow, S. *J. Am. Chem. Soc.* **1955**, *77*, 4688.



A molecule that contains just one *stereogenic carbon atom* (defined as a carbon atom connected to four different groups; also called a *chiral atom* or an *asymmetric carbon atom*) is always chiral, and hence optically active.²⁰ As seen in Fig. 4.1, such a molecule *cannot* have a plane of symmetry, whatever the identity of the four atoms or groups, as long as they are all different. However, optical activity may be present in molecules with no stereogenic atom.²¹ Some molecules with two or more stereogenic carbon atoms, however, are superimposable on their mirror images (called *meso* compounds), and hence inactive principally because there is symmetry. Examples of such compounds will be discussed subsequently.

Optically active compounds may be classified into several categories.

1. *Compounds with a Stereogenic Carbon Atom.* If there is only one such atom, the molecule must be optically active, no matter how slight the differences are among the four groups. An example is 1,12-dibromo-6-methyldodecane, which has one stereogenic carbon and will be optically active. Optical activity has been detected even in cases²² (e.g., 1-butanol-1-*d*), where one group is hydrogen and another deuterium:²³ The stereogenic carbon is connected to OH, H, D, and a propyl group.

Although enantiomers will exhibit specific rotation of equal magnitude but opposite sign, the difference may be too small to be measured accurately. In optically active compounds, the amount of rotation is greatly dependent on the nature of the four groups, in general increasing with increasing differences in polarizabilities among the groups. Alkyl groups have very similar polarizabilities²⁴ and the optical activity of 5-ethyl-5-propylundecane is too low to be measurable at any wavelength between 280 and 580 nm.²⁵

2. *Compounds with Other Quadrivalent Stereogenic Atoms.*²⁶ Any molecule with an atom that has four bonds pointing to the corners of a tetrahedron will be optically

²⁰ For discussions of the relationship between a chiral carbon and chirality, see Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, 106, 3319; Brand, D.J.; Fisher, J. *J. Chem. Educ.* **1987**, 64, 1035.

²¹ For a review of such molecules, see Nakazaki, M. *Top. Stereochem.* **1984**, 15, 199.

²² See Barth, G.; Djerassi, C. *Tetrahedron* **1981**, 24, 4123; Verbit, L. *Prog. Phys. Org. Chem.* **1970**, 7, 51; Floss, H.G.; Tsai, M.; Woodard, R.W. *Top. Stereochem.* **1984**, 15, 253.

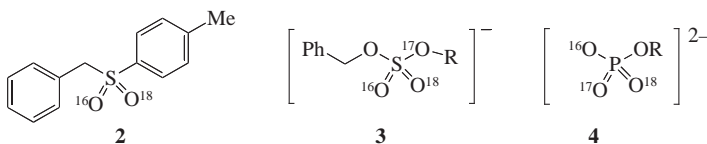
²³ Streitwieser, Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* **1956**, 78, 5597.

²⁴ For a discussion of optical activity in paraffins, see Brewster, J.H. *Tetrahedron* **1974**, 30, 1807.

²⁵ Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1980**, 45, 2754.

²⁶ For compounds with asymmetric atoms other than carbon, see Aylett, B.J. *Prog. Stereochem.* **1969**, 4, 213; Belloli, R. *J. Chem. Educ.* **1969**, 46, 640; Sokolov, V.I.; Reutov, O.A. *Russ. Chem. Rev.* **1965**, 34, 1.

active if the four groups are different. Among atoms in this category are Si,²⁷ Ge, Sn,²⁸ and N (in quaternary salts or *N*-oxides).²⁹ In sulfones, the sulfur bonds have a tetrahedral array, but since two of the groups are always oxygen, no chirality results. However, the preparation³⁰ of an optically active sulfone (**2**) in which one oxygen is ¹⁶O and the other is ¹⁸O illustrates the point that slight differences in groups are all that is necessary. This point has been taken even further with the preparation of ester **3**, both enantiomers of which have been prepared.³¹ Optically active chiral phosphates (**4**) have similarly been made.³²



3. *Compounds with Tervalent Stereogenic Atoms.* Atoms with pyramidal bonding³³ might be expected to give rise to optical activity if the atom is connected to three different groups, since the unshared pair of electrons is analogous to a fourth group, necessarily different from the others. For example, a secondary or tertiary amine



where X, Y, and Z are different and the fourth group is the electron pair would be expected to be chiral and thus resolvable. Many attempts have been made to resolve such compounds, but until 1968 all of them failed because of *pyramidal inversion* (also called *fluxional inversion*), which is a rapid oscillation of the unshared pair from one side of the XYZ plane to the other, thus converting the molecule into its enantiomer.³⁴ For ammonia, there are 2×10^{11} inversions every second. The inversion is less rapid in substituted ammonia derivatives³⁵ (amines, amides, etc.). The interconversion barrier for endo versus exo methyl in *N*-methyl-2-azabicyclo[2.2.1]heptane, for example, is $0.3 \text{ kcal mol}^{-1}$ (1.26 kJ mol^{-1}).³⁶ In this case, torsional strain plays a significant role, along with angle strain, in determining inversion barriers. Two types of nitrogen atom

²⁷ See Corriu, R.J.P.; Guérin, C.; Moreau, J.J.E. in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 1, Wiley, NY, **1989**, pp. 305–370; *Top. Stereochem.* **1984**, *15*, 43; Maryanoff, C.A.; Maryanoff, B.E. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, **1984**, pp. 355–374.

²⁸ See Gielen, M. *Top. Curr. Chem.* **1982**, *104*, 57; *Top. Stereochem.* **1981**, *12*, 217.

²⁹ See Davis, F.A.; Jenkins Jr., R.H. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, **1984**, pp. 313–353; Pope, W. J.; Peachey, S.J. *J. Chem. Soc.* **1899**, 75, 1127.

³⁰ Stirling, C.J.M. *J. Chem. Soc.* **1963**, 5741; Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* **1969**, *91*, 3603; Annunziata, R.; Cinquini, M.; Colonna, S. *J. Chem. Soc. Perkin Trans. 1* **1972**, 2057.

³¹ Lowe, G.; Parratt, M.J. *J. Chem. Soc. Chem. Commun.* **1985**, 1075.

³² Abbott, S.J.; Jones, S.R.; Weinman, S.A.; Knowles, J.R. *J. Am. Chem. Soc.* **1978**, *100*, 2558; Cullis, P.M.; Lowe, G. *J. Chem. Soc. Chem. Commun.* **1978**, 512. See Lowe, G. *Acc. Chem. Res.* **1983**, *16*, 244.

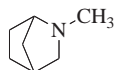
³³ For a review of the stereochemistry at trivalent nitrogen, see Raban, M.; Greenblatt, J. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, **1982**, pp. 53–83.

³⁴ See Lambert, J.B. *Top. Stereochem.* **1971**, *6*, 19; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* **1970**, *9*, 400; Lehn, J.M. *Fortschr. Chem. Forsch.* **1970**, *15*, 311.

³⁵ For example, see Stackhouse, J.; Baechler, R.D.; Mislow, K. *Tetrahedron Lett.* **1971**, 3437, 3441.

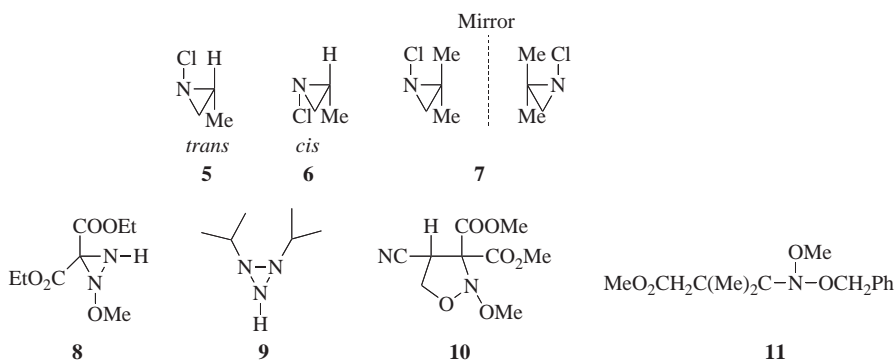
³⁶ Forsyth, D.A.; Zhang, W.; Hanley, J.A. *J. Org. Chem.* **1996**, *61*, 1284. Also see, Adams, D.B. *J. Chem. Soc. Perkin Trans. 2* **1993**, 567.

invert particularly slowly, namely, a nitrogen atom in a three-membered ring and a nitrogen atom connected to another atom bearing an



N-Methyl-2-azabicyclo[2.2.1]heptane

unshared pair. Even in such compounds, however, pyramidal inversion proved too rapid to permit isolation of separate isomers for many years. This goal was accomplished²⁹ only when compounds were synthesized in which both features are combined: a nitrogen atom in a three-membered ring connected to an atom containing an unshared pair. For example, the two isomers of 1-chloro-2-methylaziridine (**5** and **6**) were separated and do not interconvert at room temperature.³⁷ In suitable cases, this barrier to inversion can result in compounds that are optically active solely because of a chiral tervalent nitrogen atom. For example, **7** has been resolved into its separate enantiomers.³⁸ Note that in this case too, the nitrogen is connected to an atom with an unshared pair. Conformational stability has also been demonstrated for oxaziridines,³⁹ diaziridines (e.g., **8**),⁴⁰ triaziridines (e.g., **9**),⁴¹ and 1,2-oxazolidines (e.g., **10**),⁴² even though in this case the ring is five membered. However, note that the nitrogen atom in **10** is connected to two oxygen atoms.



³⁷ Brois, S.J. *J. Am. Chem. Soc.* **1968**, 90, 506, 508. See also, Shustov, G.V.; Kadorkina, G.K.; Kostyanovsky, R.G.; Rauk, A. *J. Am. Chem. Soc.* **1988**, 110, 1719; Lehn, J.M.; Wagner, J. *Chem. Commun.* **1968**, 148; Felix, D.; Eschenmoser, A. *Angew. Chem. Int. Ed.* **1968**, 7, 224. For a review, see Brois, S.J. *Trans. N.Y. Acad. Sci.* **1969**, 31, 931.

³⁸ Schurig, V.; Leyrer, U. *Tetrahedron Asymm.* **1990**, 1, 865.

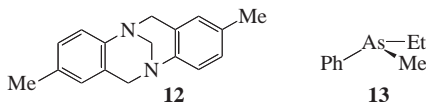
³⁹ Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G.; Brückner, S.; Malpezzi, L. *J. Chem. Soc. Perkin Trans. 2* **1988**, 1595. See also, Forni, A.; Moretti, I.; Torre, G.; Brückner, S.; Malpezzi, L.; Di Silvestro, G.D. *J. Chem. Soc. Perkin Trans. 2* **1984**, 791. See Schmitz, E. *Adv. Heterocycl. Chem.* **1979**, 24, 63.

⁴⁰ Shustov, G.V.; Denisenko, S.N.; Chervin, I.I.; Asfandiarov, N.L.; Kostyanovsky, R.G. *Tetrahedron* **1985**, 41, 5719 and cited references. See also, Mannschreck, A.; Radeaglia, R.; Gründemann, E.; Ohme, R. *Chem. Ber.* **1967**, 100, 1778.

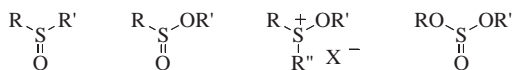
⁴¹ Hilpert, H.; Hoesch, L.; Dreiding, A.S. *Helv. Chim. Acta* **1985**, 68, 1691; **1987**, 70, 381.

⁴² See Wu, G.; Huang, M. *Chem. Rev.* **2006**, 106, 2596.

Compound **11** is another example in which nitrogen is connected to two oxygen atoms. In this case there is no ring at all, but it has been resolved into (+) and (−) enantiomers ($[\alpha]_{\text{D}}^{20} \approx \pm 3^\circ$).⁴³ This compound and several similar ones reported in the same paper are the first examples of compounds whose optical activity is solely due to an acyclic tervalent chiral nitrogen atom. However, **11** is not optically stable and racemizes at 20°C with a half-life of 1.22 h. A similar compound (**11**, with OCH_2Ph replaced by OEt) has a longer half-life, 37.5 h at 20°C.



In molecules in which the nitrogen atom is at a bridgehead, pyramidal inversion is of course prevented. Such molecules, if chiral, can be resolved even without the presence of the two structural features noted above. For example, optically active **12** (*Tröger's base*) has been prepared.⁴⁴ Phosphorus inverts more slowly and arsenic still more slowly.⁴⁵ Nonbridgehead phosphorus,⁴⁶ arsenic, and antimony compounds have also been resolved (e.g., **13**).⁴⁷ Sulfur exhibits pyramidal bonding in sulfoxides, sulfinic esters, sulfonium salts, and sulfites. Examples of each of these have been resolved.⁴⁸ An interesting example is (+)- $\text{Ph}^{12}\text{CH}_2\text{SO}^{13}\text{CH}_2\text{Ph}$, a sulfoxide in which the two alkyl groups differ only in ^{12}C versus ^{13}C , but which has $[\alpha]_{280} = +0.71^\circ$.⁴⁹ A computational study indicates that base-catalyzed inversion at sulfur in sulfoxides is possible via a tetrahedral intermediate.⁵⁰



4. *Suitably Substituted Adamantanes.* Adamantanes bearing four different substituents at the bridgehead positions are chiral and optically active and **14**, for example, has been resolved.⁵¹ This type of molecule is a kind of expanded tetrahedron and has the same symmetry properties as any other tetrahedron.

⁴³ Kostyanovsky, R.G.; Rudchenko, V.F.; Shtamburg, V.G.; Chervin, I.I.; Nasibov, S.S. *Tetrahedron* **1981**, *37*, 4245; Kostyanovsky, R.G.; Rudchenko, V.F. *Doklad. Chem.* **1982**, *263*, 121. See also, Rudchenko, V.F.; Ignatov, S.M.; Chervin, I.I.; Kostyanovsky, R.G. *Tetrahedron* **1988**, *44*, 2233.

⁴⁴ Prelog, V.; Wieland, P. *Helv. Chim. Acta* **1944**, *27*, 1127.

⁴⁵ For reviews, see Yambushev, F.D.; Savin, V.I. *Russ. Chem. Rev.* **1979**, *48*, 582; Gallagher, M.J.; Jenkins, I.D. *Top. Stereochem.* **1968**, *3*, 1; Kamai, G.; Usacheva, G.M. *Russ. Chem. Rev.* **1966**, *35*, 601.

⁴⁶ See Valentine, Jr., D.J. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, **1984**, pp. 263–312.

⁴⁷ Horner, L.; Fuchs, H. *Tetrahedron Lett.* **1962**, 203.

⁴⁸ See Andersen, K.K. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulfoxides*, Wiley, NY, **1988**, pp. 55–94; and in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, **1981**, pp. 229–312; Barbachyn, M.R.; Johnson, C.R. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, **1984**, pp. 227–261; Cinquini, M.; Cozzi, F.; Montanari, F. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, **1985**, pp. 355–407; Mikol/ajczyk, M.; Drabowicz, J. *Top. Stereochem.* **1982**, *13*, 333.

⁴⁹ Andersen, K.K.; Colonna, S.; Stirling, C.J.M. *J. Chem. Soc. Chem. Commun.* **1973**, 645.

⁵⁰ Balcells, D.; Maseras, F.; Khair, N. *Org. Lett.* **2004**, *6*, 2197.

⁵¹ Hamill, H.; McKerver, M.A. *Chem. Commun.* **1969**, 864; Applequist, J.; Rivers, P.; Applequist, D.E. *J. Am. Chem. Soc.* **1969**, *91*, 5705.

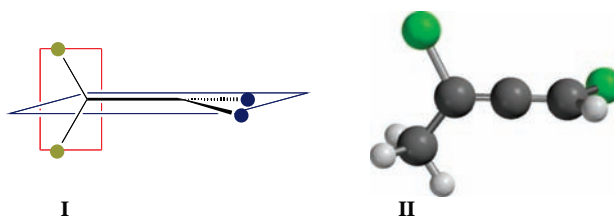
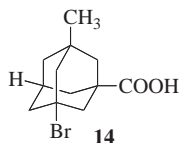
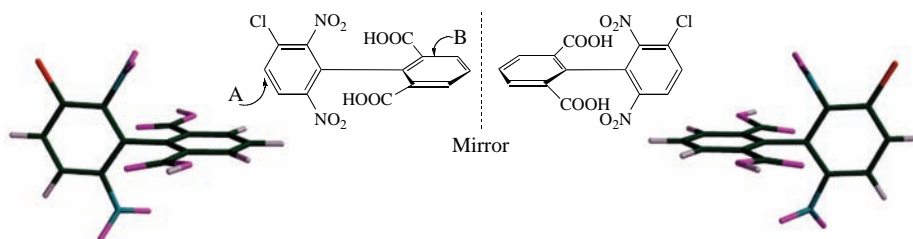


FIG. 4.2. Perpendicular dissymmetric planes and a chiral molecule with no stereogenic center.



5. *Restricted Rotation Giving Rise to Perpendicular Dissymmetric Planes.* Certain compounds that do not contain asymmetric atoms are nevertheless chiral, as illustrated in Fig. 4.2. For such compounds, there are two perpendicular planes (see I), neither of which can be bisected by a plane of symmetry (as illustrated by II). If either plane could be so bisected, the molecule would be superimposable on its mirror image, since such a plane would be a plane of symmetry. These points will be illustrated by examples.

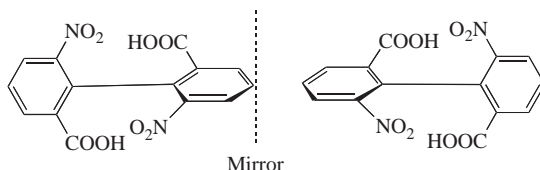
Biphenyls that contain four large groups in the ortho positions cannot freely rotate about the central bond because of steric hindrance.⁵² For example, the activation energy (rotational barrier) for the enantiomerization process of the chiral 2-carboxy-2'-methoxy-6-nitrobiphenyl was determined, $\Delta G^\ddagger = 21.8 \pm 0.1 \text{ kcal mol}^{-1}$ (91.3 kJ mol^{-1}).⁵³ In such compounds, the two rings are in perpendicular planes. If either ring is symmetrically substituted, the molecule has a plane of symmetry. For example, consider the biaryls:



Ring B is symmetrically substituted. A plane drawn perpendicular to ring B contains all the atoms and groups in ring A; hence, it is a plane of symmetry and the compound is achiral. On the other hand, consider

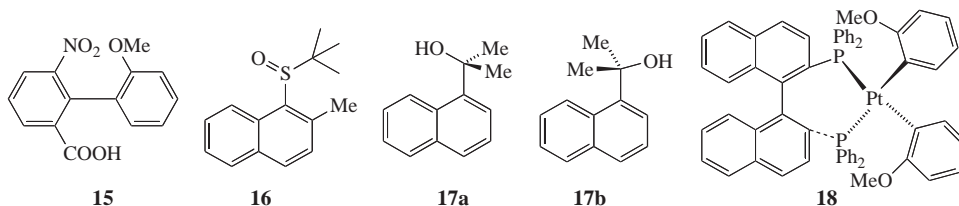
⁵² When the two rings of a biphenyl are connected by a bridge, rotation is of course impossible. For a review of such compounds, see Hall, D.M. *Prog. Stereochem.* **1969**, 4, 1.

⁵³ Ceccacci, F.; Mancini, G.; Mencarelli, P.; Villani, C. *Tetrahedron Asym.* **2003**, 14, 3117.



In this molecule, there is no plane of symmetry and the molecule is chiral; many such compounds have been resolved. Note that groups in the para position cannot cause lack of symmetry. Isomers that can be separated only because rotation about single bonds is prevented or greatly slowed are called *atropisomers*.⁵⁴ 9,9'-Bianthryls also show hindered rotation and exhibit atropisomers.⁵⁵ Low-temperature NMR is sometimes used to detect atropisomers in certain systems [1,2,4,5-tetra(*o*-tolyl)benzene, e.g.].⁵⁶ Configurationally stable atropisomers are known.⁵⁷

It is not always necessary for four large ortho groups to be present in order for rotation to be prevented. Compounds with three and even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved. An example is biphenyl-2,2'-bis-sulfonic acid.⁵⁸ In some cases, the groups may be large enough to slow rotation greatly, but not to prevent it completely. In such cases, optically active compounds can be prepared that slowly racemize on standing. Thus, **15** loses its optical activity with a half-life of 9.4 min in ethanol at 25°C.⁵⁹ Compounds with greater rotational stability can often be racemized if higher temperatures are used to supply the energy necessary to force the groups past each other.⁶⁰



Atropisomerism occurs in other systems as well, including monopyrroles.⁶¹ Sulfoxide (**16**), for example, forms atropisomers with an interconversion barrier with its atropisomer of 18–19 kcal mol⁻¹ (75.4–79.5 kJ mol⁻¹).⁶² The atropisomers of hindered naphthyl alcohols (e.g., **17**) exist as the *sp*-atropisomer (**17a**) and the *ap*-atropisomer (**17b**).⁶³ Atropisomers can also be formed in organometallic

⁵⁴ For a review, see Ōki, M. *Top. Stereochem.* **1983**, *14*, 1. Also see Miljanić, O.S.; Han, S.; Holmes, D.; Schaller, G.R.; Vollhardt, K.P.C. *Chem. Commun.* **2005**, 2606.

⁵⁵ Becker, H.-D.; Langer, V.; Sieler, J.; Becker, H.-C. *J. Org. Chem.* **1992**, *57*, 1883.

⁵⁶ Lunazzi, L.; Mazzanti, A.; Minzoni, M. *J. Org. Chem.* **2005**, *70*, 10062.

⁵⁷ Casarini, D.; Coluccini, C.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2005**, *70*, 5098.

⁵⁸ Patterson, W.I.; Adams, R. *J. Am. Chem. Soc.* **1935**, *57*, 762.

⁵⁹ Stoughton, R.W.; Adams, R. *J. Am. Chem. Soc.* **1932**, *54*, 4426.

⁶⁰ See Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**.

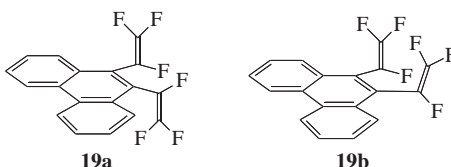
⁶¹ Boiadjev, S.E.; Lightner, S.A. *Tetrahedron Asym.* **2002**, *13*, 1721.

⁶² Casarini, D.; Foresti, E.; Gasparrini, F.; Lunazzi, L.; Macciantelli, D.; Misiti, D.; Villani, C. *J. Org. Chem.* **1993**, *58*, 5674.

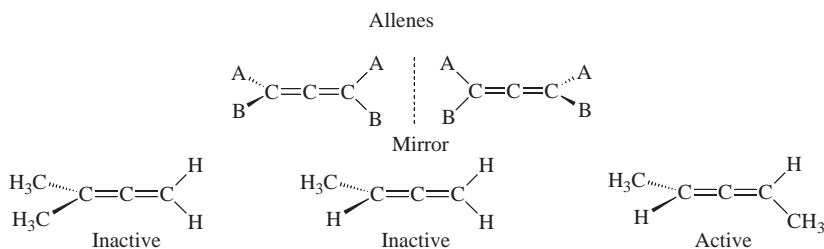
⁶³ See Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801. For a review of BINOL, see Brunel, J.M. *Chem. Rev.* **2005**, *105*, 857.

compounds, [e.g., the bis(phosphinoplatinum) complex (see **18**)] generated by reaction with (R)-BINAP [(2*R*₁ 3*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphyl, see Reaction **19-36**].⁶⁴

It is possible to isolate isomers in some cases, often due to restricted rotation. In 9,10-bis(trifluorovinyl)phenanthrene (**19**) torsional diastereomers (see Sec. 4.G) are formed. The value of *K* for interconversion of **19a** and **19b** is 0.48, with $\Delta G^0 = 15.1 \text{ kcal mol}^{-1}$.⁶⁵ The ability to isolate atropisomers can depend on interactions with solvent, as in the isolation of atropisomeric colchicinoid alkaloids, which have been isolated, characterized, and their dichroic behavior described.⁶⁶



In allenes, the central carbon is *sp* hybridized. The remaining two *p* orbitals are perpendicular to each other and each overlaps with the *p* orbital of one adjacent carbon atom, forcing the two remaining bonds of each carbon into perpendicular planes. Thus allenes fall into the category represented by Fig. 4.2. Like biphenyls, allenes are chiral *only* if both sides are unsymmetrically substituted.⁶⁷ These cases are completely different from the cis–trans isomerism of compounds with one double bond (Sec. 4.K). In the latter cases, the four groups are all in one plane, the isomers are not enantiomers, and neither is chiral, while in allenes the groups are in two perpendicular planes and the isomers are a pair of optically active enantiomers.



When a molecule has three, five, or any *odd* number of cumulative double bonds, orbital overlap causes the four groups to occupy one plane and cis–trans isomerism is observed. When four, six, or any *even* number of cumulative double bonds exist, the situation is analogous to that in the allenes and optical activity is possible. Compound **20** has been resolved.⁶⁸

⁶⁴ Alcock, N.W.; Brown, J.M.; Pérez-Torrente, J.J. *Tetrahedron Lett.* **1992**, 33, 389. See also, Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J.J.; Yamanaka, M. *Synlett* **2002**, 1561.

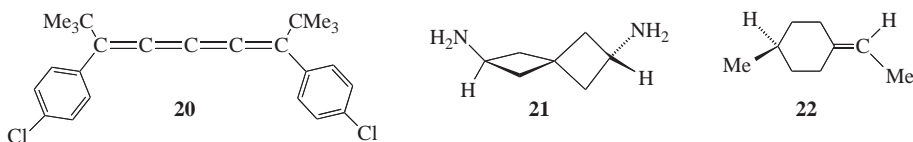
⁶⁵ Dolbier Jr., W.R.; Palmer, K.W. *Tetrahedron Lett.* **1992**, 33, 1547.

⁶⁶ Cavazza, M.; Zandomenighi, M.; Pietra, F. *Tetrahedron Lett.* **2000**, 41, 9129.

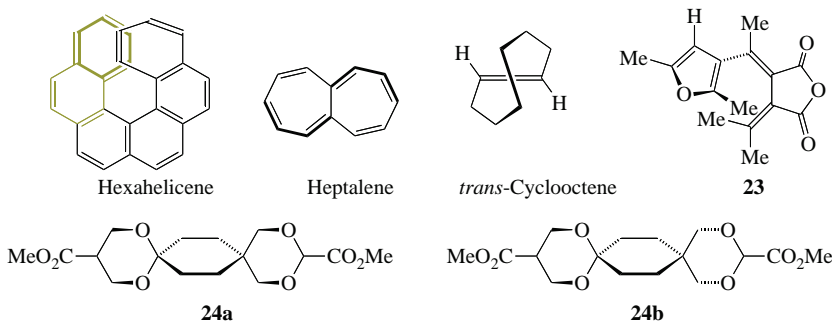
⁶⁷ For reviews of allene chirality, see Runge, W. in Landor, S.R. *The Chemistry of the Allenes*, Vol. 3, Academic Press, NY, **1982**, pp. 579–678, and in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 1, Wiley, NY, **1980**, pp. 99–154; Rossi, R.; Diversi, P. *Synthesis* **1973**, 25.

⁶⁸ Nakagawa, M.; Shingū, K.; Naemura, K. *Tetrahedron Lett.* **1961**, 802.

Other types of compounds that contain the system illustrated in Fig. 4.2 and that are similarly chiral if both sides are dissymmetric include spiranes (e.g., **21**), and compounds with exocyclic double bonds (e.g., **22**). Atropisomerism exists in (1,5)-bridgedcalix[8]arenes (see Sec. 3.C.ii).⁶⁹



6. *Chirality due to a Helical Shape.*⁷⁰ Several compounds have been prepared that are chiral because they have a shape that is actually helical and can therefore be left- or right handed in orientation. The entire molecule is usually less than one full turn of the helix, but this does not alter the possibility of left- and right handedness. An example is hexahelicene,⁷¹ in which one side of the molecule must lie above the other because of crowding.⁷² The rotational barrier for helicene is $\sim 22.9 \text{ kcal mol}^{-1}$ (95.9 kJ mol^{-1}), and significantly higher when substituents are present.⁷³ It has been shown that the dianion of helicene retains its chirality.⁷⁴ Chiral discrimination of helicenes is possible.⁷⁵ 1,16-Diazo[6]helicene has also been prepared and, interestingly, does not act as a proton sponge (see Sec. 8.F) because the helical structure leaves the basic nitrogen atoms too far apart. Heptalene is another compound that is not planar (Sec. 2.I.iii). Its twisted structure makes it chiral, but the enantiomers rapidly interconvert.⁷⁶



⁶⁹ Consoli, G.M.L.; Cunsolo, F.; Geraci, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2002**, 4, 2649.

⁷⁰ For a review, see Meurer, K.P.; Vögtle, F. *Top. Curr. Chem.* **1985**, 127, 1. See also, Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* **1984**, 125, 63; Martin, R.H. *Angew. Chem. Int. Ed.* **1974**, 13, 649.

⁷¹ Martin, R.H.; Baes, M. *Tetrahedron* **1975**, 31, 2135; Bernstein, W.J.; Calvin, M.; Buchardt, O. *J. Am. Chem. Soc.* **1973**, 95, 527; Defay, N.; Martin, R.H. *Bull. Soc. Chim. Belg.* **1984**, 93, 313; Bestmann, H.J.; Roth, W. *Chem. Ber.* **1974**, 107, 2923.

⁷² For reviews of the helicenes, see Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* **1984**, 125, 63; Martin, R.H. *Angew. Chem. Int. Ed.* **1974**, 13, 649.

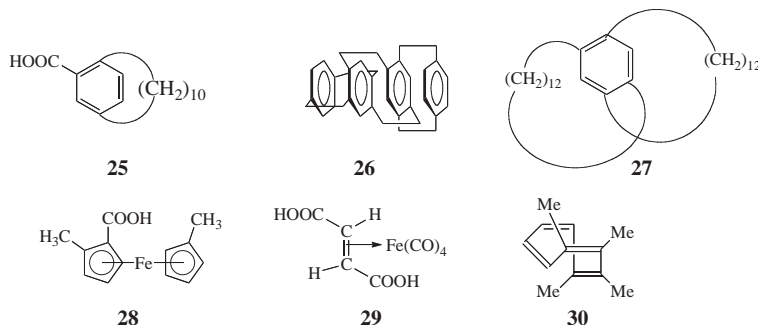
⁷³ Janke, R.H.; Haufe, G.; Würthwein, E.-U.; Borkent, J.H. *J. Am. Chem. Soc.* **1996**, 118, 6031.

⁷⁴ Frim, R.; Goldblum, A.; Rabinovitz, M. *J. Chem. Soc. Perkin Trans. 2* **1992**, 267.

⁷⁵ Murguly, E.; McDonald, R.; Branda, N.R. *Org. Lett.* **2000**, 2, 3169.

⁷⁶ Staab, H.A.; Diehm, M.; Krieger, C. *Tetrahedron Lett.* **1994**, 35, 8357.

trans-Cyclooctene (see also, Sec. 4.K.i) also exhibits helical chirality because the carbon chain must lie above the double bond on one side and below it on the other.⁷⁷ Similar helical chirality also appears in fulgide **23**⁷⁸ and dispiro-1,3-dioxane (**24**), shows two enantiomers (**24a** and **24b**).⁷⁹



7. *Optical Activity Caused by Restricted Rotation of Other Types.* Substituted paracyclophanes may be optically active⁸⁰ and **25**, for example, has been resolved.⁸¹ In this case, chirality results because the benzene ring cannot rotate in such a way that the carboxyl group goes through the alicyclic ring. Many chiral layered cyclophanes (e.g., **26**), have been prepared.⁸² Another cyclophane⁸³ with a different type of chirality is [12][12]paracyclophane (**27**), where the chirality arises from the relative orientation of the two rings attached to the central benzene ring.⁸⁴ An acetylenic cyclophane was shown to have helical chirality.⁸⁵ Metallocenes (Sec. 2.I.ii) substituted with at least two different groups on one ring are also chiral.⁸⁶ Several hundred such compounds have been resolved, one being **28**. Chirality is also found in other metallic complexes of suitable geometry.⁸⁷ Fumaric acid–iron tetracarbonyl (**29**) has been resolved,⁸⁸ and 1,2,3,4-tetramethylcyclooctatetraene (**30**) is also chiral.⁸⁹ This molecule, which exists in the tub form (Sec. 2.K), has

⁷⁷ Cope, A.C.; Ganellin, C.R.; Johnson, Jr., H.W.; Van Auken, T.V.; Winkler, H.J.S. *J. Am. Chem. Soc.* **1963**, *85*, 3276. Also see, Levin, C.C.; Hoffmann, R. *J. Am. Chem. Soc.* **1972**, *94*, 3446.

⁷⁸ Yokoyama, Y.; Iwai, T.; Yokoyama, Y.; Kurita, Y. *Chem. Lett.* **1994**, 225.

⁷⁹ Grosu, I.; Mager, S.; Plé, G.; Mesáros, E. *Tetrahedron* **1996**, *52*, 12783.

⁸⁰ For an example, see Rajakumar, P.; Srisailas, M. *Tetrahedron* **2001**, *57*, 9749.

⁸¹ Blomquist, A.T.; Stahl, R.E.; Meinwald, Y.C.; Smith, B.H. *J. Org. Chem.* **1961**, *26*, 1687. For a review of chiral cyclophanes and related molecules, see Schlögl, K. *Top. Curr. Chem.* **1984**, *125*, 27.

⁸² Nakazaki, M.; Yamamoto, K.; Tanaka, S.; Kametani, H. *J. Org. Chem.* **1977**, *42*, 287. Also see, Pelter, A.; Crump, R.A.N.C.; Kidwell, H. *Tetrahedron Lett.* **1996**, *37*, 1273. For an example of a chiral [2.2]-paracyclophane.

⁸³ For a treatise on the quantitative chirality of helicenes, see Katzenelson, O.; Edelstein, J.; Avnir, D. *Tetrahedron Asym.* **2000**, *11*, 2695.

⁸⁴ Chan, T.-L.; Hung, C.-W.; Man, T.-O.; Leung, M.-k. *J. Chem. Soc. Chem. Commun.* **1994**, 1971.

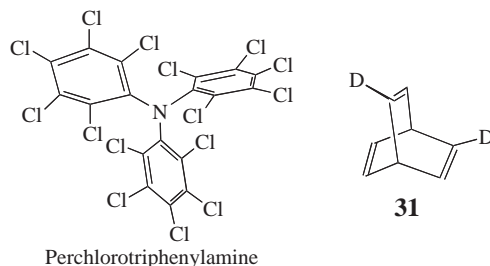
⁸⁵ Collins, S.K.; Yap, G.P.A.; Fallis, A.G. *Org. Lett.* **2000**, *2*, 3189.

⁸⁶ For reviews on the stereochemistry of metallocenes, see Schlögl, K. *J. Organomet. Chem.* **1986**, *300*, 219; *Top. Stereochem.* **1967**, *1*, 39; *Pure Appl. Chem.* **1970**, *23*, 413.

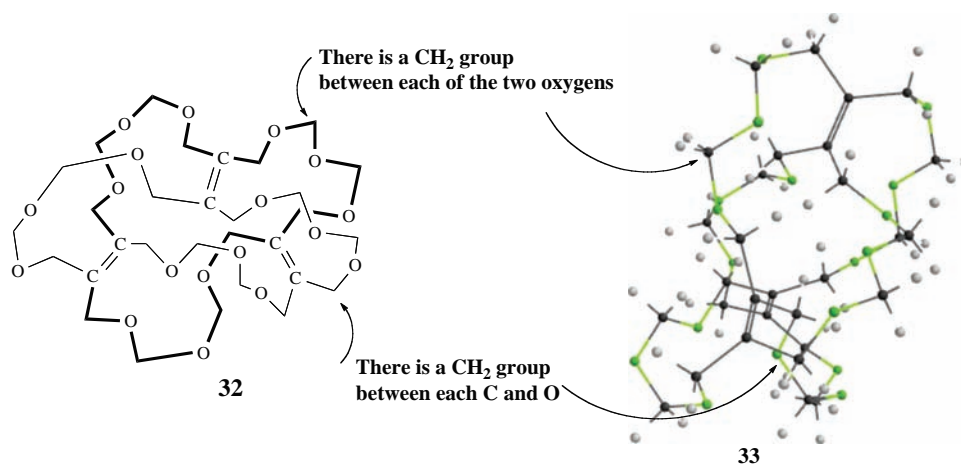
⁸⁷ For reviews of such complexes, see Paiaro, G. *Organomet. Chem. Rev. Sect. A* **1970**, *6*, 319.

⁸⁸ Paiaro, G.; Palumbo, R.; Musco, A.; Panunzi, A. *Tetrahedron Lett.* **1965**, 1067. Also see, Paiaro, G.; Panunzi, A. *J. Am. Chem. Soc.* **1964**, *86*, 5148.

⁸⁹ Paquette, L.A.; Gardlik, J.M.; Johnson, L.K.; McCullough, K.J. *J. Am. Chem. Soc.* **1980**, *102*, 5026.



neither a plane nor an alternating axis of symmetry. Another compound that is chiral solely because of hindered rotation is the propeller-shaped perchlorotriphenylamine, which has been resolved.⁹⁰ The 2,5-dideuterio derivative (**31**) of barrelene is chiral, though the parent hydrocarbon and the monodeuterio derivative are not. Compound **25** has been prepared in optically active form⁹¹ and is another case where chirality is due to isotopic substitution.



The main molecular chain in compound **32** has the form of a Möbius strip (see Fig. 15.7 and 3D model **33**).⁹² This molecule has no stereogenic carbons, nor does it have a rigid shape, a plane, nor an alternating axis of symmetry. However, **32** has been synthesized and shown to be chiral.⁹³ Rings containing 50 or more members should be able to exist as knots (**34**, and see **39** on Sec. 3.D). Such a knot would be nonsuperimposable on its mirror image. Calixarenes,⁹⁴ crown ethers,⁹⁵ catenanes, and rotaxanes (see Sec. 3.D) can also be chiral if suitably substituted.⁹⁶ For example, **40** and **41** are nonsuperimposable mirror images.

⁹⁰ Okamoto, Y.; Yashima, E.; Hatada, K.; Mislow, K. *J. Org. Chem.* **1984**, 49, 557. See Grilli, S.; Lunazzi, L.; Mazzanti, A.; Casarini, D.; Femoni, C. *J. Org. Chem.* **2001**, 66, 488.

⁹¹ Lightner, D.A.; Paquette, L.A.; Chayangkoon, P.; Lin, H.; Peterson, J.R. *J. Org. Chem.* **1988**, 53, 1969.

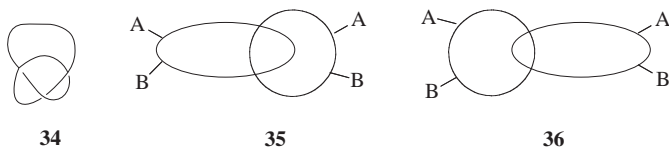
⁹² See Walba, D.M. *Tetrahedron* **1985**, 41, 3161.

⁹³ Walba, D.M.; Richards, R.M.; Haltiwanger, R.C. *J. Am. Chem. Soc.* **1982**, 104, 3219.

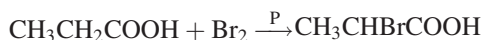
⁹⁴ Iwanek, W.; Wolff, C.; Mattay, J. *Tetrahedron Lett.* **1995**, 36, 8969.

⁹⁵ de Vries, E.F.J.; Steenwinkel, P.; Brussee, J.; Kruse, C.G.; van der Gen, A. *J. Org. Chem.* **1993**, 58, 4315; Pappalardo, S.; Palrisi, M.F. *Tetrahedron Lett.* **1996**, 37, 1493; Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, 37, 7627.

⁹⁶ See Schill, G. *Catenanes, Rotaxanes, and Knots*, Academic Press, NY, **1971**, pp. 11–18.



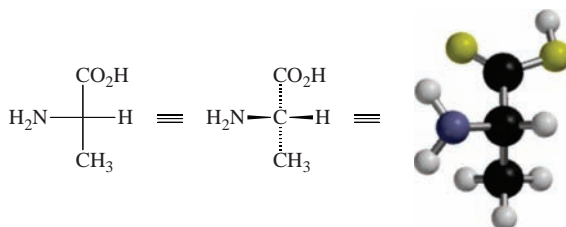
A stereogenic center may be created from an achiral molecule via a chemical reaction. One example is the α -bromination of a carboxylic acid (Hell–Volhardt–Zelenskii reaction, **12-05**) to form the α -bromo acid.



In this case, the α -carbon in the product is the stereogenic carbon. If there are no asymmetric components in the reaction, the product must be racemic. This means that no optically active material can be created if all starting materials and conditions are optically inactive.⁹⁷ This statement also holds when one begins with a racemic mixture, unless there is kinetic resolution (Sec. 4.I). Thus racemic 2-butanol, treated with HBr, must give racemic 2-bromobutane.

4.C. THE FISCHER PROJECTION

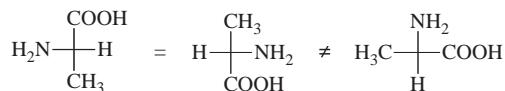
For a thorough understanding of stereochemistry, it is useful to examine molecular models (like those depicted in Fig. 4.1). However, this is not feasible when writing on paper. In 1891, Emil Fischer displayed amino acids and some carbohydrates in a particular way known as a *Fischer projection*. This is simply a method of representing and “edge-viewed” tetrahedral on paper. By this convention, the model is held so that the two bonds in front of the paper are horizontal and those behind the paper are vertical, as shown for 2-aminopropanoic acid (alanine). With modern computers, molecular models are readily available, but the ability to write structures in two dimensions to represent a 3D form remains important.



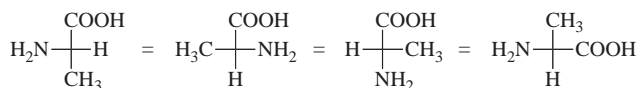
In order to obtain proper results with these formulas, remember that they are projections and must be treated differently from the models in testing for superimposability. Every

⁹⁷ There is one exception to this statement. In a very few cases, racemic mixtures may crystalize from solution in such a way that all the (+) molecules go into one crystal and the (–) molecules into another. If one of the crystals crystallizes before the other, a rapid filtration results in optically active material. For a discussion, see Pincock, R.E.; Wilson, K.R. *J. Chem. Educ.* **1973**, *50*, 455.

plane is superimposable on its mirror image; hence with these formulas there must be added the restriction that they may not be taken out of the plane of the blackboard or paper. Also, they may not be rotated 90° , although 180° rotation is permissible:



It is also permissible to keep any one group fixed and to rotate the other three clockwise or counterclockwise (because this can be done with models):

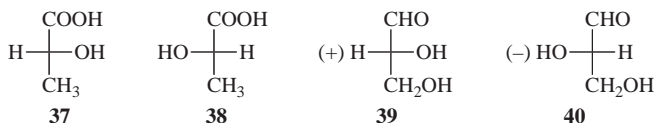


However, the *interchange* of any two groups results in the conversion of an enantiomer into its mirror image (this applies to models, as well as to the Fischer projections).

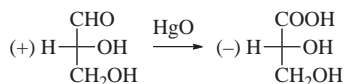
With these restrictions Fischer projections may be used instead of models to test whether a molecule containing a stereogenic carbon is superimposable on its mirror image. However, there are no such conventions for molecules whose chirality arises from anything other than chiral atoms (category 5 in Sec. 4.C).

4.D. ABSOLUTE CONFIGURATION

Suppose there are two test tubes, one containing (–)-lactic acid and the other the (+) enantiomer. One test tube contains **37** and the other **38**. How can they be distinguished?



To generate a model to answer this question, Rosanoff proposed that one compound be chosen as a standard and a configuration arbitrarily assigned to it. The compound chosen was glyceraldehyde because of its relationship to the sugars. The (+) isomer was assigned the configuration shown in **39** and given the label D. The (–) isomer, designated to be **39**, was given the label L. With a standard, other compounds could then be related to it. For example, (+)-glyceraldehyde, oxidized with mercuric oxide, gives (–)-glyceric acid:



Since it is highly improbable that the configuration at the central carbon changed, it can be concluded that (–)-glyceric acid has the same configuration as (+)-glyceraldehyde and therefore (–)-glyceric acid is also called D. This example emphasizes that molecules with

the same configuration need not rotate the plane of polarized light in the same direction. This fact should not surprise us when we remember that the same compound can rotate the plane in opposite directions under different conditions.

Once the configuration of the glyceric acids was known (in relation to the glycer-aldehydes), it was then possible to relate other compounds to either of these, and each time a new compound was related, others could be related to *it*. In this way, many thousands of compounds were related, indirectly, to D- or L-glyceraldehyde. It was determined that **37**, which has the D configuration, is the isomer that rotates the plane of polarized light to the left. Even compounds without asymmetric atoms (e.g., biphenyls and allenes), have been placed in the D or L series.⁹⁸ When a compound has been placed in the D or L series, its *absolute configuration* is said to be known.⁹⁹

In 1951, it became possible to determine that Rosanoff's guess was right. Ordinary X-ray crystallography cannot distinguish between a D and a L isomer, but by use of a special technique, Bijvoet et al.¹⁰⁰ was able to examine sodium rubidium tartrate, compared it with glyceraldehyde, and found that Rosanoff had made the correct choice. It was perhaps historically fitting that the first true absolute configuration should have been determined on a salt of tartaric acid, since Pasteur made his great discoveries on another salt of this acid.

In spite of the former widespread use of D and L to denote absolute configuration, the method is not without faults. This method does not apply to all compounds that have a stereogenic center, but only those that can be structurally related to glyceraldehyde. The DL system is rarely used, therefore, except for certain groups of compounds (e.g., carbohydrates and amino acids). A more general model is required to distinguish the stereogenic centers of enantiomers.

4.D.i. The CAHN-INGOLD-PRELOG System

The system that is used universally is the *Cahn-Ingold-Prelog* system (or the CIP system), in which the four groups on a stereogenic carbon are ranked (prioritized) according to a set of sequence rules.¹⁰¹ For the most part, only a few of these rules are sufficient to deal with the vast majority of chiral compounds.

1. Prioritize substituents in order of decreasing atomic number of the atom directly joined to the carbon.

⁹⁸ The use of small *d* and *l* is now discouraged, since some authors used it for rotation, and some for configuration. However, a racemic mixture is still a *dl* mixture, since there is no ambiguity here.

⁹⁹ For lists of absolute configurations of thousands of compounds, with references, mostly expressed as (*R*) or (*S*) rather than D or L, see Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*, 2nd ed., 2 Vols., Oxford University Press, Oxford, **1978**; Jacques, J.; Gros, C.; Bourcier, S.; Brienne, M.J.; Toullec, J. *Absolute Configurations* (Vol. 4 of Kagan, H. *Stereochemistry*), Georg Thieme Publishers, Stuttgart, **1977**.

¹⁰⁰ Bijvoet, J.M.; Peerdeman, A.F.; van Bommel, A.J. *Nature (London)* **1951**, 168, 271. For a list of organic structures whose absolute configurations have been determined by this method, see Neidle, S.; Rogers, D.; Allen, F.H. *J. Chem. Soc. C* **1970**, 2340.

¹⁰¹ For descriptions of the system and sets of sequence rules, see *Pure Appl. Chem.* **19767**, 45, 13; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, **1979** (the Blue Book); Cahn, R.S.; Ingold, C.K.; Prelog, V. *Angew. Chem. Int. Ed.* **1966**, 5, 385; Cahn, R.S. *J. Chem. Educ.* **1964**, 41, 116; Fernelius, W.C.; Loening, K.; Adams, R.M. *J. Chem. Educ.* **1974**, 51, 735. See also, Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed.* **1982**, 21, 567. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**, pp. 101–147. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 15–23.

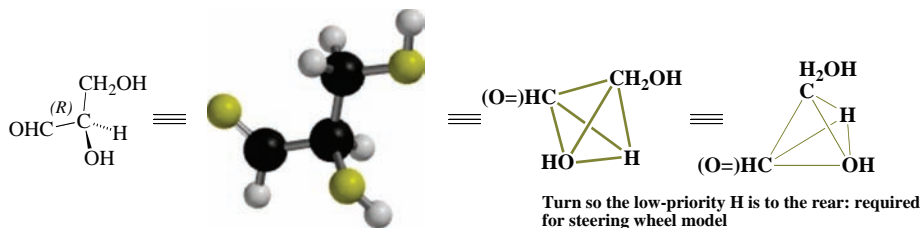
2. A tritium atom takes precedence over deuterium, which in turn takes precedence over ordinary hydrogen. Similarly, any higher isotope (e.g., ^{14}C) takes precedence over any lower one.
3. Where two or more of the atoms connected to the stereogenic carbon are the same, the atomic number of the second atom determines the order. For example, in the molecule $\text{Me}_2\text{CH}-\text{CHBr}-\text{CH}_2\text{OH}$, the CH_2OH group takes precedence over the Me_2CH group because oxygen has a higher atomic number than carbon. Note that this is so even though there are two carbons in Me_2CH , and only one oxygen in CH_2OH . If two or more atoms connected to the second atom are the same, the third atom determines the precedence, and so on.
4. All atoms except hydrogen are formally given a valence of 4. Where the actual valence is less (as in nitrogen, oxygen, or a carbanion), phantom atoms (designated by a subscript 0) are used to bring the valence up to 4. These phantom atoms are assigned an atomic number of zero and necessarily rank lowest. Thus the ligand $-\text{NHMe}_2$ ranks higher than $-\text{NMe}_2$.
5. Double and triple bonds are counted as if they were split into two or three single bonds, respectively, as in the examples in Table 4.1 (note the treatment of the phenyl group). Note that in a $\text{C}=\text{C}$ double bond, the two carbon atoms are *each* regarded as being connected to two carbon atoms and that one of the latter is counted as having three phantom substituents.

Using the four groups in Table 4.1 (aldehyde, vinyl, alkynyl, phenyl), the first atoms are connected, respectively, to (H, O, O), (H, C, C), (C, C, C), and (C, C, C). That is enough to establish that $-\text{CHO}$ ranks first and $-\text{CH}=\text{CH}_2$ last, since even one oxygen outranks three carbons and three carbons outrank two carbons and a hydrogen. To classify the remaining two groups, proceed further along the chains. Note that $-\text{C}_6\text{H}_5$ has two of its (C, C, C) carbons connected to (C, C, H), while the third is ($_{000}$) and is thus preferred to $-\text{C}\equiv\text{CH}$, which has only one (C, C, H) and two ($_{000}$)s.

TABLE 4.1 How Four Common Groups Are Treated in the Cahn-Ingold-Prelog System

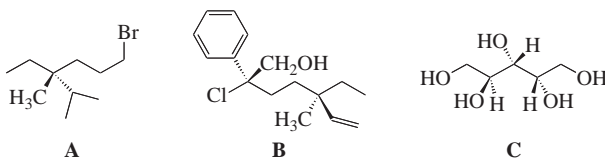
Group	Treated as if it Were	Group	Treated as if it Were
$\begin{array}{c} \text{H} \\ \diagdown \\ \text{C}=\text{O} \\ \diagup \end{array}$	$\begin{array}{c} \text{H} \\ \\ -\text{C}-\text{O}^{\text{OO}}-\text{O}^{\text{OOO}} \\ \\ \text{C}^{\text{OOO}} \end{array}$	$\begin{array}{c} \diagdown \\ \text{C}=\text{CH}_2 \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ -\text{C}-\text{C}-\text{C}^{\text{OOO}} \\ \quad \\ \text{C}^{\text{OOO}} \quad \text{H} \end{array}$
$-\text{C}\equiv\text{C}-\text{H}$	$\begin{array}{c} \text{C}^{\text{OOO}} \quad \text{H} \\ \quad \\ -\text{C}-\text{C}-\text{C}^{\text{OOO}} \\ \quad \\ \text{C}^{\text{OOO}} \end{array}$	$-\text{C}_6\text{H}_5$	$\begin{array}{c} \text{C}^{\text{OOO}} \quad \diagdown \\ \quad \\ \text{H}-\text{C}-\text{C}-\text{C}^{\text{OOO}} \\ \quad \quad \\ \text{H}-\text{C}-\text{C}-\text{C}^{\text{OOO}} \\ \quad \\ \text{C}^{\text{OOO}} \end{array}$

By application of the above rules, some groups in descending order of precedence are COOH, CPh, COMe, CHO, CH(OH)₂, *o*-tolyl, *m*-tolyl, *p*-tolyl, phenyl, C≡CH, *tert*-butyl, cyclohexyl, vinyl, isopropyl, benzyl, neopentyl, allyl, *n*-pentyl, ethyl, methyl, deuterium, and hydrogen. Using the CIP rules, the four groups of glyceraldehyde are arranged in the sequence: OH, CHO, CH₂OH, H.



Once the order is determined, a model is required to determine the absolute configuration (i.e., which structure correlates to which enantiomer). The model used is known as the *steering wheel model*, where the molecule is held so that the lowest group in the sequence is pointed away from the viewer. Once the lowest priority group is held in that position, if the other groups, in the order listed, are oriented clockwise, the molecule is designated (*R*), and if counterclockwise (*S*). For glyceraldehyde, the (+) enantiomer is shown here and the CIP rules and the steering wheel model was used to assign an absolute configuration of (*R*).

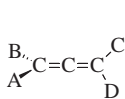
The CIP rules and steering wheel model are used to assign an absolute configuration to the following molecules. In **A**, the isopropyl carbon is higher in priority than the bromine-containing chain, and the methyl group is the lowest priority. Turning the molecule to place the methyl group to the rear makes this an (*R*) configuration. In **B**, there are two stereogenic centers, where the (*S*) center has the chain containing the (*R*) center as the lowest priority, and the (*R*) center has the methyl group as the low priority. In **C**, there are two (*S*) centers, but the hydroxyl-bearing carbon in the middle of the molecule is *not* a stereogenic carbon. Close inspection of **C** shows that this carbon has two identical groups [CH(OH)CH₂OH].



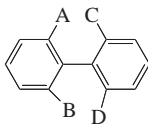
The CIP system is unambiguous and easily applicable in most cases. The CIP system also has been extended to chiral compounds that do not contain stereogenic centers, but rather have a chiral axis.¹⁰² Compounds having a chiral axis include unsymmetrical allenes, biaryls that exhibit atropisomerism (see Sec. 4.C, category 5), and alkyldiene cyclohexane derivatives, molecular propellers and gears, helicenes, cyclophanes, annulenes, *trans*-cycloalkenes, and metallocenes. A series of rules have been proposed to address these cases based on what is called an “extended tetrahedron mode”, but the rules can be ambiguous in the case of cyclophanes and a few other systems.¹⁰³

¹⁰² Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**, pp. 1119–1190. See Krow, G. *Top. Stereochem.* **1970**, *5*, 31.

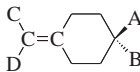
¹⁰³ Mata, P.; Lobo, A.M.; Marshall, C.; Johnson, A.P. *Tetrahedron Asym.* **1993**, *4*, 657; Perdih, M.; Razingar, M. *Tetrahedron Asym.* **1994**, *5*, 835.



Allenes



Biaryls



Alkylidenecyclohexanes

4.D.ii. Methods of Determining Configuration¹⁰⁴

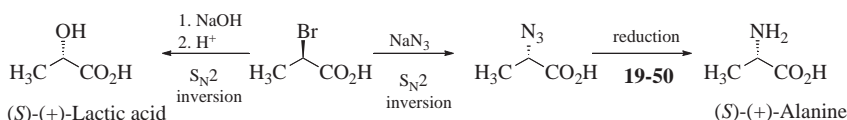
In all the methods,¹⁰⁵ it is necessary to relate the compound of unknown configuration to another whose configuration is known. The most important methods of doing this follow:

1. *Conversion of the Unknown to, or Formation of the Unknown from, a Compound of Known Configuration Without Disturbing the Stereogenic Center.* The glyceraldehyde–glyceric acid example above is



one example. The stereogenic center was not disturbed, and the configuration of the product (glyceric acid) is the same as the starting material (glyceraldehyde). Retention of the same absolute configuration such as with glyceraldehyde-to-glyceric acid is not always the case. If the reaction sequence does not disturb (change) the stereogenic center, the absolute configuration depends on the nature of the groups. For example, when (*R*)-1-bromo-2-butanol is reduced to 2-butanol without disturbing the stereogenic center, the product is the (*S*) enantiomer because CH_3CH_2 ranks lower than BrCH_2 , but higher than CH_3 .

2. *Conversion at the Stereogenic Center if the Mechanism is Known.* An $\text{S}_{\text{N}}2$ mechanism proceeds with inversion of configuration at a stereogenic carbon (Sec. 10.A.i). Indeed, a series of such transformations allowed the stereogenic center in lactic acid to be correlated to that in alanine.

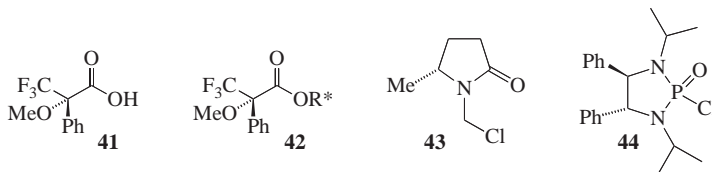


3. *Biochemical Methods.* In a series of similar compounds (e.g., amino acids or certain types of steroids), a given enzyme will usually attack only molecules with one kind of configuration. If the enzyme attacks only the L form of eight amino acids, say, then attack on the unknown ninth amino acid will demonstrate that it is also the L form.

¹⁰⁴ See Kagan, H.B. *Determination of Configuration by Chemical Methods* (Vol. 3 of Kagan, H.B. *Stereochemistry*), Georg Thieme Publishers, Stuttgart, **1977**; Brewster, J.H. in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 3, Wiley, NY, **1972**, pp. 1–249; Klyne, W.; Scopes, P.M. *Prog. Stereochem.* **1969**, *4*, 97; Schlenk, Jr., W. *Angew. Chem. Int. Ed.* **1965**, *4*, 139. Also see Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Top. Stereochem.* **1986**, *16*, 1.

¹⁰⁵ Except the X-ray method of Bijvoet.

4. *Optical Comparison.* It is sometimes possible to use the sign and extent of rotation to determine which isomer has which configuration. In a homologous series, the rotation usually changes gradually and in one direction. If the configurations of enough members of the series are known, the configurations of the missing ones can be determined by extrapolation. Also, certain groups contribute more or less fixed amounts to the rotation of the parent molecule, especially when the parent is a rigid system (e.g., a steroid).
5. *The Special X-Ray Method of Bijvoet.* This method gives direct answers and has been used in a number of cases.⁸⁶
6. *Derivatize the Alcohol with a Chiral Nonracemic Reagent and Examine the Ratio of Resulting Diastereomers by Gas Chromatography.*¹⁰⁶ This method is one of the most useful for determining enantiomeric composition. Many derivatizing agents are available, but one class widely used are derivatives of α -methoxy- α -trifluoromethylphenyl acetic acid (MTPA, Mosher's acid, **41**).¹⁰⁷ Reaction with a chiral nonracemic alcohol (R^*OH) generates a Mosher's ester (**42**) that can be analyzed for diastereomeric composition by 1H or ^{19}F NMR, as well as by chromatographic techniques.¹⁰⁸ Complexation with lanthanide shift reagents allow the signals of the MTPA ester to be resolved and used to determine enantiomeric composition.¹⁰⁹ This NMR method, as well as other related methods,¹¹⁰ are effective for determining the absolute configuration of an alcohol of interest (R^*OH , where R^* is a group containing a stereogenic center).¹¹¹ Two, of many other reagents that have been developed to determine the enantiopurity of alcohols and amines, include **43** and **44**. Chloromethyl lactam (**43**) reacts with R^*OH or R^*NHR (R^*NH_2),¹¹² forming derivatives that allow analysis by 1H NMR and **44** reacts with alkoxides (R^*O^-)¹¹³ to form a derivative that can be analyzed by ^{31}P NMR. For a more detailed discussion of methods to determine optical purity, see Section 4.J.



¹⁰⁶ Parker, D. *Chem. Rev.* **1991**, 91, 1441.

¹⁰⁷ Dale, J. A.; Dull, D.L.; Mosher, H. S. *J. Org. Chem.* **1969**, 34, 2543; Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, 95, 512.

¹⁰⁸ See Mori, K.; Akao, H. *Tetrahedron Lett.* **1978**, 4127; Plummer, E.L.; Stewart, T.E.; Byrne, K.; Pearce, G.T.; Silverstein, R.M. *J. Chem. Ecol.* **1976**, 2, 307. See also, Seco, J.M.; Quiñoá, E.; Riguera, R. *Tetrahedron Asymm.* **2000**, 11, 2695.

¹⁰⁹ Yamaguchi, S.; Yasuhara, F.; Kabuto, K. *Tetrahedron* **1976**, 32, 1363; Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* **1980**, 21, 2827; Yamaguchi, S.; Yasuhara, F. *Tetrahedron Lett.* **1977**, 89.

¹¹⁰ Latypov, S.K.; Ferreiro, M.J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, 120, 4741; Latypov, S.K.; Seco, J.M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, 60, 1538.

¹¹¹ Seco, J.M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, 104, 17.

¹¹² Smith, M.B.; Dembofsky, B.T.; Son, Y.C. *J. Org. Chem.* **1994**, 59, 1719; Latypov, S.K.; Riguera, R.; Smith, M. B.; Polivkova, J. *J. Org. Chem.* **1998**, 63, 8682. For a chiral compound used to determine the enantiomeric purity of primary amines, see Pérez-Fuertes, Y.; Kelly, A.M.; Johnson, A.L.; Arimori, S.; Bull, S.D.; James, T.D. *Org. Lett.* **2006**, 8, 609.

¹¹³ Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, 57, 1224.

7. *Other Methods.* Other methods have also been used for determining absolute configuration in a variety of molecules, including optical rotatory dispersion,¹¹⁴ circular dichroism (CD),¹¹⁵ and asymmetric synthesis (Sec. 4.H). Optical rotatory dispersion (ORD) is a measurement of specific rotation $[\alpha]$ as a function of wavelength.¹¹⁶ The change of specific rotation $[\alpha]$ or molar rotation $[\Phi]$ with wavelength is measured, and a plot of either versus wavelength is often related to the sense of chirality or the substance under consideration. In general, the absolute value of the rotation increases as the wavelength decreases. The plot of CD is the differential absorption of left and right circularly polarized radiation by a nonracemic sample, taking place only in spectral regions in which absorption bands are found in the isotropic UV or visible (vis) electronic spectrum.¹¹⁷ The primary application of both ORD and CD is for the assignment of configuration or conformation.¹¹⁸ Configurational and conformational analyses have been carried out using IR and vibrational circular dichroism (VCD) spectroscopies.¹¹⁹

One example, and one of the more effective methods for derivatizing 1,2-diols, is the method employing dimolybdenum tetraacetate $[\text{Mo}_2(\text{AcO})_4]$ developed by Snatzke and Frelek.¹²⁰ Exposure of the resulting complex to air leads, in most cases, to a significant induced CD spectrum (known as ICD). The method can be used for a variety of 1,2-diols.¹²¹

8. *NMR Databases.* Kishi and co-worker's¹²² developed an NMR database¹²³ of various molecules in chiral solvents, for the assignment of relative and absolute stereochemistry without derivatization or degradation. Kishi referred to this database as a "universal NMR database."¹²⁴ The diagram provided for diols **45** illustrates the method (see Fig. 4.3). The graph presents the difference in

¹¹⁴ See Ref. 277 for books and reviews on optical rotatory dispersion and CD. For predictions about anomalous ORD, see Polavarapu, P.L.; Zhao, C. *J. Am. Chem. Soc.* **1999**, *121*, 246.

¹¹⁵ Gawronski, J.; Grajewski, J. *Org. Lett.* **2003**, *5*, 3301. See Ref. 277; Stephens, P.J.; Aamouche, A.; Devlin, F.J.; Superchi, S.; Donnoli, M.I.; Rosini, C. *J. Org. Chem.* **2001**, *66*, 3671; McCann, D.M.; Stephens, P.J. *J. Org. Chem.* **2006**, *71*, 6074.

¹¹⁶ Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**, pp. 1203, 999–1003.

¹¹⁷ Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**, pp. 1195, 1003–1007.

¹¹⁸ Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**, pp. 1007–1071; Nakanishi, K.; Berova, N.; Woody, R.W. *Circular Dichroism: Principles and Applications*, VCH, NY, **1994**; Purdie, N.; Brittain, H.G. *Analytical Applications of Circular Dichroism*, Elsevier, Amsterdam, The Netherlands, **1994**.

¹¹⁹ Devlin, F.J.; Stephens, P.J.; Osterle, C.; Wiberg, K.B.; Cheeseman, J.R.; Frisch, M.J. *J. Org. Chem.* **2002**, *67*, 8090.

¹²⁰ Frelek, J.; Geiger, M.; Voelter, W. *Curr. Org. Chem.* **1999**, *3*, 117–146 and references cited therein; Snatzke, G.; Wagner, U.; Wolff, H. P. *Tetrahedron* **1981**, *37*, 349; Pakulski, Z.; Zamojski, A. *Tetrahedron Asymm.* **1996**, *7*, 1363; Frelek, J.; Ikekawa, N.; Takatsuto, S.; Snatzke, G. *Chirality* **1997**, *9*, 578.

¹²¹ Di Bari, L.; Pescitelli, G.; Pratelli, C.; Pini, D.; Salvadori, P. *J. Org. Chem.* **2001**, *66*, 4819.

¹²² Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2245; Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2249; Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2253.

¹²³ For another protocol, see Dambruoso, P.; Bassarello, C.; Bifulco, G.; Appendino, G.; Battaglia, A.; Fontana, G.; Gomez-Paloma, L. *Org. Lett.* **2005**, *7*, 983.

¹²⁴ Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 2076.

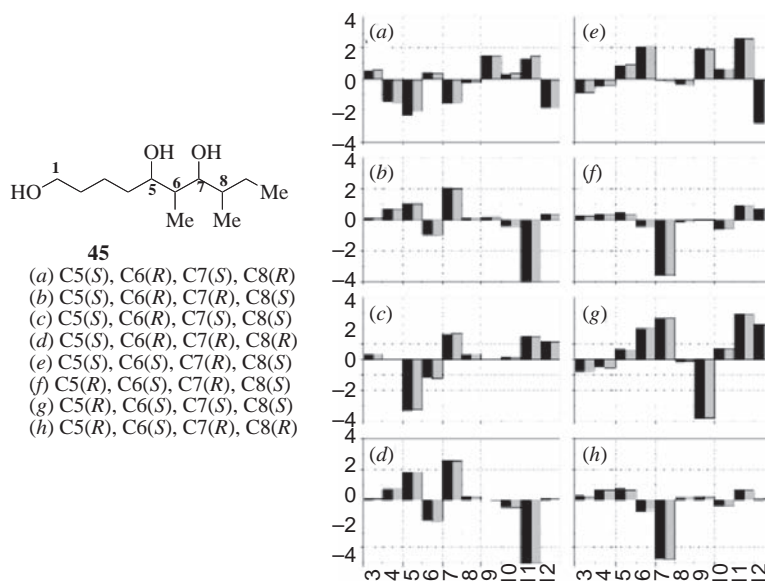


FIG. 4.3. Proton NMR analysis for assignment of stereochemistry.

carbon chemical shifts between the average and the values for **45** (100 MHz) in DMBA (*N*, α -dimethylbenzylamine). Spectra were recorded in both enantiomers of the solvent, where the solid bar was recorded in (*R*)-DMBA and the shaded bar in (*S*)-DMBA. The *x*- and *y*-axes represent the carbon number and $\Delta\delta$ ($\delta_{45a-h} - \delta_{ave}$ in ppm), respectively. The graphs are taken from “the ^{13}C NMR database in (*R*)- and (*S*)-DMBA as a deviation in chemical shift for each carbon of a given diastereomer from the average chemical shift of the carbon in question. Each diastereomer exhibits an almost identical NMR profile for (*R*)- and (*S*)-DMBA, but shows an NMR profile distinct and differing from the other diastereomers, demonstrating that the database in (*R*)- and/or (*S*)-DMBA can be used for prediction of the relative stereochemistry of structural motifs in an intact form.”¹²⁵

A ^1H NMR analysis method has been developed that leads to the assignment of the stereochemistry of β -hydroxy ketones, by visual inspection of the ABX patterns for the (*R*)-methylene unit of the β -hydroxyketones.¹²⁶ Since β -hydroxy ketones are derived from the aldol reaction (**16-34**), this method is particularly useful in organic synthesis. A method has also been developed that uses ^{13}C NMR to determine the relative stereochemistry of 2,3-dialkylpentenoic acids.¹²⁷

¹²⁵ Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* **2001**, 3, 2245.

¹²⁶ Roush, W.R.; Bannister, T.D.; Wendt, M.D.; VanNieuwenhze, M.S.; Gustin, D.J.; Dilley, G.J.; Lane, G.C.; Scheidt, K.A.; Smith, III, W.J. *J. Org. Chem.* **2002**, 67, 4284.

¹²⁷ Hong, S.-p.; McIntosh, M.C. *Tetrahedron* **2002**, 57, 5055.

4.E. THE CAUSE OF OPTICAL ACTIVITY

The question may be asked: Just why does a chiral molecule rotate the plane of polarized light? Theoretically, the answer to this question is known, and in a greatly simplified form may be explained as follows.¹²⁸

Whenever any light hits any molecule in a transparent material, the light is slowed because of interactions with the molecule. This phenomenon on a gross scale is responsible for the refraction of light, and the decrease in velocity is proportional to the refractive index of the material. The extent of interaction depends on the polarizability of the molecule. Plane-polarized light may be regarded as being made up of two kinds of circularly polarized light. Circularly polarized light has the appearance (or would have, if one could see the wave) of a helix propagating around the axis of light motion, and one kind is a left and the other is a right-handed helix. As long as the plane-polarized light is passing through a symmetrical region, the two circularly polarized components travel at the same speed. However, a chiral molecule has a different polarizability depending on whether it is approached from the left or the right. One circularly polarized component approaches the molecule, so to speak, from the left and sees a different polarizability (hence on a gross scale, a different refractive index) than the other and is slowed to a different extent. This would seem to mean that the left- and right-handed circularly polarized components travel at different velocities, since each has been slowed to a different extent. However, it is not possible for two components of the same light to be traveling at different velocities. What actually takes place, therefore, is that the faster component “pulls” the other toward it, resulting in rotation of the plane. Empirical methods for the prediction of the sign and amount of rotation based on bond refractions and polarizabilities of groups in a molecule have been devised,¹²⁹ and have given fairly good results in many cases.

In liquids and gases, the molecules are randomly oriented. A molecule that is optically inactive because it has a plane of symmetry will very seldom be oriented so that the plane of the polarized light coincides with the plane of symmetry. When it is so oriented, that particular molecule does not rotate the plane, but all others not oriented in that manner do rotate the plane, even though the molecules are achiral. There is no net rotation because even though the molecules are present in large numbers and randomly oriented, there will always be another molecule later on in the path of the light that is oriented exactly opposite and will rotate the plane back again. Even if nearly all molecules rotate the plane individually, the total rotation is zero. For chiral molecules, however (if there is no racemic mixture), no opposite orientation is present and there is a net rotation.

An interesting phenomenon was observed when the CD of chiral molecules was measured in achiral solvents. The chiral solvent contributed as much as 10–20% to the

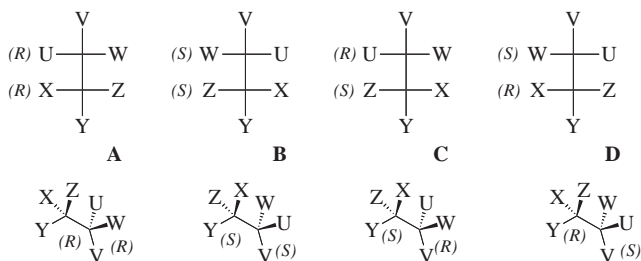
¹²⁸ See Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**, pp. 93–94, 992–999; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, **1960**, pp. 204–211; Caldwell, D.J.; Eyring, H. *The Theory of Optical Activity* Wiley, NY, **1971**; Buckingham, A.D.; Stiles, P.J. *Acc. Chem. Res.* **1974**, 7, 258; Mason, S.F. *Q. Rev. Chem. Soc.* **1963**, 17, 20.

¹²⁹ Brewster, J.H. *Top. Stereochem.* **1967**, 2, 1, *J. Am. Chem. Soc.* **1959**, 81, 5475, 5483, 5493; Sathyanarayana, B. K.; Stevens, E.S. *J. Org. Chem.* **1987**, 52, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* **1988**, 110, 4144.

CD intensity in some cases. Apparently, the chiral compound can induce a solvation structure that is chiral, even when the solvent molecules themselves are achiral.¹³⁰

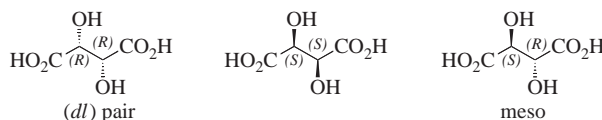
4.F. MOLECULES WITH MORE THAN ONE STEREOGENIC CENTER

When a molecule has two stereogenic centers, each has its own configuration and can be classified (*R*) or (*S*) by the CIP method. There are a total of four isomers, since the first center may be (*R*) or (*S*) and so may the second. Each is drawn as both the Fischer projection and in the extended conformation. Since a molecule can have only one mirror image, only one of the other three can be the enantiomer of **A**. This enantiomer is **B** [the mirror image of an (*R*) center is *always* an (*S*) center]. Both **C** and **D** are a second pair of enantiomers and the relationship of **C** and **D** to **A** and **B** is designated by the term *diastereomer*. Diastereomers may be defined as *stereoisomers that are not enantiomers (they are stereoisomers that are not mirror images, and not superimposable)*. Since **C** and **D** are enantiomers, they must have identical properties, except as noted in Section 4.A, and the same is true for **A** and **B**. However, the properties of **A** and **B** are not identical with those of **C** and **D**. They are different compounds, which means that they have different melting points, boiling points, solubilities, reactivity, and all other physical, chemical, and spectral properties. The properties are usually *similar*, but not *identical*. In particular, diastereomers have different specific rotations; indeed one diastereomer may be chiral and rotate the plane of polarized light while another may be achiral and not rotate at all (an example is presented below).



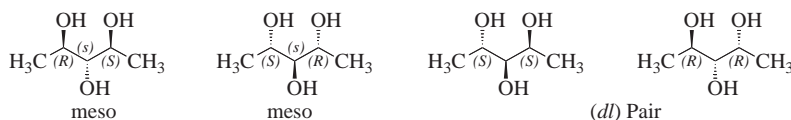
It is now possible to see why, as mentioned in Section 4.A, enantiomers react at different rates with other chiral molecules, but at the same rate with achiral molecules. In the latter case, the activated complex formed from the (*R*) enantiomer and the other molecule is the mirror image of the activated complex formed from the (*S*) enantiomer and the other molecule. Since the two activated complexes are enantiomeric, their energies are the same and the rates of the reactions in which they are formed must be the same (see Chapter 6). However, when an (*R*) enantiomer reacts with a chiral molecule that has, say, the (*R*) configuration, the activated complex has two chiral centers with configurations (*R*) and (*R*), while the activated complex formed from the (*S*) enantiomer has the configurations (*S*) and (*R*). The two activated complexes are diastereomeric, do not have the same energies, and consequently are formed at different rates.

¹³⁰ Fidler, J.; Rodger, P.M.; Rodger, A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 235.



The three stereoisomers of tartaric acid

Although four is the maximum possible number of isomers when the compound has two stereogenic centers (chiral compounds without a stereogenic carbon, or with one stereogenic carbon and another type of stereogenic center, also follow the rules described here), some compounds have fewer. When the three groups on one stereogenic atom are the same as those on the other, one of the isomers (called a *meso* form) has a plane of symmetry, and hence is optically inactive, even though it has two stereogenic carbons. Tartaric acid is a typical case. As shown, there are only three isomers of tartaric acid: a pair of enantiomers and an inactive *meso* form. For compounds that have two stereogenic atoms, *meso* forms are found only where the four groups on one of the chiral atoms are the same as those on the other chiral atom.



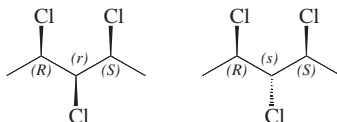
In compounds with two or more stereogenic centers, the maximum number of isomers can be calculated from the formula 2^n , where n is the number of stereogenic centers. The actual number may be less than this, owing to *meso* forms,¹³¹ but never more. An interesting case is that of 2,3,4-pentanetriol (or any similar molecule). The middle carbon is not asymmetric when the 2- and 4-carbons are both (*R*) [or both (*S*)]; labeled the *dl* pair. The compound when one of them is (*R*) and the other (*S*) is asymmetric (labeled *meso*). The middle carbon in such compounds is called a *pseudoasymmetric* carbon. In such cases, there are four isomers: two *meso* forms and one *dl* pair. Remember that the *meso* forms are superimposable on their mirror images, and that there are no other stereoisomers. Two diastereomers that have a different configuration at only one chiral center are called *epimers*.

The small letters used for the pseudoasymmetric center are assigned using established rules. An atom that is tetrahedrally substituted and bonded to four different entities, two and only two of which have opposite configurations, is stereogenic. The descriptors “*r*” and “*s*” are used to denote such centers; they are assigned in accordance with Sequence Rule 5, taking into consideration that “(*R*)” has precedence over “(*S*)” in the order of priority.¹³² Step 1: configuration “(*R*)” or “(*S*)” is assigned to stereogenic centers C-2 and C-4; Using 1,2,3-trichloropentane as an example, Step 2: Configuration at C-3 is assigned by applying sequence rule, “(*R*)” precedes “(*S*)”, and if (*R*) precedes (*S*), then Cl is the highest priority, followed by (*R*) and then (*S*): C-3 is *r*. The exchange of the

¹³¹ For a method of generating all stereoisomers consistent with a given empirical formula, suitable for computer use, see Nourse, J.G.; Carhart, R.E.; Smith, D.H.; Djerassi, C. *J. Am. Chem. Soc.* **1979**, 101, 1216; **1980**, 102, 6289.

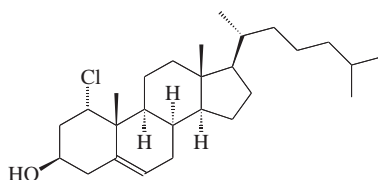
¹³² Available at http://old.iupac.org/reports/provisional/abstract04/favre_310305.html, Preferred IUPAC Names, Chapter 9, September, 2004, p. 6.

Cl and H atoms at C-3 of the compound on the left generates the compound on the right, and “3*r*” becomes “3*s*”



In compounds with two or more stereogenic centers, the absolute configuration must be separately determined for each center. The usual procedure is to determine the configuration at one center by the methods discussed in Section 4.E.ii, and then to relate the configuration at that center to the others in the molecule. One method is X-ray crystallography, which, as previously noted, cannot be used to determine the absolute configuration at any stereogenic center. This method does give *relative configurations* of all the stereogenic centers in a molecule, and if the absolute configuration of one stereogenic center is independently determined, the absolute configurations of all are then known. Other physical and chemical methods have also been used for this purpose.

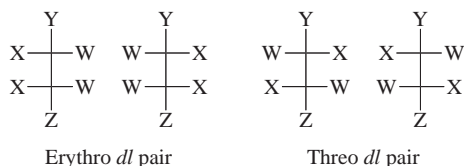
How to name the different stereoisomers of a compound when there are more than two is potentially a problem.² Enantiomers have the same IUPAC name, being distinguished by (*R*) and (*S*) or D and L or (+) or (–). In the early days of organic chemistry, it was customary to give each pair of enantiomers a different name or at least a different prefix (e.g., *epi*-, *peri*-, etc.). Thus the aldohexoses are called glucose, mannose, idose, and so on, although they are all 2,3,4,5,6-pentahydroxyhexanal (in their open-chain forms). This practice was partially due to lack of knowledge about which isomers had which configurations.¹³³ Today it is customary to describe *each chiral position* separately as either (*R*) or (*S*) or, in special fields, to use other symbols. Thus, in the case of steroids, groups above the “plane” of the ring system are designated β, and those below it α. Solid lines are typically used to depict β groups and dashed lines for α groups. An example is 1α-chloro-5-cholesten-3β-ol, showing the OH group on the top side of the molecule (up) and the chlorine atom on the bottom side (down).



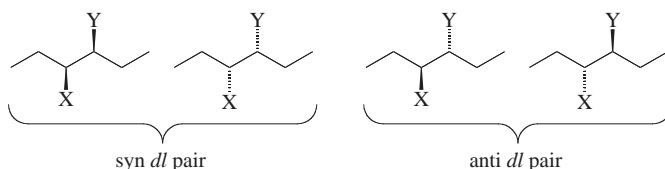
1α-Chloro-5-cholesten-3β-ol

For many open-chain compounds, prefixes are used that are derived from the names of the corresponding sugars and that describe the whole system rather than each chiral center separately. Two such common prefixes are *erythro*- and *threo*-, which are applied to systems containing two stereogenic carbons when two of the

¹³³ A method has been developed for the determination of stereochemistry in six-membered chair-like rings using residual dipolar couplings. See Yan, J.; Kline, A. D.; Mo, H.; Shapiro, M. J.; Zartler, E. R. *J. Org. Chem.* **2003**, 68, 1786.



groups are the same and the third is different.¹³⁴ The erythro pair has the identical groups on the same side when drawn in the Fischer convention, and if Y were changed to Z, it would be meso. The threo pair has them on opposite sides, and if Y were changed to Z, it would still be a *dl* pair. Another system¹³⁵ for designating stereoisomers¹³⁶ uses the terms *syn* and *anti*. The “main chain” of the molecule is drawn in the common zigzag manner. Then if two non-hydrogen substituents are on the same side of the plane defined by the main chain, the designation is *syn*; otherwise it is *anti*.



4.G. ASYMMETRIC SYNTHESIS

Organic chemists often wish to synthesize a chiral compound in the form of a single enantiomer or diastereomer, rather than as a mixture of stereoisomers. There are two basic ways in which this can be done.¹³⁷ The first way, which is more common, is to begin with a single stereoisomer, and to use a synthesis that does not affect the stereogenic center (or centers). The optically active starting compound can be obtained by a previous synthesis, or by resolution of a racemic mixture (Sec. 4.I). If possible, the starting material is obtained from Nature, since many compounds (e.g., amino acids, sugars, and steroids), are present in Nature in the form of a single enantiomer or diastereomer. These compounds have been referred to as a *chiral pool*; that is, readily available compounds that can be used as starting materials.¹³⁸ This term is not used much now.

¹³⁴ See Carey, F.A.; Kuehne, M.E. *J. Org. Chem.* **1982**, 47, 3811; Boguslavskaya, L.S. *J. Org. Chem. USSR* **1986**, 22, 1412; Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* **1982**, 21, 654; Brewster, J.H. *J. Org. Chem.* **1986**, 51, 4751. See also, Tavernier, D. *J. Chem. Educ.* **1986**, 63, 511; Brook, M.A. *J. Chem. Educ.* **1987**, 64, 218.

¹³⁵ For still another system, see Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* **1982**, 21, 654.

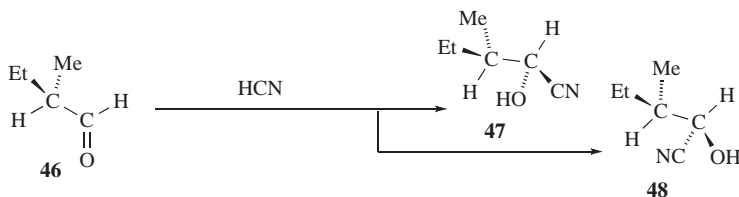
¹³⁶ Masamune, S.; Kaiho, T.; Garvey, D.S. *J. Am. Chem. Soc.* **1982**, 104, 5521.

¹³⁷ See Morrison, J.D.; Scott, J.W. *Asymmetric Synthesis*, Vol. 4; Academic Press, NY, **1984**; Williams, R.M. *Synthesis of Optically Active α -Amino Acids*, Pergamon, Elmsford, NY, **1989**; Crosby, J. *Tetrahedron* **1991**, 47, 4789; Mori, K. *Tetrahedron* **1989**, 45, 3233.

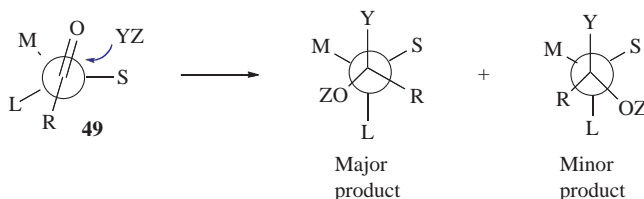
¹³⁸ See Coppola, G.M.; Schuster, H.F. *Asymmetric Synthesis*, Wiley, NY, **1987**; Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon, Elmsford, NY, **1983**; Hanessian, S. *Aldrichim. Acta* **1989**, 22, 3; Jurczak, J.; Gotebiowski, A. *Chem. Rev.* **1989**, 89, 149.

The other basic method is called *asymmetric synthesis*,¹³⁹ or *stereoselective synthesis*. As mentioned earlier, optically active materials cannot be created from inactive starting materials and conditions, except in the manner previously noted.⁹⁷ However, when a new stereogenic center is created, the two possible enantiomers need not be formed in equal amounts if anything is present that is not symmetric. Asymmetric synthesis may be categorized into four headings:

1. *Active Substrate*. If a new stereogenic center is created in a molecule that is already optically active, the product will generate diastereomers and the two diastereomers may not (except fortuitously) be formed in equal amounts. The reason is that the direction of attack by the reagent is determined by the groups already there. For certain additions to the carbon–oxygen double bond of ketones containing an asymmetric α carbon, *Cram's rule* predicts which of two diastereomers will predominate (diastereoselectivity).^{140,141} The reaction of **46**, which has a stereogenic center at the α -carbon, and HCN can generate two possible diastereomers (**47** and **48**).



If **46** is observed along its axis, it may be represented as in **49** (Sec. 4.O.i), where S, M, and L stand for small, medium, and large, respectively. The oxygen of the carbonyl orients itself between the small- and the medium-sized groups. The rule requires that the incoming group preferentially attacks on the side of the plane containing the small group. By this rule, it can be predicted that **48** will be formed in larger amounts than **47**.

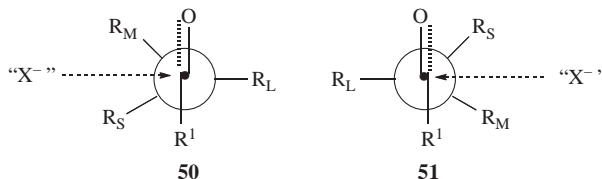


¹³⁹ See Morrison, J.D. *Asymmetric Synthesis* 5 Vols. [Vol. 4 coedited by Scott, J.W.], Academic Press, NY, **1983–1985**; Nográdi, M. *Stereoselective Synthesis*, VCH, NY, **1986**; Eliel, E.L.; Otsuka, S. *Asymmetric Reactions and Processes in Chemistry*, American Chemical Society, Washington, **1982**; Morrison, J.D.; Mosher, H.S. *Asymmetric Organic Reactions*, Prentice-Hall, Englewood Cliffs, NJ, **1971**, paperback reprint, American Chemical Society, Washington, **1976**. For reviews, see Ward, R.S. *Chem. Soc. Rev.* **1990**, 19, 1; Whitesell, J. K. *Chem. Rev.* **1989**, 89, 1581; Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* **1989**, 45, 1; Kochetkov, K.A.; Belikov, V.M. *Russ. Chem. Rev.* **1987**, 56, 1045; Oppolzer, W. *Tetrahedron* **1987**, 43, 1969; Seebach, D.; Imwinkelried, R.; Weber, T. *Mod. Synth. Methods*, **1986**, 4, 125; ApSimon, J.W.; Collier, T.L. *Tetrahedron* **1986**, 42, 5157.

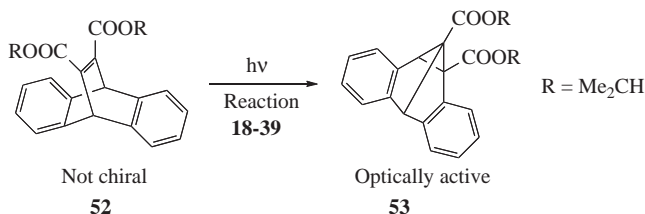
¹⁴⁰ Leitereg, T.J.; Cram, D.J. *J. Am. Chem. Soc.* **1968**, 90, 4019. For discussions, see Anh, N.T. *Top. Curr. Chem.*, **1980**, 88, 145, pp. 151–161; Eliel, E.L. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, **1983**, pp. 125–155. See Smith, R.J.; Trzoss, M.; Bühl, M.; Bienz, S. *Eur. J. Org. Chem.* **2002**, 2770.

¹⁴¹ See Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, **1962**, pp. 68–74; Bartlett, P.A. *Tetrahedron* **1980**, 36, 2, pp. 22–28; Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* **1975**, 75, 521; Goller, E.J. *J. Chem. Educ.* **1974**, 51, 182; Toromanoff, E. *Top. Stereochem.* **1967**, 2, 157.

Another model uses transition state models **50** and **51** to predict diastereoselectivity in what is known as the *Felkin–Anh model*.¹⁴² This model assumes the favored transition state will be that with the greatest separation between the incoming group and any electronegative substituent at the α -carbon. The so-called *Cornforth model* has also been presented as a model for carbonyl addition to halogenated compounds,¹⁴³ and it assumes that the electron pairs on the carbonyl oxygen and on the halogen repel and assume an anti-conformation.



Many reactions of this type are known, and in some the extent of favoritism approaches 100% (e.g., see Reaction **12-12**).¹⁴⁴ The farther away the reaction site is from the chiral center, the less influence the latter has and the more equal the amounts of diastereomers formed. There are many examples of asymmetric induction via nucleophilic acyl addition to carbonyl compounds (Reactions **16-24** and **16-25**). Enolborane addition to α -heteroatom substituted aldehydes has been evaluated using the Cornforth and the Felkin–Anh models.¹⁴⁵



In a special case of this type of asymmetric synthesis, a compound (**52**) with achiral molecules, but whose crystals are chiral, was converted by UV light to a single enantiomer of a chiral product (**53**).¹⁴⁶

It is often possible to convert an achiral compound to a chiral compound by (1) addition of a chiral group; (2) running an asymmetric synthesis, and (3) cleavage of the original chiral group. The original chiral group is called a *chiral auxiliary*.

¹⁴² Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199; Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205; Anh, N.T.; Eisenstein, O. *Nov. J. Chem.* **1977**, 1, 61. For experiments that show explanations for certain systems based on the Felkin–Anh model to be weak, see Yadav, V.K.; Gupta, A.; Balamurugan, R.; Sriramurthy, V.; Kumar, N.V. *J. Org. Chem.* **2006**, 71, 4178.

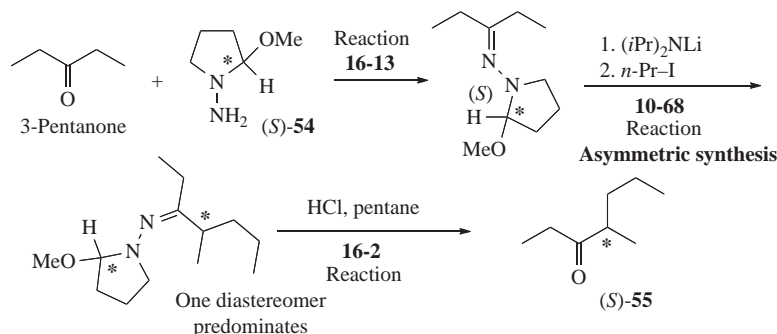
¹⁴³ Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. *J. Chem. Soc.* **1959**, 112; Evans, D.A.; Siska, S.J.; Cee, V.J. *Angew. Chem. Int. Ed.* **2003**, 42, 1761.

¹⁴⁴ See Eliel, E.L. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, **1983**, pp. 125–155; Eliel, E.L.; Koskimies, J.K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, 100, 1614; Still, W.C.; McDonald, J.H. *Tetrahedron Lett.* **1980**, 21, 1031; Still, W.C.; Schneider, J.A. *Tetrahedron Lett.* **1980**, 21, 1035.

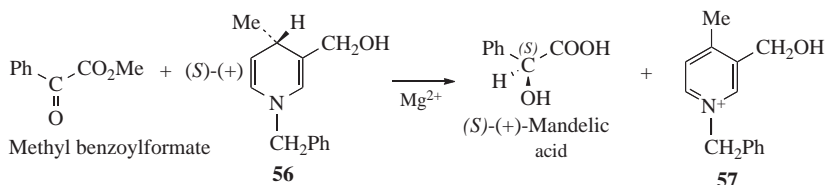
¹⁴⁵ Cee, V.J.; Cramer, C.J.; Evans, D.A. *J. Am. Chem. Soc.* **2006**, 128, 2920.

¹⁴⁶ Evans, S.V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J.R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* **1986**, 108, 5648; Garcia-Garibay, M.; Scheffer, J.R.; Trotter, J.; Wireko, F. *Tetrahedron Lett.* **1987**, 28, 4789. For an earlier example, see Penzien, K.; Schmidt, G.M.J. *Angew. Chem. Int. Ed.* **1969**, 8, 608.

An example is conversion of the achiral 2-pentanone to the chiral 4-methyl-3-heptanone, (**55**).¹⁴⁷ In this case, >99% of the product was the (*S*) enantiomer. As noted, compound **54** is called a *chiral auxiliary* because it is used to induce asymmetry and is then removed.



2. *Active Reagent*. A pair of enantiomers can be separated by an active reagent that reacts faster with one of them than it does with the other (this is also a method of resolution). If the absolute configuration of the reagent is known, the configuration of the enantiomers can often be determined by a knowledge of the mechanism and



by determining which diastereomer is preferentially formed.¹⁴⁸ Creation of a new stereogenic center in an inactive molecule can also be accomplished with an optically active reagent, although it is rare for 100% selectivity to be observed. An example^{149,150} is the reduction of methyl benzoylformate with optically active *N*-benzyl-3-(hydroxymethyl)-4-methyl-1,4-dihydropyridine (**56**) to produce mandelic acid (after hydrolysis) that contained ~97.5% of the (*S*)-(+)-isomer and 2.5% of the (*R*)-(–)-isomer (for another example, see Reaction 15-16). Note that the other product, (**57**), is not chiral. Reactions like this, in which one reagent (in this case **56**) gives up its chirality to another, are called *self-immolative*.

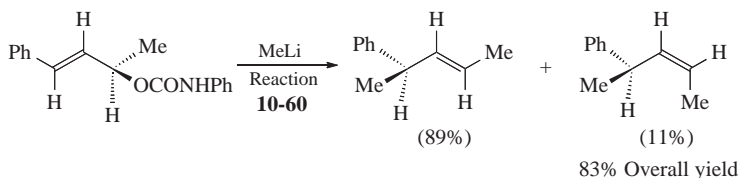
¹⁴⁷ Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K.A.M. *Tetrahedron* **1984**, *40*, 1345.

¹⁴⁸ See Brockmann, Jr., H.; Risch, N. *Angew. Chem. Int. Ed.* **1974**, *13*, 664; Potapov, V.M.; Gracheva, R.A.; Okulova, V.F. *J. Org. Chem. USSR* **1989**, *25*, 311.

¹⁴⁹ Meyers, A.I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989. For reviews of asymmetric reduction, see Morrison, J.D. *Surv. Prog. Chem.* **1966**, *3*, 147; Yamada, S.; Koga, K. *Sel. Org. Transform.*, **1970**, *1*, 1. See also, Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, **1983**.

¹⁵⁰ See, in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, **1985**, the reviews by Halpern, J. pp. 41–69; Koenig, K.E. pp. 71–101; Harada, K. pp. 345–383; Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901, pp. 6902–6916; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, **1986**, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* **1983**, *16*, 106; Brunner, H. *Angew. Chem. Int. Ed.* **1983**, *22*, 897; Sathyanarayana, B.K.; Stevens, E.S. *J. Org. Chem.* **1987**, *52*, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* **1988**, *110*, 4144.

In another example:



chirality is transferred from one atom to another in the same molecule.¹⁵¹

A reaction in which an inactive substrate is converted selectively to one of two enantiomers is called an *enantioselective* reaction, and the process is called *asymmetric induction*. These terms apply to reactions in this category and in categories 3 and 4.

When an optically active substrate reacts with an optically active reagent to form two new stereogenic centers, it is possible for both centers to be created in the desired sense. This type of process is called *double asymmetric synthesis*¹⁵² (for an example, see Reaction 16-34).

3. *Optically Active Catalyst or Solvent.*¹⁵³ Many such examples are found in the literature, among them reduction of ketones and substituted alkenes to optically active (though not optically pure) secondary alcohols and substituted alkanes by treatment with hydrogen and a chiral homogeneous hydrogenation catalyst (reactions 16-23 and 15-11),¹⁵⁴ the treatment of aldehydes or ketones with organometallic compounds in the presence of a chiral catalyst (see Reaction 16-24), and the conversion of alkenes to optically active epoxides by treatment with a hydroperoxide and a chiral catalyst (see Reaction 15-50). In some instances, the ratio of enantiomers prepared in this way is 99:1 or more.¹⁵⁵ Other examples of the use of a chiral catalyst or solvent are the conversion of chlorofumaric acid (in the form of its diion) to the (–)-*threo* isomer of the diion of chloromalic acid by treatment with H₂O and the enzyme fumarase,¹⁵⁶ as well as the preparation of

¹⁵¹ Goering, H.L.; Kantner, S.S.; Tseng, C.C. *J. Org. Chem.* **1983**, *48*, 715.

¹⁵² For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1.

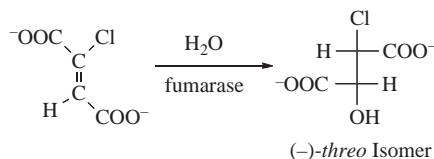
¹⁵³ For a monograph, see Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, **1985**. For reviews, see Tomioka, K. *Synthesis* **1990**, 541; Consiglio, G.; Waymouth, R.M. *Chem. Rev.* **1989**, *89*, 257; Brunner, H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 5, Wiley, NY, **1989**, pp. 109–146; Noyori, R.; Kitamura, M. *Mod. Synth. Methods* **1989**, *5*, 115; Pfaltz, A. *Mod. Synth. Methods* **1989**, *5*, 199; Kagan, H.B. *Bull. Soc. Chim. Fr.* **1988**, 846; Brunner, H. *Synthesis* **1988**, 645; Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.

¹⁵⁴ For reviews of these and related topics, see Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, **1988**; Brunner, H. *J. Organomet. Chem.* **1986**, *300*, 39; Bosnich, B.; Fryzuk, M.D. *Top. Stereochem.* **1981**, *12*, 119.

¹⁵⁵ See Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, **1994**. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**. For random examples, see Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418; Berhal, F.; Wu, Z.; Genet, J.-P.; Ayad, T.; Ratovelomanana-Vidal, V. *J. Org. Chem.* **2011**, *76*, 6320; He, P.; Liu, X.; Shi, J.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 936; Yang, H.-M.; Li, L.; Li, F.; Jiang, K.-Z.; Shang, J.-Y.; Lai, G.-Q.; Xu, L.-W. *Org. Lett.* **2011**, *13*, 6508.

¹⁵⁶ Findeis, M.A.; Whitesides, G.M. *J. Org. Chem.* **1987**, *52*, 2838; Réty, J.; Robinson, J.A. *Stereospecificity in Organic Chemistry and Enzymology*, Verlag Chemie, Deerfield Beach, FL, **1982**. For reviews, see Klibanov, A.M. *Acc. Chem. Res.* **1990**, *23*, 114; Jones, J.B. *Tetrahedron* **1986**, *42*, 3351; Jones, J.B. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, **1985**, pp. 309–344.

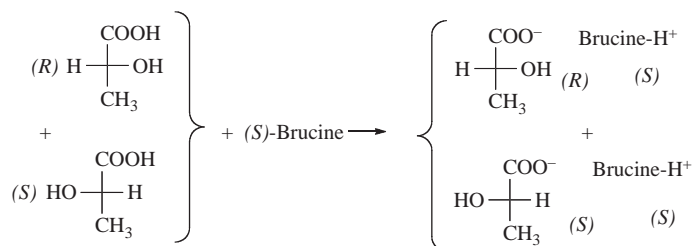
optically active aldols (aldol condensation, see Reaction **16-35**) by the condensation of enolate anions with optically active substrates.¹⁵⁷



4. *Reactions in the Presence of Circularly Polarized Light.*¹⁵⁸ If the light used to initiate a photochemical reaction (see Chap. 7) of achiral reagents is circularly polarized, then, in theory, a chiral product richer in one enantiomer might be obtained. However, such experiments have not proved fruitful. In certain instances, the use of left- and right-circularly polarized light *has* given products with opposite rotations¹⁵⁹ (showing that the principle is valid), but up to now the extent of favoritism has always been <1%.

4.H. METHODS OF RESOLUTION¹⁶⁰

A pair of enantiomers can be separated in several ways, but conversion to diastereomers and separation of these by fractional crystallization or chromatographic methods are used most often. In this method and in some of the others, both isomers can be recovered, but in some methods it is necessary to destroy one.



1. *Conversion to Diastereomers.* If the racemic mixture to be resolved contains a carboxyl group (and no strongly basic group), it is possible to form a salt with an optically active base. Since the base used is, say, the (S) form, there will be a mixture of two salts produced having the configurations (SS) and (RS). Although the acids are enantiomers, the salts are diastereomers and have different properties. The property most often used for separation is differential solubility. The mixture of diastereomeric salts is allowed to crystallize from a suitable solvent.

¹⁵⁷ Heathcock, C.H.; White, C.T. *J. Am. Chem. Soc.* **1979**, *101*, 7076.

¹⁵⁸ For a review, See Buchardt, O. *Angew. Chem. Int. Ed.* **1974**, *13*, 179. For a discussion, see Barron L.D. *J. Am. Chem. Soc.* **1986**, *108*, 5539.

¹⁵⁹ See Bernstein, W.J.; Calvin, M.; Buchardt, O. *J. Am. Chem. Soc.* **1973**, *95*, 527; Nicoud, J.F.; Kagan, J.F. *Isr. J. Chem.* **1977**, *15*, 78. See also, Zandomenighi, M.; Cavazza, M.; Pietra, F. *J. Am. Chem. Soc.* **1984**, *106*, 7261.

¹⁶⁰ Faigl, F.; Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J. *Tetrahedron Asymm.* **2008**, *19*, 519. See Wilen, S.H.; Collet, A.; Jacques, J. *Tetrahedron* **1977**, *33*, 2725; Boyle, P.H. *Q. Rev. Chem. Soc.* **1971**, *25*, 323; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**, pp. 297–424; Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, and Resolutions*, Wiley, NY, **1981**.

Since the solubilities are different, the initial crystals formed will be richer in one diastereomer. Filtration at this point will already have achieved a partial resolution. Unfortunately, the difference in solubility is rarely if ever great enough to effect total separation with one crystallization. When fractional crystallizations must be used, the process is long and tedious. Fortunately, naturally occurring optically active bases (mostly alkaloids) are readily available. Among the most commonly used are brucine, ephedrine, strychnine, and morphine. Once the two diastereomers have been separated, it is easy to convert the salts back to the free acids and the recovered base can be used again.

Most resolution of this type is done on carboxylic acids and often, when a molecule does not contain a carboxyl group, it is converted to a carboxylic acid before resolution is attempted. Racemic compounds (e.g., 2-aminocyclohexanol derivatives) react with carboxylic acids (e.g., optically active mandelic acid), to give diastereomers that are separated and then converted to enantiopure compounds.¹⁶¹ Racemic bases can be converted to diastereomeric salts with active acids. The principle of conversion to diastereomers is not confined to carboxylic acids, and other functional groups¹⁶² may be coupled to an optically active reagent.¹⁶³ Alcohols¹⁶⁴ can be converted to diastereomeric esters, aldehydes to diastereomeric hydrazones, and so on. Amino alcohols have been resolved using boric acid and chiral binaphthols.¹⁶⁵ Phosphine oxides¹⁶⁶ and chiral calix[4]arenes¹⁶⁷ have been resolved. Chiral crown ethers have been used to separate mixtures of enantiomeric alkylammonium and arylammonium ions, by the formation of diastereomeric complexes¹⁶⁸ (see also, category 3, below). Even hydrocarbons can be converted to diastereomeric inclusion compounds,¹⁶⁹ with urea. Urea is not chiral, but the cage structure is.¹⁷⁰ Racemic unsaturated hydrocarbons have been resolved as inclusion complex crystals with a chiral host compound derived from tartaric acid.¹⁷¹ *trans*-Cyclooctene (Sec. 4.C, category 6) was resolved by conversion to a Pt complex containing an optically active amine.¹⁷²

¹⁶¹ Schiffrers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2320.

¹⁶² See Boyle, P.H. *Q. Rev. Chem. Soc.* **1971**, *25*, 323; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**, pp. 322–424.

¹⁶³ For an extensive list of reagents that have been used for this purpose and of compounds resolved, see Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions*, University of Notre Dame Press, Notre Dame, IN, **1972**.

¹⁶⁴ See Klyashchitskii, B.A.; Shvets, V.I. *Russ. Chem. Rev.* **1972**, *41*, 592.

¹⁶⁵ Periasamy, M.; Kumar, N.S.; Sivakumar, S.; Rao, V.D.; Ramanathan, C.R.; Venkatraman, L. *J. Org. Chem.* **2001**, *66*, 3828.

¹⁶⁶ Andersen, N.G.; Ramsden, P.D.; Che, D.; Parvez, M.; Keay, B.A. *J. Org. Chem.* **2001**, *66*, 7478.

¹⁶⁷ Caccamese, S.; Bottino, A.; Cunsolo, F.; Parlato, S.; Neri, P. *Tetrahedron Asym.* **2000**, *11*, 3103.

¹⁶⁸ See Slingenfelter, D.S.; Helgeson, R.C.; Cram, D.J. *J. Org. Chem.* **1981**, *46*, 393; Davidson, R.B.; Bradshaw, J.S.; Jones, B.A.; Dalley, N.K.; Christensen, J.J.; Izatt, R.M.; Morin, F.G.; Grant, D.M. *J. Org. Chem.* **1984**, *49*, 353.

¹⁶⁹ See Prelog, V.; Kovačević, M.; Egli, M. *Angew. Chem. Int. Ed.* **1989**, *28*, 1147; Worsch, D.; Vögtle, F. *Top. Curr. Chem.* **1987**, *140*, 21; Toda, F. *Top. Curr. Chem.* **1987**, *140*, 43; Stoddart, J.F. *Top. Stereochem.* **1987**, *17*, 207; Arad-Yellin, R.; Green, B.S.; Knossow, M.; Tsoucaris, G. in Atwood, J.L.; Davies, J.E.D.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, **1984**, pp. 263–295.

¹⁷⁰ See Schlenk, Jr., W. *Liebigs Ann. Chem.* **1973**, 1145, 1156, 1179, 1195. See Arad-Yellin, R.; Green, B.S.; Knossow, M.; Tsoucaris, G. *J. Am. Chem. Soc.* **1983**, *105*, 4561.

¹⁷¹ Miyamoto, H.; Sakamoto, M.; Yoskioka, K.; Takaoka, R.; Toda, F. *Tetrahedron Asym.* **2000**, *11*, 3045.

¹⁷² For a review, see Tsuji, J. *Adv. Org. Chem.* **1969**, *6*, 109, see p. 220.

Fractional crystallization has always been the most common method for the separation of diastereomers. When it can be used, binary phase diagrams for the diastereomeric salts have been used to calculate the efficiency of optical resolution.¹⁷³ However, it is tedious and the fact that it is limited to solids prompted a search for other methods. Fractional distillation has given only limited separation, but gas chromatography (GC)¹⁷⁴ and preparative liquid chromatography using chiral columns¹⁷⁵ have proved to be more useful. In many cases, they have supplanted fractional crystallization, especially where the quantities to be resolved are small.¹⁷⁶

2. *Differential Absorption.* When a racemic mixture is placed on a chromatographic column, if the column consists of chiral substances, then in principle the enantiomers should move along the column at different rates and should be separable without having to be converted to diastereomers.¹⁷⁶ This has been successfully accomplished with paper, column, thin-layer,¹⁷⁷ and gas and liquid chromatography.¹⁷⁸ For example, racemic mandelic acid has been almost completely resolved by column chromatography on starch.¹⁷⁹ Many workers have achieved separations with gas and liquid chromatography by the use of columns packed with chiral absorbents.¹⁸⁰ Columns packed with chiral materials are now commercially available and are capable of separating the enantiomers of certain types of compounds.¹⁸¹
3. *Chiral Recognition.* The use of chiral hosts to form diastereomeric inclusion compounds was mentioned above. But in some cases it is possible for a host to form an inclusion compound with one enantiomer of a racemic guest, but not the other. This is called *chiral recognition*. One enantiomer fits into the chiral host cavity, the other does not. More often, both diastereomers are formed, but one forms more rapidly than the other, so that if the guest is removed it is already partially resolved (this is a form of kinetic resolution, see category 6). An example is use of the chiral crown ether (**58**) partially to resolve the racemic amine salt (**59**).¹⁸² When an

¹⁷³ Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc. Perkin Trans. 2* **1992**, 549.

¹⁷⁴ See Westley, J.W.; Halpern, B.; Karger, B.L. *Anal. Chem.* **1968**, *40*, 2046; Kawa, H.; Yamaguchi, F.; Ishikawa, N. *Chem. Lett.* **1982**, 745.

¹⁷⁵ See Meyers, A.I.; Slade, J.; Smith, R.K.; Mihelich, E.D.; Hershenson, F.M.; Liang, C.D. *J. Org. Chem.* **1979**, *44*, 2247; Goldman, M.; Kustanovich, Z.; Weinstein, S.; Tishbee, A.; Gil-Av, E. *J. Am. Chem. Soc.* **1982**, *104*, 1093.

¹⁷⁶ See Lough, W.J. *Chiral Liquid Chromatography*; Blackie and Sons: London, **1989**; Krstulović, A.M. *Chiral Separations by HPLC*, Ellis Horwood, Chichester, **1989**; Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, **1988**. For a review, see Karger, B.L. *Anal. Chem.* **1967**, *39*(8), 24A.

¹⁷⁷ Weinstein, S. *Tetrahedron Lett.* **1984**, *25*, 985.

¹⁷⁸ See Allenmark, S.G. *Chromatographic Enantioseparation*, Ellis Horwood, Chichester, **1988**; König, W.A. *The Practice of Enantiomer Separation by Capillary Gas Chromatography*, Hüthig, Heidelberg, **1987**. For reviews, see Schurig, V.; Nowotny, H. *Angew. Chem. Int. Ed.* **1990**, *29*, 939; Pirkle, W.H.; Pochapsky, T.C. *Chem. Rev.* **1989**, *89*, 347; Blaschke, G. *Angew. Chem. Int. Ed.* **1980**, *19*, 13; Rogozhin, S.V.; Davankov, V.A. *Russ. Chem. Rev.* **1968**, *37*, 565. See also, many articles in the journal *Chirality*.

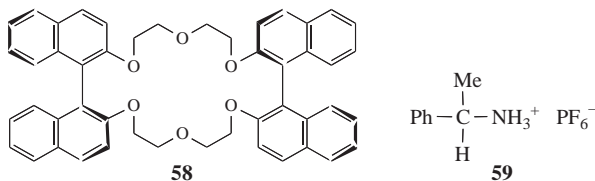
¹⁷⁹ Ohara, M.; Ohta, K.; Kwan, T. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 76. See also, Blaschke, G.; Donow, F. *Chem. Ber.* **1975**, *108*, 2792; Hess, H.; Burger, G.; Musso, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 612.

¹⁸⁰ See Schurig, V.; Nowotny, H.; Schmalzing, D. *Angew. Chem. Int. Ed.* **1989**, *28*, 736; Oi, S.; Shijo, M.; Miyano, S. *Chem. Lett.* **1990**, 59; Erlandsson, P.; Marle, I.; Hansson, L.; Isaksson, R.; Pettersson, C.; Pettersson, G. *J. Am. Chem. Soc.* **1990**, *112*, 4573.

¹⁸¹ See, for example, Pirkle, W.H.; Welch, C.J. *J. Org. Chem.* **1984**, *49*, 138.

¹⁸² Kanoh, S.; Hongoh, Y.; Katoh, S.; Motoi, M.; Suda, H. *J. Chem. Soc. Chem. Commun.* **1988**, 405; Bradshaw, J.S.; Huszthy, P.; McDaniel, C.W.; Zhu, C.Y.; Dalley, N.K.; Izatt, R.M.; Lifson, S. *J. Org. Chem.* **1990**, *55*, 3129.

aqueous solution of **59** was mixed with a solution of optically active **58** in chloroform, and the layers separated, the chloroform layer contained about twice as much of the complex between **58** and (*R*)-**59** as of the diastereomeric complex. Many other chiral crown ethers and cryptands have been used, as have been cyclodextrins,¹⁸³ cholic acid,¹⁸⁴ and other kinds of hosts.¹⁶⁹ Of course, enzymes are generally very good at chiral recognition, and much of the work in this area has been an attempt to mimic the action of enzymes.



4. *Biochemical Processes.*¹⁸⁵ Reactions catalyzed by enzymes can be utilized for this kind of resolution.¹⁸⁶ Biological molecules may react at different rates with the two enantiomers. For example, a certain bacterium may digest one enantiomer, but not the other. Pig liver esterase has been used for the selective cleavage of one enantiomeric ester.¹⁸⁷ This method is limited, since it is necessary to find the proper organism and since one of the enantiomers is destroyed in the process. However, when the proper organism is found, the method leads to a high extent of resolution since biological processes are usually very stereoselective. This process has been called chemoenzymatic dynamic kinetic resolution.¹⁸⁸
5. *Mechanical Separation.*¹⁸⁹ This is the method by which Pasteur proved that racemic tartaric acid was actually a mixture of (+)- and (–)-tartaric acids.¹⁹⁰ In the case of racemic sodium ammonium tartrate, the enantiomers crystallize separately: all the (+) molecules going into one crystal and all the (–) into another. Since the crystals too are nonsuperimposable, their appearance is not identical and a trained crystallographer can separate them with tweezers.¹⁹¹ However, this is seldom a practical method, since few compounds crystallize in this manner. Even sodium ammonium tartrate does so only when it is crystallized

¹⁸³ See, for example, Hamilton, J.A.; Chen, L. *J. Am. Chem. Soc.* **1988**, *110*, 5833.

¹⁸⁴ See Miyata, M.; Shibakana, M.; Takemoto, K. *J. Chem. Soc. Chem. Commun.* **1988**, 655.

¹⁸⁵ For a review, see Sih, C.J.; Wu, S. *Top. Stereochem.* **1989**, *19*, 63.

¹⁸⁶ See Nakamura, K.; Inoue, Y.; Ohno, A. *Tetrahedron Lett.* **1994**, *35*, 4375; Kazlauskas, R.J. *J. Am. Chem. Soc.* **1989**, *111*, 4953; Schwartz, A.; Madan, P.; Whitesell, J.K.; Lawrence, R.M. *Org. Synth.* **69**, 1. For resolution with Subtilisin, see Savile, C.K.; Magloire, V.P.; Kazlauskas, R.J. *J. Am. Chem. Soc.* **2005**, *127*, 2104. For the chemoenzymatic kinetic resolution of primary amines, see Paetzold, J.; Bäckvall, J.E. *J. Am. Chem. Soc.* **2005**, *127*, 17620.

¹⁸⁷ For an example, see Gais, H.-J.; Jungen, M.; Jadhav, V. *J. Org. Chem.* **2001**, *66*, 3384.

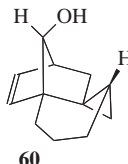
¹⁸⁸ For an example of the resolution of acyloins, see Ödman, P.; Wessjohann, L.A.; Bornscheuer, U.T. *J. Org. Chem.* **2005**, *70*, 9551.

¹⁸⁹ For reviews, see Collet, A.; Brienne, M.; Jacques, J. *Chem. Rev.* **1980**, *80*, 215; *Bull. Soc. Chim. Fr.* **1972**, 127; **1977**, 494. For a discussion, see Curtin, D.Y.; Paul, I.C. *Chem. Rev.* **1981**, *81*, 525 pp. 535–536.

¹⁹⁰ Besides discovering this method of resolution, Pasteur also discovered the method of conversion to diastereomers and separation by fractional crystallization and the method of biochemical separation (and, by extension, kinetic resolution).

¹⁹¹ This is a case of optically active materials arising from inactive materials. However, it may be argued that an optically active investigator is required to use the tweezers. Perhaps a hypothetical human being constructed entirely of inactive molecules would be unable to tell the difference between left- and right-handed crystals.

$<27^{\circ}\text{C}$. A more useful variation of the method, although still not very common, is the seeding of a racemic solution with something that will cause only one enantiomer to crystallize.¹⁹² An interesting example of the mechanical separation technique was reported in the isolation of heptahelicene (Sec. 4.C. Category 7). One enantiomer of this



compound, which incidentally has the extremely high rotation of $[\alpha]_{\text{D}}^{20} = +6200^{\circ}$ spontaneously crystallizes from benzene.¹⁹³ In the case of 1,1'-binaphthyl, optically active crystals can be formed simply by heating polycrystalline racemic samples of the compound at $76\text{--}150^{\circ}\text{C}$. A phase change from one crystal form to another takes place.¹⁹⁴ Note that 1,1'-binaphthyl is one of the few compounds that can be resolved by the Pasteur tweezer method. In some cases, resolution can be achieved by enantioselective crystallization in the presence of a chiral additive.¹⁹⁵ Spontaneous resolution has also been achieved by sublimation. In the case of the norborneol derivative **60**, when the racemic solid is subjected to sublimation, the (+) molecules condense into one crystal and the (−) molecules into another.¹⁹⁶ In this case, the crystals are superimposable, unlike the situation with sodium ammonium tartrate, but the investigators were able to remove a single crystal, which proved optically active.

6. *Kinetic Resolution.*¹⁹⁷ Since enantiomers react with chiral compounds at different rates, it is sometimes possible to effect a partial separation by stopping the reaction before completion. This method is very similar to the asymmetric syntheses discussed in Section 4.C, category 5. A method has been developed to evaluate the enantiomeric ratio of kinetic resolution using only the extent of substrate conversion.¹⁹⁸ An important application of this method is the resolution of racemic alkenes by treatment with optically active diisopinocampheylborane,¹⁹⁹ since alkenes do not easily lend themselves to conversion to diastereomers if no

¹⁹² For a review of the seeding method, see Secor, R.M. *Chem. Rev.* **1963**, 63, 297.

¹⁹³ Martin, R.H.; Baes, M. *Tetrahedron* **1975**, 31, 2135. See also, Wynberg, H.; Groen, M.B. *J. Am. Chem. Soc.* **1968**, 90, 5339; McBride, J.M.; Carter, R.L. *Angew. Chem. Int. Ed.* **1991**, 30, 293.

¹⁹⁴ Kress, R.B.; Duesler, E.N.; Etter, M.C.; Paul, I.C.; Curtin, D.Y. *J. Am. Chem. Soc.* **1980**, 102, 7709. See also, Gottarelli, G.; Spada, G.P. *J. Org. Chem.* **1991**, 56, 2096. For a discussion and other examples, see Agranat, I.; Perlmutter-Hayman, B.; Tapuhi, Y. *Nouv. J. Chem.* **1978**, 2, 183.

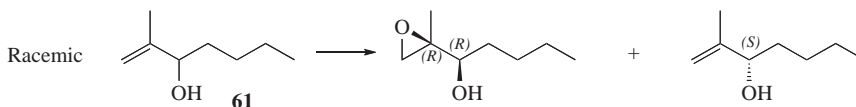
¹⁹⁵ Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* **1982**, 104, 4610. See also, Weissbuch, I.; Addadi, L.; Berkovitch-Yellin, Z.; Gati, E.; Weinstein, S.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1983**, 105, 6615.

¹⁹⁶ Paquette, L.A.; Lau, C.J. *J. Org. Chem.* **1987**, 52, 1634.

¹⁹⁷ For reviews, see Pellissier, H. *Tetrahedron* **2008**, 64, 1563; Ward, R.S. *Tetrahedron Asymm.* **1995**, 6, 1475; Pellissier, H. *Tetrahedron* **2003**, 59, 8291.

¹⁹⁸ Lu, Y.; Zhao, X.; Chen, Z.-N. *Tetrahedron Asymm.* **1995**, 6, 1093.

¹⁹⁹ Brown, H.C.; Ayyangar, N.R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, 86, 397.



other functional groups are present. Another example is the resolution of allylic alcohols (e.g., **61**) with one enantiomer of a chiral epoxidation agent (see Reaction **15-50**).²⁰⁰ In the case of **61**, the discrimination was extreme. One enantiomer was converted to the epoxide and the other was not, the rate ratio (hence the selectivity factor) being >100 . Of course, in this method only one of the enantiomers of the original racemic mixture is obtained, but there are at least two possible ways of getting the other: (1) use of the other enantiomer of the chiral reagent and (2) conversion of the product to the starting compound by a reaction that preserves the stereochemistry.

Kinetic resolution of racemic allylic acetates²⁰¹ has been accomplished via asymmetric dihydroxylation (Reaction **15-48**), and 2-oxoimidazolidine-4-carboxylates have been developed as new chiral auxiliaries for the kinetic resolution of amines.²⁰² A planar chiral cyclic ether was found to be stable at ambient temperatures, but resolved by kinetic resolution.²⁰³

7. *Deracemization*. In this type of process, one enantiomer is converted to the other, so that a racemic mixture is converted to a pure enantiomer, or to a mixture enriched in one enantiomer (*enantioenriched*). This finding is not quite the same as the methods of resolution previously mentioned, although an outside optically active substance is required. To effect the deracemization, two conditions are necessary: (1) the enantiomers must complex differently with the optically active substance and (2) they must interconvert under the conditions of the experiment. When racemic thioesters were placed in solution with a specific optically active amide for 28 days, the solution contained 89% of one enantiomer and 11% of the other.²⁰⁴ In this case, the presence of a base (Et_3N) was necessary for the interconversion to take place. Biocatalytic deracemization processes induce deracemization of chiral secondary alcohols.²⁰⁵ In a specific example, *Sphingomonas paucimobilis* NCIMB 8195 catalyzes the efficient deracemization of many secondary alcohols in up to 90% yield of the (*R*)-alcohol.²⁰⁶

²⁰⁰ Carlier, P.R.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *110*, 2978; Discordia, R.P.; Dittmer, D.C. *J. Org. Chem.* **1990**, *55*, 1414. For other examples, see Katamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron Asymm.* **1990**, *1*, 1; Hayashi, M.; Miwata, H.; Oguni, N. *J. Chem. Soc. Perkin Trans. 2* **1991**, 1167.

²⁰¹ Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* **1993**, *34*, 3911.

²⁰² Kubota, H.; Kubo, A.; Nunami, K. *Tetrahedron Lett.* **1994**, *35*, 3107.

²⁰³ Tomooka, K.; Komine, N.; Fujiki, D.; Nakai, T.; Yanagitsuru, S. *J. Am. Chem. Soc.* **2005**, *127*, 12182.

²⁰⁴ Pirkle, W.H.; Reno, D.S. *J. Am. Chem. Soc.* **1987**, *109*, 7189. For another example, see Reider, P.J.; Davis, P.; Hughes, D.L.; Grabowski, E.J.J. *J. Org. Chem.* **1987**, *52*, 955.

²⁰⁵ Stecher, H.; Faber, K. *Synthesis* **1997**, 1.

²⁰⁶ Allan, G. R.; Carnell, A. J. *J. Org. Chem.* **2001**, *66*, 6495.

4.I. OPTICAL PURITY²⁰⁷

An attempt to resolve a racemic mixture by one of the methods described in Section 4.I has given either a pure compound or a new mixture. How can the purity of the two enantiomers obtained be determined? If the (+) isomer is contaminated by, say, 20% of the (–) isomer, how can this be determined? If the value of $[\alpha]$ for the pure material ($[\alpha]_{\max}$) is known, the purity of a sample is easily determined by measuring its rotation. For example, if $[\alpha]_{\max}$ is $+80^\circ$ and the resolved (+) enantiomer contains 20% of the (–) isomer, $[\alpha]$ for the sample will be $+48^\circ$.²⁰⁸ Optical purity is defined as

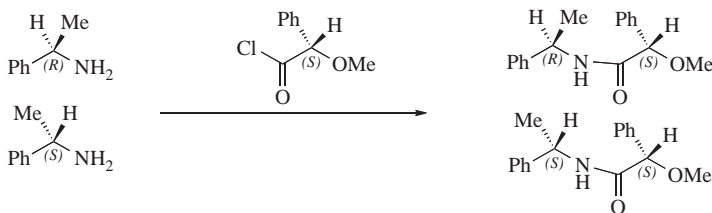
$$\text{Percent optical purity} = \frac{[\alpha]_{\text{obs}}}{[\alpha]_{\max}} \times 100$$

Assuming a linear relationship between $[\alpha]$ and concentration, which is true for most cases, the optical purity is equal to the percent excess of one enantiomer over the other:

$$\text{Optical purity} = \text{percent enantiomeric excess (\%ee)}^{209} = \frac{[R] - [S]}{[R] + [S]} \times 100 = (\%R) - (\%S)$$

How is the value of $[\alpha]_{\max}$ determined? It is plain that we have two related problems here; namely, what are the optical purities of our two samples and what is the value of $[\alpha]_{\max}$. Finding the properties of one also gives the other. Several methods for solving these problems are known.

One of these methods involves the use of NMR²¹⁰ (see Sec. 4.E.ii, category 7). If there is a nonracemic mixture of two enantiomers and the proportions constitute an unknown, convert the mixture into a mixture of diastereomers with an optically pure reagent and look at the NMR spectrum of the resulting mixture, for example,



²⁰⁷ For a review, see Raban, M.; Mislow, K. *Top. Stereochem.* **1967**, 2, 199.

²⁰⁸ If a sample contains 80% (+) and 20% (–) isomer, the (–) isomer cancels an equal amount of (+) isomer and the mixture behaves as if 60% of it were (+) and the other 40% inactive. Therefore the rotation is 60% of 80° or 48° . This type of calculation, however, is not valid for cases in which $[\alpha]$ is dependent on concentration (Sec. 4.B); see Horeau, A. *Tetrahedron Lett.* **1969**, 3121.

²⁰⁹ For a method to measure %ee using electrooptics, see Walba, D.M.; Eshdat, L.; Korblova, E.; Shao, R.; Clark, N.A. *Angew. Chem. Int. Ed.* **2007**, 46, 1473.

²¹⁰ Raban, M.; Mislow, K. *Tetrahedron Lett.* **1965**, 4249, **1966**, 3961; Jacobus, J.; Raban, M. *J. Chem. Educ.* **1969**, 46, 351; Tokles, M.; Snyder, J.K. *Tetrahedron Lett.* **1988**, 29, 6063. For a review, see Yamaguchi, S. in Morrison, J. D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, **1983**, pp. 125–152. See also, Raban, M.; Mislow, K. *Top. Stereochem.* **1967**, 2, 199.

If the NMR spectrum of the starting mixture is examined, only one peak would be found (split into a doublet by the C—H) for the Me protons, since enantiomers give identical NMR spectra.²¹¹ But the two amides are not enantiomers and each Me gives its own doublet. From the intensity of the two peaks, the relative proportions of the two diastereomers (and hence of the original enantiomers) can be determined. Alternatively, the “unsplit” OMe peaks could have been used. This method was satisfactorily used to determine the optical purity of a sample of 1-phenylethylamine (the case shown above),²¹² as well as other cases, but it is obvious that sometimes corresponding groups in diastereomeric molecules will give NMR signals that are too close together for resolution. In such cases, one may resort to the use of a different optically pure reagent. The ¹³C NMR can be used in a similar manner.²¹³ It is also possible to use these spectra to determine the absolute configuration of the original enantiomers by comparing the spectra of the diastereomers with those of the original enantiomers.²¹⁴ From a series of experiments with related compounds of known configurations it can be determined in which direction one or more of the ¹H or ¹³C NMR peaks are shifted by formation of the diastereomer. It is then assumed that the peaks of the enantiomers of unknown configuration will be shifted the same way.

A closely related method does not require conversion of enantiomers to diastereomers, but relies on the fact that (in principle, at least) enantiomers have different NMR spectra *in a chiral solvent*, or when mixed with a chiral molecule (in which case transient diastereomeric species may form, see Sec. 4.E.ii). In such cases, the peaks may be separated enough to permit the proportions of enantiomers to be determined from their intensities.²¹⁵ Another variation, which gives better results in many cases, is to use an achiral solvent, but with the addition of a *chiral lanthanide shift reagent* [e.g., *tris*[3-trifluoroacetyl-*d*-camphorato]europium(III)].²¹⁶ Lanthanide shift reagents have the property of spreading NMR peaks of compounds with which they can form coordination compounds (e.g., alcohols, carbonyl compounds, and amines). Chiral lanthanide shift reagents shift the peaks of the two enantiomers of many such compounds to different extents.

Another method, involving GC,²¹⁷ is similar in principle to the NMR chiral complex method. A mixture of enantiomers whose purity is to be determined is converted by means of an optically pure reagent into a mixture of two diastereomers. These diastereomers are then separated by GC and the ratios are determined from the peak areas. Once again, the

²¹¹ Though enantiomers give identical NMR spectra, the spectrum of a single enantiomer may be different from that of the racemic mixture, even in solution. See Williams, T.; Pitcher, R.G.; Bommer, P.; Gutzwiller, J.; Uskoković, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871.

²¹² Raban, M.; Mislow, K. *Top. Stereochem.* **1967**, *2*, 199, see pp. 216–218.

²¹³ For a method that relies on diastereomer formation without a chiral reagent, see Feringa, B.L.; Strijtveen, B.; Kellogg, R.M. *J. Org. Chem.* **1986**, *51*, 5484. See also, Pasquier, M.L.; Marty, W. *Angew. Chem. Int. Ed.* **1985**, *24*, 315; Luchinat, C.; Roelens, S. *J. Am. Chem. Soc.* **1986**, *108*, 4873.

²¹⁴ See Trost, B.M.; Belletire, J.L.; Godleski, S.; McDougal, P.G.; Balkovec, J.M.; Baldwin, J.J.; Christy, M.E.; Ponticello, G.S.; Varga, S.L.; Springer, J.P. *J. Org. Chem.* **1986**, *51*, 2370.

²¹⁵ For reviews of NMR chiral solvating agents, see Weisman, G.R. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, **1983**, pp. 153–171; Pirkle, W.H.; Hoover, D.J. *Top. Stereochem.* **1982**, *13*, 263. Sweeting, L.M.; Anet, F.A.L. *Org. Magn. Reson.* **1984**, *22*, 539. See also, Pirkle, W.H.; Tsipouras, A. *Tetrahedron Lett.* **1985**, *26*, 2989; Parker, D.; Taylor, R.J. *Tetrahedron* **1987**, *43*, 5451.

²¹⁶ Sweeting, L.M.; Crans, D.C.; Whitesides, G.M. *J. Org. Chem.* **1987**, *52*, 2273; Morrill, T.C. *Lanthanide Shift Reagents in Stereochemical Analysis*, VCH, NY, **1986**; Fraser, R.R. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, **1983**, pp. 173–196; Sullivan, G.R. *Top. Stereochem.* **1978**, *10*, 287.

²¹⁷ See Westley, J.W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978.

ratio of diastereomers is the same as that of the original enantiomers. High-pressure liquid chromatography has been used in a similar manner and has wider applicability.²¹⁸ The direct separation of enantiomers by gas or liquid chromatography on a chiral column has also been used to determine optical purity.²¹⁹

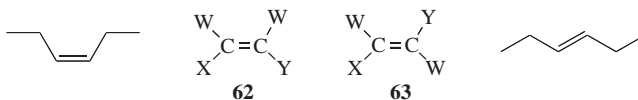
Other methods²²⁰ involve isotopic dilution,²²¹ kinetic resolution,²²² ¹³C NMR relaxation rates of diastereomeric complexes,²²³ and circular polarization of luminescence.²²⁴

4.J. *cis-trans* ISOMERISM

Compounds in which rotation is restricted may exhibit *cis-trans* isomerism.²²⁵ These compounds do not rotate the plane of polarized light (unless they also happen to be chiral), and the properties of the isomers are not identical. The two most important types are isomerism resulting from double bonds and that resulting from rings.

4.J.i. *cis-trans* Isomerism Resulting from Double Bonds

It has been mentioned (Sec. 1.D) that the two carbon atoms of a C=C double bond and the four atoms directly attached to them are all in the same plane and that the presence of the π -bond prevents rotation around the double bond. This means that in the case of a molecule WXC=CYZ, stereoisomerism exists when $W \neq X$ and $Y \neq Z$. There are two and only two isomers (**62** and **63**), each superimposable on its mirror image unless one of the groups happens to carry a stereogenic center. Note that **62** and **63** are diastereomers, by the definition given in Section 4.E.i. There are two ways to name such isomers. In the older and less versatile method, one isomer is called *cis* and the other *trans*. When each carbon of the C=C unit has an *identical group* (W in **62** and **63**), but fits the substitution pattern of **62** and **63**, the *cis-trans* nomenclature system may be applied. When the two identical groups are on the same side (W and W in **62**), it is labeled *cis*. *cis*-3-Hexene is shown as an example. When the two identical groups are on opposite side (W and W in **63**) it is labeled *trans*. *trans*-3-Hexene is shown as an example. Unfortunately, there is no obvious way to apply this method when the four groups are different.



²¹⁸ For a review, see Pirkle, W.H.; Finn, J. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, **1983**, pp. 87–124.

²¹⁹ For reviews, see in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, **1983**, the articles by Schurig, V. pp. 59–86 and Pirkle, W.H.; Finn, J. pp. 87–124.

²²⁰ See Hill, H.W.; Zens, A.P.; Jacobus, J. *J. Am. Chem. Soc.* **1979**, *101*, 7090; Matsumoto, M.; Yajima, H.; Endo, R. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4139.

²²¹ Berson, J.A.; Ben-Efraim, D.A. *J. Am. Chem. Soc.* **1959**, *81*, 4083; Andersen, K.K.; Gash, D.M.; Robertson, J.D. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, **1983**, pp. 45–57.

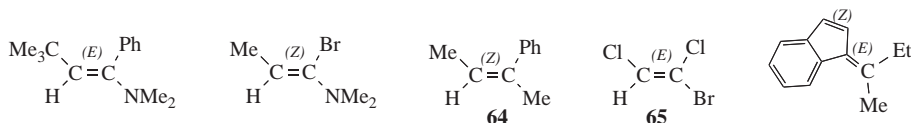
²²² Horeau, A.; Guetté, J.; Weidmann, R. *Bull. Soc. Chim. Fr.* **1966**, 3513. For a review, see Schoofs, A.R.; Guetté, J. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, **1983**, pp. 29–44.

²²³ Hofer, E.; Keuper, R. *Tetrahedron Lett.* **1984**, *25*, 5631.

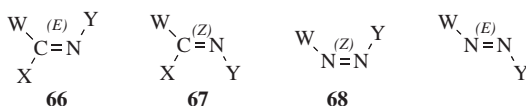
²²⁴ Schippers, P.H.; Dekkers, H.P.J.M. *Tetrahedron* **1982**, *38*, 2089.

²²⁵ *cis-trans* isomerism was formerly called *geometrical isomerism*.

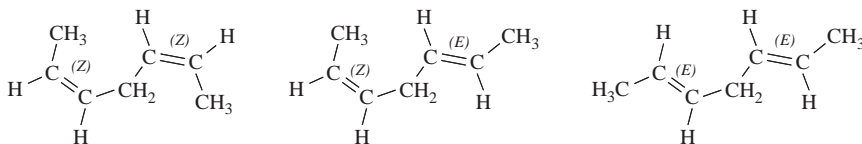
The newer and more widely applicable method can be applied to all cases, and is based on the CIP system (Sec. 4.E.i). The two groups at each carbon of the C=C unit are ranked by the sequence rules. The isomer with the two higher ranking groups on the same side of the double bond is called (*Z*) (for the German word *zusammen* meaning *together*). The isomer with the two higher ranking groups on opposite sides of the double bond is called (*E*) (for *entgegen* meaning *opposite*).²²⁶ A few examples are shown. Note that the (*Z*) isomer is not necessarily the one that would be called *cis* under the older system (e.g., **64** and **65**). Like *cis* and *trans*, (*E*) and (*Z*) are used as prefixes; for example, **65** is called (*E*)-1-bromo-1,2-dichloroethene.



This type of isomerism is also possible with other double bonds (e.g., C=N,²²⁷ N=N,²²⁸ or even C=S),²²⁹ although in these cases only two or three groups are connected to the double-bond atoms. In the case of imines, oximes, and other C=N compounds, if W = Y, **66** may be called *syn* and **67** *anti*, but (*E*) and (*Z*) are used here too.²³⁰ In azo compounds there is no ambiguity. Compound **68** is always *syn* or (*Z*) regardless of the nature of W and Y.



If there is more than one double bond²³¹ in a molecule and if $W \neq X$ and $Y \neq Z$ for each, the number of isomers in the most general case is 2^n , although this number may be decreased if some of the substituents are the same, as in the three 2,5-heptadienes shown.



When a molecule contains a double bond and a stereogenic carbon, there are four isomers, a *cis* pair of enantiomers and a *trans* pair, shown for 4-methylhex-2-ene.

²²⁶ For a complete description of the system, see *Pure Appl. Chem.* **1976**, 45, 13; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, **1979** (the Blue Book).

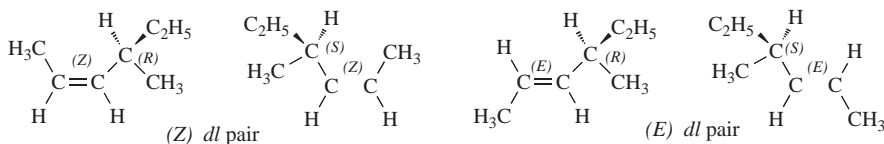
²²⁷ See in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, **1970**, the articles by McCarty, C.G. pp. 363–464 (pp. 364–408), and Wettermark, G. pp. 565–596 (pp. 574–582).

²²⁸ Wang, Y.-N.; Bohle, D.S.; Bonifant, C.L.; Chmurny, G.N.; Collins, J.R.; Davies, K.M.; Deschamps, J.; Flippen-Anderson, J.L.; Keefer, L.K.; Klose, J.R.; Saavedra, J.E.; Waterhouse, D.J.; Ivancic, J. *J. Am. Chem. Soc.* **2005**, 127, 5388.

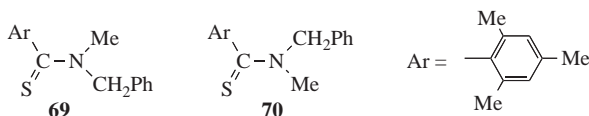
²²⁹ King, J.F.; Durst, T. *Can. J. Chem.* **1966**, 44, 819.

²³⁰ A mechanism has been reported for the acid-catalyzed *Z/E* isomerization of imines. See Johnson, J.E.; Morales, N.M.; Gorczyca, A.M.; Dolliver, D.D.; McAllister, M.A. *J. Org. Chem.* **2001**, 66, 7979.

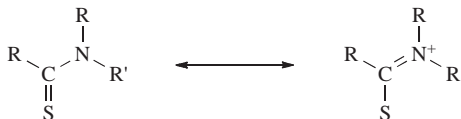
²³¹ This rule does not apply to allenes, which do not show *cis-trans* isomerism (see Sec. 4.C, category 5).



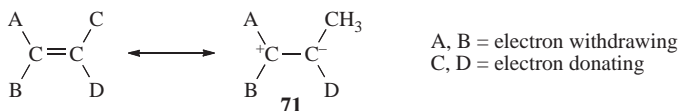
Double bonds in small rings are so constrained that they must be *cis*. From cyclopropene (a known system) to cycloheptene, double bonds in a stable ring *cannot* be *trans*. However, the cyclooctene ring is large enough to permit *trans* double bonds to exist (see Sec. 4.C, category 7), and for rings larger than 10- or 11-membered, *trans* isomers are more stable²³² (see also, Sec. 4.Q.ii).



In a few cases, single-bond rotation is so slowed that *cis* and *trans* isomers can be isolated even where no double bond exists²³³ (see also, Sec. 4.Q.iv). One example is *N*-methyl-*N*-benzylthiomesitylylide (**69** and **70**).²³⁴ The isomers are stable in the crystalline state, but interconvert with a half-life of ~ 25 h in CDCl_3 at 50°C .²³⁵ This type of isomerism is rare; it is found chiefly in certain amides and thioamides, because resonance gives the single-bond some double-bond character and slows rotation.⁵⁴ (For other examples of restricted rotation about single bonds, see Sec. 4.Q.iv.)



Conversely, there are compounds in which nearly free rotation is possible around what are formally $\text{C}=\text{C}$ double bonds. These compounds, called *push-pull* or *captodative* ethylenes, have two electron-withdrawing groups on one carbon and two electron-donating groups on the other (**71**).²³⁶ The contribution of diionic



²³² Cope, A.C.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* **1959**, *81*, 3153.

²³³ Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**, pp. 41–71.

²³⁴ Mannschreck, A. *Angew. Chem. Int. Ed.* **1965**, *4*, 985. See also, Völter, H.; Helmchen, G. *Tetrahedron Lett.* **1978**, 1251; Walter, W.; Hühnerfuss, H. *Tetrahedron Lett.* **1981**, *22*, 2147.

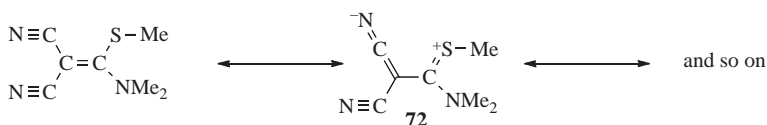
²³⁵ This is another example of atropisomerism (Sec. 4.C, category 5).

²³⁶ For reviews, see Sandström, J. *Top. Stereochem.* **1983**, *14*, 83; Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**, pp. 111–125.

TABLE 4.2 Some Properties of Maleic and Fumaric Acids

	Maleic Acid	Fumaric Acid
Property	Maleic Acid	Fumaric Acid
Melting point (°C)	130	286
Solubility in water at 25 °C (g L ⁻¹)	788	7
K_1 (at 25°C)	1.5×10^{-2}	1×10^{-3}
K_2 (at 25°C)	2.6×10^{-7}	3×10^{-5}

canonical forms, such as the one shown, decreases the double-bond character and allows easier rotation. For example, compound **72** has a barrier to rotation of 13 kcal mol⁻¹ (55 kJ mol⁻¹),²³⁷ compared to a typical value of ~62–65 kcal mol⁻¹ (260–270 kJ mol⁻¹) for simple alkenes.



Since they are diastereomers, *cis-trans* isomers always differ in properties; the differences may range from very slight to considerable. The properties of maleic acid are so different from those of fumaric acid (Table 4.2) that it is not surprising that they have different names. Since they generally have more symmetry than *cis* isomers, *trans* isomers in most cases have higher melting points and lower solubilities in inert solvents. The *cis* isomer usually has a higher heat of combustion, which indicates a lower thermochemical stability. Other noticeably different properties are densities, acid strengths, boiling points, and various types of spectra, but the differences are too involved to be discussed here.

It is also important to note that *trans*-alkenes are often more stable than *cis*-alkenes due to diminished steric hindrance (Sec. 4.Q.iv), but this is not always the case. It is known, for example, that *cis*-1,2-difluoroethene is thermodynamically more stable than *trans*-1,2-difluoroethene. This appears to be due to delocalization of halogen lone-pair electrons and an antiperiplanar effect between vicinal antiperiplanar bonds.²³⁸

4.J.ii *cis-trans* Isomerism of Monocyclic Compounds

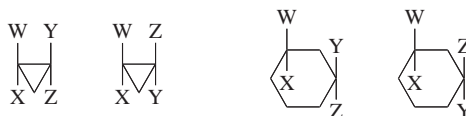
Although rings of four carbons and larger are not generally planar (see Sec. 4.O), they will be treated as such in this section, since the correct number of isomers can be determined when this is done²³⁹ and the principles are easier to visualize (see Sec. 4.O).

²³⁷ Sandström, J.; Wennerbeck, I. *Acta Chem. Scand. Ser. B*, **1978**, 32, 421.

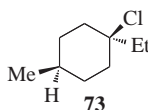
²³⁸ Yamamoto, T.; Tomoda, S. *Chem. Lett.* **1997**, 1069.

²³⁹ See Leonard, J.E.; Hammond, G.S.; Simmons, H.E. *J. Am. Chem. Soc.* **1975**, 97, 5052.

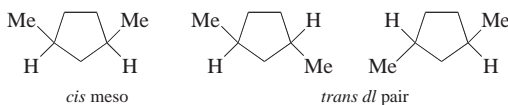
The presence of a ring, like that of a double bond, prevents rotation. *cis* and *trans* isomers are possible whenever there are two carbons on a ring, each of which is substituted by two different groups. The two carbons need not be adjacent. Examples follow:



In some cases, the two stereoisomers can interconvert. In *cis*- and *trans*-disubstituted cyclopropanones, for example, there is reversible interconversion that favors the more stable *trans* isomer. This fluxional isomerization occurs via ring opening to an unseen oxyallyl *valence bond* isomer.²⁴⁰



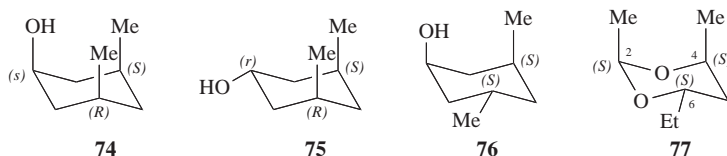
While *cis* and *trans* isomers are possible for rings, the restrictions are that W may equal Y and X may equal Z, but W may not equal X and Y may not equal Z. There is an important difference from the double-bond case: The substituted carbons may be stereogenic carbons. This means that there may be more than two isomers. In the most general case, where W, X, Y, and Z are all different, there are four isomers since neither the *cis* nor the *trans* isomer is superimposable on its mirror image. This is true regardless of ring size or which carbons are involved, except that in rings of even-numbered size when W, X, Y, and Z are at opposite corners. Cyclohexane derivative **73**, for example, has no stereogenic carbons because there is a plane of symmetry. Imagine a focus on the chlorine-bearing carbon, and view each “arm” of the ring as a group. There are two identical groups so the carbon will not be stereogenic. When W = Y and X = Z, the *cis* isomer is always superimposable on its mirror image. Hence, this isomer is a meso compound, while the *trans* isomer consists of a *dl* pair, except in the case noted above. Again, the *cis* isomer has a plane of symmetry while the *trans* does not.



Rings with more than two differently substituted carbons can be dealt with using similar principles. In some cases, it is not easy to tell the number of isomers by inspection.¹⁰⁷ The best method may be to count the number *n* of differently substituted carbons (these will usually be asymmetric, but not always, e.g., in **73**), and then to draw 2^n structures, crossing out those that can be superimposed on others (usually the easiest method is to look for a plane of symmetry). By this means, it can be determined that for 1,2,3-cyclohexanetriol there are two meso compounds and a *dl* pair; and for 1,2,3,4,5,6-hexachlorocyclohexane there are seven meso compounds and a *dl* pair. Similar principles apply to heterocyclic rings as long as there are carbons (or other ring atoms) containing two different groups.

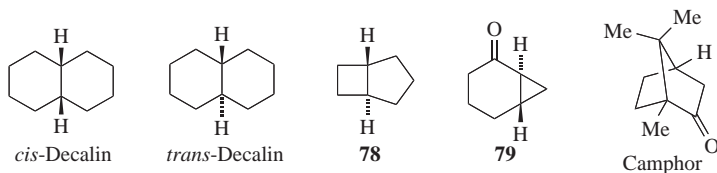
²⁴⁰ Sorensen, T.S.; Sun, F. *J. Chem. Soc. Perkin Trans. 2* **1998**, 1053.

Cyclic stereoisomers containing only two differently substituted carbons are named either *cis* or *trans*, as previously indicated. The (*Z*, *E*) system is not used for cyclic compounds. However, *cis-trans* nomenclature will not suffice for compounds with more than two differently substituted atoms. For these compounds, a system is used in which the configuration of each group is given with respect to a reference group, which is chosen as the group attached to the lowest-numbered ring member bearing a substituent giving rise to *cis-trans* isomerism. The reference group is indicated by the symbol *r*. Three stereoisomers named according to this system are 3(*S*), 5(*R*)-dimethylcyclohexan-*s*-1-ol (**74**), 3(*S*), 5(*R*)-dimethylcyclohexan-*r*-1-ol (**75**), and 3(*S*), 5(*S*)-dimethylcyclohexan-*s*-1-ol (**76**). The last example demonstrates the rule that when there are two otherwise equivalent ways of going around the ring, one chooses the path that gives the *cis* designation to the first substituent after the reference. Another example is 2(*S*), 4(*S*)-dimethyl-6*s*-ethyl-1,3-dioxane (**77**).



4.J.iii. *cis-trans* Isomerism of Fused and Bridged Ring Systems

Fused bicyclic systems are those in which two rings share two and only two atoms. In such systems, there is no new principle. The fusion may be *cis* or *trans*, as illustrated by *cis*- and *trans*-decalin. However, when the rings are small enough, the *trans* configuration is impossible and the junction must be *cis*. The smallest *trans* junction that has been prepared when one ring is four membered is a four–five junction; *trans*-bicyclo[3.2.0]heptane (**78**) is known.²⁴¹ For the bicyclo[2.2.0] system (a four–four fusion), only *cis* compounds have been made. The smallest known *trans* junction when one ring is three membered is a six–three junction (a bicyclo[4.1.0] system). An example is **79**.²⁴² When one ring is three-membered and the other eight-membered (an eight–three junction), the *trans*-fused isomer is more stable than the corresponding *cis*-fused isomer.²⁴³



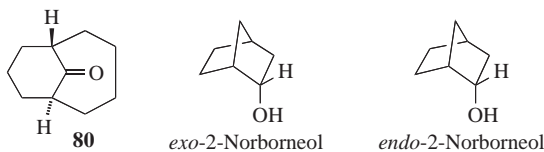
In *bridged* bicyclic ring systems, two rings share more than two atoms. In these cases, there may be fewer than 2^n isomers, because of the structure of the system. For example, there are only two isomers of camphor (a pair of enantiomers), although it has two stereogenic carbons. In both isomers, the methyl and hydrogen are *cis*. The *trans* pair of

²⁴¹ Meinwald, J.; Tufariello, J.J.; Hurst, J.J. *J. Org. Chem.* **1964**, 29, 2914.

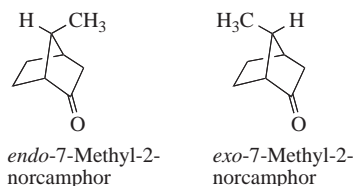
²⁴² Paukstelis, J.V.; Kao, J. *J. Am. Chem. Soc.* **1972**, 94, 4783. For references to other examples, see Dixon, D.A.; Gassman, P.G. *J. Am. Chem. Soc.* **1988**, 110, 2309.

²⁴³ Corbally, R.P.; Perkins, M.J.; Carson, A.S.; Laye, P.G.; Steele, W.V. *J. Chem. Soc. Chem. Commun.* **1978**, 778.

enantiomers is impossible in this case, since the bridge *must* be cis. The smallest bridged system so far prepared in which the bridge is trans is the [4.3.1] system; the trans ketone (**80**) has been prepared.²⁴⁴ In this case, there are four isomers, since both the trans and the cis, which has also been prepared, are pairs of enantiomers.



When one of the bridges contains a substituent, the question arises as to how to name the isomers involved. When the two bridges that do *not* contain the substituent are of unequal length, the rule generally followed is that the prefix *endo*- is used when the substituent is closer to the longer of the two unsubstituted bridges; the prefix *exo*- is used when the substituent is closer to the shorter bridge; for example, When the two bridges not containing the substituent are of equal length, this convention cannot be applied, but in some cases a decision can still be made. For example, if one of the two bridges contains a functional group, the *endo* isomer is the one in which the substituent is closer to the functional group:



4.K. OUT-IN ISOMERISM

Another type of stereoisomerism, called *out-in* isomerism (or *in-out*),²⁴⁵ is found in salts of tricyclic diamines with nitrogen at the bridgeheads. In medium-sized bicyclic ring systems, *in-out* isomerism is possible,²⁴⁶ and the bridgehead nitrogen atoms adopt the arrangement that is more stable.²⁴⁷ A focus on the nitrogen lone pairs reveals that 1,4-diazabicyclo[2.2.2]octane (**81**) favors the *out-out* isomer, that 1,6-diazabicyclo[4.4.4]tetradecane (**82**) the *in-in*,²⁴⁸ that 1,5-diazabicyclo[3.3.3]undecane (**83**) has nearly planar nitrogen atoms,²⁴⁹ and that 1,9-diazabicyclo[7.3.1]tridecane (**84**) is *in-out*.²⁵⁰ One can also focus on the NH unit in the case of ammonium salts.

²⁴⁴ Winkler, J.D.; Hey, J.P.; Williard, P.G. *Tetrahedron Lett.* **1988**, 29, 4691.

²⁴⁵ See Alder, R.W. *Acc. Chem. Res.* **1983**, 16, 321.

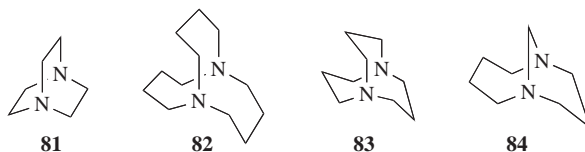
²⁴⁶ Alder, R.W.; East, S.P. *Chem. Rev.* **1996**, 96, 2097.

²⁴⁷ Alder, R.W. *Tetrahedron* **1990**, 46, 683.

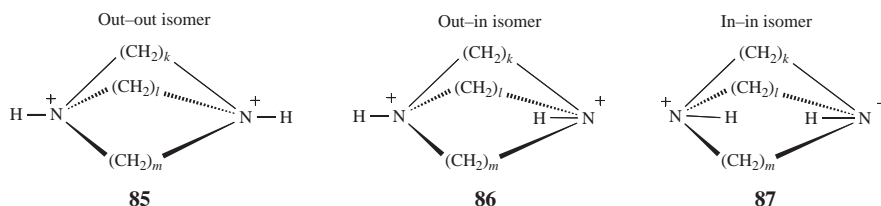
²⁴⁸ Alder, R.W.; Orpen, A.G.; Sessions, R.B. *J. Chem. Soc., Chem. Commun.* **1983**, 999.

²⁴⁹ Alder, R.W.; Goode, N.C.; King, T.J.; Mellor, J.M.; Miller, B.W. *J. Chem. Soc., Chem. Commun.* **1976**, 173; Alder, R.W.; Arrowsmith, R.J.; Casson, A.; Sessions, R.B.; Heilbronner, E.; Kovac, B.; Huber, H.; Taagepera, M. *J. Am. Chem. Soc.* **1981**, 103, 6137.

²⁵⁰ Alder, R.W.; Heilbronner, E.; Honegger, E.; McEwen, A.B.; Moss, R.E.; Olefirowicz, E.; Petillo, P.A.; Sessions, R.B.; Weisman, G.R.; White, J.M.; Yang, Z.-Z. *J. Am. Chem. Soc.* **1993**, 115, 6580.



In the examples **85–87**, when k , l , and $m > 6$, the N—H bonds can be inside the molecular cavity or outside, giving rise to three isomers, as shown. Simmons and Park²⁵¹ isolated several such isomers with k , l , and m varying from 6 to 10. In the 9,9,9 compound, the cavity of the in-in isomer is large enough to encapsulate a



chloride ion that is hydrogen bonded to the two N—H groups. The species thus formed is a cryptate, but differs from the cryptates discussed at Section 3.C.ii in that there is a negative rather than a positive ion enclosed.²⁵² Even smaller ones (e.g., the 4,4,4 compound) have been shown to form mono-inside-protonated ions.²⁵³ In compound **88**, which has four quaternary nitrogen atoms, a halide ion has been encapsulated without a hydrogen being present on a nitrogen.²⁵⁴ This ion does not display *in-out* isomerism. *Out-in* and *in-in* isomers have also been prepared in analogous all-carbon tricyclic systems.²⁵⁵

It is known that chiral phosphanes are more pyramidal and that inversion is more difficult, usually requiring temperatures well over 100°C for racemization.²⁵⁶ Alder and Read²⁵⁷ found that deprotonation of bis(phosphorane) **89**, which is known to have an *in-out* structure with significant P—P bonding, leads to a rearrangement and the *out-out* diphosphane **90**. Reprotonation gives **89**,²⁵⁸ with inversion at the nonprotonated phosphorus atom occurring at room temperature.

²⁵¹ Simmons, H.E.; Park, C.H. *J. Am. Chem. Soc.* **1968**, *90*, 2428; Park, C.H.; Simmons, H.E. *J. Am. Chem. Soc.* **1968**, *90*, 2429, 2431; Simmons, H.E.; Park, C.H.; Uyeda, R.T.; Habibi, M.F. *Trans. N.Y. Acad. Sci.* **1970**, *32*, 521. See also, Dietrich, B.; Lehn, J.M.; Sauvage, J.P. *Tetrahedron* **1973**, *29*, 1647; Dietrich, B.; Lehn, J.M.; Sauvage, J.P.; Blanzat, J. *Tetrahedron* **1973**, *29*, 1629.

²⁵² See Schmidtchen, F.P.; Gleich, A.; Schummer, A. *Pure. Appl. Chem.* **1989**, *61*, 1535; Pierre, J.; Baret, P. *Bull. Soc. Chim. Fr.* **1983**, II-367. See also, Hosseini, M.W.; Lehn, J. *Helv. Chim. Acta* **1988**, *71*, 749.

²⁵³ Dietrich, B.; Lehn, J.M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* **1989**, *30*, 4125; Wallon, A.; Peter-Katalinić, J.; Werner, U.; Müller, W.M.; Vögtle, F. *Chem. Ber.* **1990**, *123*, 375.

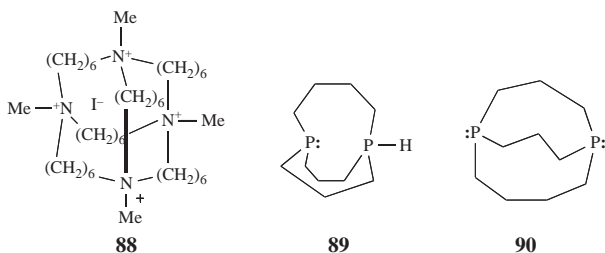
²⁵⁴ Schmidtchen, F.P.; Müller, G. *J. Chem. Soc. Chem. Commun.* **1984**, 1115. See also, Schmidtchen, F.P. *J. Am. Chem. Soc.* **1986**, *108*, 8249, *Top. Curr. Chem.* **1986**, *132*, 101.

²⁵⁵ McMurry, J.E.; Hodge, C.N. *J. Am. Chem. Soc.* **1984**, *106*, 6450; Winkler, J.D.; Hey, J.P.; Williard, P.G. *J. Am. Chem. Soc.* **1986**, *108*, 6425.

²⁵⁶ See Baechler, R.D.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 3090; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* **1970**, *9*, 400.

²⁵⁷ Alder, R.W.; Read, D. *Angew. Chem. Int. Ed.* **2000**, *39*, 2879.

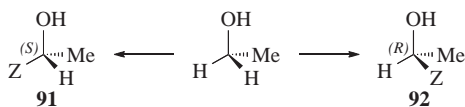
²⁵⁸ Alder, R.W.; Ellis, D.D.; Gleiter, R.; Harris, C.J.; Lange, H.; Orpen, A.G.; Read, D.; Taylor, P.N. *J. Chem. Soc., Perkin Trans. I* **1998**, 1657.



4.L. ENANTIOTOPIC AND DIASTEREOTOPIC ATOMS, GROUPS, AND FACES²⁵⁹

Many molecules contain atoms or groups that appear to be equivalent, but a close inspection will show them to be actually different. We can test whether two atoms are equivalent by replacing each of them in turn with some other atom or group. If the new molecules created by this process are identical, the original atoms are equivalent; otherwise they are not. There are three cases.

1. In the case of malonic acid [$\text{CH}_2(\text{COOH})_2$], propane (CH_2Me_2), or any other molecule of the form CH_2Y_2 ,²⁶⁰ replacing either of the CH_2 hydrogens by a group Z will give the identical compound. The two hydrogens are thus equivalent. Equivalent atoms and groups need not, of course, be located on the same carbon atom. For example, all the chlorine atoms of hexachlorobenzene are equivalent as are the two bromine atoms of 1,3-dibromopropane.
2. In the case of ethanol, replacing one of the CH_2 hydrogens by a group Z will give one enantiomer of the compound ZCHMeOH (**91**), while replacement of the other hydrogen gives the *other* enantiomer (**92**). Since the two compounds that result upon replacement of H by Z (**91** and **92**) are not identical but enantiomeric, the hydrogens are *not* equivalent. Two atoms or groups that upon replacement with a third group give enantiomers are defined as *enantiotopic*. In any symmetrical environment, the two hydrogens behave as equivalent, but in a dissymmetrical environment they may behave differently. For example, in a reaction



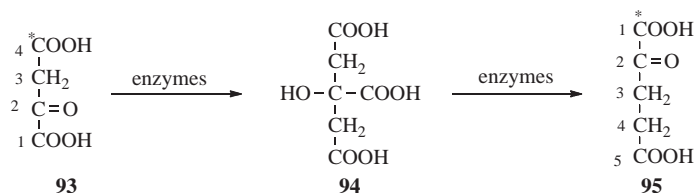
with a chiral reagent they may be attacked at different rates. This has important consequences in enzymatic reactions,²⁶¹ since enzymes are capable of much greater discrimination than ordinary chiral reagents. An example is found in the Krebs

²⁵⁹ These terms were coined by Mislow. See Eliel, E.L. *Top. Curr. Chem.* **1982**, 105, 1; Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, 1, 1. See also, Jennings, W.B. *Chem. Rev.* **1975**, 75, 307.

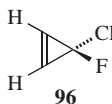
²⁶⁰ In the case where Y is itself a chiral group, this statement is only true when the two Y groups have the same configuration.

²⁶¹ For a review, see Benner, S.A.; Glasfeld, A.; Piccirilli, J.A. *Top. Stereochem.* **1989**, 19, 127. For a nonenzymatic example, see Job, R.C.; Bruce, T.C. *J. Am. Chem. Soc.* **1974**, 96, 809.

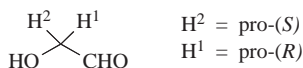
cycle, in biological organisms, where oxaloacetic acid (**93**) is converted to α -oxoglutaric acid (**95**) by a sequence that includes citric acid (**94**) as an intermediate. When **93** is labeled with ^{14}C at the 4 position, the label is found only at C-1 of **95**, despite the fact that **94** is not chiral. The two



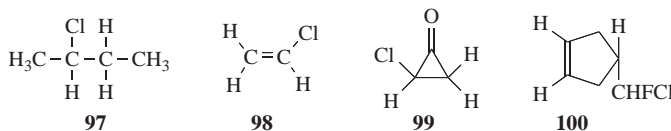
CH_2COOH groups of **94** are enantiotopic and the enzyme easily discriminates between them.²⁶² Note that the X atoms or groups of any molecule of the form CX_2WY are always enantiotopic if neither W nor Y is chiral. However, enantiotopic atoms and groups may also be found in other molecules (e.g., the hydrogen atoms in 3-fluoro-3-chlorocyclopropene, **96**). In this case, substitution of an H by a group Z makes the C-3 atom asymmetric and substitution at C-1 gives the opposite enantiomer from substitution at C-2.



The term *prochiral*²⁶³ is used for a compound or group that has two enantiotopic atoms or groups (e.g., CX_2WY). That atom or group X that would lead to an R compound if preferred to the other is called *pro-(R)*. The other is *pro-(S)*; for example,



3. Where two atoms or groups in a molecule are in such positions that replacing each of them in turn by a group Z gives rise to diastereomers, the atoms or groups are called *diastereotopic*. Some examples are the CH_2 groups of 2-chlorobutane (**97**), vinyl chloride (**98**), and chlorocyclopropanone (**99**), as well as the two alkenyl hydrogens

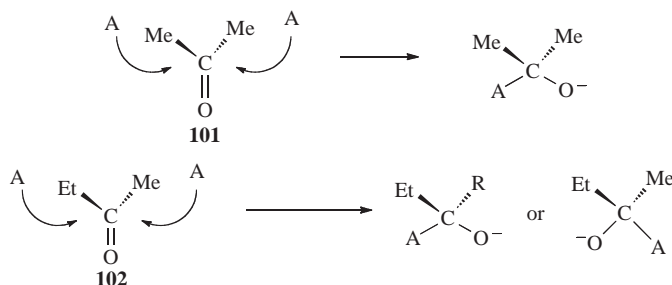


of **100**. Diastereotopic atoms and groups are different in any environment, chiral or achiral. These hydrogens react at different rates with achiral reagents, but an even

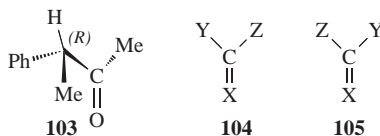
²⁶² The experiments were carried out by Evans Jr., E.A.; Slotin, L. *J. Biol. Chem.* **1941**, 141, 439; Wood, H.G.; Werkman, C.H.; Hemingway, A.; Nier, A.O. *J. Biol. Chem.* **1942**, 142, 31. The correct interpretation was given by Ogston, A.G. *Nature (London)* **1948**, 162, 963. For discussion, see Eliel, E.L. *Top. Curr. Chem.* **1982**, 105, 1, pp. 5–7, 45–70.

²⁶³ Hirschmann, H.; Hanson, K.R. *Tetrahedron* **1974**, 30, 3649.

more important consequence is that in NMR spectra, diastereotopic hydrogens theoretically give different peaks and split each other. This is in sharp contrast to equivalent or enantiotopic hydrogens, which are indistinguishable in the NMR, except when chiral solvents are used, in which case enantiotopic (but not equivalent) protons give different peaks.²⁶⁴ The term *isochronous* is used for hydrogens that are indistinguishable in the NMR.²⁶⁵ In practice, the NMR signals from diastereotopic protons are often found to be indistinguishable, but this is merely because they are very close together. Theoretically they are distinct, and they have been resolved in many cases. When they appear together, it is sometimes possible to resolve them by the use of lanthanide shift reagents (Sec. 4.J) or by changing the solvent or concentration. Note that X atoms or groups (CX_2WY) are diastereotopic if either W or Y is chiral.



Just as there are enantiotopic and diastereotopic atoms and groups, *enantiotopic and diastereotopic faces* in trigonal molecules may be distinguished. Again, there are three cases: (1) In formaldehyde or acetone (**101**), attack by an achiral reagent A from either face of the molecule gives rise to the same transition state and product; the two faces are thus equivalent and there is only one product. (2) In 2-butanone (**102**) or acetaldehyde, attack by an achiral A at one face gives a chiral transition state and the enantiomeric products arise from attack at one or the other face. Such faces are *enantiotopic*. Attack at an enantiotopic face by a chiral reagent will generate another stereogenic center, which gives diastereomers that may not be formed in equal amounts. (3) In a case like **103**, the two faces are obviously not equivalent and are called *diastereotopic*. Enantiotopic and diastereotopic faces can be named by an extension of the CIP system (Sec. 4.E.i).²⁶³ If the three groups as arranged by the sequence rules have the order $X > Y > Z$, that face in which the groups in this sequence are clockwise (as in **104**) is the *Re* face (from Latin *rectus*), whereas **105** shows the *Si* face (from Latin *sinister*).



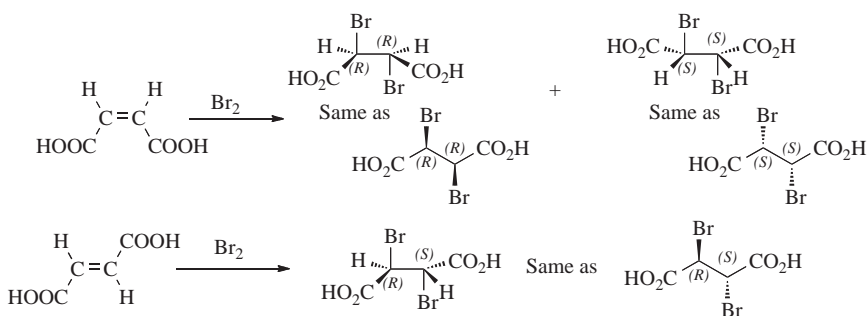
²⁶⁴ Pirkle, W.H. *J. Am. Chem. Soc.* **1966**, 88, 1837; Burlingame, T.G.; Pirkle, W.H. *J. Am. Chem. Soc.* **1966**, 88, 4294; Pirkle, W.H.; Burlingame, T.G. *Tetrahedron Lett.* **1967**, 4039.

²⁶⁵ For a review of isochronous and nonisochronous nuclei in NMR, see van Gorkom, M.; Hall, G.E. *Q. Rev. Chem. Soc.* **1968**, 22, 14. For a discussion, see Silverstein, R.M.; LaLonde, R.T. *J. Chem. Educ.* **1980**, 57, 343.

Note that new terminology has been proposed.²⁶⁶ The concept of sphericity is used, and the terms homospheric, enantiospheric, and hemispheric have been coined to specify the nature of an orbit (an equivalent class) assigned to a coset representation.²⁶⁷ Using these terms, prochirality can be defined: If a molecule has at least one enantiospheric orbit, the molecule is defined as being prochiral.²⁵⁸

4.M. STEREOSPECIFIC AND STEREOSELECTIVE SYNTHESSES

Any reaction in which only one of a set of stereoisomers is formed predominantly is called a *stereoselective* synthesis.²⁶⁸ The same term is used when a mixture of two or more stereoisomers is exclusively or predominantly formed at the expense of other stereoisomers. In a *stereospecific* reaction, a given isomer leads to one product while another stereoisomer leads to the opposite product. All stereospecific reactions are necessarily stereoselective, but the converse is not true. These terms are best illustrated by examples. Thus, if maleic acid treated with bromine gives the *dl* pair of 2,3-dibromosuccinic acid while fumaric acid gives the meso isomer (this is the case), the reaction is stereospecific as well as stereoselective because two opposite isomers give two opposite isomers. However, if both maleic and fumaric acid gave the *dl* pair or a mixture in which the *dl* pair predominated, the reaction would be stereoselective, but not stereospecific. If more or less equal amounts of *dl* and meso forms were produced in each case, the reaction would be nonstereoselective. A consequence of these definitions is that if a reaction is carried out on a compound that has no stereoisomers, it cannot be stereospecific, but at most stereoselective. For example, addition of bromine to methylacetylene could (and does) result in preferential formation of *trans*-1,2-dibromopropene, but this can be only a stereoselective, not a stereospecific reaction.



4.N. CONFORMATIONAL ANALYSIS

For acyclic molecules with single covalent bonds, there is rotation about those bonds. As a practical matter, such rotation leads to different arrangements of the atoms with respect to a given bond, but all arrangements constitute the same molecule. The different

²⁶⁶ Fujita, S. *J. Org. Chem.* **2002**, 67, 6055.

²⁶⁷ Fujita, S. *J. Am. Chem. Soc.* **1990**, 112, 3390.

²⁶⁸ For a further discussion of these terms and of stereoselective reactions in general, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**, pp. 835–990.

arrangements for a molecule due to such rotation are called *rotamers*. In principle, there is rotation about every single bond and a near infinite number of rotamers. If two different 3D spatial arrangements of the atoms in an acyclic molecule are interconvertible merely by free rotation about bonds, they are called *conformations*.²⁶⁹ If they are not interconvertible, they are called *configurations*.²⁷⁰ Configurations represent *isomers* that can be separated, as previously discussed in this chapter. Conformations represent *conformers*, which are rapidly interconvertible and thus nonseparable. The terms “conformational isomer” or more commonly “rotamer”²⁷¹ are used to identify one of many structures that result from rotation about single covalent bonds. Typically, the conformation is the average of the collection of lower energy rotamers for an acyclic compound. A number of methods have been used to determine conformations.²⁷² These include X-ray and electron diffraction, IR, Raman, UV, NMR,²⁷³ and microwave spectra,²⁷⁴ PES,²⁷⁵ supersonic molecular jet spectroscopy,²⁷⁶ and ORD and CD measurements.²⁷⁷ Ring current NMR anisotropy has been applied to conformational analysis,²⁷⁸ as has chemical shift simulation.²⁷⁹ Some of these methods are useful only for solids. It must be kept in mind that the conformation of a molecule in the solid state is not necessarily the same as in solution.²⁸⁰ Conformations can be *calculated* by a method called molecular mechanics (Sec. 4.P). A method was reported that characterized six-membered ring conformations as a linear combination of ideal basic conformations.²⁸¹ The term absolute conformation has been introduced for molecules where

²⁶⁹ See Bonchev, D.; Rouvray, D.H. *Chemical Topology*, Gordon and Breach, Australia, **1999**.

²⁷⁰ See Dale, J. *Stereochemistry and Conformational Analysis*, Verlag Chemie, Deerfield Beach, FL, **1978**; Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, **1971**; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, **1965**; Hanack, M. *Conformation Theory*, Academic Press, NY, **1965**. For reviews, see Dale, J. *Top. Stereochem.* **1976**, 9, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* **1976**, 5, 411; Eliel, E.L. *J. Chem. Educ.* **1975**, 52, 762; Bastiansen, O.; Bushweller, C.H.; Gianni, M.H. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, **1980**, pp. 215–278.

²⁷¹ Öki, M. *The Chemistry of Rotational Isomers*, Springer-Verlag, Berlin, **1993**.

²⁷² For a review, see Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, **1965**, pp. 129–188.

²⁷³ See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**; Marshall, J.L. *Carbon–Carbon and Carbon–Proton NMR Couplings*, VCH, NY, **1983**. For reviews, see Anet, F.A.L.; Anet, R. in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, **1971**, pp. 343–420; Kessler, H. *Angew. Chem. Int. Ed.* **1970**, 9, 219; Ivanova, T.M.; Kugatova-Shemyakina, G.P. *Russ. Chem. Rev.* **1970**, 39, 510; See also, Whitesell, J.K.; Minton, M. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*, Chapman and Hall, NY, **1987**.

²⁷⁴ For a review see Wilson, E.B. *Chem. Soc. Rev.* **1972**, 1, 293.

²⁷⁵ For a review, see Klessinger, M.; Rademacher, P. *Angew. Chem. Int. Ed.* **1979**, 18, 826.

²⁷⁶ Breen, P.J.; Warren, J.A.; Bernstein, E.R.; Seeman, J.I. *J. Am. Chem. Soc.* **1987**, 109, 3453.

²⁷⁷ See Kagan, H.B. *Determination of Configurations by Dipole Moments, CD, or ORD* (Vol. 2 of Kagan, H.B. *Stereochemistry*), Georg Thieme Publishers, Stuttgart, **1977**; Crabbé, P. *ORD and CD in Chemistry and Biochemistry*, Academic Press, NY, **1972**; Sneath, G. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Sadtler Research Laboratories, Philadelphia, **1967**; Velluz, L.; Legrand, M.; Grosjean, M. *Optical Circular Dichroism*, Academic Press, NY, **1965**. For reviews, see Smith, H.E. *Chem. Rev.* **1983**, 83, 359; Håkansson, R. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, **1979**, pp. 67–120; Hudec, J.; Kirk, D.N. *Tetrahedron* **1976**, 32, 2475; Schellman, J.A. *Chem. Rev.* **1975**, 75, 323.

²⁷⁸ Chen, J.; Cammers-Goodwin, A. *Eur. J. Org. Chem.* **2003**, 3861.

²⁷⁹ Iwamoto, H.; Yang, Y.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **2001**, 42, 49.

²⁸⁰ See Kessler, H.; Zimmermann, G.; Förster, H.; Engel, J.; Oepen, G.; Sheldrick, W.S. *Angew. Chem. Int. Ed.* **1981**, 20, 1053.

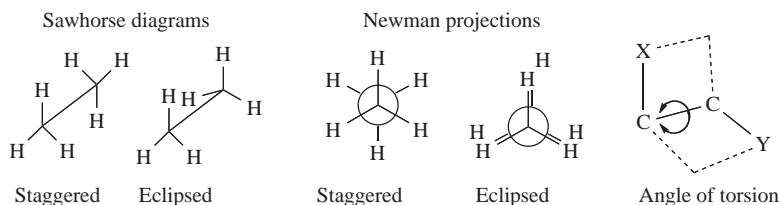
²⁸¹ Bérces, A.; Whitfield, D.M.; Nukada, T. *Tetrahedron* **2001**, 57, 477.

one conformation is optically inactive but, by internal rotation about a $C(sp^3)–C(sp^3)$ bond, optically active conformers are produced.²⁸²

Note that “free” rotation about single bonds is not possible in cyclic molecules, but rather pseudorotation that leads to different conformations. This discussion will therefore separate rotation in acyclic molecules from pseudorotation in cyclic molecules.

4.N.i. Conformation in Open-Chain Systems²⁸³

For any open-chain molecule with a single bond that connects two sp^3 carbon atoms, an infinite number of rotamers are possible, each of which has a certain energy associated with it, which leads to an infinite number of conformations. As a practical matter, the number of conformations is much less. If one ignores duplications due to symmetry, the number of conformations can be *estimated* as being $> 3^n$, where n = the number of internal C—C bonds. For example, *n*-pentane, has 11, *n*-hexane 35, *n*-heptane 109, *n*-octane 347, *n*-nonane 1101, and *n*-decane 3263.²⁸⁴ For ethane, there are two important rotamers that are taken as the extremes, a conformation of highest (marked eclipsed) and one of lowest (marked staggered) potential energy, depicted in two ways as sawhorse diagrams or Newman projections. In *Newman projection formulas*, the observer looks at the C—C bond head on. The three lines emanating from the center of the circle represent the bonds coming from the front carbon, with respect to the observer.



The staggered conformation is the conformation of lowest potential energy for ethane. As rotation about the bond occurs, the energy gradually increases until the eclipsed conformation is reached, when the energy is at a maximum. Further rotation decreases the energy again. Figure 4.4 illustrates this finding. The *angle of torsion*, which is a dihedral angle, is the angle between the X—C—C and the C—C—Y planes, as shown in the diagram. For ethane, the difference in energy is $\sim 2.9 \text{ kcal mol}^{-1}$ (12 kJ mol^{-1}).²⁸⁵ This difference is called the *energy barrier or rotational barrier*,²⁸⁶ since in free rotation about a single bond there must be enough rotational energy present to cross the barrier every time two hydrogen atoms are opposite each other. There was

²⁸² Öki, M.; Toyota, S. *Eur. J. Org. Chem.* **2004**, 255.

²⁸³ See Berg, U.; Sandström, J. *Adv. Phys. Org. Chem.* **1989**, 25, 1. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**, pp. 597–664. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 35–47.

²⁸⁴ Goto, H.; Osawa, E.; Yamato, M. *Tetrahedron* **1993**, 49, 387.

²⁸⁵ Lide Jr., D.R. *J. Chem. Phys.* **1958**, 29, 1426; Weiss, S.; Leroi, G.E. *J. Chem. Phys.* **1968**, 48, 962; Hirota, E.; Saito, S.; Endo, Y. *J. Chem. Phys.* **1979**, 71, 1183.

²⁸⁶ Mo, Y.; Gao, J. *Acc. Chem. Res.* **2007**, 40, 113.

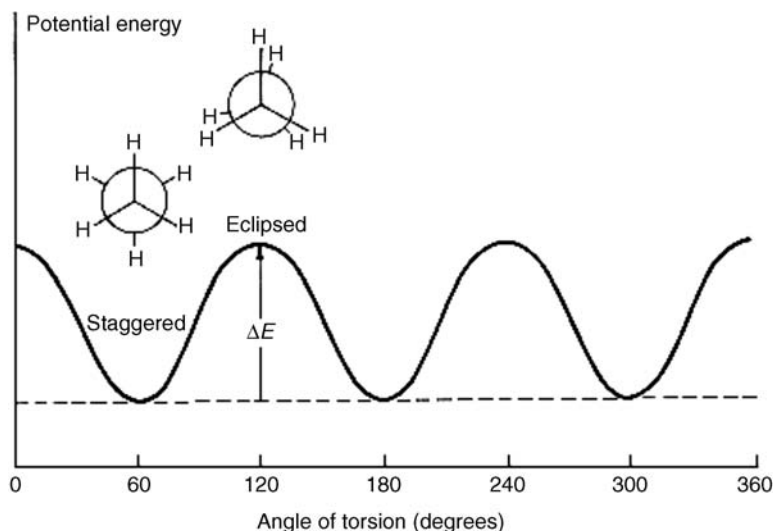


FIG. 4.4. Conformational energy diagram for ethane.

much speculation about the cause of the barriers and many explanations have been suggested.²⁸⁷ It has been concluded from MO calculations (see Sec. 4.P) that the barrier is caused by repulsion between overlapping filled molecular orbitals.²⁸⁸ The staggered conformation of ethane is lowest in energy because the orbitals of the C—H bonds in this conformation have the least amount of overlap with the C—H orbitals of the adjacent carbon.

At ordinary temperatures, enough rotational energy is present for the ethane molecule to rotate rapidly, but it spends most of its time at or near the energy minimum. Groups larger than hydrogen cause larger barriers, presumably due to steric interactions between the larger units.²⁸⁹ When the barriers are large enough, as in the case of suitably substituted biphenyls (Sec. 4.C, category 5) or the diadamantyl compound mentioned (see **107** and **108**) rotation at room temperature is completely prevented, which is described as a *q* configuration not *a* conformations. Even for compounds with small barriers, cooling to low temperatures may remove enough rotational energy for what would otherwise be conformational isomers to become configurational isomers.

A 1,2-disubstituted ethane ($\text{YCH}_2\text{—CH}_2\text{Y}$ or $\text{YCH}_2\text{—CH}_2\text{X}$,²⁹⁰ e.g., *n*-butane),²⁹¹ is somewhat more complicated. There are four extremes: a fully staggered conformation, called *anti*, *trans*, or *antiperiplanar*; another staggered conformation, called *gauche* or *synclinal*; and two types of eclipsed conformations, called *synperiplanar* and *anticlinal*.

²⁸⁷ See Lowe, J.P. *Prog. Phys. Org. Chem.* **1968**, 6, 1; Oosterhoff, L.J. *Pure Appl. Chem.* **1971**, 25, 563; Wyn-Jones, E.; Pethrick, R.A. *Top. Stereochem.* **1970**, 5, 205; Pethrick, R.A.; Wyn-Jones, E. *Q. Rev. Chem. Soc.* **1969**, 23, 301; Brier, P.N. *J. Mol. Struct.* **1970**, 6, 23; Lowe, J.P. *Science*, **1973**, 179, 527.

²⁸⁸ See Pitzer, R.M. *Acc. Chem. Res.* **1983**, 16, 207. See, however, Bader, R.F.W.; Cheeseman, J.R.; Laidig, K.E.; Wiberg, K.B.; Breneman, C. *J. Am. Chem. Soc.* **1990**, 112, 6530.

²⁸⁹ See Bader, W.; Cortés-Guzmán, F. *Can. J. Chem.* **2009**, 87, 1583.

²⁹⁰ See Wiberg, K.B.; Murcko, M.A. *J. Am. Chem. Soc.* **1988**, 110, 8029; Allinger, N.L.; Grev, R.S.; Yates, B.F.; Schaefer, III, H.F. *J. Am. Chem. Soc.* **1990**, 112, 114.

²⁹¹ Cormanich, R.A.; Freitas, M.P. *J. Org. Chem.* **2009**, 74, 8384; Mo, Y. *J. Org. Chem.* **2010**, 75, 2733.

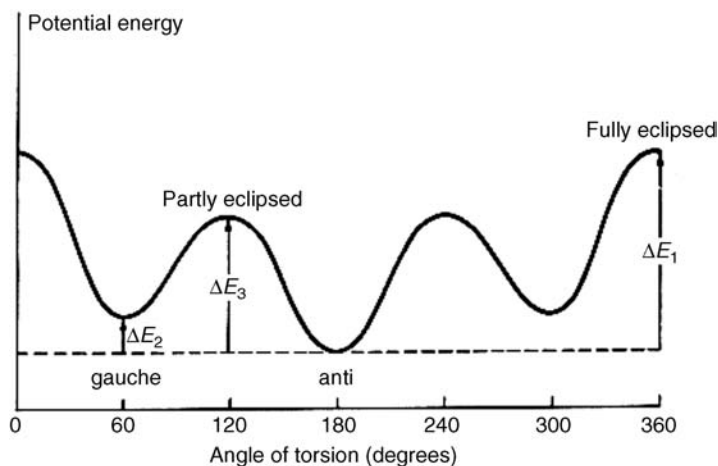
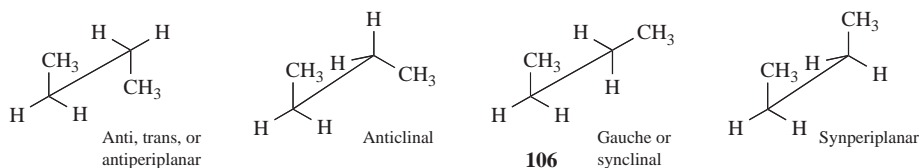


FIG. 4.5. Conformational energy for $\text{YCH}_2\text{—CH}_2\text{Y}$ or $\text{YCH}_2\text{—CH}_2\text{X}$. For *n*-butane, $\Delta E_1 = 4\text{--}6$, $\Delta E_2 = 0.9$, and $\Delta E_3 = 3.4 \text{ kcal mol}^{-1}$ (17–25, 3.8, 14 kJ mol^{-1} , respectively).



An energy diagram for this system is given in Fig. 4.5. Although there is constant rotation about the central bond, it is possible to estimate what percentage of the molecules are in each conformation at a given time. For example, a consideration of dipole moment and polarizability measurements led to the conclusion that for 1,2-dichloroethane in CCl_4 solution at 25°C $\sim 70\%$ of the molecules are in the *anti* and $\sim 30\%$ in the *gauche* conformation.²⁹² The corresponding figures for 1,2-dibromoethane are 89% *anti* and 11% *gauche*.²⁹³ The eclipsed conformations are unpopulated and serve only as pathways from one staggered conformation to another. Solids normally consist of a single conformer.

It may be observed that the *gauche* conformation of butane (see **106**), or any other similar molecule, appears to be chiral. It is not. The lack of optical activity in such compounds arises from the fact that **106** is not a static molecule, but is in dynamic equilibrium with many other conformations, including its mirror image. In effect, they interconvert too rapidly for separation.

For butane and for most other molecules of the forms $\text{YCH}_2\text{—CH}_2\text{Y}$ and $\text{YCH}_2\text{—CH}_2\text{X}$, the *anti* conformer is the most stable, but exceptions are known. One group of exceptions consists of molecules containing small electronegative atoms, especially

²⁹² Le Fèvre, R.J.W.; Orr, B.J. *Aust. J. Chem.* **1964**, *17*, 1098.

²⁹³ See Schrumpf, G. *Angew. Chem. Int. Ed.* **1982**, *21*, 146.

fluorine and oxygen. Thus 2-fluoroethanol,²⁹⁴ 1,2-difluoroethane,²⁹⁵ and 2-fluoroethyl trichloroacetate (FCH₂CH₂OCOCCL₃)²⁹⁶ exist predominantly in the *gauche* form and compounds, such as, 2-chloroethanol and 2-bromoethanol,²⁹⁴ also prefer the *gauche* form. It has been proposed that the preference for the *gauche* conformation in these molecules is an example of a more general phenomenon, known as the *gauche effect*; that is, a tendency to adopt that structure that has the maximum number of *gauche* interactions between adjacent electron pairs or polar bonds.²⁹⁷ It was believed that the favorable *gauche* conformation of 2-fluoroethanol was the result of intramolecular hydrogen bonding, but this explanation does not do for molecules like 2-fluoroethyl trichloroacetate. It has in fact been ruled out for 2-fluoroethanol as well.²⁹⁸ The effect of β -substituents in Y—C—C—OX systems where Y = F or SiR₃ has been examined and there is a small bond shortening effect on C—OX that is greatest when OX is a good leaving group. Bond lengthening was also observed with the β -silyl substituent.²⁹⁹ Other exceptions are known, where small electronegative atoms are absent. For example 1,1,2,2-tetrachloroethane and 1,1,2,2-tetrabromoethane both prefer the *gauche* conformation,³⁰⁰ even though 1,1,2,2-tetrafluoroethane prefers the *anti*.³⁰¹ Also, both 2,3-dimethylpentane and 3,4-dimethylhexane prefer the *gauche* conformation,³⁰² and 2,3-dimethylbutane shows no preference for either.³⁰³ Furthermore, the solvent can exert a powerful effect. For example, the compound 2,3-dinitro-2,3-dimethylbutane exists entirely in the *gauche* conformation in the solid state, but in benzene, the *gauche/anti* ratio is 79:21; while in CCl₄ the *anti* form is actually favored (*gauche/anti* ratio 42:58).³⁰⁴ In many cases, there are differences in the conformation of these molecules between the gas and the liquid phase (as when X = Y = OMe) because of polar interactions with the solvent.³⁰⁵

In one case, two conformational isomers of a single aliphatic hydrocarbon, 3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane, have proven stable enough for isolation at room temperature.³⁰⁶ The two isomers **107** and **108** were separately crystallized, and the structures were proven by X-ray crystallography. The actual dihedral angles are distorted from the 60° angles shown in the drawings, due to steric hindrance between the large adamantyl and *tert*-butyl groups.

²⁹⁴ See Davenport, D.; Schwartz, M. *J. Mol. Struct.* **1978**, *50*, 259; Huang, J.; Hedberg, K. *J. Am. Chem. Soc.* **1989**, *111*, 6909.

²⁹⁵ See Friesen, D.; Hedberg, K. *J. Am. Chem. Soc.* **1980**, *102*, 3987; Fernholt, L.; Kveseth, K. *Acta Chem. Scand. Ser. A* **1980**, *34*, 163.

²⁹⁶ Abraham, R.J.; Monasterios, J.R. *Org. Magn. Reson.* **1973**, *5*, 305.

²⁹⁷ See Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102. See also, Phillips, L.; Wray, V. *J. Chem. Soc. Chem. Commun.* **1973**, 90; Radom, L.; Hehre, W.J.; Pople, J.A. *J. Am. Chem. Soc.* **1972**, *94*, 2371; Zefirov, N.S. *J. Org. Chem. USSR* **1974**, *10*, 1147; Juaristi, E. *J. Chem. Educ.* **1979**, *56*, 438.

²⁹⁸ Griffith, R.C.; Roberts, J.D. *Tetrahedron Lett.* **1974**, 3499.

²⁹⁹ Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc. Perkin Trans. 2* **1992**, 549.

³⁰⁰ Kagarise, R.E. *J. Chem. Phys.* **1956**, *24*, 300.

³⁰¹ Brown, D.E.; Beagley, B. *J. Mol. Struct.* **1977**, *38*, 167.

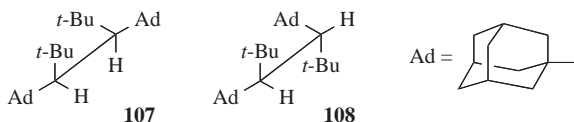
³⁰² Ritter, W.; Hull, W.; Cantow, H. *Tetrahedron Lett.* **1978**, 3093.

³⁰³ Lunazzi, L.; Macciantelli, D.; Bernardi, F.; Ingold, K.U. *J. Am. Chem. Soc.* **1977**, *99*, 4573.

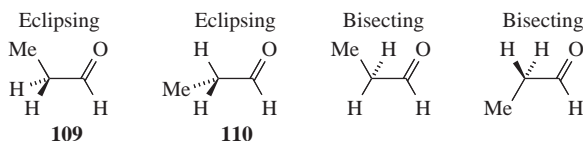
³⁰⁴ Tan, B.; Chia, L.H.L.; Huang, H.; Kuok, M.; Tang, S. *J. Chem. Soc. Perkin Trans. 2* **1984**, 1407.

³⁰⁵ Smith, G.D.; Jaffe, R.L.; Yoon, D.Y. *J. Am. Chem. Soc.* **1995**, *117*, 530. For an analysis of *N,N*-dimethylacetamide, see Mack, H.-G.; Oberhammer, H. *J. Am. Chem. Soc.* **1997**, *119*, 3567.

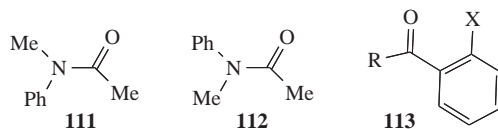
³⁰⁶ Flamm-ter Meer; Beckhaus, H.; Peters, K.; von Schnering, H.; Fritz, H.; Rüchardt, C. *Chem. Ber.* **1986**, *119*, 1492; Rüchardt, C.; Beckhaus, H. *Angew. Chem. Int. Ed.* **1985**, *24*, 529.



All the conformations so far discussed have involved rotation about sp^3-sp^3 bonds. Many studies have also been made of compounds with sp^3-sp^2 bonds.³⁰⁷ For example, propanal (or any similar molecule) has four extreme conformations, two of which are called *eclipsing* and the other two *bisecting*. For propanal, the eclipsing conformations have lower energy than the other two, with **109** favored over **110** by ~ 1 kcal mol⁻¹ (4 kJ mol⁻¹).³⁰⁸ As already pointed out (Sec. 4.K.i), for a few of these compounds, rotation is slow enough to permit *cis-trans* isomerism, although for simple compounds rotation is rapid. The *cis* conformer of acetic acid was produced in solid Ar,³⁰⁹ and it was reported that acetaldehyde has a lower rotational barrier (~ 1 kcal mol⁻¹ or 4 kJ mol⁻¹) than ethane.³¹⁰ Calculations have examined the rotational barriers around the CO and CC bonds in formic acid, ethanedial, and glycolaldehyde molecules.³¹¹



Other carbonyl compounds exhibit rotation about sp^3-sp^3 bonds, including amides.³¹² In *N*-acetyl-*N*-methylaniline, the *cis*-conformation (**111**) is more stable than the *trans*-conformation (**112**) by 3.5 kcal mol⁻¹ (14.6 kJ mol⁻¹).³¹³ This is due to destabilization of (*S*) due to steric hindrance between two methyl groups, and to electronic repulsion between the carbonyl lone-pair electrons and the phenyl π -electrons in the twisted phenyl orientation.³¹³



³⁰⁷ See Sinegovskaya, L.M.; Keiko, V.V.; Trofimov, B.A. *Sulfur Rep.* **1987**, 7, 337 (for enol ethers and thioethers); Karabatsos, G.J.; Fenoglio, D.J. *Top. Stereochem.* **1970**, 5, 167; Jones, G.I.L.; Owen, N.L. *J. Mol. Struct.* **1973**, 18, 1 (for carboxylic esters). See also, Cossé-Barbi, A.; Massat, A.; Dubois, J.E. *Bull. Soc. Chim. Belg.* **1985**, 94, 919; Dorigo, A.E.; Pratt, D.W.; Houk, K.N. *J. Am. Chem. Soc.* **1987**, 109, 6591.

³⁰⁸ Allinger, N.L.; Hickey, M.J. *J. Mol. Struct.* **1973**, 17, 233; Gupta, V.P. *Can. J. Chem.* **1985**, 63, 984.

³⁰⁹ Macoas, E.M.S.; Khriatchchev, L.; Pettersson, M.; Fausto, R.; Rasanen, M. *J. Am. Chem. Soc.* **2003**, 125, 16188.

³¹⁰ Davidson, R.B.; Allen, L.C. *J. Chem. Phys.* **1971**, 54, 2828.

³¹¹ Ratajczyk, T.; Pecul, M.; Sadlej, J. *Tetrahedron* **2004**, 60, 179.

³¹² Avalos, M.; Babiano, R.; Barneto, J.L.; Bravo, J.L.; Cintas, P.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* **2001**, 66, 7275. Also see Modarresi-Alam, A.R.; Najafi, P.; Rostamizadeh, M.; Keykha, H.; Bijanzadeh, H.-R.; Kleinpeter, E. *J. Org. Chem.* **2007**, 72, 2208.

³¹³ Saito, S.; Toriumi, Y.; Tomioka, A.; Itai, A. *J. Org. Chem.* **1995**, 60, 4715.

A similar conformational analysis has been done with formamide derivatives,³¹⁴ with secondary amides,³¹⁵ and for hydroxamide acids.³¹⁶ It is known that thioformamide has a larger rotational barrier than formamide, which can be explained by a traditional picture of amide “resonance” that is more appropriate for the thioformamide than formamide itself.³¹⁷ Torsional barriers in α -keto amides have been reported,³¹⁸ and the C—N bond of acetamides,³¹⁹ thioamides,³²⁰ enamides³²¹ carbamates (R_2N-CO_2R'),³²² and enolate anions derived from amides³²³ have been examined. It is known that substituents influence rotational barriers.³²⁴

In Section 4.C, category 5, atropisomerism was possible when ortho substituents on biphenyl derivatives and certain other aromatic compounds prevented rotation about the $C^{sp^3}-C^{sp^3}$ bond. The presence of ortho-substituents can also influence the conformation of certain groups.³²⁵ In **113**, R = alkyl and the carbonyl unit is planar, with the *trans* C=O \cdots F conformer is more stable when X = F. When X = CF₃, the *cis* and *trans* are planar and the *trans* predominates.³²⁶ When R = alkyl, there is one orthogonal conformation, but there are two interconverting nonplanar conformations when R = *O*-alkyl.³²⁶ In 1,2-diacylbenzenes, the carbonyl units tend to adopt a twisted conformation to minimize steric interactions.³²⁷

4.N.ii. Conformation in Six-Membered Rings³²⁸

For cyclic compounds, complete rotation (360°) about a single bond is impossible. However, repulsion between atoms and groups leads to motion about each bond called pseudorotation. Pseudorotation leads to a variety of different conformations, depending on the size of the ring. In many such conformations, the ring is said to be puckered. For cyclohexane, there are two extreme conformations in which all the angles are tetrahedral (the C—C—C angles in cyclohexane are actually 111.5°).³²⁹ These are called the *boat* and the *chair* conformations. The chair conformation is the low-energy structure that participates in a dynamic equilibrium (there are two chair conformations that are

³¹⁴ Axe, F.U.; Renugopalakrishnan, V.; Hagler, A.T. *J. Chem. Res.* **1998**, 1. For an analysis of DMF see Wiberg, K.B.; Rablen, P.R.; Rush, D.J.; Keith, T.A. *J. Am. Chem. Soc.* **1995**, 117, 4261.

³¹⁵ Avalos, M.; Babiano, R.; Barneto, J.L.; Cintas, P.; Clemente, F.R.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* **2003**, 68, 1834.

³¹⁶ Kakkar, R.; Grover, R.; Chadha, P. *Org. Biomol. Chem.* **2003**, 1, 2200.

³¹⁷ Wiberg, K.B.; Rablen, P.R. *J. Am. Chem. Soc.* **1995**, 117, 2201.

³¹⁸ Bach, R.D.; Mintcheva, I.; Kronenberg, W.J.; Schlegel, H.B. *J. Org. Chem.* **1993**, 58, 6135.

³¹⁹ Ilieva, S.; Hadjieva, B.; Galabov, B. *J. Org. Chem.* **2002**, 67, 6210.

³²⁰ Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, 123, 2038; *J. Org. Chem.* **2002**, 67, 826.

³²¹ Rablen, P.R.; Miller, D.A.; Bullock, V.R.; Hutchinson, P.H.; Gorman, J.A. *J. Am. Chem. Soc.* **1999**, 121, 218.

³²² Deetz, M.J.; Forbes, C.C.; Jonas, M.; Malerich, J.P.; Smith, B.D.; Wiest, O. *J. Org. Chem.* **2002**, 67, 3949.

³²³ Kim, Y.-J.; Streitwieser, A.; Chow, A.; Fraenkel, G. *Org. Lett.* **1999**, 1, 2069.

³²⁴ Smith, B.D.; Goodenough-Lashua, D.M.; D'Souza, C.J.E.; Norton, K.J.; Schmidt, L.M.; Tung, J.C. *Tetrahedron Lett.* **2004**, 45, 2747.

³²⁵ For an analysis of barriers to rotation in such compounds, see Mazzanti, A.; Lunazzi, L.; Minzoni, M.; Anderson, J.E. *J. Org. Chem.* **2006**, 71, 5474.

³²⁶ Abraham, R.J.; Angioloni, S.; Edgar, M.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* **1997**, 41.

³²⁷ Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1997**, 62, 7592.

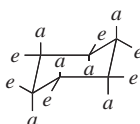
³²⁸ See Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* **1971**, 3, 139; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**, pp. 686–753. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 54–67.

³²⁹ See Geise, H.J.; Buys, H.R.; Mijlhoff, F.C. *J. Mol. Struct.* **1971**, 9, 447; Bastiansen, O.; Fernholt, L.; Seip, H.M.; Kambara, H.; Kuchitsu, K. *J. Mol. Struct.* **1973**, 18, 163.

equivalent in energy for cyclohexane), and the boat form is a higher energy form³³⁰ in equilibrium with a somewhat more stable form



known as the *twist* conformation. The twist form is $\sim 1.5 \text{ kcal mol}^{-1}$ (6.3 kJ mol^{-1}) more stable than the boat because it has less eclipsing interaction (see below).³³¹ The chair form is more stable than the twist form by $\sim 5 \text{ kcal mol}^{-1}$ (21 kJ mol^{-1}).³³² In the vast majority of compounds containing a cyclohexane ring, the molecules exist almost entirely as equilibrating chair forms.³³³ It is known that the boat or twist form exists transiently. In some cases, chair and twist–boat conformations have actually been observed (*cis*-1,4-di-*tert*-butylcyclohexane, e.g.).³³⁴



Axial and equatorial bonds
in chair cyclohexane

An inspection of the chair form shows that six of its bonds are directed differently from the other six. On each carbon, one bond is directed up or down and the other more or less in the “plane” of the ring. The up or down bonds are called *axial* and the others are *equatorial*. The axial bonds point alternately up and down. If a molecule were frozen into a chair form, there would be isomerism in monosubstituted cyclohexanes. For example, there would be an equatorial methylcyclohexane and an axial isomer. This result is incorrect, however, as it has never been possible to isolate isomers of this type at room temperature.³³⁵ In order for the two types of methylcyclohexane to be nonseparable, there must be rapid inter-conversion of one chair form to another (in which all axial bonds become equatorial and vice versa) and this is possible only if the boat or twist conformations are transient species. Conversion of one chair form to another requires an activation energy of $\sim 10 \text{ kcal mol}^{-1}$ (42 kJ mol^{-1})³³⁶ and is very rapid at room temperature.³³⁷ However, by working at low temperatures, Jensen and Bushweller³³⁸ were able to obtain the pure equatorial conformers of chlorocyclohexane and trideuteriomethoxycyclohexane as solids and in solution. Equatorial chlorocyclohexane has a half-life of 22 years in solution at -160°C .

³³⁰ See Dunitz, J.D. *J. Chem. Educ.* **1970**, 47, 488.

³³¹ For a review of nonchair forms, see Kellie, G.M.; Riddell, F.G. *Top. Stereochem.* **1974**, 8, 225.

³³² Squillacote, M.; Sheridan, R.S.; Chapman, O.L.; Anet, F.A.L. *J. Am. Chem. Soc.* **1975**, 97, 3244.

³³³ See Wiberg, K.B.; Castejon, H.; Bailey, W.F.; Ochterski, J. *J. Org. Chem.* **2000**, 65, 1181.

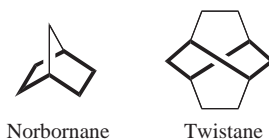
³³⁴ Gill, G.; Pawar, D.M.; Noe, E.A. *J. Org. Chem.* **2005**, 70, 10726.

³³⁵ See Wehle, D.; Fitjer, L. *Tetrahedron Lett.* **1986**, 27, 5843.

³³⁶ See Anet, F.A.L.; Bourn, A.J.R. *J. Am. Chem. Soc.* **1967**, 89, 760. See also, Strauss, H.L. *J. Chem. Educ.* **1971**, 48, 221.

³³⁷ See Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**, pp. 287–307; Anderson, J.E. *Top. Curr. Chem.* **1974**, 45, 139.

³³⁸ See Jensen, F.R.; Bushweller, C.H.; *J. Chem. Soc.* **1969**, 91, 3223.



In some molecules, the twist conformation is actually preferred.³³⁹ Of course, in certain bicyclic compounds, the six-membered ring is forced to maintain a boat or twist conformation, as in norbornane or twistane.

In monosubstituted cyclohexanes, the substituent normally prefers the equatorial position because there is an interaction between the substituent and the axial hydrogens in the axial 3 and 5 positions, but the extent of this preference depends greatly on the nature of the group.³⁴⁰ Alkyl groups have a greater preference for the equatorial position than polar groups. For alkyl groups, the preference increases with size, although size seems to be unimportant for polar groups. Both the large HgBr ³⁴¹ and HgCl ³⁴² groups and the small F group have been reported to have little or no conformational preference (the HgCl group actually shows a slight preference for the axial position). Table 4.3 gives approximate values of the free energy required for various groups to go from the equatorial position to the axial (these are called *A* values),³⁴³ although it must be kept in mind that they vary somewhat with physical state, temperature, and solvent.³⁴⁴ Values for other groups in kcal mol^{-1} include D ³⁴⁵ (0.008), NH_2 ³⁴⁶ (1.4), $\text{CH}=\text{CH}_2$ ³⁴⁷ (1.7), CH_3 ³⁴⁸ (1.74), C_6H_{11} ³⁴⁹ (2.15), $\text{Si}(\text{CH}_3)$ ³⁵⁰ (2.4–2.6), OCH_3 ³⁵¹ (0.75), C_6H_5 ³⁵² (2.7), and $t\text{-(CH}_3)_3\text{C}$ ³⁵³ (4.9).

For alkyl groups in disubstituted compounds, the conformation is such that as many groups as possible adopt the equatorial position. This conformation will minimize the axial interactions (known as $\text{A}^{1,3}$ -strain), and will be the lower energy conformation. The preference for one chair conformation over the other depends on the groups attached to the cyclohexane ring, and their relative positions on that ring. In a *cis*-1,2-disubstituted cyclohexane, one substituent must be axial and the other equatorial. In a *trans*-1,2,

³³⁹ Weiser, J.; Golan, O.; Fitjer, L.; Biali, S.E. *J. Org. Chem.* **1996**, *61*, 8277.

³⁴⁰ For a study of thioether, sulfoxide and sulfone substituents, see Juaristi, E.; Labastida, V.; Antúnez, S. *J. Org. Chem.*, **2000**, *65*, 969.

³⁴¹ Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* **1959**, *81*, 6337.

³⁴² Anet, F.A.L.; Krane, J.; Kitching, W.; Dodderel, D.; Praeger, D. *Tetrahedron Lett.* **1974**, 3255.

³⁴³ These values are from Corey, E.J.; Feiner, N.F. *J. Org. Chem.* **1980**, *45*, 765. Also see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* **1971**, *3*, 139. See also, Schneider, H.; Hoppen, V. *Tetrahedron Lett.* **1974**, 579 and see Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 54–67.

³⁴⁴ See Ford, R.A.; Allinger, N.L. *J. Org. Chem.* **1970**, *35*, 3178. For a critical review of the methods used to obtain these values, see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* **1971**, *3*, 139.

³⁴⁵ Anet, F.A.L.; O'Leary, D.J. *Tetrahedron Lett.* **1989**, *30*, 1059.

³⁴⁶ Buchanan, G.W.; Webb, V.L. *Tetrahedron Lett.* **1983**, *24*, 4519.

³⁴⁷ Eliel, E.L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.

³⁴⁸ Booth, H.; Everett, J.R. *J. Chem. Soc. Chem. Commun.* **1976**, 278.

³⁴⁹ Hirsch, J.A. *Top. Stereochem.* **1967**, *1*, 199.

³⁵⁰ Kitching, W.; Olszowy, H.A.; Drew, G.M.; Adcock, W. *J. Org. Chem.* **1982**, *47*, 5153.

³⁵¹ Schneider, H.; Hoppen, V. *Tetrahedron Lett.* **1974**, 579.

³⁵² Squillacote, M.E.; Neth, J.M. *J. Am. Chem. Soc.* **1987**, *109*, 198. Values of 2.59–2.92 kcal mol^{-1} (10.84–12.23 kJ mol^{-1}) were determined for 4-X- C_6H_4 — substituents (X = NO_2 , Cl, MeO): see Kirby, A.J.; Williams, N. *H. J. Chem. Soc. Chem. Commun.* **1992**, 1285, 1286.

³⁵³ Manoharan, M.; Eliel, E.L. *Tetrahedron Lett.* **1984**, *25*, 3267.

TABLE 4.3 Free-Energy Differences between Equatorial and Axial Substituents on a Cyclohexane Ring^{a,b}

Group	A (kcal mol ⁻¹)	kJ mol ⁻¹	Group	A (kcal mol ⁻¹)	kJ mol ⁻¹
H	0		N=	0.5	2.09
F	0.2	0.84	N≡	0.2	0.84
Cl	0.4	1.67	NO ₂	1.1	4.61
Br	0.4	1.67	C≡	0.2	0.84
I	0.4	1.67	aryl	3.0	12.56
PR ₃	1.6	6.7	CO ₂ ⁻	2.0	8.37
SR	0.8	3.35	CHO	0.8	3.35
S(O)R	1.9	7.95	C=	1.3	5.44
S(O ₂)R	2.5	10.47	CR ₃	6.0	25.11
OR	0.8	3.35	CHR ₂	2.1	8.79
NH ₃ ⁺	2.0	8.37	CH ₂ R	1.8	7.54
NR ₃ ⁺	2.1	8.79			
NHR	1.3	5.44			

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^aSee Ref. 343.

^bThe A values or A^{1,3}-strain.

compound both may be equatorial or both axial. This finding is also true for 1,4-disubstituted cyclohexanes, but the reverse holds for 1,3-compounds: the *trans* isomer must have the *age* conformation and the *cis* isomer may be *a* or *ee*. For alkyl groups, the *ee* conformation predominates over the *a*, but for other groups this is not necessarily so. For example, both *trans*-1,4-dibromocyclohexane and the corresponding dichloro compound have the *ee* and *a* conformations about equally populated³⁵⁴ and most *trans*-1,2-dihalo-cyclohexanes exist predominantly in the *a* conformation.³⁵⁵ Note that in the latter case the two halogen atoms are anti in the *a* conformation, but *gauche* in the *ee* conformation.³⁵⁶

Since compounds with alkyl equatorial substituents are generally more stable, *trans*-1,2 compounds, which can adopt the *ee* conformation, are thermodynamically more stable than their *cis*-1,2 isomers, which must exist in the *age* conformation. For the 1,2-dimethylcyclohexanes, the difference in stability is ~2 kcal mol⁻¹ (8 kJ mol⁻¹). Similarly, *trans*-1,4 and *cis*-1,3 compounds are more stable than their stereoisomers.

An interesting anomaly is *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane, in which the six isopropyl groups prefer the axial position, although the six ethyl groups of the corresponding hexaethyl compound prefer the equatorial position.³⁵⁷ The alkyl groups of these compounds can of course only be all axial or all equatorial, and it is likely that the molecule prefers the all-axial conformation because of unavoidable strain in the other conformation.

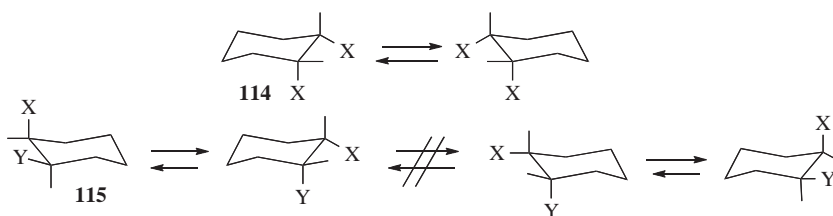
³⁵⁴ Abraham, R.J.; Rossetti, Z.L. *J. Chem. Soc. Perkin Trans. 2* **1973**, 582. See also, Hammarström, L.; Berg, U.; Liljefors, T. *Tetrahedron Lett.* **1987**, 28, 4883.

³⁵⁵ Abraham, M.H.; Xodo, L.E.; Cook, M.J.; Cruz, R. *J. Chem. Soc. Perkin Trans. 2* **1982**, 1503; Samoshin, V.V.; Svyatkin, V.A.; Zefirov, N.S. *J. Org. Chem. USSR* **1988**, *24*, 1080, and references cited therein. See Zefirov, N.S.; Samoshin, V.V.; Subbotin, O.A.; Sergeev, N.M. *J. Org. Chem. USSR* **1981**, *17*, 1301.

³⁵⁶ For a case of a preferential diaxial conformation in 1,3 isomers, see Ochiai, M.; Iwaki, S.; Ukita, T.; Matsuura, Y.; Shiro, M.; Nagao, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4606.

³⁵⁷ Golan, O.; Goren, Z.; Biali, S.E. *J. Am. Chem. Soc.* **1990**, *112*, 9300.

Incidentally, it is now apparent, at least in one case, why the correct number of stereoisomers could be predicted by assuming planar rings, even though they are not planar (Sec. 4.K.ii). In the case of both a *cis*-1,2-X,X-disubstituted and a *cis*-1,2-X,Y-disubstituted cyclohexane, the molecule is nonsuperimposable on its mirror image; neither has a plane of symmetry. However, in the former case (**114**) conversion of one chair form to the other which of course happens rapidly, turns the molecule into its mirror image, while in the latter case (**115**) rapid interconversion does not give the mirror image, but merely the conformer in which the original axial and equatorial substituents exchange places. Thus the optical inactivity of **114** is not due to a plane of symmetry, but to a rapid interconversion of the molecule and its mirror image. A similar situation holds for *cis*-1,3 compounds. However, for *cis*-1,4 isomers (both X,X and X,Y) optical inactivity arises from a plane of symmetry in both conformations. All *trans*-1,2- and *trans*-1,3-disubstituted cyclohexanes are chiral (whether X,X or X,Y), while *trans*-1,4 compounds (both X,X and X,Y) are achiral, since all conformations have a plane of symmetry. It has been shown that the equilibrium is very dependent on both the solvent and the concentration of the disubstituted cyclohexane.³⁵⁸ A theoretical study of the 1,2-dihalides showed a preference for the diaxial form with X = Cl, but predicted that the energy difference between diaxial and diequatorial was small when X = F.³⁵⁹



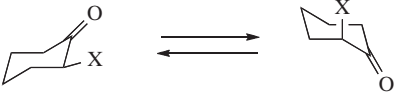
The conformation of a group can be frozen into a desired position by putting a large alkyl group into the ring (most often *tert*-butyl), which introduces significant $A^{1,3}$ -strain and leads to a preference for the chair with the groups in the equatorial position.³⁶⁰ It is known that silylated derivatives of *trans*-1,4- and *trans*-1,2-dihydroxycyclohexane, some monosilyloxycyclohexanes and some silylated sugars have unusually large populations of chair conformations with axial substituents.³⁶¹ Adjacent silyl groups in the 1,2-disubstituted series show a stabilizing interaction in all conformations, generally leading to unusually large axial populations.

³⁵⁸ Abraham, R.J.; Chambers, E.J.; Thomas, W.A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1061.

³⁵⁹ Wiberg, K.B. *J. Org. Chem.* **1999**, 64, 6387.

³⁶⁰ This idea was suggested by Winstein, S.; Holness, N.J. *J. Am. Chem. Soc.* **1955**, 77, 5561. See Saunders, M.; Wolfsberg, M.; Anet, F.A.L.; Kronja, O. *J. Am. Chem. Soc.* **2007**, 129, 10276.

³⁶¹ Marzabadi, C. H.; Anderson, J. E.; Gonzalez-Outeirino, J.; Gaffney, P. R. J.; White, C. G. H.; Tocher, D. A.; Todaro, L. J. *J. Am. Chem. Soc.* **2003**, 125, 15163.

TABLE 4.4 Proportion of Axial Conformation in 2-Substituted Cyclohexanones, in CDCl_3 ^a


X	% Axial Conformation
F	17 ± 3
Cl	45 ± 4
Br	71 ± 4
I	88 ± 5
MeO	28 ± 4
MeS	85 ± 7
MeSe	(92)
Me ₂ N	44 ± 3
Me	(26)

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^aSee Ref. 366.

The principles involved in the conformational analysis of six-membered rings containing one or two trigonal atoms. For example, cyclohexanone and cyclohexene, are similar.^{362–364} The barrier to interconversion in cyclohexane has been calculated to be 8.4–12.1 kcal mol^{−1} (35.2–50.7 kJ mol^{−1}).³⁶⁵ Cyclohexanone derivatives also assume a chair-conformation. Substituents at C-2 can assume an axial or equatorial position depending on steric and electronic influences. The proportion of the conformation with an axial X group is shown in Table 4.4 for a variety of substituents (X) in 2-substituted cyclohexanones.³⁶⁶

³⁶² See Rabideau, P.W. *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*, VCH, NY, **1989**; Vereshchagin, A.N. *Russ. Chem. Rev.* **1983**, 52, 1081; Johnson, F. *Chem. Rev.* **1968**, 68, 375. See also, Lambert, J.B.; Cliekman, R.R.; Taba, K.M.; Marko, D.E.; Bosch, R.J.; Xue, L. *Acc. Chem. Res.* **1987**, 20, 454.

³⁶³ See Dale, J. *Stereochemistry and Conformational Analysis*, Verlag Chemie, Deerfield Beach, FL, **1978**; Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, **1971**; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, **1965**; Dale, J. *Top. Stereochem.* **1976**, 9, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* **1976**, 5, 411; Eliel, E.L. *J. Chem. Educ.* **1975**, 52, 762; Bushweller, C.H.; Gianni, M.H. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, **1980**, pp. 215–278.

³⁶⁴ See Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* **1971**, 3, 139; Robinson, D.L.; Theobald, D.W. *Q. Rev. Chem. Soc.* **1967**, 21, 314; Eliel, E.L. *Angew. Chem. Int. Ed.* **1965**, 4, 761; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**, pp. 686–753. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 61–65.

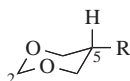
³⁶⁵ Laane, J.; Choo, J. *J. Am. Chem. Soc.* **1994**, 116, 3889.

³⁶⁶ Basso, E.A.; Kaiser, C.; Rittner, R.; Lambert, J.B. *J. Org. Chem.* **1993**, 58, 7865.

4.N.iii. Conformation in Six-Membered Rings Containing Heteroatoms

In six-membered rings containing heteroatoms,³⁶⁷ the basic principles are the same; that is, there are chair, twist, and boat forms, axial, and equatorial groups. The conformational equilibrium for tetrahydropyridines, for example, has been studied.³⁶⁸ In certain compounds, a number of new factors enter the picture. Only two of these will be examined.³⁶⁹

1. In 5-alkyl-substituted 1,3-dioxanes, the 5-substituent has a much smaller preference for the equatorial position than in cyclohexane derivatives;³⁷⁰ the $A^{1,3}$ -strain is much lower. This fact indicates that the lone pairs on the oxygens have a smaller steric requirement than the C—H bonds in the corresponding cyclohexane derivatives. There is some evidence of a homoanomeric interaction in these systems.³⁷¹ Similar behavior is found in the 1,3-dithianes,³⁷² and 2,3-disubstituted-1,4-dithianes have also been examined.³⁷³ With certain non-alkyl substituents (e.g., F, NO₂, SOMe,³⁷⁴ NMe₃⁺) the axial position is actually preferred.³⁷⁵



Substituted 1,3-dioxanes

2. An alkyl group located on a carbon α to a heteroatom prefers the equatorial position, which is of course the normally expected behavior, but a *polar* group in such a location prefers the *axial* position. An example of this phenomenon, known as the *anomeric effect*,³⁷⁶ is the greater stability of α -glucosides over β -glucosides. A number of explanations have been offered for the anomeric

³⁶⁷ See Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycle*, VCH, NY, **1988**; Riddell, F.G. *The Conformational Analysis of Heterocyclic Compounds*, Academic Press, NY, **1980**; Juaristi, E. *Acc. Chem. Res.* **1989**, *22*, 357; Crabb, T.A.; Katritzky, A.R. *Adv. Heterocycl. Chem.* **1984**, *36*, 1; Eliel, E.L. *Angew. Chem. Int. Ed.* **1972**, *11*, 739; *Pure Appl. Chem.* **1971**, *25*, 509; *Acc. Chem. Res.* **1970**, *3*, 1; Lambert, J.B. *Acc. Chem. Res.* **1971**, *4*, 87.

³⁶⁸ Bachrach, S.M.; Liu, M. *Tetrahedron Lett.* **1992**, *33*, 6771.

³⁶⁹ These factors are discussed by Eliel, E.L. *Angew. Chem. Int. Ed.* **1972**, *11*, 739.

³⁷⁰ Riddell, F.G.; Robinson, M.J.T. *Tetrahedron* **1967**, *23*, 3417; Eliel, E.L.; Knoeber, M.C. *J. Am. Chem. Soc.* **1968**, *90*, 3444. See also, Eliel, E.L.; Alcudia, F. *J. Am. Chem. Soc.* **1974**, *96*, 1939. See Cieplak, P.; Howard, A.E.; Powers, J.P.; Rychnovsky, S.D.; Kollman, P.A. *J. Org. Chem.* **1996**, *61*, 3662 for conformational energy differences in 2,2,6-trimethyl-4-alkyl-1,3-dioxane.

³⁷¹ Cai, J.; Davies, A.G.; Schiesser, C.H. *J. Chem. Soc. Perkin Trans. 2* **1994**, 1151.

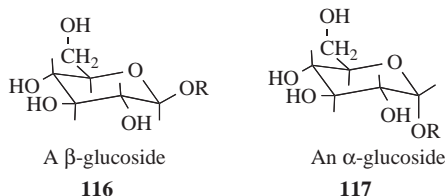
³⁷² Hutchins, R.O.; Eliel, E.L. *J. Am. Chem. Soc.* **1969**, *91*, 2703. See also, Juaristi, E.; Cuevas, G. *Tetrahedron* **1999**, *55*, 359.

³⁷³ Strelenko, Y.A.; Samoshin, V.V.; Troyansky, E.I.; Demchuk, D.V.; Dmitriev, D.E.; Nikishin, G.I.; Zefirov, N.S. *Tetrahedron* **1994**, *50*, 10107.

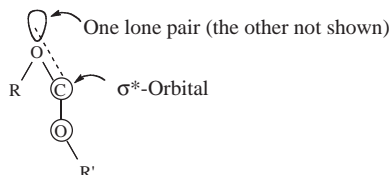
³⁷⁴ Gordillo, B.; Juaristi, E.; Mat3nez, R.; Toscano, R.A.; White, P.S.; Eliel, E.L. *J. Am. Chem. Soc.* **1992**, *114*, 2157.

³⁷⁵ Kaloustian, M.K.; Dennis, N.; Mager, S.; Evans, S.A.; Alcudia, F.; Eliel, E.L. *J. Am. Chem. Soc.* **1976**, *98*, 956. See also, Eliel, E.L.; Kandasamy, D.; Sechrest, R.C. *J. Org. Chem.* **1977**, *42*, 1533.

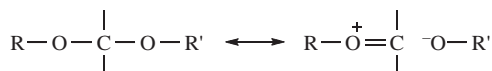
³⁷⁶ See Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, **1983**; Szarek, W.A.; Horton, D. *Anomeric Effect*, American Chemical Society, Washington, **1979**; Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Elmsford, NY, **1983**, pp. 4–26; Zefirov, N.S. *Tetrahedron* **1977**, *33*, 3193; Lemieux, R.U. *Pure Appl. Chem.* **1971**, *27*, 527.



effect.³⁷⁷ The one³⁷⁸ that has received the most acceptance³⁷⁹ is that one of the lone pairs of the polar atom connected to the carbon (an oxygen atom in the case of **117**) can be stabilized by overlapping with an antibonding orbital of the bond between the carbon and the other polar atom:



This can happen only if the two orbitals are in the positions shown. The situation can also be represented by this type of hyperconjugation (called “negative hyperconjugation,” see Sec. 2.M):



It is possible that simple repulsion between parallel dipoles in **116** also plays a part in the greater stability of **117**. It has been shown that aqueous solvation effects reduce anomeric stabilization in many systems, particularly for tetrahydropyrans. In contrast to cyclic acetals, simple acyclic acetals rarely adopt the anomeric conformation, apparently because the eclipsed conformation better accommodates steric interactions of groups linked by relatively short carbon–oxygen bonds.³⁸¹ In all *cis*-2,5-di-*tert*-butyl-1,4-cyclohexanediol, hydrogen bonding stabilizes the otherwise high-energy form³⁸² and 1,3-dioxane (**118**) exists largely as the twist conformation shown.³⁸³ The conformational preference of 1-methyl-1-silacyclohexane (**121**) has been studied.³⁸⁴ A strongly decreased activation barrier in

³⁷⁷ Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, 48, 5019.

³⁷⁸ See Romers, C.; Altona, C.; Buys, H.R.; Havinga, E. *Top. Stereochem.* **1969**, 4, 39, pp. 73–77; Wolfe, S.; Whangbo, M.; Mitchell, D.J. *Carbohydr. Res.* **1979**, 69, 1.

³⁷⁹ See Praly, J.; Lemieux, R.U. *Can. J. Chem.* **1987**, 65, 213; Booth, H.; Khedhair, K.A.; Readshaw, S.A. *Tetrahedron* **1987**, 43, 4699. For evidence against it, see Box, V.G.S. *Heterocycles* **1990**, 31, 1157.

³⁸⁰ Cramer, C.J. *J. Org. Chem.* **1992**, 57, 7034; Booth, H.; Dixon, J.M.; Readshaw, S.A. *Tetrahedron* **1992**, 48, 6151.

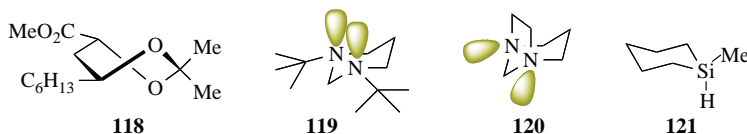
³⁸¹ Anderson, J.E. *J. Org. Chem.* **2000**, 65, 748.

³⁸² Stolow, R.D. *J. Am. Chem. Soc.* **1964**, 86, 2170; Stolow, R.D.; McDonagh, P.M.; Bonaventura, M.M. *J. Am. Chem. Soc.* **1964**, 86, 2165. Also see Fitjer, L.; Scheuermann, H.; Klages, U.; Wehle, D.; Stephenson, D.S.; Binsch, G. *Chem. Ber.* **1986**, 119, 1144.

³⁸³ Rychnovsky, S.D.; Yang, G.; Powers, J.P. *J. Org. Chem.* **1993**, 58, 5251.

³⁸⁴ Arnason, I.; Kvaran, A.; Jonsdottir, S.; Gudnason, P. I.; Oberhammer, H. *J. Org. Chem.* **2002**, 67, 3827.

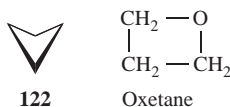
silacyclohexane was observed, as compared to that in the parent ring, and is explained by the longer endocyclic Si—C bonds.



Second-row heteroatoms are known to show a substantial anomeric effect.³⁸⁵ There appears to be evidence for a reverse anomeric effect in 2-aminotetrahydropyrans,³⁸⁶ but it has been called into question whether a reverse anomeric effect exists at all.³⁸⁷ In **119**, the lone-pair electrons assume an axial conformation and there is an anomeric effect.³⁸⁸ In **120**, however, the lone-pair electron orbitals are oriented *gauche* to both the axial and equatorial α -CH bond and there is no anomeric effect.³⁸⁸

4.N.iv. Conformation in Other Rings³⁸⁹

Three-membered saturated rings are usually planar, but other small rings can have some flexibility. Cyclobutane³⁹⁰ is not planar, but exists as in **122**, with an angle between the planes of $\sim 35^\circ$.³⁹¹ The deviation from planarity is presumably caused by eclipsing in the planar form (see Sec. 4.Q.i). Oxetane is closer to



planarity because there is less eclipsing, with an angle between the planes of $\sim 10^\circ$.³⁹² Cyclopentane might be expected to be planar, since the angles of a regular pentagon are 108° , but it is not so, also because of eclipsing effects.³⁹³ There are two puckered conformations for cyclopentane, the *envelope* and the *half-chair*. There is little energy difference between these two forms and many five-membered ring systems have

³⁸⁵ Salzner, U.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1993**, *115*, 10231; Aggarwal, V.K.; Worrall, J.M.; Adams, H.; Alexander, R.; Taylor, B.F. *J. Chem. Soc. Perkin Trans. 1* **1997**, 21.

³⁸⁶ Salzner, U.; Schleyer, P.v.R. *J. Org. Chem.* **1994**, *59*, 2138.

³⁸⁷ Perrin, C.L. *Tetrahedron* **1995**, *51*, 11901.

³⁸⁸ Anderson, J.E.; Cai, J.; Davies, A.G. *J. Chem. Soc. Perkin Trans. 2* **1997**, 2633. For some controversy concerning the anomeric effect a related system, see Perrin, C.L.; Armstrong, K.B.; Fabian, M.A. *J. Am. Chem. Soc.* **1994**, *116*, 715; Salzner, U. *J. Org. Chem.* **1995**, *60*, 986.

³⁸⁹ Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, **1994**, pp. 675–685 and 754–770.

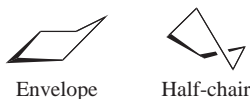
³⁹⁰ For reviews of the stereochemistry of four-membered rings, see Legon, A.C. *Chem. Rev.* **1980**, *80*, 231; Moriarty, R.M. *Top. Stereochem.* **1974**, *8*, 271; Cotton, F.A.; Frenz, B.A. *Tetrahedron* **1974**, *30*, 1587.

³⁹¹ Miller, F.A.; Capwell, R.J.; Lord, R.C.; Rea, D.G. *Spectrochim. Acta Part A*, **1972**, *28*, 603. However, see Margulis, T.N. *J. Am. Chem. Soc.* **1971**, *93*, 2193.

³⁹² Luger, P.; Buschmann, J. *J. Am. Chem. Soc.* **1984**, *106*, 7118.

³⁹³ See Fuchs, B. *Top. Stereochem.* **1978**, *10*, 1; Legon, A.C. *Chem. Rev.* **1980**, *80*, 231.

conformations somewhere in between them.³⁹⁴ Although in the envelope conformation one carbon is shown above the others,



ring motions cause each of the carbons in rapid succession to assume this position. The puckering rotates around the ring in what is called a *pseudorotation*³⁹⁵ (see Sec. 4.O.ii). In substituted cyclopentanes and five-membered rings in which at least one atom does not contain two substituents [e.g., tetrahydrofuran (THF), cyclopentanone, C₃- and C₇-monosubstituted and disubstituted hexahydroazepin-2-ones (caprolactams),³⁹⁶ tetrahydrothiophene *S*-oxide³⁹⁷], one conformer may be more stable than the others. The barrier to planarity in cyclopentane has been reported to be 5.2 kcal mol⁻¹ (22 kJ mol⁻¹).³⁹⁸ Contrary to previous reports, there is only weak stabilization (<2 kcal mol⁻¹; <8 kJ mol⁻¹) of three-, four-, and five-membered rings by *gem*-dialkoxycarbonyl substituents (e.g., COOR).³⁹⁹

Rings larger than six-membered are always puckered⁴⁰⁰ unless they contain a large number of *sp*² atoms (see the section on strain in medium rings, Sec. 4.Q.ii). The energy and conformations of the alkane series cycloheptane to cyclodecane has been reported.⁴⁰¹ The conformation shown for oxacyclooctane (**123**), for example, appears to be the most abundant one.⁴⁰² The conformations of other large-ring compounds have been studied, including cycloundecane,⁴⁰³ 11-membered ring lactones,⁴⁰⁴ 10- and 11-membered ring ketones,⁴⁰⁵ and 11- and 14-membered ring lactams.⁴⁰⁶ Dynamic NMR was used to determine the conformation large-ring cycloalkenes and lactones,⁴⁰⁷ and C—H coupling constants have been used for conformational analysis.⁴⁰⁸ Strain estimates have been made

³⁹⁴ Willy, W.E.; Binsch, G.; Eliel, E.L. *J. Am. Chem. Soc.* **1970**, 92, 5394; Lipnick, R.L. *J. Mol. Struct.* **1974**, 21, 423.

³⁹⁵ Lipnick, R.L. *J. Mol. Struct.* **1974**, 21, 411; Poupko, R.; Luz, Z.; Zimmermann, H. *J. Am. Chem. Soc.* **1982**, 104, 5307; Riddell, F.G.; Cameron K.S.; Holmes, S.A.; Strange, J.H. *J. Am. Chem. Soc.* **1997**, 119, 7555.

³⁹⁶ Matallana, A.; Kruger, A.W.; Kingsbury, C.A. *J. Org. Chem.* **1994**, 59, 3020.

³⁹⁷ Abraham, R.J.; Pollock, L.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* **1994**, 2329.

³⁹⁸ Carreira, L.A.; Jiang, G.J.; Person, W.B.; Willis, Jr., J.N. *J. Chem. Phys.* **1972**, 56, 1440.

³⁹⁹ Verevkin, S.P.; Kümmerlin, M.; Beckhaus, H.-D.; Galli, C.; Rüchardt, C. *Eur. J. Org. Chem.* **1998**, 579.

⁴⁰⁰ See Arshinova, R.P. *Russ. Chem. Rev.* **1988**, 57, 1142; Ounsworth, J.P.; Weiler, L. *J. Chem. Educ.* **1987**, 64, 568; Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**, pp. 307–321; Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* **1975**, 911; Anet, F.A.L. *Top. Curr. Chem.* **1974**, 45, 169; Dunitz, J.D. *Pure Appl. Chem.* **1971**, 25, 495. See Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycles* VCH, NY, **1988**.

⁴⁰¹ Wiberg, K.B. *J. Org. Chem.* **2003**, 68, 9322.

⁴⁰² Meyer, W.L.; Taylor, P.W.; Reed, S.A.; Leister, M.C.; Schneider, H.-J.; Schmidt, G.; Evans, F.E.; Levine, R.A. *J. Org. Chem.* **1992**, 57, 291.

⁴⁰³ Pawar, D.M.; Brown II, J.; Chen, K.-H.; Allinger, N.L.; Noe, E.A. *J. Org. Chem.* **2006**, 71, 6512.

⁴⁰⁴ Spracklin, D.K.; Weiler, L. *J. Chem. Soc. Chem. Commun.* **1992**, 1347; Keller, T.H.; Neeland, E.G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* **1988**, 110, 7858.

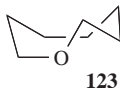
⁴⁰⁵ Pawar, D.M.; Smith, S.V.; Moody, E.M.; Noe, E.A. *J. Am. Chem. Soc.* **1998**, 120, 8241.

⁴⁰⁶ Borgen, G.; Dale, J.; Gundersen, L.-L.; Krivokapic, A.; Rise, F.; Øverås, A.T. *Acta Chem. Scand. B*, **1998**, 52, 1110.

⁴⁰⁷ Pawar, D.M.; Davids, K.L.; Brown, B.L.; Smith, S.V.; Noe, E.A. *J. Org. Chem.* **1999**, 64, 4580; Pawar, D.M.; Moody, E.M.; Noe, E.A. *J. Org. Chem.* **1999**, 64, 4586.

⁴⁰⁸ Kleinpeter, E.; Koch, A.; Pihlaja, K. *Tetrahedron* **2005**, 61, 7349.

for small-ring cyclic allenes and butatrienes.⁴⁰⁹ Note that axial and equatorial hydrogens are found only in the chair conformations of six-membered rings. In rings of other sizes, the hydrogens protrude at angles that generally do not lend themselves to classification in this way,⁴¹⁰ although in some cases the terms “pseudo-axial” and “pseudo-equatorial” have been used to classify hydrogens in rings of other sizes.⁴¹¹



4.O. MOLECULAR MECHANICS⁴¹²

Molecular Mechanics⁴¹³ describes a molecule in terms of a collection of bonded atoms that have been distorted from some idealized geometry due to nonbonded van der Waals (steric) and Coulombic (charge–charge) interactions. This approach is fundamentally different from MO theory that is based on quantum mechanics and that make no reference whatsoever to chemical bonding. The success of molecular mechanics depends on the ability to represent molecules in terms of unique valence structures, on the notion that bond lengths and angles may be transferred from one molecule to another and on a predictable dependence of geometrical parameters on the local atomic environment.

The molecular mechanics energy of a molecule is given as a sum of contributions arising from distortions from ideal bond distances (stretch contributions), bond angles (bend contributions) and torsion angles (torsion contributions), together with contributions from non-bonded interactions. This energy is commonly referred to as a *strain energy*, meaning that it reflects the inherent strain in a real molecule relative to a hypothetical idealized (strain-free) form.

$$E^{\text{strain}} = E_{\text{A}}^{\text{stretch}} + E_{\text{A}}^{\text{bend}} + E_{\text{A}}^{\text{torsion}} + E_{\text{AB}}^{\text{nonbonded}} \quad (4.1)$$

Stretch and bend terms are most simply given in terms of quadratic (Hooke's law) forms:

$$E^{\text{strain}}(r) = \frac{1}{2} k^{\text{stretch}} (r - r^{\text{eq}})^2 \quad (4.2)$$

$$E^{\text{bend}}(\alpha) = \frac{1}{2} k^{\text{bend}} (\alpha - \alpha^{\text{eq}})^2 \quad (4.3)$$

⁴⁰⁹ Daoust, K.J.; Hernandez, S.M.; Konrad, K.M.; Mackie, I.D.; Winstanley, Jr., J.; Johnson, R.P. *J. Org. Chem.* **2006**, *71*, 5708.

⁴¹⁰ For definitions of axial, equatorial, and related terms for rings of any size, see Anet, F.A.L. *Tetrahedron Lett.* **1990**, *31*, 2125.

⁴¹¹ For a discussion of the angles of the ring positions, see Cremer, D. *Isr. J. Chem.* **1980**, *20*, 12.

⁴¹² Thanks to Dr. Warren Hehre, Wavefunction, Inc., Irvine, CA. Personal communication. See Hehre, W.J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations*, Wavefunction, Inc., Irvine, CA, **2003**, pp. 56–57.

⁴¹³ For a review, see Rappe, A.K.; Casewit, C.J. *Molecular Mechanics Across Chemistry*, University Science Books, Sausalito, CA, **1997**.

r and α are the bond distance and angle, respectively, and r^{eq} and α^{eq} are the ideal bond length and angle, respectively.

Torsion terms need to properly reflect the inherent periodicity of the particular bond involved in a rotation. For example, the threefold periodicity of the carbon–carbon bond in ethane may be represented by a simple cosine form.

$$E^{\text{torsion}}(\omega) = k^{\text{torsion}3}[1 - \cos 3(\omega - \omega^{\text{eq}})] \quad (4.4)$$

Ω is the torsion angle, ω^{eq} is the ideal torsion angle and k^{torsion} is a parameter. Torsion contributions to the strain energy usually will also need to include contributions that are onefold and twofold periodic. These can be represented in the same manner as the threefold term.

$$E^{\text{torsion}}(\omega) = k^{\text{torsion}1}[1 - \cos(\omega - \omega^{\text{eq}})] + k^{\text{torsion}2}[1 - \cos 2(\omega - \omega^{\text{eq}})] + k^{\text{torsion}3}[1 - \cos 3(\omega - \omega^{\text{eq}})] \quad (4.5)$$

Nonbonded interactions involve a sum of van der Waals (VDW) interactions and Coulombic interactions. The Coulombic term accounts for charge–charge interactions.

$$E^{\text{nonbonded}}(r) = E^{\text{VDW}}(r) + E^{\text{Coulombic}}(r) \quad (4.6)$$

The VDW is made up of two parts, the first to account for strong repulsion on nonbonded atoms as they closely approach, and the second to account for weak long-range attraction, r is the nonbonded distance.

Molecular mechanics methods differ both in the form of the terms that make up the strain energy and in their detailed parameterization. Older methods (e.g., SYBYL⁴¹⁴) use very simple forms and relatively few parameters, while newer methods (e.g., MM3,⁴¹⁵ MM4,⁴¹⁶ and MMFF⁴¹⁷) use more complex forms and many more parameters. In general, the more complex the form of the strain energy terms and the more extensive the parameterization, the better the results. Of course, more parameters mean that more (experimental) data will be needed in their construction. Because molecular mechanics is not based on “physical fundamentals,” but rather is essentially an interpolation scheme, its success depends on the availability of either experimental or high-quality theoretical data for parameterization. A corollary is that molecular mechanics would not be expected to lead to good results for “new” molecules, that is, molecules outside the range of their parameterization.

The two most important applications of molecular mechanics are geometry calculations on very large molecules (e.g., on proteins) and conformational analysis on molecules for which there may be hundreds, thousands, or even tens of thousands of distinct structures. It is here that methods based on quantum mechanics are simply not (yet) practical. It should be no surprise that equilibrium geometries obtained from molecular mechanics are generally in good accord with experimental values. There are ample data with which to

⁴¹⁴ Clark, M.; Cramer, III, R.D.; van Opdenbosch, N. *J. Computational Chem.* **1989**, *10*, 982.

⁴¹⁵ Allinger, N.L.; Li, F.; Yun, Y.H. *J. Computational Chem.* **1990**, *11*, 855, and later papers in this series.

⁴¹⁶ Allinger, N.L.; Chen, K.; Lii, J.-H. *J. Computational Chem.* **1996**, *17*, 642, and later papers in this series.

⁴¹⁷ Halgren, T.A. *J. Computational Chem* **1996**, *17*, 490, and later papers in this series.

parameterize and evaluate the methods. However, because there are very few experimental data relating to the equilibrium conformations of molecules and energy differences among different conformations, molecular mechanics calculations for these quantities need to be viewed with a very critical eye. In time, high-quality data from quantum mechanics will provide the needed data and allow more careful parameterization (and assessment) than now possible.

The most important limitation of molecular mechanics is its inability to provide thermochemical data. The reason for this is that the mechanics strain energy is specific to a given molecule (it provides a measure of how much this molecule deviates from an ideal arrangement), and different molecules have different ideal arrangements. For example, acetone and methyl vinyl ether have different bonds and would be referenced to different standards. The only exception occurs for conformational energy differences or, more generally, for energy comparisons among molecules with exactly the same bonding (e.g., *cis*- and *trans*-2-butene).

Because a molecular mechanics calculation reveals nothing about the distribution of electrons or distribution of charge in molecules, and because mechanics methods have not (yet) been parameterized to reproduce transition state geometries, they are of limited value in describing either chemical reactivity or product selectivity. There are, however, situations where steric considerations associated with either the product or reactants are responsible for trends in reactivity and selectivity, and here molecular mechanics would be expected to be of some value.

Because of the different strengths and limitations of molecular mechanics and quantum chemical calculations, it is now common practice to combine the two, for example, to use molecular mechanics to establish conformation (or at least a set of reasonable conformations) and then to quantum calculations to evaluate energy differences.

In practical terms, molecular mechanics calculations may easily be performed on molecules comprising several thousand atoms. Additionally, molecular mechanics calculations are sufficiently rapid to permit extensive conformational searching on molecules containing upward of a hundred atoms. Modern graphical based programs for desktop computers make the methods available to all chemists.

4.P. STRAIN

Steric strain⁴¹⁸ exists in a molecule when bonds are forced to make abnormal angles, usually due to repulsion of large atoms or groups attached to those bonds, but not always. This repulsion results in a higher energy than would be the case in the absence of the angle distortions. It has been shown that there is a good correlation between the ¹³C—H coupling constants in NMR and the bond angles and bond force angles in strained organic molecules.⁴¹⁹ There are, in general, two kinds of structural features that result in sterically caused abnormal bond angles. One of these is found in small-ring compounds, where the angles must be less than those resulting from normal orbital overlap.⁴²⁰ Such strain is called *small-angle strain* or *Baeyer strain*. The other arises when nonbonded

⁴¹⁸ See Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, 1978; Wiberg, K.B. *Angew. Chem. Int. Ed.* **1986**, 25, 312; Greenberg, A.; Stevenson, T.A. *Mol. Struct. Energ.* **1986**, 3, 193; Liebman, J.F.; Greenberg, A. *Chem. Rev.* **1976**, 76, 311; Cremer, D.; Kraka, E. *Mol. Struct. Energ.* **1988**, 7, 65.

⁴¹⁹ Zhao, C.-Y.; Duan, W.-S.; Zhang, Y.; You, X.-Z. *J. Chem. Res. (S)* **1998**, 156.

⁴²⁰ Wiberg, K.B. *Accs. Chem. Res.* **1996**, 29, 229.

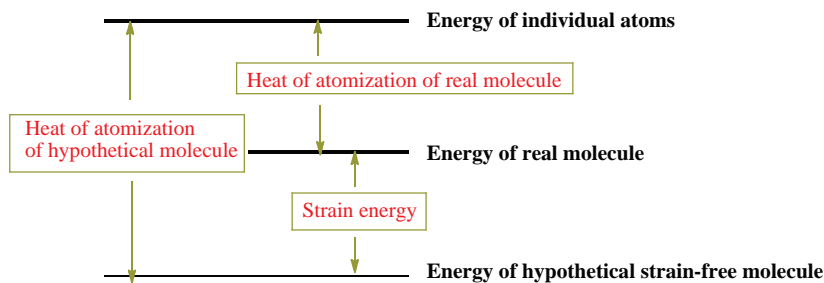


FIG. 4.6. Strain energy calculation.

atoms are forced into close proximity by the geometry of the molecule. These are called *nonbonded interactions*. This latter type of strain is most often associated with the term steric strain.

Strained molecules possess *strain energy*. That is, their potential energies are higher than they would be if strain were absent.⁴²¹ The strain energy for a particular molecule can be estimated from heat of atomization or heat of combustion data. A strained molecule has a lower heat of atomization than it would have if it were strain-free (Fig. 4.6). As in the similar case of resonance energies (Sec. 2.B), strain energies cannot be known exactly, because the energy of a real molecule can be measured, but not the energy of a hypothetical unstrained model. It is also possible to calculate strain energies by molecular mechanics, not only for real molecules, but also for those that cannot be made.⁴²²

4.P.i Strain in Small Rings

Three-membered rings have a great deal of angle strain (also called *Baeyer strain*), since 60° angles represent a large departure from the “normal” tetrahedral angles. Calculations have been interpreted to say that Baeyer strain in small ring systems originates from a decrease in nucleus–electron attraction compared to acyclic compounds,⁴²³ but this has been challenged in later work.⁴²⁴ However, in sharp contrast to other ethers, ethylene oxide is quite reactive, the ring being opened by many reagents (see Sec. 10.G.iii). Ring opening, of course, relieves the strain.⁴²⁵ Cyclopropane,⁴²⁶ which is even more strained⁴²⁷ than ethylene oxide, is also cleaved more easily than would be expected for an alkane.⁴²⁸ Thus,

⁴²¹ For discussions, see Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* **1987**, 109, 985, 1001.

⁴²² For a review, see Rüchardt, C.; Beckhaus, K. *Angew. Chem. Int. Ed.* **1985**, 24, 529. See also, Burkert, U.; Allinger, N.L. *Molecular Mechanisms*, American Chemical Society, Washington, **1982**, pp. 169–194; Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, 13, 1, 45–47.

⁴²³ Barić, D.; Maksić, Z.B. *Theor. Chem. Acc.* **2005**, 114, 222.

⁴²⁴ Hohlneicher, G.; Packschies, L. *Tetrahedron Lett.* **2007**, 48, 6429. However, see Barić, D.; Maksić, Z.B. *Tetrahedron Lett.* **2008**, 49, 1428.

⁴²⁵ For reviews of reactions of cyclopropanes and cyclobutanes, see Trost, B.M. *Top. Curr. Chem.* **1986**, 133, 3; Wong, H.N.C.; Lau, C.D.H.; Tam, K. *Top. Curr. Chem.* **1986**, 133, 83.

⁴²⁶ For a treatise, see Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts.; Wiley, NY, **1987**.

⁴²⁷ See in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts, Wiley, NY, **1987**, the papers by Wiberg, K.B. pt. 1., pp. 1–26; Liebman, J.F.; Greenberg, A. pt. 2, pp. 1083–1119; Liebman, J.F.; Greenberg, A. *Chem. Rev.* **1989**, 89, 1225.

⁴²⁸ See Wong, H.N.C.; Hon, M.; Ts, C.e; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, 89, 165; Reissig, H. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, **1987**, pp. 375–443.

pyrolysis at 450–500°C converts it to propene, bromination gives 1,3-dibromopropane,⁴²⁹ and it can be hydrogenated to propane (though at high pressure).⁴³⁰ Other three-membered rings are similarly reactive.⁴³¹ Alkyl substituents influence the strain energy of small ring compounds,⁴³² and carbonyl substitution also influences the strain energy.⁴³³ *gem*-Dimethyl substitution, for example, “lowers the strain energy of cyclopropanes, cyclobutanes, epoxides, and dimethyldioxirane by 6–10 kcal mol⁻¹ (25–42 kJ mol⁻¹) relative to an unbranched acyclic reference molecule.”⁴³² The CH bond dissociation energy also tends to increase ring strain in small-ring alkenes.⁴³⁴ Computation of the ring strain energy of 1,1-dimethylcyclobutane, however, shows “no significant enthalpic component of the *gem*-dimethyl effect as measured by the ring strain energy.”⁴³⁵

There is much evidence, chiefly derived from NMR coupling constants, that the bonding in cyclopropanes is not the same as in compounds that lack small-angle strain.⁴³⁶ For a normal carbon atom, one *s* and three *p* orbitals are hybridized to give four approximately equivalent *sp*³ orbitals, each containing ~25% *s* character. But for a cyclopropane carbon atom, the four hybrid orbitals are far from equivalent. The two orbitals directed to the outside bonds have more *s* character than a normal *sp*³ orbital, while the two orbitals involved in ring bonding have less, because the more *p*-like they are the more they resemble ordinary *p* orbitals, whose preferred bond angle is 90° rather than 109.5°. Since the small-angle strain in cyclopropanes is the difference between the preferred angle and the real angle of 60°, this additional *p* character relieves some of the strain. The external orbitals have ~33% *s* character, so that they are ~*sp*² orbitals, while the internal orbitals have ~17% *s* character, so that they may be called ~*sp*⁵ orbitals.⁴³⁷ Each of the three carbon–carbon bonds of cyclopropane is therefore formed by overlap of two *sp*⁵ orbitals. Molecular-orbital calculations show that such bonds are not completely *s* in character. In normal C—C bonds, *sp*³ orbitals overlap in such a way that the straight line connecting the nuclei becomes an axis about which the electron density is symmetrical. But in cyclopropane, the electron density is directed *away from the ring*.⁴³⁸ Figure 4.7 shows the direction of orbital overlap.⁴³⁹ For cyclopropane, the angle (marked θ) is 21°. Cyclobutane exhibits the same phenomenon but to a lesser extent, θ being 7°. ⁴³⁹ Molecular orbital calculations also show that the maximum electron densities of the C—C σ orbitals are bent away from the ring, with $\theta = 9.4^\circ$ for cyclopropane and 3.4° for cyclobutane.⁴⁴⁰ The bonds in cyclopropane are called *bent bonds* (sometimes, *banana bonds*), and are intermediate

⁴²⁹ Ogg, Jr., R.A.; Priest, W.J. *J. Am. Chem. Soc.* **1938**, 60, 217.

⁴³⁰ Shortridge, R.W.; Craig, R.A.; Greenlee, K.W.; Derfer, J.M.; Boord, C.E. *J. Am. Chem. Soc.* **1948**, 70, 946.

⁴³¹ See Frey, H.M. *Adv. Phys. Org. Chem.* **1966**, 4, 147.

⁴³² Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* **2002**, 67, 2588.

⁴³³ Bach, R.D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2006**, 128, 4598.

⁴³⁴ Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, 126, 4444; Tian, Z.; Fattahi, A.; Lis, L.; Kass, S.R. *J. Am. Chem. Soc.* **2006**, 128, 17087.

⁴³⁵ Bachrach, S.M. *J. Org. Chem.* **2008**, 73, 2466. Also see Ringer, A.L.; Magers, D.H. *J. Org. Chem.* **2007**, 72, 2533.

⁴³⁶ See Cremer, D.; Kraka, E. *J. Am. Chem. Soc.* **1985**, 107, 3800, 3811; Slee, T.S. *Mol. Struct. Energ.* **1988**, 5, 63; Casaarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1997**, 62, 7592.

⁴³⁷ Randić, M.; Maksić, Z. *Theor. Chim. Acta* **1965**, 3, 59; Weigert, F.J.; Roberts, J.D. *J. Am. Chem. Soc.* **1967**, 89, 5962.

⁴³⁸ Wiberg, K.B. *Accs. Chem. Res.* **1996**, 29, 229.

⁴³⁹ See Hoffmann, R.; Davidson, R.B. *J. Am. Chem. Soc.* **1971**, 93, 5699. See also Ref. 438

⁴⁴⁰ Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* **1987**, 109, 985, 1001.

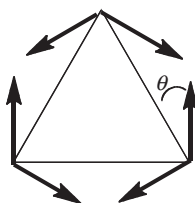


FIG. 4.7. Orbital overlap in cyclopropane. The arrows point toward the center of electron density.

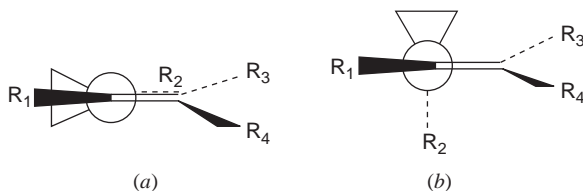


FIG. 4.8. Conformations of α -cyclopropylalkenes. Conformation (a) leads to maximum conjugation and conformation (b) to minimum conjugation

in character between σ and π , so that cyclopropanes behave in some respects like double-bond compounds.⁴⁴¹ For one thing, there is much evidence, chiefly from UV spectra,⁴⁴² that a cyclopropane ring is conjugated with an adjacent double bond. The conjugation is greatest for the conformation shown in Fig. 4.8a and is least or absent for the conformation shown in 4.8b, since overlap of the double-bond π orbital with two of the p -like orbitals of the cyclopropane ring is greatest in conformation a. However, the conjugation between a cyclopropane ring and a double bond is less than that between two double bonds.⁴⁴³ For other examples of the similarities in behavior of a cyclopropane ring and a double bond (see Sec. 4.O.iv).

Four-membered rings also exhibit angle strain, but much less than three-membered rings, and for that reason are less easily opened. Cyclobutane is more resistant than cyclopropane to bromination, and although it can be hydrogenated to butane, more strenuous conditions are required. Nevertheless, pyrolysis at 420°C gives two molecules of ethylene. As mentioned earlier (Sec. 4.O.iv), cyclobutane is not planar.

Many highly strained compounds containing small rings in fused systems have been prepared,⁴⁴⁴ showing that organic molecules can exhibit much more strain than simple cyclopropanes or cyclobutanes.⁴⁴⁵ Table 4.5 shows a few of these compounds.⁴⁴⁶

⁴⁴¹ See Tidwell, T.T. in Rappoport, Z. *The Chemistry of the Cyclopropyl Groups*, pt. 1, Wiley, NY, **1987**, pp. 565–632; Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, pp. 511–610, Wiley, NY, **1970**.

⁴⁴² See Tsuji, T.; Shibata, T.; Hienuki, Y.; Nishida, S. *J. Am. Chem. Soc.* **1978**, *100*, 1806; Drumright, R.E.; Mas, R.H.; Merola, J.S.; Tanko, J.M. *J. Org. Chem.* **1990**, *55*, 4098.



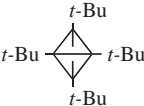


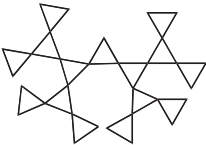


⁴⁴³ Staley, S.W. *J. Am. Chem. Soc.* **1967**, *89*, 1532; Pews, R.G.; Ojha, N.D. *J. Am. Chem. Soc.* **1969**, *91*, 5769. See, however, Noe, E.A.; Young, R.M. *J. Am. Chem. Soc.* **1982**, *104*, 6218.

⁴⁴⁴ See the reviews in *Chem. Rev.* **1989**, *89*, 975, and the following: Jefford, C.W. *J. Chem. Educ.* **1976**, *53*, 477; Seebach, D. *Angew. Chem. Int. Ed.* **1965**, *4*, 121; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, **1978**, pp. 210–220; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley–Interscience, NY, **1994**, pp. 771–811.

⁴⁴⁵ For a useful classification of strained polycyclic systems, see Gund, P.; Gund, T.M. *J. Am. Chem. Soc.* **1981**, *103*, 4458.

⁴⁴⁶ For a computer program that generates IUPAC names for complex bridged systems, see Rücker, G.; Rücker, C. *Chimia* **1990**, *44*, 116.

TABLE 4.5 Some Strained Small-Ring Compounds

Structural Formula of Compound Prepared	Systematic Name of Ring System	Common Name if Any	Reference
	Bicyclo[1.1.0]butane	Bicyclobutane	447
	$\Delta^{1,4}$ -Bicyclo[2.2.0]hexene		448
	Tricyclo[1.1.0.0 ^{2,4}]butane	Tetrahedrane	449
	Pentacyclo[5.1.0.0 ^{2,4} .0 ^{3,5} .0 ^{6,8}]octane	Octabisvalene	450
	Tricyclo[1.1.1.0 ^{1,3}]pentane	a [1.1.1] Propellane	364
	Tetradecaspiro [2.0.2.0.0.0.0.0.2.0.2.0.0.0.2.0.2. 0.0.1.0.0.2.0.2.0.0.0]untriacontane	[15] Triangulane	451
	Tetracyclo[2.2.0.0 ^{2,6} .0 ^{3,5}]hexane	Prismane	452
	Pentacyclo[4.2.0.0 ^{2,5} .0 ^{3,8} .0 ^{4,7}]octane	Cubane	453

⁴⁴⁷ Lemal, D.M.; Menger, F.M.; Clark, G.W. *J. Am. Chem. Soc.* **1963**, 85, 2529; Wiberg, K.B.; Lampman, G.M. *Tetrahedron Lett.* **1963**, 2173; Hoz, S. in Rappoport, Z *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, **1987**, pp. 1121–1192; Wiberg, K.B. *Adv. Alicyclic Chem.* **1968**, 2, 185. For a review of [n.1.1] systems, see Meinwald, J.; Meinwald, Y.C. *Adv. Alicyclic Chem.* **1966**, 1, 1.

⁴⁴⁸ Casanova, J.; Bragin, J.; Cottrell, F.D. *J. Am. Chem. Soc.* **1978**, 100, 2264.

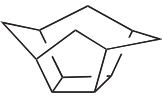
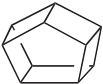

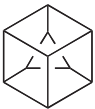
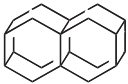
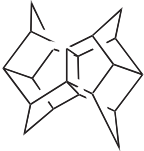
⁴⁴⁹ Irngartinger, H.; Goldmann, A.; Jahn, R.; Nixdorf, M.; Rodewald, H.; Maier, G.; Malsch, K.; Emrich, R. *Angew. Chem. Int. Ed.* **1984**, 23, 993; Maier, G.; Fleischer, F. *Tetrahedron Lett.* **1991**, 32, 57. Also see Maier, G. *Angew. Chem. Int. Ed.* **1988**, 27, 309; Maier, G.; Rang, H.; Born, D. in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, **1990**, pp. 219–259; Maier, G.; Born, D. *Angew. Chem. Int. Ed.* **1989**, 28, 1050.

⁴⁵⁰ Rücker, C.; Trupp, B. *J. Am. Chem. Soc.* **1988**, 110, 4828.

⁴⁵¹ Von Seebach, M.; Kozhushkov, S.I.; Boese, R.; Benet-Buchholz, J.; Yufit, D.S.; Howard, J.A.K.; de Meijere, A. *Angew. Chem. Int. Ed.* **2000**, 39, 2495.

⁴⁵² Katz, T.J.; Acton, N. *J. Am. Chem. Soc.* **1973**, 95, 2738. See also, Wilzbach, K.E.; Kaplan, L. *J. Am. Chem. Soc.* **1965**, 87, 4004.

TABLE 4.5 (Continued)

Structural Formula of Compound Prepared	Systematic Name of Ring System	Common Name if Any	Reference
	Pentacyclo[5.4.1.0 ³ , ¹ .0 ⁵ .0 ⁸ , ¹¹] dodecane	4[Peristylane]	454
	Hexacyclo[5.3.0.0 ² , ⁶ .0 ³ , ¹⁰ .0 ⁴ , ⁹ .0 ⁵ , ⁸] decane	Pentaprismane	455
	Tricyclo[3.1.1.1 ² , ⁴]octane	Diasterane	456
	Hexacyclo[4.4.0.0 ² , ⁴ .0 ³ , ⁹ .0 ⁵ , ⁸ .0 ⁷ , ¹⁰] decane		457
	Nonacyclo[10.8.0 ² , ¹¹ .0 ⁴ , ⁹ .0 ⁴ , ¹⁹ .0 ⁶ , ¹⁷ .-0 ⁷ , ¹⁶ .0 ⁹ , ¹⁴ .0 ¹⁴ , ¹⁹]icosane	A double tetraesterane	458
	Undecacyclo[9.9.0.0 ¹ , ⁵ .0 ² , ¹² .0 ² , ¹⁸ .0 ³ , ⁷ .-0 ⁶ , ¹⁰ .0 ⁸ , ¹² .0 ¹¹ , ¹⁵ .0 ¹³ , ¹⁷ .0 ¹⁶ , ²⁰]icosane	Pagodane	459

⁴⁵³ Hedberg, L.; Hedberg, K.; Eaton, P.E.; Nodari, N.; Robiette, A.G. *J. Am. Chem. Soc.* **1991**, *113*, 1514. For a review of cubanes, see Griffin, G.W.; Marchand, A.P. *Chem. Rev.* **1989**, *89*, 997.

⁴⁵⁴ Paquette, L.A.; Fischer, J.W.; Browne, A.R.; Doecke, C.W. *J. Am. Chem. Soc.* **1985**, *105*, 686.

⁴⁵⁵ Eaton, P.E.; Or, Y.S.; Branca, S.J.; Shankar, B.K.R. *Tetrahedron* **1986**, *42*, 1621. See also, Dauben, W.G.; Cunningham Jr., A.F. *J. Org. Chem.* **1983**, *48*, 2842.

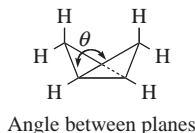
⁴⁵⁶ Otterbach, A.; Musso, H. *Angew. Chem. Int. Ed.* **1987**, *26*, 554.

⁴⁵⁷ Allred, E.L.; Beck, B.R. *J. Am. Chem. Soc.* **1973**, *95*, 2393.

⁴⁵⁸ Hoffmann, V.T.; Musso, H. *Angew. Chem. Int. Ed.* **1987**, *26*, 1006.

⁴⁵⁹ Rihs, G. *Tetrahedron Lett.* **1983**, *24*, 5857. See Mathew, T.; Keller, M.; Hunkler, D.; Prinzbach, H. *Tetrahedron Lett.* **1996**, *37*, 4491 for the synthesis of azapagodanes (also called azadodecahedranes).

Perhaps the most interesting are cubane, prismane,⁴⁶⁰ and the substituted tetrahedrane, since preparation of these ring systems had been the object of much endeavor. Prismane is tetracyclo[2.2.0.0^{2,6}.0^{3,5}]hexane and many derivatives are known,⁴⁶¹ including bis (homohexaprismane) derivatives.⁴⁶² The bicyclobutane molecule is bent, with the angle θ between the planes equal to $126 \pm 3^\circ$.⁴⁶³ The rehybridization effect, described above for cyclopropane, is even more extreme in this molecule. Calculations have shown that the central bond is essentially formed by overlap of two p orbitals with little or no



s character.⁴⁶⁴ *Propellanes* are compounds in which two carbons, directly connected, are also connected by three other bridges. [1.1.1]Propellane is in the table and it is the smallest possible propellane.⁴⁶⁵ It is in fact more stable than the larger [2.1.1]propellane and [2.2.1]propellane, which have been isolated only in solid matrixes at low temperature.⁴⁶⁶ The bicyclo[1.1.1]pentanes are related to the propellanes except that the central connecting bond is missing, and several derivatives are known.⁴⁶⁷ Even more complex systems are known.⁴⁶⁸

In certain small-ring systems, including small propellanes, the geometry of one or more carbon atoms is so constrained that all four of their valences are directed to the same side of a plane (inverted tetrahedron), as in **124**.⁴⁶⁹ An example is 1,3-dehydroadamantane, **125**, which is also a propellane.⁴⁷⁰ X-ray crystallography of the 5-cyano derivative of **125** shows that the four carbon valences at C-1 and C-3 are all directed “into” the molecule and none point outside.⁴⁷¹ Compound **125** is quite reactive; it is unstable in air, readily adds hydrogen, water, bromine, or acetic acid to the C-1—C-3 bond, and is easily polymerized. When two such atoms are connected by a bond (as in **125**), the bond is very long (the C-1—C-3 bond length in the 5-cyano derivative of **125** is 1.64 Å), as the atoms try to compensate in this way for their enforced angles. The high reactivity of the C-1—C-3 bond of **125** is not only caused by strain, but also by the fact that reagents find it easy to approach these atoms since there are no bonds (e.g., C—H bonds on C-1 or C-3) to get in the way.

⁴⁶⁰ Gribanova, T.N.; Minyaev, R.M.; Minkin, V.I. *Russ. J. Org. Chem.* **2007**, *43*, 1144.

⁴⁶¹ Gleiter, R.; Treptow, B.; Irngartinger, H.; Oeser, T. *J. Org. Chem.* **1994**, *59*, 2787.

⁴⁶² Golobish, T.D.; Dailey, W.P. *Tetrahedron Lett.* **1996**, *37*, 3239.

⁴⁶³ Haller, I.; Srinivasan, R. *J. Chem. Phys.* **1964**, *41*, 2745.

⁴⁶⁴ Newton, M.D.; Schulman, J.M. *J. Am. Chem. Soc.* **1972**, *94*, 767.

⁴⁶⁵ Wiberg, K.B.; Waddell, S.T. *J. Am. Chem. Soc.* **1990**, *112*, 2194; Seiler, S.T. *Helv. Chim. Acta* **1990**, *73*, 1574; Bothe, H.; Schlüter, A. *Chem. Ber.* **1991**, *124*, 587; Lynch, K.M.; Dailey, W.P. *J. Org. Chem.* **1995**, *60*, 4666. See Wiberg, K.B. *Chem. Rev.* **1989**, *89*, 975; Ginsburg, D. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, **1987**, pp. 1193–1221; Ginsburg, D. *Top. Curr. Chem.* **1987**, *137*, 1. For a discussion of charge density and bonding, see Coppens, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 6810.

⁴⁶⁶ Wiberg, K.B.; Walker, F.H.; Pratt, W.E.; Michl, J. *J. Am. Chem. Soc.* **1983**, *105*, 3638.

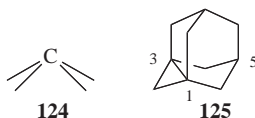
⁴⁶⁷ Della, E.W.; Taylor, D.K. *J. Org. Chem.* **1994**, *59*, 2986.

⁴⁶⁸ See Kuck, D.; Krause, R.A.; Gestmann, D.; Postheuer, F.; Schuster, A. *Tetrahedron* **1998**, *54*, 5247.

⁴⁶⁹ For a review, see Wiberg, K.B. *Acc. Chem. Res.* **1984**, *17*, 379.

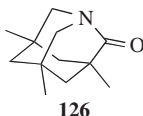
⁴⁷⁰ Scott, W.B.; Pincock, R.E. *J. Am. Chem. Soc.* **1973**, *95*, 2040.

⁴⁷¹ Gibbons, C.S.; Trotter, J. *Can. J. Chem.* **1973**, *51*, 87.



4.P.ii. Strain in Other Rings⁴⁷²

In rings larger than four-membered, there is no strain due to small bond angles, but there are three other kinds of strain. In the chair form of cyclohexane, which does not exhibit any of the three kinds of strain, all six carbon–carbon bonds have the two attached carbons in the *gauche* conformation. However, in five-membered rings and in rings containing from 7 to 13 carbons, any conformation in which all the ring bonds are *gauche* contains transannular interactions, that is, interactions between the substituents on C-1 and C-3 or C-1 and C-4, and so on. These interactions occur because the internal space is not large enough for all the quasi-axial hydrogen atoms to fit without coming into conflict. The molecule can adopt other conformations in which this *transannular strain* is reduced, but then some of the carbon–carbon bonds must adopt eclipsed or partially eclipsed conformations. The strain resulting from eclipsed conformations is called *Pitzer strain*. For saturated rings from 3- to 13-membered (except for the chair form of cyclohexane) there is no escape from at least one of these two types of strain. In practice, each ring adopts conformations that minimize both sorts of strain as much as possible. For cyclopentane, as seen in Section 4.O. iv, this means that the molecule is not planar. In rings larger than nine-membered, Pitzer strain seems to disappear, but transannular strain is still present.⁴⁷³ For 9- and 10-membered rings, some of the transannular and Pitzer strain may be relieved by the adoption of a third type of strain, *large-angle strain*. Thus, C—C—C angles of 115–120° have been found in X-ray diffraction of cyclononylamine hydrobromide and 1,6-diaminocyclodecane dihydrochloride.⁴⁷⁴



Strain can exert other influences on molecules. 1-Aza-2-adamantanone (**126**) is an extreme case of a twisted amide.⁴⁷⁵ The overlap of the lone-pair electrons on nitrogen with the π -system of the carbonyl is prevented.⁴⁷⁵ In chemical reactions, **126** reacts more or less like a ketone, giving a Wittig reaction (**16-44**) and it can form a ketal (**16-7**). A twisted biadamantylidene compound has been reported.⁴⁷⁶

The amount of strain in cycloalkanes is shown in Table 4.6,⁴⁷⁷ which lists heats of combustion per CH₂ group. As can be seen, cycloalkanes > 13-membered are as strain-free as cyclohexane.

⁴⁷² See Raphael, R.A. *Proc. Chem. Soc.* **1962**, 97; Sicher, J. *Prog. Stereochem.* **1962**, 3, 202.

⁴⁷³ Huber-Buser, E.; Dunitz, J.D. *Helv. Chim. Acta* **1960**, 43, 760.

⁴⁷⁴ Dunitz, J.D.; Venkatesan, K. *Helv. Chim. Acta* **1961**, 44, 2033.

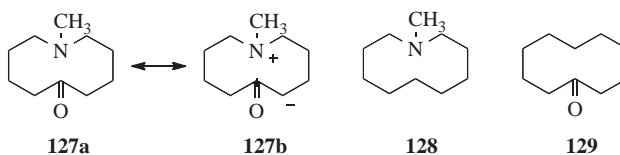
⁴⁷⁵ Kirby, A.J.; Komarov, I.V.; Wothers, P.D.; Feeder, N. *Angew. Chem. Int. Ed.*, **1998**, 37, 785. Also see Maddar, R.D.; Kim, C.-Y.; Chandra, P.P.; Doyon, J.B.; Barid, Jr., T.A.; Fierke, C.A.; Christianson, D.W.; Voet, J.G.; Jain, A. *J. Org. Chem.* **2002**, 67, 582.

⁴⁷⁶ Okazaki, T.; Ogawa, K.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* **2002**, 67, 5981.

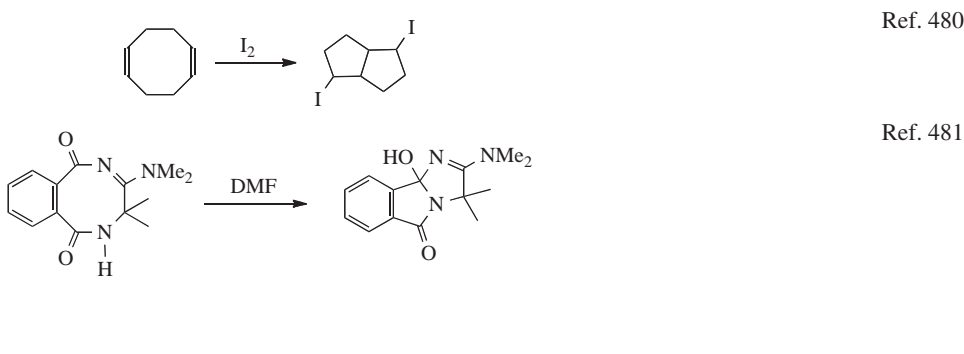
⁴⁷⁷ Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* **1960**, 29, 214, p. 218.

TABLE 4.6 Heats of Combustion in the Gas Phase for Cycloalkanes, per CH₂ Group^a

Size of Ring	$-\Delta H_c$ (g)		Size of Ring	$-\Delta H_c$ (g)	
	kcal mol ⁻¹	kJ mol ⁻¹		kcal mol ⁻¹	kJ mol ⁻¹
3	166.3	695.8	10	158.6	663.6
4	163.9	685.8	11	158.4	662.7
5	158.7	664.0	12	157.8	660.2
6	157.4	658.6	13	157.7	659.8
7	158.3	662.3	14	157.4	658.6
8	158.6	663.6	15	157.5	659.0
9	158.8	664.4	16	157.5	659.0

[Reprinted with permission. Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* **1960**, 29, 214, p. 218].^aSee Ref. 472.

Transannular interactions can exist across rings from 8- to 11-membered and even larger.⁴⁷⁸ Such interactions can be detected by dipole and spectral measurements. For example, that the carbonyl group in **127a** is affected by the nitrogen (**127b** is probably another canonical form) has been demonstrated by photoelectron spectroscopy, which shows that the ionization potentials of the nitrogen *n* and C=O π orbitals in **127** differ from those of the two comparison molecules **128** and **129**.⁴⁷⁹ It is significant that when **127** donates electrons to a proton, it goes to the oxygen rather than to the nitrogen. Many examples of transannular reactions are known, including the following:



where DMF = *N*, *N*-dimethylformamide (Solvent)

⁴⁷⁸ For a review, see Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* **1966**, 20, 119.

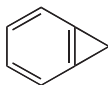
⁴⁷⁹ Spanka, G.; Rademacher, P. *J. Org. Chem.* **1986**, 51, 592. See also, Spanka, G.; Rademacher, P.; Duddeck, H. *J. Chem. Soc. Perkin Trans. 2* **1988**, 2119.

In summary, saturated rings may be divided into four groups, of which the first and third are more strained than the other two.⁴⁸²

1. *Small rings* (three- and four-membered). Small-angle strain predominates.
2. *Common rings* (five-, six-, and seven-membered). Largely unstrained. The strain that is present is mostly Pitzer strain.
3. *Medium rings* (8- to 11-membered). Considerable strain; Pitzer, transannular, and large-angle strain.
4. *Large rings* (12-membered and larger). Little or no strain.⁴⁸³

4.P.iii. Unsaturated Rings⁴⁸⁴

Double bonds can exist in rings of any size. As expected, the most highly strained are the three-membered rings (e.g., cyclopropene). Small-angle strain, which is so important in cyclopropane, is even greater in cyclopropene⁴⁸⁵ because the ideal angle is more distorted. In cyclopropane, the bond angle is forced to be 60° , $\sim 50^\circ$ smaller than the tetrahedral angle; but in cyclopropene, the angle, also $\sim 60^\circ$, is now $\sim 60^\circ$ smaller than the ideal angle of 120° for an alkene. Thus, the angle of cyclopropene is $\sim 10^\circ$ more strained than in cyclopropane. However, this additional strain is offset by a decrease in strain arising from another factor. Cyclopropene, lacking two hydrogens, has none of the eclipsing strain present in cyclopropane. Cyclopropene has been prepared⁴⁸⁶ and is stable at liquid-nitrogen temperatures, although on warming even to -80°C it rapidly polymerizes. Many other cyclopropenes are stable at room temperature and above.⁴⁶⁴ The highly strained benzocyclopropene,⁴⁸⁷ in which the cyclopropene ring is fused to a benzene ring, has been prepared⁴⁸⁸ and is stable for weeks at room temperature, although it decomposes on distillation at atmospheric pressure.



Benzocyclopropene

⁴⁸² See Granik, V.G. *Russ. Chem. Rev.* **1982**, 51, 119.

⁴⁸³ An example is the calculated strain of $1.4\text{--}3.2\text{ kcal mol}^{-1}$ ($5.9\text{--}13.4\text{ kJ mol}^{-1}$) in cyclotetradecane. See Chickos, J.S.; Hesse, D.G.; Panshin, S.Y.; Rogers, D.W.; Saunders, M.; Uffer, P.M.; Liebman, J.F. *J. Org. Chem.* **1992**, 57, 1897.

⁴⁸⁴ For a review of strained double bonds, see Zefirov, N.S.; Sokolov, V.I. *Russ. Chem. Rev.* **1967**, 36, 87. For a review of double and triple bonds in rings, see Johnson, R.P. *Mol. Struct. Energ.* **1986**, 3, 85.

⁴⁸⁵ See Baird, M.S. *Top. Curr. Chem.* **1988**, 144, 137; Halton, B.; Banwell, M.G. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, **1987**, pp. 1223–1339; Closs, G.L. *Adv. Alicyclic Chem.* **1966**, 1, 53; For a discussion of the bonding and hybridization, see Allen, F.H. *Tetrahedron* **1982**, 38, 645.

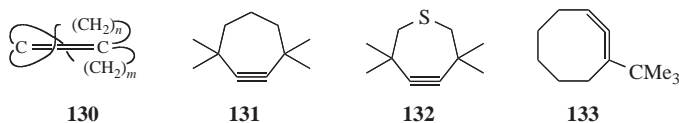
⁴⁸⁶ Dem'yanov, N.Ya.; Doyarenko, M.N. *Ber.* **1923**, 56, 2200; Schlatter, M.J. *J. Am. Chem. Soc.* **1941**, 63, 1733; Stigliani, W.M.; Laurie, V.W.; Li, J.C. *J. Chem. Phys.* **1975**, 62, 1890.

⁴⁸⁷ See Halton, B. *Chem. Rev.* **1989**, 89, 1161; **1973**, 73, 113; Billups, W.E.; Rodin, W.A.; Haley, M.M. *Tetrahedron* **1988**, 44, 1305; Billups, W.E. *Acc. Chem. Res.* **1978**, 11, 245.

⁴⁸⁸ Vogel, E.; Grimme, W.; Korte, S. *Tetrahedron Lett.* **1965**, 3625. Also see Müller, P.; Bernardinelli, G.; Thi, H. C.G. *Chimia* **1988**, 42, 261; Neidlein, R.; Christen, D.; Poignée, V.; Boese, R.; Bläser, D.; Gieren, A.; Ruiz-Pérez, C.; Hübner, T. *Angew. Chem. Int. Ed.* **1988**, 27, 294.

As previously mentioned, double bonds in relatively small rings must be *cis*. A stable *trans* double bond⁴⁸⁹ first appears in an eight-membered ring (*trans*-cyclooctene, Sec. 4.C, category 6), although the transient existence of *trans*-cyclohexene and cycloheptene has been demonstrated.⁴⁹⁰ Above ~11 members, the *trans* isomer is more stable than the *cis*.²³² It has proved possible to prepare compounds in which a *trans* double bond is shared by two cycloalkene rings (e.g., **130**). Such compounds have been called [*m.n*] *betweenanenes*, and several have been prepared with *m* and *n* values from 8 to 26.⁴⁹¹ The double bonds of the smaller *betweenanenes*, as might be expected from the fact that they are deeply buried within the bridges, are much less reactive than those of the corresponding *cis*-*cis* isomers.

The smallest unstrained cyclic triple bond is found in cyclononyne.⁴⁹² Cyclooctyne has been isolated,⁴⁹³ but its heat of hydrogenation shows that it is considerably strained. There have been a few compounds isolated with triple bonds in seven-membered rings. 3,3,7,7-Tetramethylcycloheptyne (**131**) is known and dimerizes within 1 h at room temperature,⁴⁹⁴ but the thia derivative (**132**), in which the C—S bonds are longer than the corresponding C—C bonds in **131**, is indefinitely stable even at 140°C.⁴⁹⁵ Cycloheptyne itself has not been isolated, although its transient existence has been shown.⁴⁹⁶ Cyclohexyne⁴⁹⁷ and its 3,3,6,6-tetramethyl derivative⁴⁹⁸ have been trapped at 77 K, and in an Ar π matrix at 12 K, respectively. Its IR spectra have also been



obtained. Transient six- and even five-membered rings containing triple bonds have also been demonstrated.⁴⁹⁹ A derivative of cyclopentyne has been trapped in a matrix.⁵⁰⁰ Although cycloheptyne and cyclohexyne have not been isolated at room temperatures, Pt(0) complexes of these compounds have been prepared and are stable.⁵⁰¹ The smallest

⁴⁸⁹ For reviews of *trans* cycloalkenes, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* **1984**, 125, 1; Marshall, J.A. *Acc. Chem. Res.* **1980**, 13, 213.

⁴⁹⁰ Wallraff, G.M.; Michl, J. *J. Org. Chem.* **1986**, 51, 1794; Squillacote, M.; Bergman, A.; De Felippis, J. *Tetrahedron Lett.* **1989**, 30, 6805.

⁴⁹¹ Marshall, J.A.; Flynn, K.E. *J. Am. Chem. Soc.* **1983**, 105, 3360. For reviews, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* **1984**, 125, 1; Marshall, J.A. *Acc. Chem. Res.* **1980**, 13, 213. For a review of these and similar compounds, see Borden, W.T. *Chem. Rev.* **1989**, 89, 1095.

⁴⁹² See Meier, H. *Adv. Strain Org. Chem.* **1991**, 1, 215; Krebs, A.; Wilke, J. *Top. Curr. Chem.* **1983**, 109, 189; Nakagawa, M. in Patai, S. *The Chemistry of the C≡C Triple Bond*, pt. 2, Wiley, NY, **1978**, pp. 635–712; Krebs, A. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 987–1062. See Meier, H.; Hanold, N.; Molz, T.; Bissinger, H.J.; Kolshorn, H.; Zountsas, J. *Tetrahedron* **1986**, 42, 1711.

⁴⁹³ Blomquist, A.T.; Liu, L.H. *J. Am. Chem. Soc.* **1953**, 75, 2153. See also, Bühl, H.; Gugel, H.; Kolshorn, H.; Meier, H. *Synthesis* **1978**, 536.

⁴⁹⁴ Schmidt, H.; Schweig, A.; Krebs, A. *Tetrahedron Lett.* **1974**, 1471.

⁴⁹⁵ Krebs, A.; Kimling, H. *Tetrahedron Lett.* **1970**, 761.

⁴⁹⁶ Bottini, A.T.; Frost II, K.A.; Anderson, B.R.; Dev, V. *Tetrahedron* **1973**, 29, 1975.

⁴⁹⁷ Wentrup, C.; Blanch, R.; Briehl, H.; Gross, G. *J. Am. Chem. Soc.* **1988**, 110, 1874.

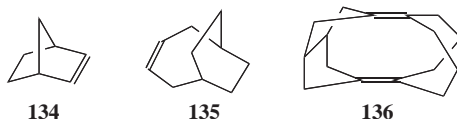
⁴⁹⁸ See Sander, W.; Chapman, O.L. *Angew. Chem. Int. Ed.* **1988**, 27, 398.

⁴⁹⁹ See Bolster, J.M.; Kellogg, R.M. *J. Am. Chem. Soc.* **1981**, 103, 2868; Gilbert, J.C.; Baze, M.E. *J. Am. Chem. Soc.* **1983**, 105, 664.

⁵⁰⁰ Chapman, O.L.; Gano, J.; West, P.R.; Regitz, M.; Maas, G. *J. Am. Chem. Soc.* **1981**, 103, 7033.

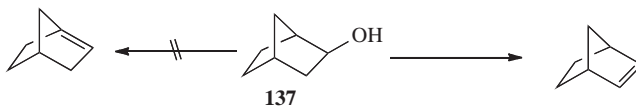
⁵⁰¹ Bennett, M.A.; Robertson, G.B.; Whimp, P.O.; Yoshida, T. *J. Am. Chem. Soc.* **1971**, 93, 3797.

cyclic allene⁵⁰² so far isolated is 1-*tert*-butyl-1,2-cyclooctadiene (**133**).⁵⁰³ The parent 1,2-cyclooctadiene has not been isolated. It has been shown to exist as a transient species, but rapidly dimerizes.⁵⁰⁴ Incorporation of the *tert*-butyl group apparently prevents this. The transient existence of 1,2-cycloheptadiene has also been shown,⁵⁰⁵ and both 1,2-cyclooctadiene and 1,2-cycloheptadiene have been isolated in Pt complexes.⁵⁰⁶ 1,2-Cyclohexadiene has been trapped at low temperatures, and its structure has been proved by spectral studies.⁵⁰⁷ Cyclic allenes in general are less strained than their acetylenic isomers.⁵⁰⁸ The cyclic cumulene 1,2,3-cyclononatriene also has been synthesized and is reasonably stable in solution at room temperature in the absence of air.⁵⁰⁹



There are many examples of polycyclic molecules and bridged molecules that have one or more double bonds. There is flattening of the ring containing the C=C unit, and this can have a significant effect on the molecule. Norbornene (bicyclo[2.2.1]hept-2-ene, **134**) is a simple example and it has been calculated that it contains a distorted π -face.⁵¹⁰ The double bond can appear away from the bridgehead carbon atoms, as in bicyclo[4.2.2]dec-3-ene (**135**), which flattens that part of the molecule. The C=C units in pentacyclo[8.2.1.1^{2,5}.1^{4,7}.1^{8,11}]hexadeca-1,7-diene (**136**) are held in a position where there is significant π - π interactions across the molecule.⁵¹¹

Double bonds at the bridgehead of bridged bicyclic compounds are impossible in small systems. This result is the basis of *Bredt's rule*,⁵¹² which states that elimination to give a double bond in a bridged bicyclic system (e.g., **137**) always leads away from the bridgehead. This rule no longer applies when the rings are large enough. In



⁵⁰² See Johnson, R.P. *Chem. Rev.* **1989**, 89, 1111; Thies, R.W. *Isr. J. Chem.* **1985**, 26, 191; Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*; Wiley, NY, **1984**, pp. 38–56.

⁵⁰³ Price, J.D.; Johnson, R.P. *Tetrahedron Lett.* **1986**, 27, 4679.

⁵⁰⁴ See Marquis, E.T.; Gardner, P.D. *Tetrahedron Lett.* **1966**, 2793.

⁵⁰⁵ Wittig, G.; Dorsch, H.; Meske-Schüller, J. *Liebigs Ann. Chem.* **1968**, 711, 55.

⁵⁰⁶ Visser, J.P.; Ramakers, J.E. *J. Chem. Soc. Chem. Commun.* **1972**, 178.

⁵⁰⁷ Wentrup, C.; Gross, G.; Maquestiau, A.; Flammang, R. *Angew. Chem. Int. Ed.* **1983**, 22, 542. 1,2,3-Cyclohexatriene has also been trapped: Shakespeare, W.C.; Johnson, R.P. *J. Am. Chem. Soc.* **1990**, 112, 8578.

⁵⁰⁸ Moore, W.R.; Ward, H.R. *J. Am. Chem. Soc.* **1963**, 85, 86.

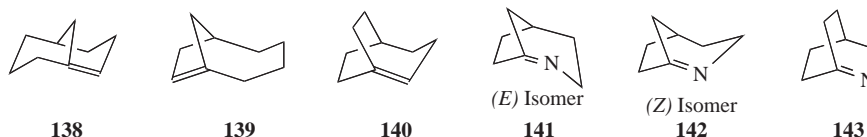
⁵⁰⁹ Angus Jr., R.O.; Johnson, R.P. *J. Org. Chem.* **1984**, 49, 2880.

⁵¹⁰ Ohwada, T. *Tetrahedron* **1993**, 49, 7649.

⁵¹¹ Lange, H.; Schäfer, W.; Gleiter, R.; Camps, P.; Vázquez, S. *J. Org. Chem.* **1998**, 63, 3478.

⁵¹² See Shea, K.J. *Tetrahedron* **1980**, 36, 1683; Buchanan, G.L. *Chem. Soc. Rev.* **1974**, 3, 41; Köbrich, G. *Angew. Chem. Int. Ed.* **1973**, 12, 464. See Billups, W.E.; Haley, M.M.; Lee, G. *Chem. Rev.* **1989**, 89, 1147; Warner, P.M. *Chem. Rev.* **1989**, 89, 1067; Keese, R. *Angew. Chem. Int. Ed.* **1975**, 14, 528. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 553–555.

determining whether a bicyclic system is large enough to accommodate a bridgehead double bond, the most reliable criterion is the size of the ring in which the double bond is located.⁵¹³ Bicyclo[3.3.1]non-1-ene⁵¹⁴ (**138**) and bicyclo[4.2.1]non-1(8)ene⁵¹⁵ (**139**) are stable compounds. Both can be looked upon as derivatives of *trans*-cyclooctene, which is of course a known compound. Compound **138** has been shown to have a strain



energy of the same order of magnitude as that of *trans*-cyclooctene.⁵¹⁶ On the other hand, in bicyclo[3.2.2]non-1-ene (**140**), the largest ring that contains the double bond is a *trans*-cycloheptene, which is as yet unknown. Compound **140** has been prepared, but dimerized before it could be isolated.⁵¹⁷ Even smaller systems ([3.2.1] and [2.2.2]), but with imine double bonds (**141–143**), have been obtained in matrixes at low temperatures.⁵¹⁸ These compounds are destroyed on warming. Compounds **141** and **142** are the first reported example of (*E–Z*) isomerism at a strained bridgehead double bond.⁵¹⁹

4.P.iv. Strain Due to Unavoidable Crowding⁵²⁰

In some molecules, large groups are so close to each other that they cannot fit into the available space in such a way that normal bond angles are maintained. It has proved possible to prepare compounds with a high degree of this type of strain. For example, success has been achieved in synthesizing benzene rings containing *ortho tert*-butyl groups. Two examples that have been prepared, of several, are 1,2,3-tri-*tert*-butyl compound **144**⁵²¹ and the 1,2,3,4-tetra-*tert*-butyl compound **145**.⁵²² That these molecules are strained is demonstrated by UV and IR spectra, which show that the ring is not planar in 1,2,4-tri-*tert*-butylbenzene, and by a comparison of the heats of reaction of this compound and its 1,3,5 isomer, which show that the 1,2,4 compound possesses $\sim 22 \text{ kcal mol}^{-1}$ (92 kJ mol^{-1}) more strain energy than its isomer⁵²³ (see also Reaction **18-27**). Although SiMe_3 groups are larger

⁵¹³ See Maier, W.F.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.

⁵¹⁴ Kim, M.; White, J.D. *J. Am. Chem. Soc.* **1975**, *97*, 451; Becker, K.B. *Helv. Chim. Acta* **1977**, *60*, 81. See Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* **1979**, *44*, 2438.

⁵¹⁵ Wiseman, J.R.; Chan, H.; Ahola, C.J. *J. Am. Chem. Soc.* **1969**, *91*, 2812; Carruthers, W.; Qureshi, M.I. *Chem. Commun.* **1969**, 832; Becker, K.B. *Tetrahedron Lett.* **1975**, 2207.

⁵¹⁶ Lesko, P.M.; Turner, R.B. *J. Am. Chem. Soc.* **1968**, *90*, 6888; Burkert, U. *Chem. Ber.* **1977**, *110*, 773.

⁵¹⁷ Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* **1969**, *91*, 7775.

⁵¹⁸ Sheridan, R.S.; Ganzer, G.A. *J. Am. Chem. Soc.* **1983**, *105*, 6158; Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* **1985**, *107*, 2799.

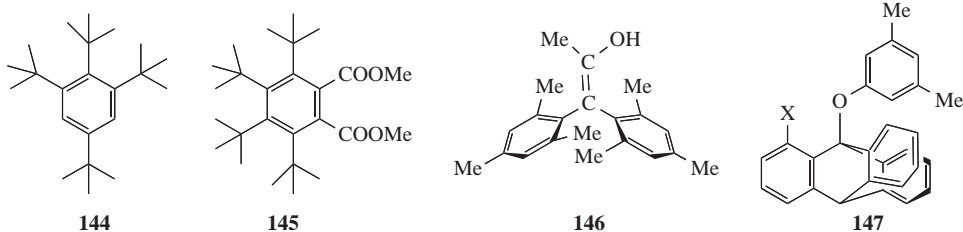
⁵¹⁹ Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* **1985**, *107*, 2799.

⁵²⁰ See Tidwell, T.T. *Tetrahedron* **1978**, *34*, 1855; Mosher, H.S.; Tidwell, T.T. *J. Chem. Educ.* **1990**, *67*, 9. For a review of van der Waals radii, see Zefirov, Yu.V.; Zorkii, P.M. *Russ. Chem. Rev.* **1989**, *58*, 421.

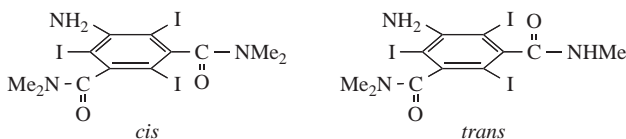
⁵²¹ Arnett, E.M.; Bollinger, J.M. *Tetrahedron Lett.* **1964**, 3803.

⁵²² Maier, G.; Schneider, K. *Angew. Chem. Int. Ed.* **1980**, *19*, 1022. For another example, see Krebs, A.; Franken, E.; Müller, S. *Tetrahedron Lett.* **1981**, *22*, 1675.

⁵²³ Arnett, E.M.; Sanda, J.C.; Bollinger, J.M.; Barber, M. *J. Am. Chem. Soc.* **1967**, *89*, 5389. See also, Barclay, L.R.C.; Brownstein, S.; Gabe, E.J.; Lee, F.L. *Can. J. Chem.* **1984**, *62*, 1358.



than CMe_3 groups, it has proven possible to prepare $\text{C}_6(\text{SiMe}_3)_6$. This compound has a chair-shaped ring in the solid state, and a mixture of chair and boat forms in solution.⁵²⁴ Even smaller groups can sterically interfere in ortho positions. In hexaisopropylbenzene, the six isopropyl groups are so crowded that they cannot rotate, but are lined up around the benzene ring, all pointed in the same direction.⁵²⁵ This compound is an example of a *geared molecule*.⁵²⁶ The isopropyl groups fit into each other in the same manner as interlocked



gears. Another example is **146**, which is a stable enol.⁵²⁷ In this case, each ring can rotate about its C–aryl bond only by forcing the other to rotate as well. In the case of triptycene derivatives (e.g., **147**), a complete 360° rotation of the aryl group around the O–aryl bond requires the aryl group to pass over three rotational barriers; one of which is the C–X bond and the other two the “top” C–H bonds of the other two rings. As expected, the C–X barrier is the highest, ranging from $10.3 \text{ kcal mol}^{-1}$ (43.1 kJ mol^{-1}) for $\text{X} = \text{F}$ to $17.6 \text{ kcal mol}^{-1}$ (73.6 kJ mol^{-1}) for $\text{X} = \text{tert-butyl}$.⁵²⁸ In another instance, it has proved possible to prepare *cis* and *trans* isomers of 5-amino-2,4,6-triiodo-*N,N,N',N''*-tetramethylisophthalamide because there is no room for the CONMe_2 groups to rotate, caught as they are between two bulky iodine atoms.⁵²⁹ The *trans* isomer is chiral and has been resolved, while the *cis* isomer is a meso form. Another example of *cis-trans* isomerism resulting from restricted rotation about single bonds⁵³⁰ is found in 1,8-di-*o*-tolynaphthalene⁵³¹ (see also, Sec. 4.K.i).

⁵²⁴ Sakurai, H.; Ebata, K.; Kabuto, C.; Sekiguchi, A. *J. Am. Chem. Soc.* **1990**, *112*, 1799.

⁵²⁵ Siegel, J.; Gutiérrez, A.; Schweizer, W.B.; Ermer, O.; Mislow, K. *J. Am. Chem. Soc.* **1986**, *108*, 1569. Also see Kahr, B.; Biali, S.E.; Schaefer, W.; Buda, A.B.; Mislow, K. *J. Org. Chem.* **1987**, *52*, 3713.

⁵²⁶ See Iwamura, H.; Mislow, K. *Acc. Chem. Res.* **1988**, *21*, 175; Mislow, K. *Chemtracts: Org. Chem.* **1989**, *2*, 151; Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* **1985**, *18*, 80.

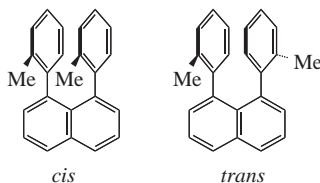
⁵²⁷ Nugiel, D.A.; Biali, S.E.; Rappoport, Z. *J. Am. Chem. Soc.* **1984**, *106*, 3357.

⁵²⁸ Yamamoto, G.; Öki, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3597. See Yamamoto, G. *Pure Appl. Chem.* **1990**, *62*, 569; Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**, pp. 269–284.

⁵²⁹ Ackerman, J.H.; Laidlaw, G.M.; Snyder, G.A. *Tetrahedron Lett.* **1969**, 3879; Ackerman, J.H.; Laidlaw, G.M. *Tetrahedron Lett.* **1969**, 4487. See also, Cuyegkeng, M.A.; Mannschreck, A. *Chem. Ber.* **1987**, *120*, 803.

⁵³⁰ See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**; Förster, H.; Vögtle, F. *Angew. Chem. Int. Ed.* **1977**, *16*, 429; Öki, M. *Angew. Chem. Int. Ed.* **1976**, *15*, 87.

⁵³¹ Clough, R.L.; Roberts, J.D. *J. Am. Chem. Soc.* **1976**, *98*, 1018. For a study of rotational barriers in this system, see Cosmo, R.; Sternhell, S. *Aust. J. Chem.* **1987**, *40*, 1107.



There are many other cases of intramolecular crowding that result in the distortion of bond angles. Hexahelicene (Sec. 4.C, category 6) and bent benzene rings (Sec. 2.G) have been mentioned previously. The compounds tri-*tert*-butylamine, and tetra-*tert*-butylmethane are as yet unknown. In the latter, there is no way for the strain to be relieved and it is questionable whether this compound can ever be made. In tri-*tert*-butylamine, the crowding can be eased somewhat if the three bulky groups assume a planar instead of the normal pyramidal configuration. In tri-*tert*-butylcarbinol, coplanarity of the three *tert*-butyl groups is prevented by the presence of the OH group, and yet this compound has been prepared.⁵³² Tri-*tert*-butylamine should have less steric strain than tri-*tert*-butylcarbinol and it should be possible to prepare it.⁵³³ The tetra-*tert*-butylphosphonium cation (*t*-Bu)₄P⁺ has been prepared.⁵³⁴ Although steric effects are nonadditive in crowded molecules, a quantitative measure has been proposed by DeTar, based on molecular mechanics calculations. This is called *formal steric enthalpy* (FSE), and values have been calculated for alkanes, alkenes, alcohols, ethers, and methyl esters.⁵³⁵ For example, some FSE values for alkanes are butane 0.00; 2,2,3,3-tetramethylbutane 7.27; 2,2,4,4,5-pentamethylhexane 11.30; and tri-*tert*-butylmethane 38.53.

The two carbon atoms of a C=C double bond and the four groups attached to them are normally in a plane, but if the groups are large enough, significant deviation from planarity can result.⁵³⁶ The compound tetra-*tert*-butylethene (**148**) has not been prepared,⁵³⁷ but the tetraaldehyde (**149**), which should have about the same amount of strain, has been made. X-ray crystallography shows that **149** is twisted out of a planar shape by an angle of 28.6°.⁵³⁸ Also, the C=C double bond distance is 1.357 Å, significantly longer than normal C=C bond of 1.32 Å (Table 1.5). (*Z*)-1,2-Bis(*tert*-butyldimethylsilyl)-1,2-bis(trimethylsilyl)ethene (**150**) has an even greater twist, but could not be made to undergo conversion to the (*E*) isomer, probably because the groups are too large to slide past each other.⁵³⁹ A different kind of double-bond strain is found in tricyclo[4.2.2.2^{2,5}]dodeca-1,5-

⁵³² Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* **1968**, *90*, 4421.

⁵³³ See Back, T.G.; Barton, D.H.R. *J. Chem. Soc. Perkin Trans 1*, **1977**, 924; Kopka, I.E.; Fataftah, Z.A.; Rathke, M.W. *J. Org. Chem.* **1980**, *45*, 4616.

⁵³⁴ Schmidbaur, H.; Blaschke, G.; Zimmer-Gasser, B.; Schubert, U. *Chem. Ber.* **1980**, *113*, 1612.

⁵³⁵ DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* **1985**, *50*, 2826, 5298, 5304.

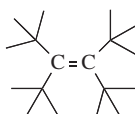
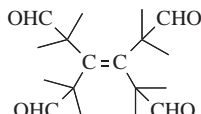
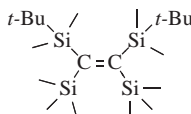
⁵³⁶ For reviews, see Luef, W.; Keese, R. *Top. Stereochem.* **1991**, *20*, 231; Sandström, J. *Top. Stereochem.* **1983**, *14*, 83, pp. 160–169.

⁵³⁷ For a list of crowded alkenes that have been made, see Drake, C.A.; Rabjohn, N.; Tempesta, M.S.; Taylor, R.B. *J. Org. Chem.* **1988**, *53*, 4555. See also, Garratt, P.J.; Payne, D.; Tocher, D.A. *J. Org. Chem.* **1990**, *55*, 1909.

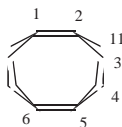
⁵³⁸ Krebs, A.; Nickel, W.; Tikwe, L.; Kopf, J. *Tetrahedron Lett.* **1985**, *26*, 1639.

⁵³⁹ Sakurai, H.; Ebata, K.; Kabuto, C.; Nakadaira, Y. *Chem. Lett.* **1987**, 301.

diene (**151**),⁵⁴⁰ cubene (**152**),⁵⁴¹ and homocub-4(5)-ene (**153**).⁵⁴² In these molecules, the four groups on the

**148****149****150**

double bond are all forced to be on one side of the double-bond plane.⁵⁴³ In **151**, the angle between the line C1–C2 (extended) and the plane defined by C2, C3, and C11 is 27°. An additional source of strain in this molecule is the fact that the two double bonds are pushed into close proximity by the four bridges. In an effort to alleviate this sort of strain, the bridge bond distances (C-3—C-4) are 1.595 Å, which is considerably longer than the 1.53 Å expected for a normal sp^3 – sp^3 C—C bond (Table 1.5). Compounds **152** and **153** have *not* been isolated, but have been generated as intermediates that were trapped by reaction with other compounds.^{541,542}

**151****152****153**

⁵⁴⁰ Wiberg, K.B.; Matturo, M.G.; Okarma, P.J.; Jason, M.E. *J. Am. Chem. Soc.* **1984**, *106*, 2194; Wiberg, K.B.; Adams, R.D.; Okarma, P.J.; Matturo, M.G.; Segmuller, B. *J. Am. Chem. Soc.* **1984**, *106*, 2200.

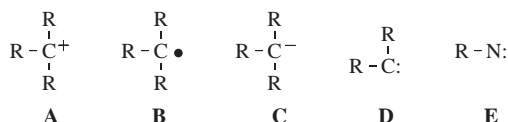
⁵⁴¹ Eaton, P.E.; Maggini, M. *J. Am. Chem. Soc.* **1988**, *110*, 7230.

⁵⁴² Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* **1988**, *110*, 7229.

⁵⁴³ For a review of such molecules, see Borden, W.T. *Chem. Rev.* **1989**, *89*, 1095. See also, Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* **1988**, *110*, 4710.

Carbocations, Carbanions, Free Radicals, Carbenes, and Nitrenes

There are four types of organic species in which a carbon atom has a valence of only 2 or 3.¹ They are usually very short-lived, and most exist only as intermediates that are quickly converted to more stable molecules. However, some are more stable than others and fairly stable examples have been prepared for three of the four types. The four types of species are *carbocations (A)*, *carbon radicals (B)*, *carbanions (C)*, and *carbenes (D)*. Of the four, only carbanions have a complete octet around the carbon. There are many other organic ions and radicals with charges and unpaired electrons on atoms other than carbon, but only *nitrenes (E)*, the nitrogen analogues of carbenes, will be discussed. Each of these five types is discussed in a separate section, which in each case includes brief summaries of the ways in which the species form and react. These summaries are short and schematic. The generation and fate of the five types are more fully treated for the appropriate specific reactions in Part II.



5.A. CARBOCATIONS²

5.A.i. Nomenclature

First, the nomenclature of carbocations (A) is discussed. For many years, these species were called “carbonium ions,” although it was suggested³ as long ago as 1902 that this was

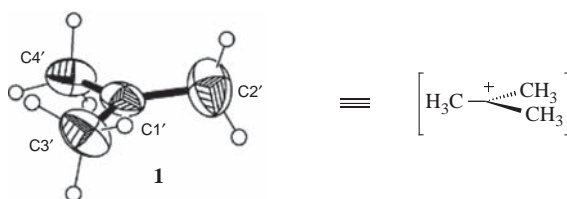
¹ For general references, see Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, **1974**; McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, **1973**. Two serial publications devoted to review articles on this subject are *Reactive Intermediates (Wiley)* and *Reactive Intermediates (Plenum)*.

² See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, 5 Vols., Wiley, NY, **1968–1976**; Vogel, P. *Carbocation Chemistry*, Elsevier, NY, **1985**. See Saunders, M.; Jiménez-Vázquez, H.A. *Chem. Rev.* **1991**, *91*, 375; Arnett, E.M.; Hofelich, T.C.; Schriver, G.W. *React. Intermed. (Wiley)* **1987**, *3*, 189. For reviews of dicarbocations, see Lammertsma, K.; Schleyer, P.v.R.; Schwarz, H. *Angew. Chem. Int. Ed.* **1989**, *28*, 1321. See also, the series *Advances in Carbocation Chemistry*.

³ Gomberg, M. *Ber.* **1902**, *35*, 2397.

inappropriate because “-onium” usually refers to a covalency higher than that of the neutral atom. Nevertheless, the name “carbonium ion” was well established and created few problems⁴ until some years ago, when Olah and co-workers^{2,5} found evidence for another type of intermediate in which there is a positive charge at a carbon atom, but in which the formal covalency of the carbon atom is five rather than three. The simplest example is the methanonium ion (CH_5^+ ; see Reaction 12-01). Olah⁵ proposed that the name “carbonium ion” be henceforth reserved for pentacoordinated positive ions, and that **A** be called a “carbenium ions.” He also proposed the term “carbocation” to encompass both types. IUPAC has accepted these definitions.⁶ For the most part, intermediates such as **A** are called *carbenium ions* or *carbocations*, but the latter term will be used more often in this book.

5.A.ii. Stability and Structure of Carbocations



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Carbocations are intermediates in several kinds of reactions.⁷ The more stable ones have been prepared in solution and in some cases even as solid salts. X-ray crystallographic structures also have been obtained in some cases.⁸ The X-ray of the *tert*-butyl cation complexed with dichloromethane was reported,⁹ for example, and is presented as **1** with the solvent molecules removed for clarity. The IR spectrum of the *tert*-butyl cation has been recorded in the gas phase.¹⁰ An isolable dioxo-stabilized pentadienylium ion was isolated and its structure was determined by ¹H NMR, ¹³C NMR, mass spectrometry, and IR.¹¹ A β-fluoro substituted 4-methoxyphenethyl cation has been observed directly by laser flash photolysis.¹² In solution, the carbocation may be free (this is more likely in polar solvents,

⁴ For a history of the term “carbonium ion”, see Traynham, J.G. *J. Chem. Educ.* **1986**, 63, 930.

⁵ Olah, G.A. *CHEMTECH* **1971**, 1, 566; *J. Am. Chem. Soc.* **1972**, 94, 808.

⁶ Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *Compendium of Chemical Terminology, IUPAC Recommendations*, Blackwell Scientific Publications, Oxford, **1987**.

⁷ Olah, G.A. *J. Org. Chem.* **2001**, 66, 5943. See Olah, G.A.; Prakash, G.K.S. (Eds.), *Carbocation Chemistry*, Wiley Interscience, Hoboken, NJ, **2004**.

⁸ See Laube, T. *J. Am. Chem.* **2004**, 126, 10904 and references therein. For the X-ray of a vinyl carbocation see Müller, T.; Juhasz, M.; Reed, C.A. *Angew. Chem. Int. Ed.* **2004**, 43, 1543.

⁹ Kato, T.; Reed, C.A. *Angew. Chem. Int. Ed.* **2004**, 43, 2908.

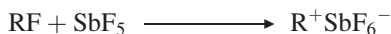
¹⁰ Douberly, G.E.; Ricks, A.M.; Ticknor, B.W.; Schleyer, P.v.R.; Duncan, M.A. *J. Am. Chem. Soc.* **2007**, 129, 13782.

¹¹ Lüning, U.; Baumstark, R. *Tetrahedron Lett.* **1993**, 34, 5059.

¹² McClelland, R.A.; Cozens, F.L.; Steenken, S.; Amyes, T.L.; Richard, J.P. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1717.

in which it is solvated) or it may exist as an ion pair,¹³ which means that it is closely associated with a negative ion, called a *counterion* or *gegenion*. Ion pairs are more likely in nonpolar solvents.

Among simple alkyl carbocations,¹⁴ the order of stability is tertiary > secondary > primary. There are many known examples of rearrangements of primary or secondary carbocations to tertiary, both in solution and in the gas phase (see Sec. 18.A.ii). Since simple alkyl cations are unstable in ordinary strong-acid solutions (e.g., H₂SO₄), the study of these species was greatly facilitated by the discovery that many of them could be kept indefinitely as stable solutions in mixtures of fluorosulfuric acid and antimony pentafluoride. Such mixtures, usually dissolved in SO₂ or SO₂ClF, are among the strongest acidic solutions known and are often called *superacids*.¹⁵ The original experiments involved the addition of alkyl fluorides to SbF₅.¹⁶



Subsequently, it was found that the same carbocations could also be generated from alcohols in superacid-SO₂ at -60 °C¹⁷ and from alkenes by the addition of a proton from superacid or HF-SbF₅ in SO₂ or SO₂ClF at low temperatures.¹⁸ Even alkanes give carbocations in superacid by loss of H⁻. For example,¹⁹ 2-methylpropane gives the *tert*-butyl cation.



No matter how they are generated, study of the simple alkyl carbocations has provided dramatic evidence for the stability order.²⁰ Both propyl fluorides gave the isopropyl cation; all four butyl fluorides²¹ gave the *tert*-butyl cation, and all seven of the pentyl fluorides examined gave the *tert*-pentyl cation. *n*-Butane, in superacid, gave only the *tert*-butyl cation. To date, no primary cation has survived long enough for detection. Neither methyl nor ethyl fluoride gave the corresponding carbocations when treated with SbF₅. At low temperatures, methyl fluoride gave chiefly the methylated sulfur dioxide salt [(CH₃OSO)⁺SbF₆]⁻,²² while ethyl fluoride rapidly formed the *tert*-butyl and *tert*-hexyl cations by addition of the initially formed ethyl cation to ethylene molecules also formed.²³ At room temperature, methyl fluoride also gave the *tert*-butyl cation.²⁴ In accord with the

¹³ For a treatise, see Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, 2 Vols., Wiley, NY, **1972–1974**.

¹⁴ For a review, see Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1969**, pp. 715–782. Also see, Farcasiu, D.; Norton, S.H. *J. Org. Chem.* **1997**, 62, 5374.

¹⁵ See Olah, G.A.; Prakash, G.K.S.; Sommer, J. in *Superacids*, Wiley, NY, **1985**, pp. 65–175.

¹⁶ Olah, G.A.; Baker, E.B.; Evans, J.C.; Tolgyesi, W.S.; McIntyre, J.S.; Bastien, I.J. *J. Am. Chem. Soc.* **1964**, 86, 1360; Kramer, G.M. *J. Am. Chem. Soc.* **1969**, 91, 4819.

¹⁷ Olah, G.A.; Sommer, J.; Namanworth, E. *J. Am. Chem. Soc.* **1967**, 89, 3576.

¹⁸ Olah, G.A.; Halpern, Y. *J. Org. Chem.* **1971**, 36, 2354. See also, Herlem, M. *Pure Appl. Chem.* **1977**, 49, 107.

¹⁹ Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* **1967**, 89, 4739.

²⁰ See Amyes, T.L.; Stevens, I.W.; Richard, J.P. *J. Org. Chem.* **1993**, 58, 6057 for a recent study.

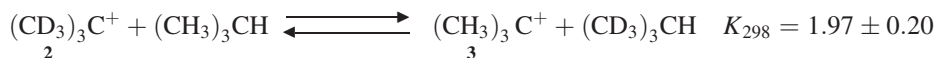
²¹ See Saunders, M.; Hagen, E.L.; Rosenfeld, J. *J. Am. Chem. Soc.* **1968**, 90, 6882; Saunders, M.; Cox, D.; Lloyd, J.R. *J. Am. Chem. Soc.* **1979**, 101, 6656; Myhre, P.C.; Yannoni, C.S. *J. Am. Chem. Soc.* **1981**, 103, 230.

²² Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* **1978**, 100, 5163.

²³ Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1969**, p. 722.

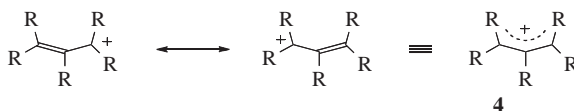
²⁴ Bacon, J.; Gillespie, R.J. *J. Am. Chem. Soc.* **1971**, 91, 6914.

stability order, hydride ion is abstracted from alkanes by superacid most readily from tertiary and least readily from primary positions.



The stability order can be explained by the polar effect and by hyperconjugation (Sec. 2.M). In the polar effect, nonconjugated substituents exert an influence on stability through bonds (inductive effect) or through space (field effect). Since a tertiary carbocation has more carbon substituents on the positively charged carbon, relative to a primary, there is a greater polar effect that leads to great stability. In the hyperconjugation explanation,²⁵ a primary carbocation is compared with a tertiary, and “*the hyperconjugation concept arises from model-building procedures* (see Sec. 2.M). In general, this means that the model must be corrected by including some delocalization in order to get a good enough description.”²⁶ Evidence used to support the hyperconjugation explanation is that the equilibrium constant for this reaction involving **2** and **3** is 1.97, showing that **3** is more stable than **2**.²⁷ Due to a β secondary isotope effect, there is less hyperconjugation in **2** than in **3** (see Sec. 6.J.V.ii for isotope effects).²⁸ The field effect explanation is that the electron-donating effect of alkyl groups increases the electron density at the charge-bearing carbon, reducing the net charge on the carbon, and in effect spreading the charge over the α carbons. It is a general rule that the more concentrated any charge is, the less stable the species bearing it will be. There are several structural types of delocalization, as summarized in Table 5.1.²⁹

The most stable of the simple alkyl cations is the *tert*-butyl cation. Even the relatively stable *tert*-pentyl and *tert*-hexyl cations fragment at higher temperatures to produce the *tert*-butyl cation, as do all other alkyl cations with four or more carbons to date studied.³⁰ Methane,³¹ ethane, and propane, in superacid, also yield *tert*-butyl cations as the main product (see Reaction 12-20). Even paraffin wax and polyethylene give a *tert*-butyl cation. Solid salts of *tert*-butyl and *tert*-pentyl cations, [e.g., $\text{Me}_3\text{C}^+ \text{SbF}_6^-$], have been prepared from superacid solutions and are stable below -20°C .³²



²⁵ See Radom, L.; Poppinger, D.; Haddon, R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, **1976**, pp. 2303–2426.

²⁶ Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., HarperCollins, NY, **1987**, p. 68.

²⁷ Meot-Ner, M. *J. Am. Chem. Soc.* **1987**, 109, 7947.

²⁸ If only the field effect were operating, **2** would be more stable than **3**, since deuterium is electron-donating with respect to hydrogen (Sec. 1.J), assuming that the field effect of deuterium could be felt two bonds away.

²⁹ Lambert, J.B.; Ciro, S.M. *J. Org. Chem.* **1996**, 61, 1940.

³⁰ Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* **1967**, 89, 4739; Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1969**, pp. 750–764.

³¹ Olah, G.A.; Klopman, G.; Schlosberg, R.H. *J. Am. Chem. Soc.* **1969**, 91, 3261. See also, Hogeveen, H.; Gaasbeek, C.J. *Recl. Trav. Chim. Pays-Bas* **1968**, 87, 319.

³² Olah, G.A.; Svoboda, J.J.; Ku, A.T. *Synthesis* **1973**, 492; Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* **1967**, 89, 4739.

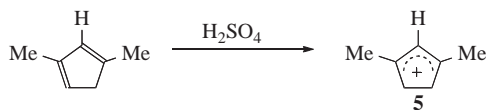
TABLE 5.1 Structural Types of Delocalization^a

Valence Structures	Abbreviation	Name
	$\pi\pi$	Simple conjugation
	$\sigma\pi$	Hyperconjugation
	$\pi\sigma$	Homoconjugation
	$\sigma\sigma$	Homohyperconjugation
	$\sigma\pi/\pi\pi$	Hyperconjugation/ conjugation
	$\sigma\pi/\sigma\pi$	Double hyperconjugation

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^aSee Ref. 25.

In carbocations, where the positive carbon is in conjugation with a double bond, as in allylic cations (the allyl cation is **4**, R = H), the stability is greater because of increased delocalization due to resonance³³ where the positive charge is spread over several atoms instead of being concentrated on one (see the molecular orbital picture of **4** in Sec. 2.C, category 2). Each of the terminal atoms in **4** has a charge of $\frac{1}{2}$ (the charge is exactly $\frac{1}{2}$ if all of the R groups are the same). Stable cyclic and acyclic allylic-type carbocations³⁴ have been prepared by dissolving conjugated dienes in concentrated sulfuric acid; the cyclopentadienyl cation, (**5**) is an example.³⁵



Stable allylic carbocations have also been obtained by the reaction between alkyl halides, alcohols, or alkenes (by hydride extraction) and SbF₅ in SO₂ or SO₂ClF.³⁶ Bis(allylic) cations³⁷ are more stable than the simple allylic type, and some of these have been prepared in concentrated sulfuric acid.³⁸ Arenium ions (Sec. 11.A.i) are

³³ See Barbour, J.B.; Karty, J.M. *J. Org. Chem.* **2004**, 69, 648; Mo, Y. *J. Org. Chem.* **2004**, 69, 5563 and references cited therein.

³⁴ For reviews, see Deno, N.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2 Wiley, NY, **1970**, pp. 783–806; Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, **1970**, pp. 39–114.

³⁵ Deno, N.C.; Richey, Jr., H.G.; Friedman, N.; Hodge, J.D.; Houser, J.J.; Pittman, Jr., C.U. *J. Am. Chem. Soc.* **1963**, 85, 2991.

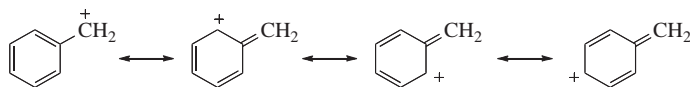
³⁶ Olah, G.A.; Spear, R.J. *J. Am. Chem. Soc.* **1975**, 97, 1539 and references cited therein.

³⁷ For a review of divinylmethyl and trivinylmethyl cations, see Sorensen, T.S. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, pp. 807–835.

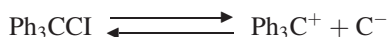
³⁸ Deno, N.C.; Pittman, Jr., C.U. *J. Am. Chem. Soc.* **1964**, 86, 1871.

familiar examples of this type. Propargyl cations ($\text{RC}\equiv\text{CC}^+\text{R}_2$) have also been prepared.³⁹

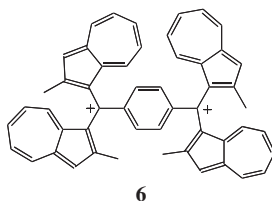
Canonical forms can be drawn for benzylic carbocations, as shown,⁴⁰ and they are similar to those shown above for allylic cations.



A number of benzylic carbocations have been obtained in solution as SbF_6^- salts.⁴¹ Diarylmethyl and triarylmethyl cations are even more stable because more canonical forms are possible (i.e., there is more extensive delocalization, hence greater stability). Chlorotriphenylmethane ionizes in polar solvents to give the stable triphenylmethyl cation (trityl cation, see **18**), for example, because the solvent does not react with the ion,



whereas water does react with the ion. In liquid SO_2 , for example, the ion remains stable for many years. Both triphenylmethyl and diphenylmethyl cations have been isolated as solid salts.⁴² In fact, $\text{Ph}_3\text{C}^+ \text{BF}_4^-$ and related salts are available commercially. Arylmethyl cations are further stabilized if they have electron-donating substituents in ortho or para positions.⁴³ Dications⁴⁴ and trications are also possible, including the particularly stable dication (**6**), where each positively charged benzylic carbon is stabilized by two azulene rings.⁴⁵ A related trication is known where two azulene rings stabilize each benzylic cationic center.⁴⁶



Cyclopropylmethyl carbocations⁴⁷ are even more stable than benzylic carbocations. Carbocations **7**, **8**, and similar ions have been prepared by dissolution of the alcohols in $\text{FSO}_3\text{H}-\text{SO}_2-\text{SbF}_5$,⁴⁸ and **9** has been prepared from the corresponding alcohol in

³⁹ Olah, G.A.; Spear, R.J.; Westerman, P.W.; Denis, J. *J. Am. Chem. Soc.* **1974**, *96*, 5855.

⁴⁰ For a review of benzylic, diarylmethyl, and triarylmethyl cations, see Freedman, H.H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, **1971**, pp. 1501–1578.

⁴¹ Olah, G.A.; Porter, R.D.; Jeuell, C.L.; White, A.M. *J. Am. Chem. Soc.* **1972**, *94*, 2044.

⁴² Volz, H.; Schnell, H.W. *Angew. Chem. Int. Ed.* **1965**, *4*, 873.

⁴³ Deno, N.C.; Schriesheim, A. *J. Am. Chem. Soc.* **1955**, *77*, 3051.

⁴⁴ Prakash, G.K.S. *Pure Appl. Chem.* **1998**, *70*, 2001.

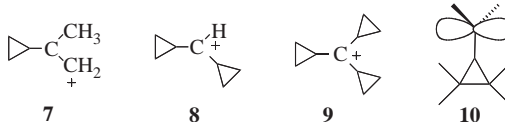
⁴⁵ Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* **1992**, *33*, 3773.

⁴⁶ Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* **1994**, *35*, 751.

⁴⁷ For reviews, see in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, **1972**; Richey, Jr., H.G. pp. 1201–294; Wiberg, K.B.; Hess, Jr., B.A.; Ashe, III, A.H. pp. 1295–1345.

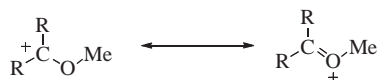
⁴⁸ Pittman, Jr., C.U.; Olah, G.A. *J. Am. Chem. Soc.* **1965**, *87*, 2998; Deno, N.C.; Liu, J.S.; Turner, J.O.; Lincoln, D.N.; Fruit, Jr., R.E. *J. Am. Chem. Soc.* **1965**, *87*, 3000.

96% H_2SO_4 .⁴⁹ This special stability, which increases with each additional cyclopropyl group, is



a result of conjugation between the bent orbitals of the cyclopropyl rings (Sec. 4.Q.i) and the vacant p orbital of the cationic carbon (see **10**). Nuclear magnetic resonance and other studies have shown that the vacant p orbital lies parallel to the C-2—C-3 bond of the cyclopropane ring and not perpendicular to it.⁵⁰ In this respect, the geometry is similar to that of a cyclopropane ring conjugated with a double bond (Sec. 4.Q.i). Cyclopropylmethyl cations are further discussed in Section 10.C.i, category 4. The stabilizing effect just discussed is unique to cyclopropyl groups. Cyclobutyl and larger cyclic groups are about as effective at stabilizing a carbocation as ordinary alkyl groups.⁵¹

Another structural feature that increases carbocation stability is the presence, adjacent to the cationic center, of a heteroatom bearing an unshared pair⁵² (e.g., oxygen,⁵³ nitrogen,⁵⁴ or halogen).⁵⁵ Such ions are stabilized by resonance, as with the oxocarbenium ion ($\text{R}_2\text{C}=\text{O}^+\text{Me}$).



This methoxymethyl cation can be obtained as a stable solid, $\text{MeOCH}_2^+ \text{SbF}_6^-$.⁵⁶ Carbocations containing either α , β , or γ silicon atom are also stabilized,⁵⁷ relative to similar ions without the silicon atom. γ -Silyl cyclobutylcarbocations are known.⁵⁸ In superacid solution, ions [e.g., CX_3^+ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$)] have been prepared.⁵⁹ Vinyl-stabilized halonium ions are also known.⁶⁰

⁴⁹ Deno, N.C.; Richey, Jr., H.G.; Liu, J.S.; Hodge, J.D.; Houser, H.J.; Wisotsky, M.J. *J. Am. Chem. Soc.* **1962**, *84*, 2016.

⁵⁰ See Poulter, C.D.; Spillner, C.J. *J. Am. Chem. Soc.* **1974**, *96*, 7591; Childs, R.F.; Kostyk, M.D.; Lock, C.J.L.; Mahendran, M. *J. Am. Chem. Soc.* **1990**, *112*, 8912.

⁵¹ Sorensen, T.S.; Miller, I.J.; Ranganayakulu, K. *Aust. J. Chem.* **1973**, *26*, 311.

⁵² See Hevesi, L. *Bull. Soc. Chim. Fr.* **1990**, 697; Olah, G.A.; Liang, G.; Mo, Y.M. *J. Org. Chem.* **1974**, *39*, 2394; Borch, R.F. *J. Am. Chem. Soc.* **1968**, *90*, 5303; Rabinovitz, M.; Bruck, D. *Tetrahedron Lett.* **1971**, 245.

⁵³ For a review of ions of the form $\text{R}_2\text{C}^+-\text{OR}'$, see Rakhmankulov, D.L.; Akhmatdinov, R.T.; Kantor, E.A. *Russ. Chem. Rev.* **1984**, *53*, 888. For a review of ions of the form $\text{R}'\text{C}^+(\text{OR})_2$ and $\text{C}^+(\text{OR})_3$, see Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* **1987**, *16*, 75.

⁵⁴ For a review of such ions where nitrogen is the heteroatom, see Scott, F.L.; Butler, R.N. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, **1974**, pp. 1643–1696.

⁵⁵ See Allen, A.D.; Tidwell, T.T. *Adv. Carbocation Chem.* **1989**, *1*, 1. See also, Teberekidis, V.I.; Sigalas, M.P. *Tetrahedron* **2003**, *59*, 4749.

⁵⁶ Olah, G.A.; Svoboda, J.J. *Synthesis* **1973**, 52.

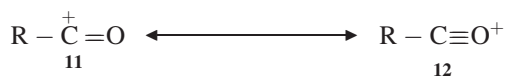
⁵⁷ See Lambert, J.B. *Tetrahedron* **1990**, *46*, 2677; Lambert, J.B.; Zhao, Y.; Emblidge, R.W.; Salvador, L.A.; Liu, X.; So, J.-H.; Chelius, E.C. *Acc. Chem. Res.* **1999**, *32*, 183. See also, Lambert, J.B.; Chelius, E.C. *J. Am. Chem. Soc.* **1990**, *112*, 8120.

⁵⁸ Creary, X.; Kochly, E.D. *J. Org. Chem.* **2009**, *74*, 9044.

⁵⁹ Olah, G.A.; Heiliger, L.; Prakash, G.K.S. *J. Am. Chem. Soc.* **1989**, *111*, 8020.

⁶⁰ Haubenstock, H.; Sauer, R.R. *Tetrahedron* **2004**, *60*, 1191.

Simple acyl cations (RCO^+) have been prepared⁶¹ in solution and the solid state.⁶² The acetyl cation (CH_3CO^+) is about as stable as the *tert*-butyl cation (see Table 5.1). The 2,4,6-trimethylbenzoyl and 2,3,4,5,6-pentamethylbenzoyl cations are especially stable (for steric reasons) and are easily formed in 96% H_2SO_4 .⁶³ These ions, often referred to as *acylium ions*, are stabilized by a canonical form containing a triple bond (**12**), although the positive charge is principally located on the carbon,⁶⁴ so that **11** contributes more than **12**.



The stabilities of many other stable carbocations can also be attributed to resonance. Among these are the tropylium, cyclopropenium,⁶⁵ and other aromatic cations discussed in Chapter 2. Where resonance stability is completely lacking, as in the phenyl (C_6H_5^+) or vinyl cations,⁶⁶ the ion, if formed at all, is usually very short lived.⁶⁷ Neither a vinyl⁶⁸ nor a phenyl cation has as yet been prepared as a stable species in solution.⁶⁹ However, stable alkenyl carbocations have been generated on Zeolite Y,⁷⁰ and the phenyl cation has been observed in cryogenic argon matrices.⁷¹

Various quantitative methods have been developed to express the relative stabilities of carbocations.⁷² One of the most common of these, although useful only for relatively stable carbocations that are formed by ionization of alcohols in acidic solutions, is based on the equation⁷³

$$H_{\text{R}} = \text{p}K_{\text{R}^+} - \log \frac{C_{\text{R}^+}}{C_{\text{ROH}}}$$

⁶¹ see Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* **1990**, 22, 1; Olah, G.A.; Germain, A.; White, A.M. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, **1976**, pp. 2049–2133; Lindner, E. *Angew. Chem. Int. Ed.* **1970**, 9, 114.

⁶² See Olah, G.A.; Dunne, K.; Mo, Y.K.; Szilagy, P. *J. Am. Chem. Soc.* **1972**, 94, 4200; Olah, G.A.; Svoboda, J.J. *Synthesis* **1972**, 306.

⁶³ Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* **1933**, 55, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* **1951**, 73, 3651.

⁶⁴ Boer, F.P. *J. Am. Chem. Soc.* **1968**, 90, 6706; Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B*, **1972**, 1430. See also, Olah, G.A.; Westerman, P.W. *J. Am. Chem. Soc.* **1973**, 95, 3706.

⁶⁵ See Komatsu, K.; Kitagawa, T. *Chem. Rev.* **2003**, 103, 1371. Also see, Gilbertson, R.D.; Weakley, T.J.R.; Haley, M.M. *J. Org. Chem.* **2000**, 65, 1422.

⁶⁶ See Gronheid, R.; Lodder, G.; Okuyama, T. *J. Org. Chem.* **2002**, 67, 693. For a discussion of aryl substituted vinyl cations, see Müller, T.; Margraf, D.; Syha, Y. *J. Am. Chem. Soc.* **2005**, 127, 10852.

⁶⁷ For a review of destabilized carbocations, see Tidwell, T.T. *Angew. Chem. Int. Ed.* **1984**, 23, 20.

⁶⁸ See Abram, T.S.; Watts, W.E. *J. Chem. Soc. Chem. Commun.*, **1974**, 857; Siehl, H.; Carnahan, Jr., J.C.; Eckes, L.; Hanack, M. *Angew. Chem. Int. Ed.* **1974**, 13, 675. Also see Franke, W.; Schwarz, H.; Stahl, D. *J. Org. Chem.* **1980**, 45, 3493. See also, Siehl, H.; Koch, E. *J. Org. Chem.* **1984**, 49, 575.

⁶⁹ See Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979; Hanack, M. *Pure Appl. Chem.* **1984**, 56, 1819, *Acc. Chem. Res.* **1976**, 9, 364; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* **1979**, 8, 353; Richey, Jr., H.G.; Richey, J.M. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, pp. 899–957; Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, **1970**, pp. 42–49; Stang, P.J. *Prog. Phys. Org. Chem.* **1973**, 10, 205. See also, Charton, M. *Mol. Struct. Energ.* **1987**, 4, 271. For a computational study, see Glaser, R.; Horan, C. J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* **1999**, 64, 902.

⁷⁰ Yang, S.; Kondo, J.N.; Domen, K. *Chem. Commun.* **2001**, 2008.

⁷¹ Winkler, M.; Sander, W. *J. Org. Chem.* **2006**, 71, 6357.

⁷² For reviews, see Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* **1987**, 7, 313; Bethell, D.; Gold, V. *Carbonium Ions*, Academic Press, NY, **1967**, pp. 59–87.

⁷³ Deno, N.C.; Berkheimer, H.E.; Evans, W.L.; Peterson, H.J. *J. Am. Chem. Soc.* **1959**, 81, 2344.

TABLE 5.2 $R-H \rightarrow R^+ + H^-$ Dissociation Energies in the Gas Phase

Ion	$D(R^+ - H^-)$		Reference
	kcal mol ⁻¹	kJ mol ⁻¹	
CH₃⁺	314.6	1316	76
C₂H₅⁺	276.7	1158	76
(CH₃)₂CH⁺	249.2	1043	76
(CH₃)₃C⁺	231.9	970.3	76
C₆H₅⁺	294	1230	77
H₂C=CH⁺	287	1200	77,78
H₂C=CH—CH₂⁺	256	1070	77
Cyclopentyl	246	1030	77
C₆H₅CH₂⁺	238	996	77
CH₃CHO	230	962	77

pK_{R^+} is the pK value for the reaction $R^+ + 2 H_2O \rightleftharpoons ROH + H_3O^+$ and is a measure of the stability of the carbocation. The H_R parameter is an easily obtainable measurement of the stability of a solvent (Sec. 8.C) and approaches pH at low concentrations of acid. In order to obtain pK_{R^+} , for a cation R^+ , one dissolves the alcohol ROH in an acidic solution of known H_R . Then, the concentration of R^+ and ROH are obtained, generally from spectra, and pK_{R^+} is easily calculated.⁷⁴ A measure of carbocation stability that applies to less stable ions is the dissociation energy [$D(R^+ - H^-)$] for the cleavage reaction $R-H \rightarrow R^+ + H^-$, which can be obtained from PES (Sec. 1.E) and other measurements. Some values of $D(R^+ - H^-)$ are shown in Table 5.2.⁷⁵⁻⁷⁸ Within a given class of ion, (primary, secondary, allylic, aryl, etc.), $D(R^+ - H^-)$ has been shown to be a linear function of the logarithm of the number of atoms in R^+ , with larger ions being more stable.⁷⁷

Since the central carbon of tricoordinated carbocations has only three bonds and no other valence electrons, the bonds are sp^2 and should be planar.⁷⁹ Raman, IR, and NMR spectroscopic data on simple alkyl cations show this to be so.⁸⁰ In methylcyclohexyl cations, there are two chair conformations where the carbon bearing the positive charge is planar (**13** and **14**), and there is evidence that **14** is more stable due to a difference in

⁷⁴ For a list of stabilities of 39 typical carbocations, see Arnett, E.M.; Hofelich, T.C. *J. Am. Chem. Soc.* **1983**, *105*, 2889. See also, Schade, C.; Mayr, H.; Arnett, E.M. *J. Am. Chem. Soc.* **1988**, *110*, 567; Schade, C.; Mayr, H. *Tetrahedron* **1988**, *44*, 5761.

⁷⁵ Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* **1933**, *55*, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* **1951**, *73*, 3651; Boer, F.P. *J. Am. Chem. Soc.* **1968**, *90*, 6706; Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B*, **1972**, 1430. See also, Arnett, E.M.; Petro, C. *J. Am. Chem. Soc.* **1978**, *100*, 5408; Arnett, E.M.; Pienta, N.J. *J. Am. Chem. Soc.* **1980**, *102*, 3329.

⁷⁶ Schultz, J.C.; Houle, F.A.; Beauchamp, J.L. *J. Am. Chem. Soc.* **1984**, *106*, 3917.

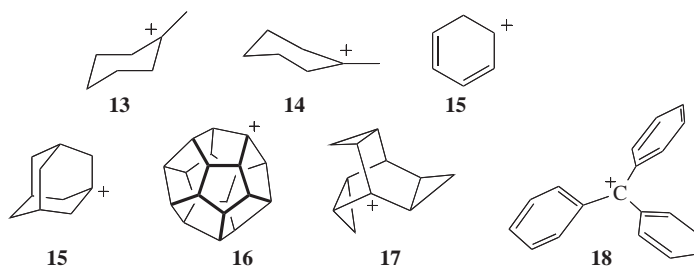
⁷⁷ Lossing, F.P.; Holmes, J.L. *J. Am. Chem. Soc.* **1984**, *106*, 6917.

⁷⁸ Vinyl cations are generated by photolysis of vinyl iodonium salts. See Slegt, M.; Gronheid, R.; van der Vlugt, D.; Ochiai, M.; Okuyama, T.; Zuilhof, H.; Overkleeft, H.S.; Lodder, G. *J. Org. Chem.* **2006**, *71*, 2227.

⁷⁹ See Schleyer, P.v.R. in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, **1971**, p. 241; Hehre, W. *J. Acc. Chem. Res.* **1975**, *8*, 369; Freedman, H.H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, **1974**, pp. 1561-574.

⁸⁰ Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* **1971**, *93*, 459; Yannoni, C.S.; Kendrick, R.D.; Myhre, P.C.; Bebout, D.C.; Petersen, B.L. *J. Am. Chem. Soc.* **1989**, *111*, 6440.

hyperconjugation.⁸¹ Arenonium ions (**15**) are also known, and are relatively stable.⁸² Other evidence is that carbocations are difficult to form at bridgehead atoms in [2.2.1] systems,⁸³ where they cannot be planar (see Sec. 10.A.ii).⁸⁴ Bridgehead carbocations are known, however, as in [2.1.1]hexanes⁸⁵ and cubyl carbocations.⁸⁶ However, larger bridgehead ions can exist. For example, the adamantyl cation (**15**) has been synthesized, as the SF_6^- salt.⁸⁷ The relative stability of 1-adamantyl cations is influenced by the number and nature of substituents. For example, the stability of the 1-adamantyl cation increases with the number of isopropyl substituents at C-3, C-5, and C-7.⁸⁸ Among other bridgehead carbocations that have been prepared in superacid solution at -78°C are the dodecahydryl cation (**16**)⁸⁹ and the 1-trishomobarrellyl cation (**17**).⁹⁰ In the latter case, the instability of the bridgehead position is balanced by the extra stability gained from the conjugation with the three cyclopropyl groups.



Triarylmethyl cations (e.g., the triphenylmethyl carbocation, **18**),⁹¹ are propeller-shaped, although the central carbon and the three ring carbons connected to it are in a plane.⁹² The three benzene rings cannot be all in the same plane due to steric hindrance, although increased resonance energy would be gained if they could.

An important tool for the investigation of carbocation structure is measurement of the ^{13}C NMR chemical shift of the carbon atom bearing the positive charge.⁹³ This shift approximately correlates with electron density on the carbon. The ^{13}C chemical shifts for a

⁸¹ Rauk, A.; Sorensen, T.S.; Maerker, C.; de M. Carneiro, J.W.; Sieber, S.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1996**, *118*, 3761.

⁸² Lawlor, D.A.; More O'Ferrall, R.A.; Rao, S.N. *J. Am. Chem. Soc.* **2008**, *130*, 17997.

⁸³ For a review of bridgehead carbocations, see Fort, Jr., R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, **1974**, pp. 1783–1835.

⁸⁴ Della, E.W.; Schiesser, C.H. *J. Chem. Soc. Chem. Commun.* **1994**, 417.

⁸⁵ Åhman, J.; Somfai, P.; Tanner, D. *J. Chem. Soc. Chem. Commun.* **1994**, 2785.

⁸⁶ Della, E.W.; Head, N.J.; Janowski, W.K.; Schiesser, C.H. *J. Org. Chem.* **1993**, *58*, 7876.

⁸⁷ Olah, G.A.; Prakash, G.K.S.; Shih, J.G.; Krishnamurthy, V.V.; Mateescu, G.D.; Liang, G.; Sipos, G.; Buss, V.; Gund, T.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1985**, *107*, 2764. See also, Kruppa, G.H.; Beauchamp, J.L. *J. Am. Chem. Soc.* **1986**, *108*, 2162; Laube, T. *Angew. Chem. Int. Ed.* **1986**, *25*, 349.

⁸⁸ Takeuchi, K.; Okazaki, T.; Kitagawa, T.; Ushino, T.; Ueda, K.; Endo, T.; Notario, R. *J. Org. Chem.* **2001**, *66*, 2034.

⁸⁹ Olah, G.A.; Prakash, G.K.S.; Fessner, W.; Kobayashi, T.; Paquette, L.A. *J. Am. Chem. Soc.* **1988**, *110*, 8599.

⁹⁰ de Meijere, A.; Schallner, O. *Angew. Chem. Int. Ed.* **1973**, *12*, 399.

⁹¹ See Sundaralingam, M.; Chwang, A.K. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, **1976**, pp. 2427–2476.

⁹² Schuster, I.I.; Colter, A.K.; Kurland, R.J. *J. Am. Chem. Soc.* **1968**, *90*, 4679.

⁹³ For reviews of the NMR spectra of carbocations, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.*, **1979**, *12*, 261; Farnum, D.G. *Adv. Phys. Org. Chem.* **1975**, *11*, 123.

TABLE 5.3 The ^{13}C NMR Chemical-Shift Values, in Parts per Million from $^{13}\text{CS}_2$, for the Charged Carbon Atom of Some Carbocations in $\text{SO}_2\text{ClF}-\text{SbF}_5$, $\text{SO}_2-\text{FSO}_3\text{H}-\text{SbF}_6$, or $\text{SO}_2-\text{SbF}_5^a$

Ion	Chemical Shift	Temperature ($^{\circ}\text{C}$)	Ion	Chemical Shift	Temperature ($^{\circ}\text{C}$)
Et_2MeC^+	-139.4	-20	$\text{C}(\text{OH})_3^+$	+28.0	-50
Me_2EtC^+	-139.2	-60	PhMe_2C^+	-61.1	-60
Me_3C^+	-135.4	-20	PhMeCH^+	-40 ⁹¹	
Me_2CH^+	-125.0	-20	Ph_2CH^+	-5.6	-60
Me_2COH^+	-55.7	-50	Ph_3C^+	-18.1	-60
$\text{MeC}(\text{OH})_2^+$	-1.6	-30	$\text{Me}_2(\text{cyclopropyl})\text{C}^+$	-86.8	-60
$\text{HC}(\text{OH})_2^+$	+17.0	-30			

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^aSee Ref. 94.

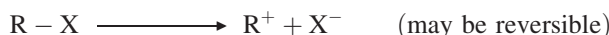
number of ions are given in Table 5.3.⁹⁴ As shown in Table 5.3, the substitution of an ethyl for a methyl or a methyl for a hydrogen atom causes a downfield shift, indicating that the central carbon becomes somewhat more positive. On the other hand, the presence of hydroxy or phenyl groups decreases the positive character of the central carbon. The ^{13}C chemical shifts are not always in exact order of carbocation stabilities, as determined in other ways. Thus the chemical shift shows that the triphenylmethyl cation has a more positive central carbon than diphenylmethyl cation, although the former is more stable. Also, the 2-cyclopropylpropyl and 2-phenylpropyl cations have shifts of -86.8 and -61.1, respectively, although we have seen that according to other criteria a cyclopropyl group is better than a phenyl group at stabilizing a carbocation.⁹⁵ The reasons for this discrepancy are not fully understood.^{88,96}

Nonclassical carbocations are discussed in section 10.C.i.

5.A.iii. The Generation and Fate of Carbocations

A number of methods are available to generate carbocations, stable or unstable.

1. A direct ionization, in which a leaving group attached to a carbon atom leaves with its pair of electrons, as in solvolysis reactions of alkyl halides (see Sec. 10.G.i) or sulfonate esters (Reaction 10-04):

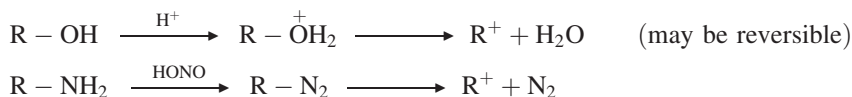


⁹⁴ Olah, G.A.; White, A.M. *J. Am. Chem. Soc.* **1968**, *90*, 1884; **1969**, *91*, 5801. For ^{13}C NMR data for additional ions, see Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* **1977**, *99*, 5026; Olah, G.A.; Prakash, G.K.S.; Liang, G. *J. Org. Chem.* **1977**, *42*, 2666.

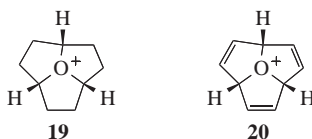
⁹⁵ Olah, G.A.; Porter, R.D.; Kelly, D.P. *J. Am. Chem. Soc.* **1971**, *93*, 464.

⁹⁶ See Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* **1977**, *99*, 1712; Kitching, W.; Adcock, W.; Aldous, G. *J. Org. Chem.* **1979**, *44*, 2652. See also, Larsen, J.W.; Bouis, P.A. *J. Am. Chem. Soc.* **1975**, *97*, 4418; Volz, H.; Shin, J.; Streicher, H. *Tetrahedron Lett.* **1975**, 1297; Larsen, J.W. *J. Am. Chem. Soc.* **1978**, *100*, 330.

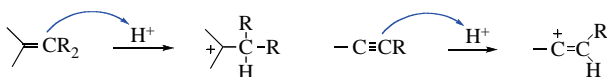
2. Ionization after an initial reaction that converts one functional group into a leaving group, as in protonation of an alcohol to give an oxonium ion (ROH_2^+) or conversion of a primary amine to a diazonium salt, both of which ionize to the corresponding carbocation:



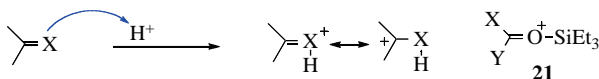
Oxonium ions are also generated by protonation of ethers,⁹⁷ including epoxides.⁹⁸ However, these ions do not always lead to carbocations via ionization, but often undergo substitution reactions (see Chap 10). Oxatriquinane, (**19**) is a fused, tricyclic alkyl oxonium ion that is remarkably stable. Oxonium ion **19** has been heated to reflux in water, can be chromatographed, and does not react with alcohols or alkyl thiols.⁹⁹ The X-ray crystal structure shows longer C—O bond distances and more acute C—O—C bond angles than any reported alkyloxonium salt. Oxatriquinene (**20**) has also been synthesized.



3. A proton or other positive species adds to one atom of an alkene or alkyne, leaving the adjacent carbon atom with a positive charge (see Chapters 11 and 15).



4. A proton or other positive species adds to one atom of a $\text{C}=\text{X}$ bond, where $\text{X} = \text{O}, \text{S}, \text{N}$ in most cases, leaving the adjacent carbon atom with a positive charge (see Chapter 16). When $\text{X} = \text{O}, \text{S}$, this ion is a resonance stabilized oxocarbenium ion ($\text{X} = \text{O}$) or thiocarbenium ion ($\text{X} = \text{S}$), as shown. When $\text{X} = \text{NR}$, protonation leads to an iminium ion ($\text{X} = \text{N}$), with the charge localized on the nitrogen. A silylated carboxonium ion (e.g., **21**) has been reported.¹⁰⁰



When formed by any of the processes 1–3, carbocations are most often short-lived transient species and react further without being isolated. Oxocarbenium ions are more stable and may be longer lived, but even oxocarbenium ions are transient intermediates. The intrinsic barriers to formation and reaction of carbocations have been studied.¹⁰¹

⁹⁷ Peterson, P.E.; Slama, F.J. *J. Am. Chem. Soc.*, **1968**, 90, 6516.

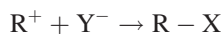
⁹⁸ Carlier, P.R.; Deora, N.; Crawford, T.D. *J. Org. Chem.* **2006**, 71, 1592.

⁹⁹ Mascall, M.; Hafezi, N.; Meher N.K.; Fetting, J.C. *J. Am. Chem. Soc.* **2008**, 130, 13532.

¹⁰⁰ Prakash, G.K.S.; Bae, C.; Rasul, G.; Olah, G.A. *J. Org. Chem.* **2002**, 67, 1297.

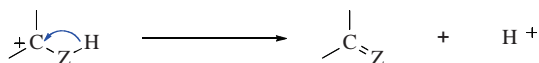
There are two principal pathways by which carbocations react to give stable products that are effectively the reverse of the two pathways just described.

1. A carbocation may combine with a species possessing an electron pair (essentially a Lewis acid–base reaction, see Chapter 8). This reaction occurs by an atom or group donating electrons to the positive carbon of the carbocation. The atom or group that donates the electrons to carbon is called a *nucleophile* (see Chapter 10):



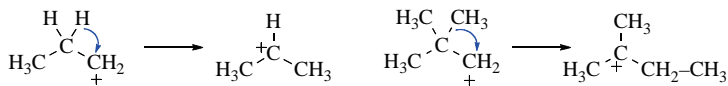
Any reasonable nucleophile will react with the carbocation, but the nucleophile may also be a neutral species with a pair to donate, in which case, of course, the immediate product must bear a positive charge (see Chapters 10, 13, 15, and 16). These reactions are very fast. A recent study measured k_s (the rate constant for reaction of a simple tertiary carbocation) to be $3.5 \times 10^{12} \text{ s}^{-1}$.¹⁰²

2. The carbocation may have a proton (or much less often, another positive ion) removed from the adjacent atom (see Chapters 11 and 17):



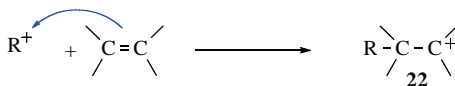
Carbocations can also adopt two other pathways that lead not to stable products, but to other carbocations:

3. *Rearrangement*. An alkyl or aryl group or a hydrogen atom (sometimes another group) migrates with its electron pair to the positive center, leaving another positive charge behind (see Chap 18):



A novel rearrangement has been observed. The 2-methyl-2-butyl-1-¹³C cation (¹³C-labeled *tert*-amyl cation) shows an interchange of the inside and outside carbons with a barrier of 19.5 kcal mol^{−1} (81.6 kJ mol^{−1}) (±2.0 kcal mol^{−1}, 8.4 kJ mol^{−1}).¹⁰³ Another unusual migratory process has been observed for the nonamethylcyclopentyl cation. It has been shown that “four methyl groups undergo rapid circumambulatory migration with a barrier <2 kcal mol^{−1} (8.4 kJ mol^{−1}) while five methyl groups are fixed to ring carbons. The process that equalizes the two sets of methyls has a barrier of 7.0 kcal mol^{−1} (29.3 kJ mol^{−1}).”¹⁰⁴

4. *Addition*. A carbocation may add to a double bond, generating a positive charge at a new position (see Chaps 11 and 15). This means that the π bond donates two electrons to a positive atom, generating positive charge on the carbon as shown:



¹⁰¹ Richard, J.P.; Amyes, T.L.; Williams, K.B. *Pure. Appl. Chem.* **1998**, 70, 2007.

¹⁰² Toteva, M.M.; Richard, J.P. *J. Am. Chem. Soc.* **1996**, 118, 11434.

¹⁰³ Vreck, V.; Saunders, M.; Kronja, O. *J. Am. Chem. Soc.* **2004**, 126, 13703.

¹⁰⁴ Kronja, O.; Kohli, T.-P.; Mayr, H.; Saunders, M. *J. Am. Chem. Soc.* **2000**, 122, 8067.

Whether formed by pathway 3 or 4, the new carbocation normally reacts further in an effort to stabilize itself, usually by pathway 1 or 2. However, **22** can add to another alkene molecule, and this product can add to still another, and so on. This is one of the mechanisms for vinyl polymerization.

5.B. CARBANIONS

5.B.i. Stability and Structure¹⁰⁵

Formally, a carbanion is a trivalent carbon atom with an unshared electron pair, and a formal charge of -1 . In fact, there are few carbanions that do not have an anion-stabilizing group attached to the carbon atom. Stabilization may be by resonance delocalization or by orbital participation of an atom with d orbitals or orbitals associated with a metal.

By definition, every carbanion possesses an unshared pair of electrons and is formally a base. When a carbanion donates an electron to a proton, it is converted to its conjugate acid (an acid–base reaction, see Chapter 8). If the carbanion ($R_3C:^-$) were available, reaction with an acid generates the conjugate acid (R_3C-H), an alkane. The stability of the carbanion is directly related to the strength of the conjugate acid. The weaker that conjugate acid, the greater the base strength of the carbanion, and the lower the stability of the carbanion.¹⁰⁶ Stability here is judged by diminished reactivity (lower electron-donating ability) with a proton. The greater the stability, the lower the electron-donating ability (lower reactivity) for reaction of the carbanion with a proton (any acid that is sufficiently strong), and hence the longer lived the carbanion. Thus the determination of the order of stability of a series of carbanions is equivalent to a determination of the inverse order of strengths of the conjugate acids, and one can obtain information about relative carbanion stability from a table of acid strengths (e.g., Table 8.1).

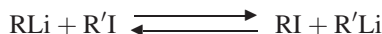
While formation of simple carbanions (e.g., CH_3^-) is rare, formation of a carbon–metal bond often generates a molecule (e.g., R_3C-M , where M = a metal atom) that has a polarized bond in which the carbon is electron rich (δ^-). An organic molecule that contains a carbon–metal bond is called an *organometallic compound*. Organometallic compounds where the metal is Mg, Li, or other metals are carbanion surrogates, and in much of their chemistry they react as if they were carbanions (see Reactions **12-22–12.39**). Many such compounds are known, and organometallic chemistry is a very large area, occupying a borderline region between organic and inorganic chemistry. This section will discuss carbanions with little reference to a metal. Section 5.B.ii will discuss the structures of organometallic compounds, which are often carbanion surrogates.

Carbanions are very strong bases, and the conjugate acids of simple unsubstituted carbanions are very weak acids, with very few exceptions. Unfortunately, it is not easy to measure acid strengths of very weak acids. There is little doubt that carbanions are very

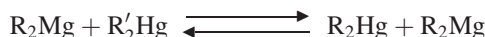
¹⁰⁵ See Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C; Elsevier, NY, **1980**, **1984**, **1987**; Bates, R.B.; Ogle, C.A. *Carbanion Chemistry*, Springer, NY, **1983**; Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, **1979**; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, **1965**; Staley, S.W. *React. Intermed. (Wiley)* **1985**, 3, 19; Staley, S.W.; Dustman, C.K. *React. Intermed. (Wiley)* **1981**, 2, 15. For reviews of NMR spectra of carbanions, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.* **1979**, 12, 261. For a review of dicarbanions, see Thompson, C.M.; Green, D.L.C. *Tetrahedron* **1991**, 47, 4223.

¹⁰⁶ See Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Pergamon, Elmsford, NY, **1978**; Fischer, H.; Rewicki, D. *Prog. Org. Chem.* **1968**, 7, 116.

unstable in solution, and in contrast to the situation with carbocations, efforts to prepare solutions in which carbanions (e.g., ethyl or isopropyl) exist in a relatively free state have not yet been successful. It has also not been possible to form these carbanions in the gas phase. Indeed, there is evidence that simple carbanions (e.g., ethyl and isopropyl) are unstable, losing an electron, which converts them to radicals.¹⁰⁷ Nevertheless, there have been several approaches to the problem. Applequist and O'Brien¹⁰⁸ studied the position of equilibrium for the reaction:



This reaction was done in ether or an ether–pentane mixture. The reasoning in these experiments was that the R group that forms the more stable carbanion would be more likely to be bonded to lithium than to iodine. Carbanion stability was found to be in the order: vinyl > phenyl > cyclopropyl > ethyl > *n*-propyl > isobutyl > neopentyl > cyclobutyl > cyclopentyl. In a somewhat similar approach, Dessy et al.¹⁰⁹ treated a number of alkylmagnesium compounds with a number of alkylmercury compounds in THF, setting up the equilibrium:



where the group of greater carbanion stability is linked to magnesium. The carbanion stability determined this way was phenyl > vinyl > cyclopropyl > methyl > ethyl > isopropyl. The two stability orders are in fairly good agreement, and they show that stability of simple carbanions decreases in the order methyl > primary > secondary. It was not possible to determine the position of *tert*-butyl by the experiments reported by Dessy et al.¹⁰⁹, but there seems little doubt that it is still less stable. This stability order can be interpreted as solely a consequence of the field effect since resonance is absent. The electron-donating alkyl groups of isopropyl result in a greater negative charge density at the central carbon atom (compared with methyl), thus decreasing its stability. The results of Applequist and O'Brien¹⁰⁸ show that β branching also decreases carbanion stability. Cyclopropyl occupies an apparently anomalous position, but this is probably due to the large amount of *s* character in the carbanionic carbon (see Sec. 5.B.i, category 2). Strongly electron-withdrawing groups (e.g., trifluoromethylsulfonyl) provide exceptional stability to carbanions.¹¹⁰

A different approach to the problem of hydrocarbon acidity, and hence carbanion stability, is that of Shatenshtein and Shapiro, who treated hydrocarbons with deuterated potassium amide and measured the rates of hydrogen exchange.¹¹¹ The experiments did not measure *thermodynamic* acidity, since rates were measured, not positions of equilibria. They measured *kinetic* acidity; that is, which compounds gave up protons most rapidly (see Sec. 6.F for the distinction between thermodynamic and kinetic control of product). Measurements of rates of hydrogen exchange enable one to compare acidities of a series of acids against a given base even where the positions of the equilibria cannot be measured

¹⁰⁷ See Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* **1988**, *110*, 607.

¹⁰⁸ Applequist, D.E.; O'Brien, D.F. *J. Am. Chem. Soc.* **1963**, *85*, 743.

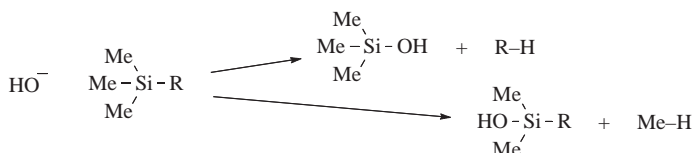
¹⁰⁹ Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* **1966**, *88*, 460.

¹¹⁰ Terrier, F.; Magnier, E.; Kizilian, E.; Wakselman, C.; Buncel, E. *J. Am. Chem. Soc.* **2005**, *127*, 5563.

¹¹¹ For reviews, see Jones, J.R. *Surv. Prog. Chem.* **1973**, *6*, 83; Shatenshtein, A.I.; Shapiro, I.O. *Russ. Chem. Rev.* **1968**, *37*, 845.

because they lie too far to the side of the starting materials; that is, where the acids are too weak to be converted to their conjugate bases in measurable amounts. Although the correlation between thermodynamic and kinetic acidity is far from perfect,¹¹² the results of the rate measurements, too, indicated that the order of carbanion stability is methyl > primary > secondary > tertiary.¹¹¹

Experiments described above were done in solution, and experiments in the gas phase gave different results. In reactions of OH^- with alkyltrimethylsilanes, it is possible to cleave either R or Me. Since the R or Me come off as a carbanion or incipient carbanion, the product ratio RH/MeH can be used to establish the relative stabilities of various R groups. From these experiments a stability order of neopentyl > cyclopropyl > *tert*-butyl > *n*-propyl > methyl > isopropyl > ethyl was found.¹¹³ On the other hand, in a different kind of gas-phase experiment, Graul and Squires¹¹⁴ were able to observe CH_3^- ions, but not the ethyl, isopropyl, or *tert*-butyl ions.

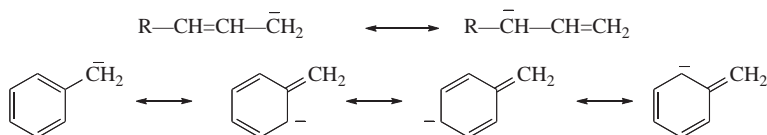


As mentioned above, carbanion-stabilizing groups can increase the stability of carbanions, which influences their ease of formation. Six structural features that lead to improved stability are listed:

1. *Conjugation of the Unshared Pair with an Unsaturated Bond.*



In cases where a double or triple bond is located α to the carbanionic carbon, the ion is stabilized by resonance in which the unshared pair overlaps with the π electrons of the double bond. This factor is responsible for the stability of the allylic¹¹⁵ and benzylic¹¹⁶ types of carbanions:



Diphenylmethyl and triphenylmethyl anions are still more stable due to extensive delocalization into the benzene rings, and can be kept in solution indefinitely if

¹¹² See Bordwell, F.G.; Matthews, W.S.; Vanier, N.R. *J. Am. Chem. Soc.* **1975**, 97, 442.

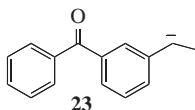
¹¹³ DePuy, C.H.; Gronert, S.; Barlow, S.E.; Bierbaum, V.M.; Damrauer, R. *J. Am. Chem. Soc.* **1989**, 111, 1968. The same order (for *t*-Bu, Me, *i*Pr, and Et) was found in gas-phase cleavages of alkoxides (Reaction 12-41): Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* **1984**, 106, 4053.

¹¹⁴ Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* **1988**, 110, 607.

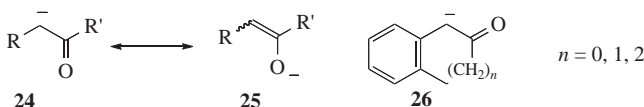
¹¹⁵ See Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, **1970**, pp. 67–77.

¹¹⁶ See Bockrath, B.; Dorfman, L.M. *J. Am. Chem. Soc.* **1974**, 96, 5708.

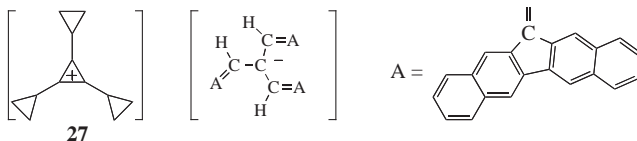
water is rigidly excluded.¹¹⁷ X-ray crystallographic structures have been obtained for Ph_2CH^- and Ph_3C^- enclosed in crown ethers.¹¹⁸ Carbanion **23** has a lifetime of several minutes (hours in a freezer at -20°C) in dry THF.¹¹⁹ Condensed aromatic rings fused to a cyclopentadienyl anion are known to stabilize the carbanion.¹²⁰



Where the carbanionic carbon is conjugated with a carbon–oxygen or carbon–nitrogen multiple bond ($\text{Y}=\text{O}$ or N), the stability of the ion is greater than that of the triarylmethyl anions, since these electronegative atoms are more capable of bearing a negative charge than carbon. However, it is questionable whether ions of this type should be called a carbanion at all, since in the case of enolate ions, for example, **25** contributes more to the hybrid than **24** although such ions react more often at the carbon than at the oxygen. In benzylic enolate anions (e.g., **26**), the conformation of the enolate can be coplanar with the aromatic ring or bent out of plane if the strain is too great.¹²¹ Enolate ions can also be maintained in solution in many cases, at least for minutes or hours at lower temperatures. In the case of carbanions at a carbon α to a nitrile, the “enolate” resonance form would be a ketene imine nitrane, but the existence of this species has been called into question.¹²² A nitro group is particularly effective in stabilizing a negative charge on an adjacent carbon, and the anions of simple nitro alkanes can exist in water. Thus the $\text{p}K_a$ for nitromethane is 10.2. Dinitromethane is even more acidic ($\text{p}K_a = 3.6$). In contrast to the stability of cyclopropylmethyl cations (Sec. 5.A.ii), the cyclopropyl group exerts only a weak stabilizing effect on an adjacent carbanionic carbon.¹²³



By combining a very stable carbanion with a very stable carbocation, Okamoto et al.¹²⁴ were able to isolate the salt (**27**), as well as several similar salts, as stable solids. These are salts that consist entirely of carbon and hydrogen atoms.



¹¹⁷ See Buncel, E.; Menon, B. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C, Elsevier, NY, **1980**, **1984**, **1987**, pp. 97–124.

¹¹⁸ Olmstead, M.M.; Power, P.P. *J. Am. Chem. Soc.* **1985**, *107*, 2174.

¹¹⁹ Laferriere, M.; Sanrame, C. N.; Scaiano, J. C. *Org. Lett.* **2004**, *6*, 873.

¹²⁰ Kinoshita, T.; Fujita, M.; Kaneko, H.; Takeuchi, K.-i.; Yoshizawa, K.; Yamabe, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1145.

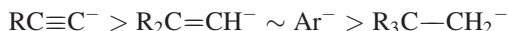
¹²¹ Eldin, S.; Whalen, D.L.; Pollack, R.M. *J. Org. Chem.* **1993**, *58*, 3490.

¹²² Abbotto, A.; Bradamante, S.; Pagani, G.A. *J. Org. Chem.* **1993**, *58*, 449.

¹²³ Perkins, M.J.; Peynircioglu, N.B. *Tetrahedron* **1985**, *41*, 225.

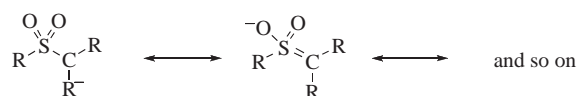
¹²⁴ Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* **1990**, *55*, 996. See also, Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc. Chem. Commun.* **1988**, 923.

2. *Carbanions Increase in Stability with an Increase in the Amount of s Character at the Carbanionic Carbon.* Thus the order of stability is



Acetylene, where the carbon is sp hybridized with 50% s character, is much more acidic than ethylene¹²⁵ (sp^2 , 33% s), which in turn is more acidic than ethane, with 25% s character. Increased s character means that the electrons are closer to the nucleus, and hence of lower energy. As previously mentioned, cyclopropyl carbanions are more stable than methyl, owing to the larger amount of s character as a result of strain (see Sec. 4.Q.i).

3. *Stabilization by Sulfur¹²⁶ or Phosphorus.* Attachment to the carbanionic carbon of a sulfur or phosphorus atom causes an increase in carbanion stability, although the reasons for this are in dispute. One theory is that there is overlap of the unshared pair with an empty d orbital¹²⁷ ($p\pi-d\pi$ bonding, see Sec. 2.H). For example, a carbanion containing the SO_2R group would be written as follows:



However, there is evidence against d -orbital overlap; and the stabilizing effects have been attributed to other causes.¹²⁸ In the case of a PhS substituent, carbanion stabilization is thought to be due to a combination of the inductive and polarizability effects of the group, and $d-p\pi$ resonance and negative hyperconjugation play a minor role, if any.¹²⁹ An α silicon atom also stabilizes carbanions.¹³⁰

4. *Field Effects.* Most of the groups that stabilize carbanions by resonance effects (either the kind discussed in paragraph 1 above or the kind discussed in paragraph 3) have electron-withdrawing field effects and thereby stabilize the carbanion further by spreading the negative charge, although it is difficult to separate the field effect from the resonance effect. However, in a nitrogen (ylid $\text{R}_3\text{N}^+-\text{CR}_2$, see Sec. 2.H), where a positive nitrogen is adjacent to the negatively charged carbon, only the field effect operates. Ylids are more stable than the corresponding simple carbanions. Carbanions are stabilized by a field effect if there is any heteroatom (O, N, or S) connected to the carbanionic carbon, provided that the heteroatom bears a positive charge in at least one important canonical form,¹³¹ for example,

¹²⁵ See Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, **1970**, pp. 49–56.

¹²⁶ See Oae, S.; Uchida, Y. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, **1988**, pp. 583–664; Wolfe, S. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, **1985**, pp. 133–190; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**, pp. 42–56; Durst, T.; Viau, R. *Intra-Sci. Chem. Rep.* **1973**, 7 (3), 63. Also see, Reich, H.J. in Liotta, DC. *Organoselenium Chemistry*, Wiley, NY, **1987**, pp. 243–276.

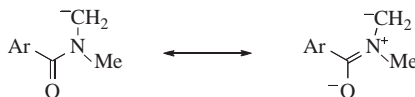
¹²⁷ See Wolfe, S.; LaJohn, L.A.; Bernardi, F.; Mangini, A.; Tonachini, G. *Tetrahedron Lett.* **1983**, 24, 3789; Wolfe, S.; Stolow, A.; LaJohn, L.A. *Tetrahedron Lett.* **1983**, 24, 4071.

¹²⁸ See Borden, W.T.; Davidson, E.R.; Andersen, N.H.; Epiotis, N.D. *J. Am. Chem. Soc.* **1978**, 100, 1604; Bernardi, F.; Bottoni, A.; Venturini, A.; Mangini, A. *J. Am. Chem. Soc.* **1986**, 108, 8171.

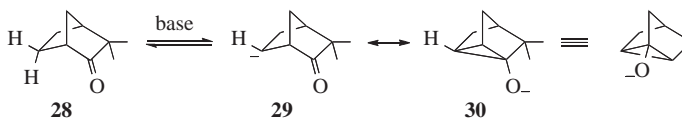
¹²⁹ Bernasconi, C.F.; Kittredge, K.W. *J. Org. Chem.* **1998**, 63, 1944.

¹³⁰ Wetzel, D.M.; Brauman, J.I. *J. Am. Chem. Soc.* **1988**, 110, 8333.

¹³¹ For a review of such carbanions, see Beak, P.; Reitz, D.B. *Chem. Rev.* **1978**, 78, 275. See also, Rondan, N.G.; Houk, K.N.; Beak, P.; Zajdel, W.J.; Chandrasekhar, J.; Schleyer, P.v.R. *J. Org. Chem.* **1981**, 46, 4108.



5. Certain Carbanions Are Stable because They Are Aromatic. See the cyclopentadienyl anion in Section 2.I.ii, and other aromatic anions in Chapter 2.
6. *Stabilization by a Nonadjacent π Bond.*¹³² In contrast to the situation with carbocations (see Sec. 2.C.i), there have been fewer reports of carbanions stabilized by interaction with a nonadjacent π bond. One that may be mentioned is **30**, formed when optically active camphenilone (**28**) was treated with a strong base (potassium *tert*-butoxide).¹³³ That **30** was truly formed was shown by the following facts: (1) A proton was abstracted: ordinary CH_2 groups are not acidic enough for this base; (2) recovered **28** was racemized: **30** is symmetrical and can be attacked equally well from either side; (3) when the experiment was performed in deuterated solvent, the rate of deuterium uptake was equal to the rate of racemization; and (4) recovered **28** contained up to three atoms of deuterium per molecule, although if **29** were the only ion, no more than two could be taken up. Ions of this type, in which a negatively charged carbon is stabilized by a carbonyl group two carbons away, are called *homoenolate ions*.



Based on these four categories, functional groups in the α position stabilize carbanions in the following order: $\text{NO}_2 > \text{RCO} > \text{COOR} > \text{SO}_2 > \text{CN} \sim \text{CONH}_2 > \text{halogen} > \text{H} > \text{R}$.

It is unlikely that free carbanions exist in solution, although some of the stabilized carbanions noted above have reasonable lifetimes in solution. Like carbocations, they usually exist as either ion pairs or they are solvated.¹³⁴ Among experiments that demonstrate ion pairing or solvation was the treatment of $\text{PhCOCHMe}^- \text{M}^+$ with ethyl iodide, where M^+ was Li^+ , Na^+ , or K^+ . The half-lives of the reaction were¹³⁵ for Li, 31×10^{-6} ; Na, 0.39×10^{-6} ; and K, 0.0045×10^{-6} , demonstrating that the species involved were not identical. Similar results¹³⁶ were obtained with Li, Na, and Cs triphenylmethides ($\text{Ph}_3\text{C}^- \text{M}^+$).¹³⁷ Where ion pairs are unimportant, carbanions are solvated. Cram¹⁰⁵ demonstrated

¹³² See Werstiuk, N.H. *Tetrahedron* **1983**, 39, 205; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, **1980**, pp. 410–437.

¹³³ See Werstiuk, N.H.; Yeroushalmi, S.; Timmins, G. *Can. J. Chem.* **1983**, 61, 1945; Lee, R.E.; Squires, R.R. *J. Am. Chem. Soc.* **1986**, 108, 5078; Peiris, S.; Ragauskas, A.J.; Stothers, J.B. *Can. J. Chem.* **1987**, 65, 789; Shiner, C. S.; Berks, A.H.; Fisher, A.M. *J. Am. Chem. Soc.* **1988**, 110, 957.

¹³⁴ For reviews of carbanion pairs, see Hogen-Esch, T.E. *Adv. Phys. Org. Chem.* **1977**, 15, 153; Jackman, L.M.; Lange, B.C. *Tetrahedron* **1977**, 33, 2737. See also, Laube, T. *Acc. Chem. Res.* **1995**, 28, 399.

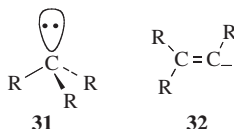
¹³⁵ Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* **1960**, 82, 1386.

¹³⁶ Solov'yanov, A.A.; Karpyuk, A.D.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* **1981**, 17, 381. See also, Solov'yanov, A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* **1983**, 19, 1964.

¹³⁷ See DePalma, V.M.; Arnett, E.M. *J. Am. Chem. Soc.* **1978**, 100, 3514; Buncel, E.; Menon, B. *J. Org. Chem.* **1979**, 44, 317; O'Brien, D.H.; Russell, C.R.; Hart, A.J. *J. Am. Chem. Soc.* **1979**, 101, 633; Streitwieser, Jr., A.; Shen, C.C.C. *Tetrahedron Lett.* **1979**, 327; Streitwieser, Jr., A. *Acc. Chem. Res.* **1984**, 17, 353.

solvation of carbanions in many solvents. There may be a difference in the structure of a carbanion depending on whether it is free (e.g., in the gas phase) or in solution. The negative charge may be more localized in solution in order to maximize the electrostatic attraction to the counterion.¹³⁸

The structure of simple unsubstituted carbanions is not known with certainty since they have not been isolated, but it is likely that the central carbon is sp^3 hybridized, with the unshared pair occupying one apex of the tetrahedron. Carbanions are expected to have pyramidal structures (e.g., **31**, similar to those of amines).



The methyl anion (CH_3^-) has been observed in the gas phase and reported to have a pyramidal structure.¹³⁹ If this is taken as a general structure for carbanions, then any carbanion in which the three R groups are different should be chiral and reactions in which it is an intermediate should give retention of configuration. Attempts have been made to demonstrate this principle, but without success.¹⁴⁰ A possible explanation is that pyramidal inversion takes place here, as in amines, so that the unshared pair and the central carbon rapidly oscillate from one side of the plane to the other. There is, however, other evidence for the sp^3 nature of the central carbon and for its tetrahedral structure. Carbons at bridgeheads, although extremely reluctant to undergo reactions in which they must be converted to carbocations, easily undergo reactions in which they must be carbanions and stable bridgehead carbanions are known.¹⁴¹ Also, reactions at vinylic carbons proceed with retention,¹⁴² indicating that the intermediate **32** has sp^2 hybridization and not the sp hybridization that would be expected in the analogous carbocation. A cyclopropyl anion can also hold its configuration.¹⁴³

Carbanions in which the negative charge is stabilized by resonance involving overlap of the unshared-pair orbital with the π electrons of a multiple bond are essentially planar, as would be expected by the necessity for planarity in resonance, although unsymmetrical solvation or ion-pairing effects may cause the structure to deviate somewhat from true planarity.¹⁴⁴ Cram¹⁴⁴ showed that where chiral carbanions possessing this type of resonance are generated, retention, inversion, or racemization can result, depending on the solvent (see Sec. 12.A.ii). This result is

¹³⁸ See Schade, C.; Schleyer, P.v.R.; Geissler, M.; Weiss, E. *Angew. Chem. Int. Ed.* **1986**, 21, 902.

¹³⁹ Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc.* **1978**, 100, 2556.

¹⁴⁰ Retention of configuration has never been observed with simple carbanions. Cram has obtained retention with carbanions stabilized by resonance. However, these carbanions are known to be planar or nearly planar, and retention was caused by asymmetric solvation of the planar carbanions (see Sec. 12.A.ii).

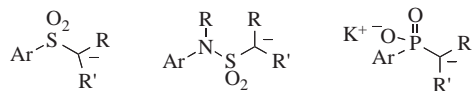
¹⁴¹ See Peoples, P.R.; Grutzner, J.B. *J. Am. Chem. Soc.* **1980**, 102, 4709.

¹⁴² See Feit, B.; Melamed, U.; Speer, H.; Schmidt, R.R. *J. Chem. Soc. Perkin Trans. 1* **1984**, 775; Chou, P.K.; Kass, S.R. *J. Am. Chem. Soc.* **1991**, 113, 4357.

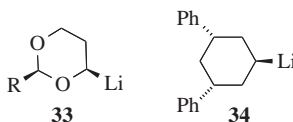
¹⁴³ Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1988**, 110, 6925; Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, **1990**. For a review, see Boche, G.; Walborsky, H.M. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, **1987**, pp. 701–808.

¹⁴⁴ See Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, **1965**, pp. 85–105.

explained by unsymmetrical solvation of planar or near-planar carbanions. However, some carbanions that are stabilized by adjacent sulfur or phosphorus, for example, are inherently chiral, since retention of configuration is observed where



they are generated, even in solvents that cause racemization or inversion with other carbanions.¹⁴⁵ It is known that in THF, PhCH(Li)Me behaves as a prochiral entity,¹⁴⁶ and **33** has been prepared as an optically pure α -alkoxyllithium reagent.¹⁴⁷ Cyclohexyllithium (**34**) shows some configurational stability, and it is known that isomerization is slowed by an increase in the strength of lithium coordination and by an increase in solvent polarity.¹⁴⁸ It is known that a vinyl anion is configurationally stable whereas a vinyl radical is not. This is due to the instability of the radical anion that must be an intermediate for conversion of one isomer of vinyl lithium to the other.¹⁴⁹ The configuration about the carbanionic carbon, at least for some of the α -sulfonyl carbanions, seems to be planar,¹⁵⁰ and the inherent chirality is caused by lack of rotation about the C—S bond.¹⁵¹



5.B.ii. The Structure of Organometallic Compounds¹⁵²

Whether a carbon–metal bond is ionic or polar-covalent is determined chiefly by the electronegativity of the metal and the structure of the organic part of the molecule. Ionic bonds become more likely as the negative charge on the metal-bearing carbon is decreased by resonance or field effects. Thus the sodium salt of acetoacetic ester has a more ionic carbon–sodium bond than methylsodium.

Most organometallic bonds are polar-covalent. Only the alkali metals have electronegativities low enough to form ionic bonds with carbon, and even here the behavior of lithium alkyls shows considerable covalent character. The simple alkyls and aryls of Na, K,

¹⁴⁵ Bordwell, F.G.; Phillips, D.D.; Williams, Jr., J.M. *J. Am. Chem. Soc.* **1968**, *90*, 426; Annunziata, R.; Cinquini, M.; Colonna, S.; Cozzi, F. *J. Chem. Soc. Chem. Commun.* **1981**, 1005; Chassaing, G.; Marquet, A.; Corset, J.; Froment, F. *J. Organomet. Chem.* **1982**, 232, 293; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, **1965**, pp. 105–113; Hirsch, R.; Hoffmann, R.W. *Chem. Ber.* **1992**, 125, 975.

¹⁴⁶ Hoffmann, R.W.; Rühl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* **1992**, 719.

¹⁴⁷ Rychnovsky, S.D.; Plzak, K.; Pickering, D. *Tetrahedron Lett.* **1994**, 35, 6799.

¹⁴⁸ Reich, H.J.; Medina, M.A.; Bowe, M.D. *J. Am. Chem. Soc.* **1992**, 114, 11003.

¹⁴⁹ Jenkins, P.R.; Symons, M.C.R.; Booth, S.E.; Swain, C.J. *Tetrahedron Lett.* **1992**, 33, 3543.

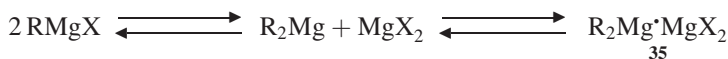
¹⁵⁰ Gais, H.; Müller, J.; Vollhardt, J.; Lindner, H.J. *J. Am. Chem. Soc.* **1991**, 113, 4002. For a contrary view, see Frost, B.M.; Schmuff, N.R. *J. Am. Chem. Soc.* **1985**, 107, 396.

¹⁵¹ Grossert, J.S.; Hoyle, J.; Cameron, T.S.; Roe, S.P.; Vincent, B.R. *Can. J. Chem.* **1987**, 65, 1407.

¹⁵² See Elschenbroich, C.; Salzer, A. *Organometallics*, VCH, NY, **1989**; Oliver, J.P. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, **1985**, pp. 789–826; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., Vol. 1, Methuen: London, **1967**; Grovenstein, Jr., E. in Buncl, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. C, Elsevier, NY, **1987**, pp. 175–221.

Rb, and Cs¹⁵³ are nonvolatile solids¹⁵⁴ insoluble in benzene or other organic solvents, while alkyllithium reagents are soluble, although they too are generally nonvolatile solids. Organolithium reagents with alkyl units (alkyllithium reagents) do not exist as monomeric species in hydrocarbon solvents or ether.¹⁵⁵ In benzene and cyclohexane, freezing-point-depression studies have shown that alkyllithium reagents are normally hexameric unless steric interactions favor tetrameric aggregates.¹⁵⁶ Nuclear magnetic resonance studies, especially measurements of ¹³C—⁶Li coupling, have also shown aggregation in hydrocarbon solvents.¹⁵⁷ Boiling-point-elevation studies have been performed in ether solutions, where alkyllithium reagents exist in two- to fivefold aggregates.¹⁵⁸ Even in the gas phase¹⁵⁹ and in the solid state,¹⁶⁰ alkyllithium reagents exist as aggregates. X-ray crystallography has shown that methylolithium has the same tetrahedral structure in the solid state as in ether solution.¹⁶⁰ However, *tert*-butyllithium is monomeric in THF, although dimeric in ether and tetrameric in hydrocarbon solvents.¹⁶¹ Neopentyllithium exists as a mixture of monomers and dimers in THF.¹⁶²

The C—Mg bond in *Grignard reagents* is covalent and not ionic. The actual structure of Grignard reagents in solution has been a matter of much controversy over the years.¹⁶³ In 1929, it was discovered¹⁶⁴ that the addition of dioxane to an ethereal Grignard solution precipitates all the magnesium halide and leaves a solution of R₂Mg in ether; (i.e., there can be no RMgX in the solution since there is no halide). The following equilibrium, now called the *Schlenk equilibrium*, was proposed as the composition of the Grignard solution:



in which **35** is a complex. Much work has demonstrated that the Schlenk equilibrium actually exists and that the position of the equilibrium depends on the identity of R, X, the

¹⁵³ See Schade, C.; Schleyer, P.v.R. *Adv. Organomet. Chem.* **1987**, 27, 169.

¹⁵⁴ For X-ray crystallography studies, see Weiss, E.; Sauermann, G. *Chem. Ber.* **1970**, 103, 265; Weiss, E.; Köster, H. *Chem. Ber.* **1977**, 110, 717.

¹⁵⁵ See Setzer, W.N.; Schleyer, P.v.R. *Adv. Organomet. Chem.* **1985**, 24, 353; Schleyer, P.v.R. *Pure Appl. Chem.* **1984**, 56, 151; Brown, T.L. *Pure Appl. Chem.* **1970**, 23, 447; *Adv. Organomet. Chem.* **1965**, 3, 365; Kovrizhnykh, E.A.; Shatenshtein, A.I. *Russ. Chem. Rev.* **1969**, 38, 840. For reviews of the structures of lithium enolate anions and related compounds, see Boche, G. *Angew. Chem. Int. Ed.* **1989**, 28, 277; Seebach, D. *Angew. Chem. Int. Ed.* **1988**, 27, 1624. Also see Günther, H.; Moskau, D.; Bast, P.; Schmalz, D. *Angew. Chem. Int. Ed.* **1987**, 26, 1212; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, **1988**, *The Chemistry of Organolithium Compounds*, Pergamon, Elmsford, NY, **1974**.

¹⁵⁶ Lewis, H.L.; Brown, T.L. *J. Am. Chem. Soc.* **1970**, 92, 4664; Brown, T.L.; Rogers, M.T. *J. Am. Chem. Soc.* **1957**, 79, 1859; Weiner, M.A.; Vogel, G.; West, R. *Inorg. Chem.* **1962**, 1, 654.

¹⁵⁷ Thomas, R.D.; Jensen, R.M.; Young, T.C. *Organometallics* **1987**, 6, 565. See also, Kaufman, M.J.; Gronert, S.; Streitwieser, Jr., A. *J. Am. Chem. Soc.* **1988**, 110, 2829.

¹⁵⁸ Wittig, G.; Meyer, F.J.; Lange, G. *Liebigs Ann. Chem.* **1951**, 571, 167. See also, Bates, T.F.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* **1988**, 110, 5109.

¹⁵⁹ Playšić, D.; Srzić, D.; Klasinc, L. *J. Phys. Chem.* **1986**, 90, 2075.

¹⁶⁰ Weiss, E.; Sauermann, G.; Thirase, G. *Chem. Ber.* **1983**, 116, 74.

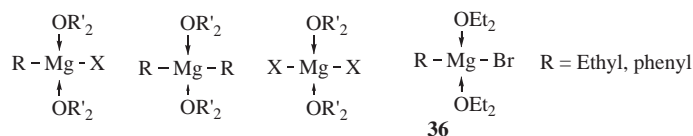
¹⁶¹ Bauer, W.; Winchester, W.R.; Schleyer, P.v.R. *Organometallics* **1987**, 6, 2371.

¹⁶² Fraenkel, G.; Chow, A.; Winchester, W.R. *J. Am. Chem. Soc.* **1990**, 112, 6190.

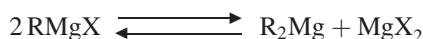
¹⁶³ For reviews, see Ashby, E.C. *Bull. Soc. Chim. Fr.* **1972**, 2133; *Q. Rev. Chem. Soc.* **1967**, 21, 259; Wakefield, B. *J. Organomet. Chem. Rev.* **1966**, 1, 131; Bell, N.A. *Educ. Chem.* **1973**, 143.

¹⁶⁴ Schlenk, W.; Schlenk, Jr., W. *Ber.* **1929**, 62B, 920.

solvent, the concentration, and the temperature.¹⁶⁵ It has been known for many years that the magnesium in a solution of a Grignard reagent, no matter whether it is RMgX , R_2Mg , or MgX_2 , can coordinate with two molecules of ether in addition to the two covalent bonds to generate the solvent-coordinated species shown.



Rundle and Guggenberger¹⁶⁶ performed X-ray diffraction studies on solid phenylmagnesium bromide dietherate and on ethylmagnesium bromide dietherate, which they obtained by cooling ordinary ethereal Grignard solutions until the solids crystallized. They found that the structures were magnesium bromides (e.g., **36**). These solids still contained ether. When ordinary ethereal Grignard solutions¹⁶⁷ prepared from bromomethane, chloromethane, bromoethane, and chloroethane were evaporated at $\sim 100^\circ\text{C}$ under vacuum so that the solid remaining contained no ether, X-ray diffraction showed *no* RMgX , but a mixture of R_2Mg and MgX_2 .¹⁶⁸ These results indicate that in the presence of ether, $\text{RMgX} \cdot 2\text{Et}_2\text{O}$ is the preferred structure, while the loss of ether drives the Schlenk equilibrium to $\text{R}_2\text{Mg} + \text{MgX}_2$. However, conclusions drawn from a study of the solid materials do not necessarily apply to the structures in solution.



Boiling-point-elevation and freezing-point-depression measurements have demonstrated that in THF at all concentrations and in ether at low concentrations (up to $\sim 0.1 \text{ M}$) Grignard reagents prepared from alkyl bromides and iodides are monomeric, (i.e., there are few or no molecules with two Mg atoms).¹⁶⁹ Thus, part of the Schlenk equilibrium is operating but not the other part (i.e., **35** is not present in measurable amounts). This was substantiated by ^{25}Mg NMR spectra of the ethyl Grignard reagent in THF, which showed the presence of three peaks, corresponding to EtMgBr , Et_2Mg , and MgBr_2 .¹⁷⁰ That the equilibrium between RMgX and R_2Mg lies far to the left for “ethylmagnesium bromide” in ether was shown by Smith and Becker,¹⁷¹ who mixed 0.1 M ethereal solutions of Et_2Mg and MgBr_2 and found that a reaction occurred with a heat evolution of $3.6 \text{ kcal mol}^{-1}$ (15 kJ mol^{-1}) of Et_2Mg , and that the product was *monomeric* (by boiling-point elevation measurements). When either solution was added little by little to the other, there was a linear output of heat until almost a 1 : 1 molar ratio was reached. Addition of an excess of either reagent gave no further heat output. These results show that at least under some conditions the Grignard reagent is largely RMgX .

¹⁶⁵ See Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* **1971**, *93*, 1206; Salinger, R.M.; Mosher, H.S. *J. Am. Chem. Soc.* **1964**, *86*, 1782.

¹⁶⁶ Guggenberger, L.J.; Rundle, R.E. *J. Am. Chem. Soc.* **1968**, *90*, 5375.

¹⁶⁷ See Sakamoto, S.; Imamoto, T.; Yamaguchi, K. *Org. Lett.* **2001**, *3*, 1793.

¹⁶⁸ Weiss, E. *Chem. Ber.* **1965**, *98*, 2805.

¹⁶⁹ Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* **1964**, *86*, 4363; Vreugdenhil, A.D.; Blomberg, C. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 453, 461.

¹⁷⁰ Benn, R.; Lehmkühl, H.; Mehler, K.; Ruffńska, A. *Angew. Chem. Int. Ed.* **1984**, *23*, 534.

¹⁷¹ Smith, M.B.; Becker, W.E. *Tetrahedron* **1966**, *22*, 3027.

(coordinated with solvent), but that the equilibrium can be driven to R_2Mg by evaporation of all the ether or by addition of dioxane.

For some aryl Grignard reagents, it is possible to distinguish separate NMR chemical shifts for $ArMgX$ and Ar_2Mg .¹⁷² From the area under the peaks, it is possible to calculate the concentrations of the two species, and from them, equilibrium constants for the Schlenk equilibrium. These data show¹⁷² that the position of the equilibrium depends very markedly on the aryl group and the solvent, but that conventional aryl Grignard reagents in ether are largely $ArMgX$. In THF the predominance of $ArMgX$ is less, and with some aryl groups there is actually more Ar_2Mg present. Separate NMR chemical shifts have also been found for alkyl $RMgBr$ and R_2Mg in HMPA¹⁷³ and in ether at low temperatures.¹⁷⁴ When Grignard reagents from alkyl bromides or chlorides are prepared in triethylamine the predominant species is $RMgX$.¹⁷⁵ Thus the most important factor determining the position of the Schlenk equilibrium is the solvent. For primary alkyl groups the equilibrium constant for the reaction as written above is lowest in Et_3N , higher in ether, and still higher in THF.¹⁷⁶

However, Grignard reagents prepared from alkyl bromides or iodides in ether at higher concentrations (0.5–1 M) contain dimers, trimers, and higher polymers, and those prepared from alkyl chlorides in ether at all concentrations are dimeric,¹⁷⁷ so that **35** is in solution, probably in equilibrium with $RMgX$ and R_2Mg (i.e., the complete Schlenk equilibrium seems to be present).

The Grignard reagent prepared from 1-chloro-3,3-dimethylpentane in ether undergoes rapid inversion of configuration at the Mg containing carbon (demonstrated by NMR; this compound is not chiral).¹⁷⁸ The mechanism of this inversion is not completely known. Despite the mechanistic ambiguity, in almost all cases, it is not possible to retain the configuration of a stereogenic carbon while forming a Grignard reagent.

Organolithium reagents (RLi) are very important reagents in organic chemistry. In recent years, a great deal has been learned about their structure¹⁷⁹ in both the solid state and in solution. X-ray analysis of complexes of *n*-butyllithium with tetramethylethylenediamine (TMEDA), THF, and 1,2-dimethoxyethane (DME) shows them to be dimers and tetramers [e.g., $(BuLi \cdot DME)_4$];¹⁸⁰ they are aggregates.¹⁸¹ X-ray analysis of isopropyllithium shows it to be a hexamer $[(iPrLi)_6]$,¹⁸² and unsolvated lithium aryls are tetramers.¹⁸³ α -Ethoxyvinyl lithium $[CH_2=C(OEt)Li]$ shows a polymeric structure with tetrameric subunits.¹⁸⁴ Aminomethyl aryllithium reagents have been shown to be

¹⁷² Evans, D.F.; Fazakerley, V. *Chem. Commun.* **1968**, 974.

¹⁷³ Ducom, J. *Bull. Chem. Soc. Fr.* **1971**, 3518, 3523, 3529.

¹⁷⁴ See Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* **1971**, 93, 1206.

¹⁷⁵ Ashby, E.C.; Walker, F. *J. Org. Chem.* **1968**, 33, 3821.

¹⁷⁶ Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* **1971**, 93, 1206.

¹⁷⁷ Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* **1964**, 86, 4363.

¹⁷⁸ Fraenkel, G.; Cottrell, C.E.; Dix, D.T. *J. Am. Chem. Soc.* **1971**, 93, 1704; Pechhold, E.; Adams, D.G.; Fraenkel, G. *J. Org. Chem.* **1971**, 36, 1368; Maercker, A.; Geuss, R. *Angew. Chem. Int. Ed.* **1971**, 10, 270.

¹⁷⁹ See Pratt, L.M.; Kass, S.R. *J. Org. Chem.* **2004**, 69, 2123.

¹⁸⁰ Nichols, M.A.; Williard, P.G. *J. Am. Chem. Soc.* **1993**, 115, 1568.

¹⁸¹ See Jones, A.C.; Sanders, A.W.; Bevan, M.J.; Reich, H.J. *J. Am. Chem. Soc.* **2007**, 129, 3492.

¹⁸² Siemeling, U.; Redecker, T.; Neumann, B.; Stammer, H.-G. *J. Am. Chem. Soc.* **1994**, 116, 5507.

¹⁸³ Ruhlandt-Senge, K.; Ellison, J.J.; Wehmschulte, R.J.; Pauer, F.; Power, P.P. *J. Am. Chem. Soc.* **1993**, 115, 11353. Also see Betz, J.; Hampel, F.; Bauer, W. *Org. Lett.* **2000**, 2, 3805.

¹⁸⁴ Sorger, K.; Bauer, W.; Schleyer, P.v.R.; Stalke, D. *Angew. Chem. Int. Ed.*, **1995**, 34, 1594.

chelated and dimeric in solvents (e.g., THF).¹⁸⁵ There are several functionalized organolithium reagents.¹⁸⁶

The dimeric, tetrameric, and hexameric structures of organolithium reagents¹⁸⁷ in the solid state is often retained in solution, but this is dependent on the solvent and complexing additives, if any. A tetrahedral organolithium compound is known,¹⁸⁸ and the X-ray of an α,α -dilithio hydrocarbon has been reported.¹⁸⁹ Phenyllithium is a mixture of tetramers and dimers in diethyl ether, but stoichiometric addition of THF, DME, or TMEDA leads to the dimer.¹⁹⁰ The solution structures of mixed aggregates of butyllithium and amino-alkaloids has been determined¹⁹¹ as well as the solution structure of sulfur-stabilized allyllithium compounds.¹⁹² Vinylithium is an 8:1 mixture of tetramer/dimer in THF at -90°C , but addition of TMEDA changes the ratio of tetramer/dimer to 1:13 at -80°C .¹⁹³ Internally solvated allylic lithium compounds have been studied, showing the coordinated lithium to be closer to one of the terminal allyl carbons.¹⁹⁴ A relative scale of organolithium stability has been established,¹⁹⁵ and the issue of configurational stability of enantioenriched organolithium reagents has been examined.¹⁹⁶

Enolate anions are an important class of carbanions that appear in a variety of important reactions, including alkylation α to a carbonyl group and the aldol (**16-34**) and *Claisen condensation* (**16-85**) reactions. Metal enolate anions of aldehydes, ketones, esters, and other acid derivatives exist as aggregates in ether solvents.¹⁹⁷ There is evidence that the lithium enolate of isobutyrophenone is a tetramer in THF,¹⁹⁸ but a dimer in DME.¹⁹⁹ X-ray crystallography of ketone enolate anions have shown that they can exist as tetramers and hexamers.²⁰⁰ There is also evidence that the aggregate structure is preserved in solution and is probably the actual reactive species. Lithium enolate anions derived from esters are as dimers in the solid state²⁰¹ that contain four THF molecules. It has also been established that the reactivity of enolate anions in alkylation and condensation reactions is influenced by the aggregate state of the enolate. It is also true that the relative proportions of (*E*) and (*Z*) enolate anions are influenced by the extent of solvation and the aggregation state.

¹⁸⁵ Reich, H.J.; Gudmundsson, B.O.; Goldenberg, W.S.; Sanders, A.W.; Kulicke, K.J.; Simon, K.; Guzei, I. A. *J. Am. Chem. Soc.* **2001**, *123*, 8067.

¹⁸⁶ Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3137.

¹⁸⁷ See Parisel, O.; Fressigne, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Org. Chem.* **2003**, *68*, 1290.

¹⁸⁸ Sekiguchi, A.; Tanaka, M. *J. Am. Chem. Soc.* **2003**, *125*, 12684.

¹⁸⁹ Linti, G.; Rodig, A.; Pritzkow, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4503.

¹⁹⁰ Reich, H.J.; Green, D.P.; Medina, M.A.; Goldenberg, W.S.; Gudmundsson, B.Ö.; Dykstra, R.R.; Phillips, N.H. *J. Am. Chem. Soc.* **1998**, *120*, 7201.

¹⁹¹ Sun, X.; Winemiller, M.D.; Xiang, B.; Collum, D.B. *J. Am. Chem. Soc.* **2001**, *123*, 8039. See also, Rutherford, J.L.; Hoffmann, D.; Collum, D.B. *J. Am. Chem. Soc.* **2002**, *124*, 264.

¹⁹² Piffl, M.; Weston, J.; Günther, W.; Anders, E. *J. Org. Chem.* **2000**, *65*, 5942.

¹⁹³ Bauer, W.; Griesinger, C. *J. Am. Chem. Soc.* **1993**, *115*, 10871.

¹⁹⁴ Fraenkel, G.; Chow, A.; Fleischer, R.; Liu, H. *J. Am. Chem. Soc.* **2004**, *126*, 3983.

¹⁹⁵ Graña, P.; Paleo, M.R.; Sardina, F.J. *J. Am. Chem. Soc.* **2002**, *124*, 12511.

¹⁹⁶ Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 717. See also, Fraenkel, G.; Duncan, J.H.; Martin, K.; Wang, J. *J. Am. Chem. Soc.* **1999**, *121*, 10538.

¹⁹⁷ Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.* **1968**, *90*, 4464; Bernstein, M.P.; Collum, D.B. *J. Am. Chem. Soc.* **1993**, *115*, 789; Collum, D.B. *Acc. Chem. Res.* **1992**, *25*, 448.

¹⁹⁸ Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* **1981**, *103*, 4494.

¹⁹⁹ Jackman, L.M.; Lange, B.C. *Tetrahedron* **1977**, *33*, 2737.

²⁰⁰ Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* **1986**, *108*, 462; Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* **1985**, *107*, 3345 and references cited therein.

²⁰¹ Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W.B.; Dunitz, J.D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.

Addition of LiBr to a lithium enolate anion in THF suppresses the concentration of monomeric enolate.²⁰² *Ab initio* studies confirm the aggregate state of acetaldehyde.²⁰³ It is also known that α -Li benzonitrile [PhCH(Li)CN] exists as a dimer in ether and with TMEDA.²⁰⁴ Mixed aggregates of *tert*-butyllithium and lithium *tert*-butoxide are known to be hexameric.²⁰⁵

It might be mentioned that matters are much simpler for organometallic compounds with less-polar bonds. Thus Et₂Hg and EtHgCl are both definite compounds, the former is a liquid and the latter is a solid. Organocalcium reagents are also known, and are formed from alkyl halides via a single electron transfer (SET) mechanism with free radical intermediates.²⁰⁶

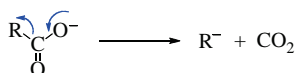
5.B.iii. The Generation and Fate of Carbanions

There are two principal ways in which most carbanions are generated.

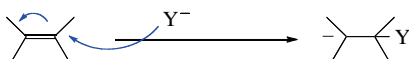
1. A Group Attached to a Carbon Leaves Without Its Electron Pair



The “leaving group” is most often a proton. In fact, the proton is removed by a suitable base, and this is a simple acid–base reaction.²⁰⁷ However, other leaving groups are known (see Chap 12), such as carboxyl:



2. A Negative Ion Adds to a Carbon–Carbon Double or Triple Bond (see Chapter 15)



The addition of a negative ion to a carbon–oxygen double bond (C=O) does not give a carbanion, but an alkoxide (R–O[−]), since the negative charge resides on the oxygen.

The most common reaction of carbanions is to donate electrons to a positive species, often a proton, or with another species that has an empty orbital in its outer shell (a Lewis acid–base reaction):



This means that carbanions react with electrophilic atoms (those functionalized so there is a δ^+ carbon atom); see Chapter 16.

²⁰² Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* **1996**, *118*, 8136.

²⁰³ Abbotto, A.; Streitwieser, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1997**, *119*, 11255.

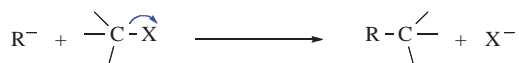
²⁰⁴ Carlier, P.R.; Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* **1994**, *116*, 11602.

²⁰⁵ DeLong, G.T.; Pannell, D.K.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* **1993**, *115*, 7013.

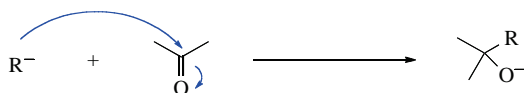
²⁰⁶ Walborsky, H.M.; Hamdouchi, C. *J. Org. Chem.* **1993**, *58*, 1187.

²⁰⁷ For a review of such reactions, see Durst, T. in Buncl, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. B, Elsevier, NY, **1984**, pp. 239–291.

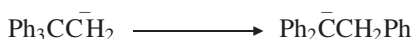
Carbanions may also form a bond with a carbon that already has four bonds, by displacing one of the four groups (S_N2 reaction, see Chapter 10):



Like carbocations, carbanions can also react in ways in which they are converted to species that are still charged. They can add to double bonds (usually C=O double bonds; see Chapters 10 and 16),



or rearrange, although this is rare (see Chapter 18),



or they are oxidized to free radicals.²⁰⁸ A system in which a carbocation [$\text{Ph}(p\text{-Me}_2\text{NC}_6\text{H}_4)_2\text{C}^+$] oxidizes a carbanion [$(p\text{-NO}_2\text{C}_6\text{H}_4)_3\text{C}^-$] to give two free radicals, reversibly, so that all four species are present in equilibrium, has been demonstrated.^{209,210}

Organometallic compounds that are not ionic but polar-covalent behave very much as if they were ionic and give similar reactions.

5.C. FREE RADICALS

5.C.i. Stability and Structure²¹¹

A *free radical* (usually just called a *radical*) may be defined as a species that contains one or more unpaired electrons. Note that this definition includes certain stable inorganic molecules (e.g., NO and NO₂), as well as many individual atoms (e.g., Na and Cl). As with carbocations and carbanions, simple alkyl radicals are very reactive and are usually transient species. For the most part, their lifetimes are extremely short in solution, but they can be kept frozen for relatively long periods of time within the crystal lattices of other

²⁰⁸ For a review, see Guthrie, R.D. in Buncl, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, **1980**, pp. 197–269.

²⁰⁹ Arnett, E.M.; Molter, K.E.; Marchot, E.C.; Donovan, W.H.; Smith, P. *J. Am. Chem. Soc.* **1987**, *109*, 3788.

²¹⁰ Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* **1990**, *55*, 996. See also, Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc. Chem. Commun.* **1988**, 923.

²¹¹ See Alfassi, Z.B. *N-Centered Radicals*, Wiley, Chichester, **1998**; Alfassi, Z.B. *Peroxy Radicals*, Wiley, Chichester, **1997**; Alfassi, Z.B. *Chemical Kinetics of Small Organic Radicals*, 4 Vols., CRC Press: Boca Raton, FL, **1988**; Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radicals*, Cambridge University Press, Cambridge, **1979**; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, Cambridge, **1974**; Kochi, J.K. *Free Radicals*, 2 Vols., Wiley, NY, **1973**; Hay, J.M. *Reactive Free Radicals*, Academic Press, NY, **1974**; For reviews, see Kaplan, L. *React. Intermed. (Wiley)* **1985**, *3*, 227; Griller, D.; Ingold, K.U. *Acc. Chem. Res.* **1976**, *9*, 13.

molecules.²¹² There are, however, many stable radicals,²¹³ some of which will be noted below. Many spectral²¹⁴ measurements have been made on radicals trapped in this manner. Even under these conditions the methyl radical decomposes with a half-life of 10–15 min in a methanol lattice at 77 K.²¹⁵ Since the lifetime of a radical depends not only on its inherent stability, but also on the conditions under which it is generated, the terms *persistent* and *stable* are usually used for the different senses. A stable radical is inherently stable; a persistent radical has a relatively long lifetime under the conditions at which it is generated, although it may not be very stable.

Radicals can be characterized by several techniques (e.g., mass spectrometry²¹⁶ or the characterization of alkoxycarbonyl radicals by Step–Scan Time-Resolved Infrared Spectroscopy).²¹⁷ Another technique makes use of the magnetic moment that is associated with the spin of an electron, which can be expressed by a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$. According to the *Pauli principle*, any two electrons occupying the same orbital must have opposite spins, so the total magnetic moment is zero for any species in which all the electrons are paired. In radicals, however, one or more electrons are unpaired, so there is a net magnetic moment and the species is paramagnetic. Radicals can therefore be detected by magnetic-susceptibility measurements, but for this technique a relatively high concentration of radicals is required.

A much more important technique is *electron spin resonance* (ESR), also called *electron paramagnetic resonance* (EPR).²¹⁸ The principle of ESR is similar to that of NMR, except that electron spin is involved rather than nuclear spin. The two electron spin states ($m_s = \frac{1}{2}$ and $m_s = -\frac{1}{2}$) are ordinarily of equal energy, but in a magnetic field the energies are different. As in NMR, a strong external field is applied and electrons are caused to flip from the lower state to the higher by the application of an appropriate radio frequency signal. Inasmuch as two electrons paired in one orbital must have opposite spins that cancel, an ESR spectrum arises only from species that have one or more unpaired electrons (i.e., free radicals).

Since only free radicals give an ESR spectrum, the method can be used to detect the presence of radicals and to determine their concentration.²¹⁹ Furthermore, information concerning the electron distribution (and hence the structure) of free radicals can be obtained from the splitting pattern of the ESR spectrum (ESR peaks are split by nearby

²¹² See Dunkin, I.R. *Chem. Soc. Rev.* **1980**, 9, 1; Jacox, M.E. *Rev. Chem. Intermed.* **1978**, 2, 1. For a review of the study of radicals at low temperatures, see Mile, B. *Angew. Chem. Int. Ed.* **1968**, 7, 507.

²¹³ See Hicks, R.G. *Org. Biomol. Chem.* **2007**, 5, 1321. See also, Hioe, J.; Zipse, H. *Org. Biomol. Chem.* **2010**, 8, 3609.

²¹⁴ See Andrews, L. *Annu. Rev. Phys. Chem.* **1971**, 22, 109.

²¹⁵ Sullivan, P.J.; Koski, W.S. *J. Am. Chem. Soc.* **1963**, 85, 384.

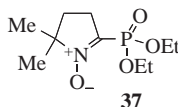
²¹⁶ Sablier, M.; Fujii, T. *Chem. Rev.* **2002**, 102, 2855.

²¹⁷ Bucher, G.; Halupka, M.; Kolano, C.; Schade, O.; Sander, W. *Eur. J. Org. Chem.* **2001**, 545.

²¹⁸ See Wertz, J.E.; Bolton, J.R. *Electron Spin Resonance*, McGraw-Hill, NY, **1972** [reprinted by Chapman and Hall, NY, and Methuen: London, **1986**]; Assenheim, H.M. *Introduction to Electron Spin Resonance*, Plenum, NY, **1967**; Bersohn, R.; Baird, J.C. *An Introduction to Electron Paramagnetic Resonance*, W.A. Benjamin, NY, **1966**. For reviews, see Bunce, N.J. *J. Chem. Educ.* **1987**, 64, 907; Hirota, N.; Ohya-Nishiguchi, H. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed., pt. 2, Wiley, NY, **1986**, pp. 605–655; Griller, D.; Ingold, K.U. *Acc. Chem. Res.* **1980**, 13, 193; Norman, R.O.C. *Chem. Soc. Rev.* **1980**, 8, 1; Fischer, H. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, pp. 435–491; Turro, N.J.; Kleinman, M.H.; Karatekin, E. *Angew. Chem. Int. Ed.* **2000**, 39, 4437; Kurreck, H.; Kirste, B.; Lubitz, W. *Angew. Chem. Int. Ed.* **1984**, 23, 173. See also, Poole, Jr., C.P. *Electron Spin Resonance. A Comprehensive Treatise on Experimental Techniques*, 2nd ed., Wiley, NY, **1983**.

²¹⁹ Davies, A.G. *Chem. Soc. Rev.* **1993**, 22, 299.

protons).²²⁰ Fortunately (for the existence of most free radicals is very short), it is not necessary for a radical to be persistent for an ESR spectrum to be obtained. Electron spin resonance spectra have been observed for radicals with lifetimes considerably <1 s. Failure to observe an ESR spectrum does not prove that radicals are not involved, since the concentration may be too low for direct observation. In such cases, the *spin-trapping* technique can be used.²²¹ In this technique, a compound is added that is able to combine with very reactive radicals to produce more persistent radicals; the new radicals can be observed by ESR. Azulenyl nitrones have been developed as chromotropic spin-trapping agents.²²² An important class of spin-trapping compounds are nitroso compounds, which react with radicals to give stable nitroxide radicals:²²³ $RN=O + R'\cdot \rightarrow RR'N-O\cdot$. An *N*-oxide spin trap has been developed [37; 2(diethylphosphino)-5,5-dimethyl-1-pyrroline-*N*-oxide], and upon trapping a reactive free radical, ³¹P NMR can be used to identify it.²²⁴ This technique is effective, and short-lived species (e.g., the oxiranylmethyl radical) have been detected by spin trapping.²²⁵ Other molecules have been used to probe the intermediacy of radicals via SET processes. They are called SET probes.²²⁶



Because there is an equal probability that a given unpaired electron will have a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$, radicals are observed as a single line in an ESR spectrum unless they interact with other electronic or nuclear spins or possess magnetic anisotropy, in which case two or more lines may appear in the spectrum.²²⁷

Another magnetic technique for the detection of free radicals uses an ordinary NMR instrument. It was discovered²²⁸ that if an NMR spectrum is taken during the course of a reaction, certain signals might be enhanced, either in a positive or negative direction; others may be reduced. When this type of behavior, called *chemically induced dynamic nuclear polarization*²²⁹ (CIDNP), is found in the NMR spectrum of the product of a reaction, it

²²⁰ See Walton, J.C. *Rev. Chem. Intermed.* **1984**, 5, 249; Kochi, J.K. *Adv. Free-Radical Chem.* **1975**, 5, 189; Bielski, B.H.J.; Gebicki, J.M. *Atlas of Electron Spin Resonance Spectra*, Academic Press, NY, **1967**.

²²¹ See Janzen, E.G.; Haire, D.L. *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, 1, 253; Perkins, M.J. *Adv. Phys. Org. Chem.* **1980**, 17, 1; Zubarev, V.E.; Belevskii, V.N.; Bugaenko, L.T. *Russ. Chem. Rev.* **1979**, 48, 729; Evans, C.A. *Aldrichimica Acta* **1979**, 12, 23; Janzen, E.G. *Acc. Chem. Res.* **1971**, 4, 31. See also, the collection of papers on this subject in *Can. J. Chem.* **1982**, 60, 1379.

²²² Becker, D.A.; Natero, R.; Echegoyen, L.; Lawson, R.C. *J. Chem. Soc. Perkin Trans. 2* **1998**, 1289. Also see, Klivenyi, P.; Matthews, R.T.; Wermer, M.; Yang, L.; MacGarvey, U.; Becker, D.A.; Natero, R.; Beal, M.F. *Experimental Neurobiology* **1998**, 152, 163.

²²³ For a series of papers on nitroxide radicals, see *Pure Appl. Chem.* **1990**, 62, 177.

²²⁴ Janzen, E.G.; Zhang, Y.-K. *J. Org. Chem.* **1995**, 60, 5441. For the preparation of a new but structurally related spin trap see Karoui, H.; Nsanzumuhire, C.; Le Moigne, F.; Tordo, P. *J. Org. Chem.* **1999**, 64, 1471.

²²⁵ Grossi, L.; Strazzari, S. *Chem. Commun.* **1997**, 917.

²²⁶ Timberlake, J.W.; Chen, T. *Tetrahedron Lett.* **1994**, 35, 6043; Tanko, J.M.; Brammer, Jr., L.E.; Hervás, M.; Campos, K. *J. Chem. Soc. Perkin Trans. 2* **1994**, 1407.

²²⁷ Harry Frank, University of Connecticut, Storrs, CT., Personal Communication.

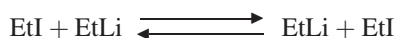
²²⁸ Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* **1969**, 91, 746; Lepley, A.R. *J. Am. Chem. Soc.* **1969**, 91, 749; Lepley, A.R.; Landau, R.L. *J. Am. Chem. Soc.* **1969**, 91, 748.

²²⁹ See Lepley, R.L.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, **1973**. Bargon, J. *Helv. Chim. Acta* **2006**, 89, 2082. For reviews, see Adrian, F.J. *Rev. Chem. Intermed.* **1986**, 7, 173; Closs, G.L.; Miller, R.J.; Redwine, O.D. *Acc. Chem. Res.* **1985**, 18, 196; Closs, G.L. *Adv. Magn. Reson.* **1974**, 7, 157; Lawler, R.G. *Acc. Chem. Res.* **1972**, 5, 25; Kaptain, R. *Adv. Free-Radical Chem.* **1975**, 5, 319.



FIG. 5.1.²³¹ (a) The NMR spectrum taken during reaction between EtI and EtLi in benzene (the region between 0.5 and 3.5 δ was scanned with an amplitude twice that of the remainder of the spectrum). The signals at 1.0–1.6 δ are due to butane, some of which is also formed in the reaction. (b) Reference spectrum of EtI. [Reprinted with permission from Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* **1969**, 91, 746. Copyright © 1969 American Chemical Society.]

means that *at least a portion of that product was formed via the intermediacy of a free radical*.²³⁰ For example, the question was raised whether radicals were intermediates in the exchange reaction between ethyl iodide and ethyllithium (Reaction 12-39):



Curve *a* in Fig. 5.1²³¹ shows an NMR spectrum taken during the course of the reaction. Curve *b* is a reference spectrum of ethyl iodide (CH_3 protons at $\delta = 1.85$; CH_2 protons at $\delta = 3.2$). Note that in curve *a* some of the ethyl iodide signals are enhanced; others go below the base line (*negative enhancement*; also called *emission*). Thus the ethyl iodide formed in the exchange shows CIDNP and so was formed via a free radical intermediate. Chemically induced dynamic nuclear polarization results when protons in a reacting molecule become dynamically coupled to an unpaired electron while traversing the path from reactants to products. Although the presence of CIDNP almost always means that a free radical is involved,²³² its absence does not prove that a free radical intermediate is

²³⁰ A related technique is called CIDEP. For a review, see Hore, P.J.; Joslin, C.G.; McLauchlan, K.A. *Chem. Soc. Rev.* **1979**, 8, 29.

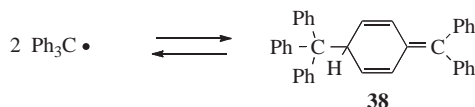
²³¹ Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* **1969**, 91, 746.

²³² It has been shown that CIDNP can also arise in cases where para hydrogen (H_2 in which the nuclear spins are opposite) is present: Eisenschmid, T.C.; Kirss, R.U.; Deutsch, P.P.; Hommeltoft, S.I.; Eisenberg, R.; Bargon, J.; Lawler, R.G.; Balch, A.L. *J. Am. Chem. Soc.* **1987**, 109, 8089.

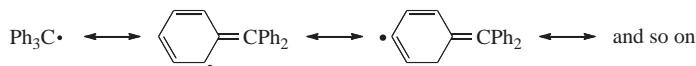
necessarily absent, since reactions involving free radical intermediates can also take place without observable CIDNP. Also, the presence of CIDNP does not prove that *all* of a product was formed via a free radical intermediate, only that some of it was. Note that dynamic nuclear polarization (DNP) enhances signal intensities in the NMR spectra of solids and liquids. In a contemporary DNP experiment, a diamagnetic sample is doped with a paramagnet and the large polarization of the electron spins is transferred to the nuclei via microwave irradiation of the EPR spectrum.²³³ Dynamic nuclear polarization has been used to examine biradicals.²³⁴

As with carbocations, the stability order of free radicals is tertiary > secondary > primary, explainable by field effects and hyperconjugation, analogous to that in carbocations (Sec. 5.A.ii).²³⁵

With resonance possibilities, the stability of free radicals increases,²³⁶ some can be kept indefinitely.²³⁷ Benzylic and allylic²³⁸ radicals for which canonical forms can be drawn similar to those shown for the corresponding cations (Sec. 5.A.ii) and anions (Sec. 5.B.i, category 1) are more stable than simple alkyl radicals, but still have only a transient existence under ordinary conditions. Note that 2-phenylethyl radicals have been shown to exhibit bridging of the phenyl group.²³⁹



The triphenylmethyl and similar radicals²⁴⁰ are stable enough to exist in solution at room temperature, although they are in equilibrium with a dimeric form. The concentration of triphenylmethyl radical in benzene solution is ~2% at room temperature. For many years, it was assumed that $\text{Ph}_3\text{C} \cdot$, the first stable free radical known,²⁴¹ dimerized to hexaphenylethane ($\text{Ph}_3\text{C}-\text{CPh}_3$),²⁴² but UV and NMR investigations have shown that the true structure is **38**.²⁴³ Although triphenylmethyl-type radicals are stabilized by resonance:



²³³ Wind, R.A.; Duijvestijn, M.J.; van der Lugt, C.; Manenschijn, A.; Vriend, J. *Prog. Nucl. Magn. Reson. Spectrosc.* **1985**, *17*, 33.

²³⁴ Hu, K.-N.; Yu, H.-h.; Swager, T. M.; Griffin, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 10844. A discussion of electronic effects is found in Wagner, P.J.; Wang, L. *Org. Lett.* **2006**, *8*, 645.

²³⁵ For a discussion of the role of alkyl substitution with respect to radical stabilization, see Gronert, S. *J. Org. Chem.* **2006**, *71*, 7045. For a discussion concerning data that hyperconjugation stabilizes alkyl radicals, see Gronert, S. *Org. Lett.* **2007**, *9*, 2211.

²³⁶ For a discussion, see Robaugh, D.A.; Stein, S.E. *J. Am. Chem. Soc.* **1986**, *108*, 3224.

²³⁷ See Forrester, A.R.; Hay, J.M.; Thomson, R.H. *Organic Chemistry of Stable Free Radicals*, Academic Press, NY, **1968**.

²³⁸ For an electron diffraction study of the allyl radical, see Vajda, E.; Tremmel, J.; Rozsondai, B.; Hargittai, I.; Mal'tsev, A.K.; Kagramanov, N.D.; Nefedov, O.M. *J. Am. Chem. Soc.* **1986**, *108*, 4352.

²³⁹ Asensio, A.; Dannenberg, J. J. *J. Org. Chem.* **2001**, *66*, 5996.

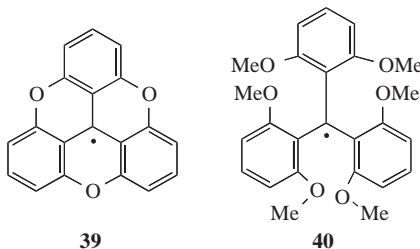
²⁴⁰ For a review, see Sholle, V.D.; Rozantsev, E.G. *Russ. Chem. Rev.* **1973**, *42*, 1011.

²⁴¹ Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757; *Ber.* **1900**, *33*, 3150.

²⁴² For hexaphenylethane derivatives, see Stein, M.; Winter, W.; Rieker, A. *Angew. Chem. Int. Ed.* **1978**, *17*, 692; Yannoni, N.; Kahr, B.; Mislow, K. *J. Am. Chem. Soc.* **1988**, *110*, 6670.

²⁴³ Volz, H.; Lotsch, W.; Schnell, H. *Tetrahedron* **1970**, *26*, 5343; McBride, J. *Tetrahedron* **1974**, *30*, 2009. See Guthrie, R.D.; Weisman, G.R. *Chem. Commun.* **1969**, 1316; Takeuchi, H.; Nagai, T.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 753; Peyman, A.; Peters, K.; von Schnering, H.G.; Rüchardt, C. *Chem. Ber.* **1990**, *123*, 1899.

steric hindrance to dimerization and not resonance is the major cause of their stability.²⁴⁴ This was demonstrated by the preparation of the radicals **39** and **40**.²⁴⁵ These radicals are electronically very similar, but **39**, being planar, has much less steric hindrance to dimerization than $\text{Ph}_3\text{C}^\bullet$, while **40**, with six groups in ortho positions, has much more. On the other hand, the planarity of **35** means that it has a maximum amount of



resonance stabilization, while **40** must have much less, since its degree of planarity should be even less than $\text{Ph}_3\text{C}^\bullet$, which itself is propeller shaped and not planar. Thus if resonance is the chief cause of the stability of $\text{Ph}_3\text{C}^\bullet$, **40** should dimerize and **39** should not, but if steric hindrance is the major cause, the reverse should happen. It was found²³³ that **40** gave no evidence of dimerization, even in the solid state, while **39** existed primarily in the dimeric form, which is dissociated to only a small extent in solution.²⁴⁶ This result indicates that steric hindrance to dimerization is the major cause for the stability of triarylmethyl radicals. A similar conclusion was reached in the case of $(\text{NC})_3\text{C}^\bullet$, which dimerizes readily although it is considerably stabilized by resonance.²⁴⁷ Nevertheless, that resonance is still an important contributing factor to the stability of radicals is shown by the facts that (1) the radical $t\text{-Bu}(\text{Ph})_2\text{C}^\bullet$ dimerizes more than $\text{Ph}_3\text{C}^\bullet$, while $p\text{-PhCOC}_6\text{H}_4(\text{Ph}_2)\text{C}^\bullet$ dimerizes less.²⁴⁸ The latter has more canonical forms than $\text{Ph}_3\text{C}^\bullet$, but steric hindrance should be about the same (for attack at one of the two rings). (2) A number of radicals $(p\text{-XC}_6\text{H}_4)_3\text{C}^\bullet$, with $\text{X}=\text{F}$, Cl , O_2N , CN , and so on, do not dimerize, but are kinetically stable.²⁴⁹ Completely chlorinated triarylmethyl radicals are more stable than the unsubstituted kind, probably for steric reasons, and many are quite inert in solution and in the solid state.²⁵⁰

Allylic radical are relatively stable, and the pentadienyl radical is particularly stable, but (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-stereoisomers can form. It has been calculated that the (*Z,Z*)-pentadienyl radical is 5.6 kcal mol^{-1} less stable than the (*E,E*)-pentadienyl radical.²⁵¹ Note that vinyl radicals have (*E*)- and (*Z*)-forms and the inversion barrier from one to the other increases as the electronegativity of substituents increase.²⁵² Conjugated propargylic radicals are calculated to have diminished stability as the

²⁴⁴ For a review of steric effects in free radical chemistry, see Rüchardt, C. *Top. Curr. Chem.* **1980**, 88, 1.

²⁴⁵ Sabacky, M.J.; Johnson, Jr., C.S.; Smith, R.G.; Gutowsky, H.S.; Martin, J.C. *J. Am. Chem. Soc.* **1967**, 89, 2054.

²⁴⁶ Müller, E.; Moosmayer, A.; Rieker, A.; Scheffler, K. *Tetrahedron Lett.* **1967**, 3877. See also, Neugebauer, F. A.; Hellwinkel, D.; Aulmich, G. *Tetrahedron Lett.* **1978**, 4871.

²⁴⁷ Kaba, R.A.; Ingold, K.U. *J. Am. Chem. Soc.* **1976**, 98, 523.

²⁴⁸ Zarkadis, A.K.; Neumann, W.P.; Marx, R.; Uzick, W. *Chem. Ber.* **1985**, 118, 450; Zarkadis, A.K.; Neumann, W.P.; Uzick, W. *Chem. Ber.* **1985**, 118, 1183.

²⁴⁹ Dünnebacke, D.; Neumann, W.P.; Penenory, A.; Stewen, U. *Chem. Ber.* **1989**, 122, 533.

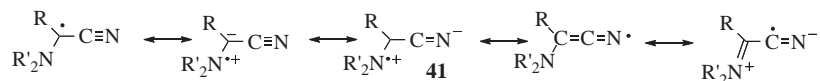
²⁵⁰ For reviews, see Ballester, M. *Adv. Phys. Org. Chem.* **1989**, 25, 267, pp. 354–405; *Acc. Chem. Res.* **1985**, 18, 380. See also, Hegarty, A.F.; O'Neill, P. *Tetrahedron Lett.* **1987**, 28, 901.

²⁵¹ Fort, Jr., R.C.; Hrovat, D.A.; Borden, W.T. *J. Org. Chem.* **1993**, 58, 211.

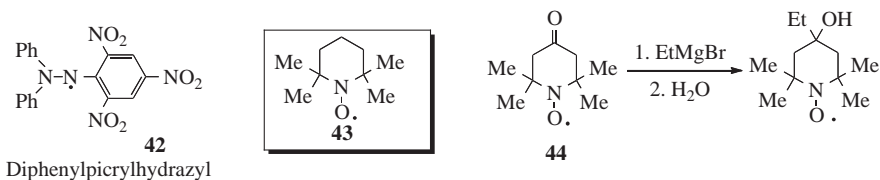
²⁵² Galli, C.; Guarnieri, A.; Koch, H.; Mencarelli, P.; Rappoport, Z. *J. Org. Chem.* **1997**, 62, 4072.

conjugation increases, in contrast to the behavior of alkenes.²⁵³ Cyclopropyl alkynes have been used as mechanistic probes to distinguish between vinyl radicals and ionic intermediates.²⁵⁴ Enolate radicals are also known.²⁵⁵

It has been postulated that the stability of free radicals is enhanced by the presence at the radical center of *both* an electron-donating and an electron-withdrawing group.²⁵⁶ This finding is called the *push–pull* or *captodative effect* (see also, Sec. 4.K.i). The effect arises from increased resonance, as in **41**.



There is some evidence in favor²⁵⁷ of the captodative effect, some of it from ESR studies.²⁵⁸ However, there is also experimental²⁵⁹ and theoretical²⁶⁰ evidence against it. There is evidence that while $\text{FCH}_2\cdot$ and $\text{F}_2\text{CH}\cdot$ are more stable than $\text{CH}_3\cdot$, the radical $\text{CF}_3\cdot$ is less stable; that is, the presence of the third F destabilizes the radical.²⁶¹



Certain radicals with unpaired electron on a carbon are also very stable.²⁶² Radicals can be stabilized by intramolecular hydrogen bonding.²⁶³ Diphenylpicrylhydrazyl (**42**) is a solid that can be kept for years, and stable neutral azine radicals have been prepared.²⁶⁴ Nitroxide radicals were mentioned previously,²⁶⁵ and the commercially available TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) free radical (**43**) is a stable nitroxyl radical used in

²⁵³ Rogers, D.W.; Matsunaga, N.; Zavitsas, A.A. *J. Org. Chem.* **2006**, 71, 2214.

²⁵⁴ Gottschling, S.E.; Grant, T.N.; Milnes, K.K.; Jennings, M.C.; Baines, K.M. *J. Org. Chem.* **2005**, 70, 2686.

²⁵⁵ Giese, B.; Damm, W.; Wetterich, F.; Zeltz, H.-G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* **1993**, 34, 5885.

²⁵⁶ For reviews, see Sustmann, R.; Korth, H. *Adv. Phys. Org. Chem.* **1990**, 26, 131; Viehe, H.G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, 18, 148.

²⁵⁷ See Pasto, D.J. *J. Am. Chem. Soc.* **1988**, 110, 8164. See also, Ashby, E.C. *Bull. Soc. Chim. Fr.* **1972**, 2133; Bell, N.A. *Educ. Chem.* **1973**, 143.

²⁵⁸ See Sakurai, H.; Kyushin, S.; Nakadaira, Y.; Kira, M. *J. Phys. Org. Chem.* **1988**, 1, 197; Rhodes, C.J.; Roduner, E. *Tetrahedron Lett.* **1988**, 29, 1437; Viehe, H.G.; Merényi, R.; Janousek, Z. *Pure Appl. Chem.* **1988**, 60, 1635; Bordwell, F.G.; Lynch, T. *J. Am. Chem. Soc.* **1989**, 111, 7558.

²⁵⁹ See Bordwell, F.G.; Bausch, M.J.; Cheng, J.P.; Cripe, T.H.; Lynch, T.-Y.; Mueller, M.E. *J. Org. Chem.* **1990**, 55, 58; Bordwell, F.G.; Harrelson, Jr., J.A. *Can. J. Chem.* **1990**, 68, 1714.

²⁶⁰ See Pasto, D.J. *J. Am. Chem. Soc.* **1988**, 110, 8164.

²⁶¹ Jiang, X.; Li, X.; Wang, K. *J. Org. Chem.* **1989**, 54, 5648.

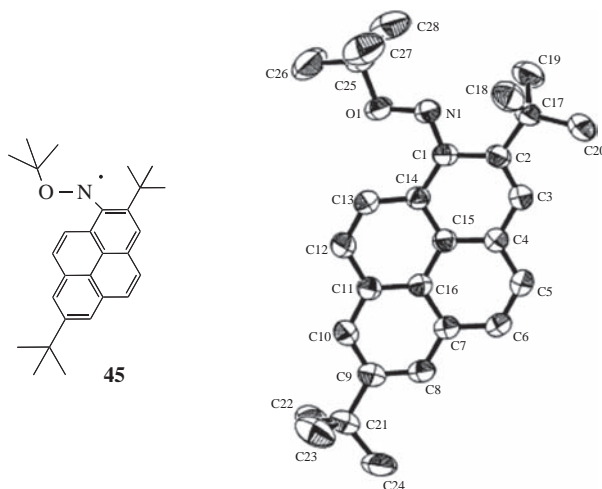
²⁶² For reviews of radicals with the unpaired electron on atoms other than carbon, see, in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, the reviews by Nelson, S.F. pp. 527–593 (*N*-centered); Bentrude, W.G. pp. 595–663 (*P*-centered); Kochi, J.K. pp. 665–710 (*O*-centered); Kice, J.L. pp. 711–740 (*S*-centered); Sakurai, H. pp. 741–807 (Si, Ge, Sn, and Pb centered).

²⁶³ Maki, T.; Araki, Y.; Ishida, Y.; Onomura, O.; Matsumura, Y. *J. Am. Chem. Soc.* **2001**, 123, 3371.

²⁶⁴ Jeromin, G.E. *Tetrahedron Lett.* **2001**, 42, 1863.

²⁶⁵ See Novak, I.; Harrison, L.J.; Kovač, B.; Pratt, L.M. *J. Org. Chem.* **2004**, 69, 7628.

chemical reactions (e.g., oxidations),²⁶⁶ or as a spin trap.²⁶⁷ Nitroxyl radical **44** is a nitroxide radical so stable that reactions can be performed on it (e.g., the *Grignard reaction* shown with **44**; see Reaction 16-24) without affecting the unpaired electron²⁶⁸ (the same is true for some of the chlorinated triarylmethyl radicals mentioned above²⁶⁹). Several nitrogen-containing groups are known to stabilize radicals, and the most effective radical stabilization is via spin delocalization.²⁷⁰ A number of persistent *N-tert*-butoxy-1-aminopyrenyl radicals (e.g., **45**) have been isolated as monomeric radical crystals (see **46**, the X-ray crystal



structure of **45**),²⁷¹ and monomeric *N*-alkoxyarylaminylns have been isolated.²⁷² α -Trichloromethylbenzyl(*tert*-butyl)aminoxyl (**47**) is extremely stable.²⁷³ In aqueous media it is stable for > 30 days, and in solution in an aromatic hydrocarbon solvent it has survived for >90 days.²⁷³ Although the stable nitroxide radicals have the α -carbon blocked to prevent radical formation there, stable nitroxide radicals are also known with hydrogen at the α -carbon,²⁷⁴ and long-lived vinyl nitroxide radicals are known.²⁷⁵ A stable

²⁶⁶ See Anelli, P.L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, 69, 212; Fritz-Langhals, E. *Org. Process Res. Dev.* **2005**, 9, 577. See also, Rychnovsky, S.D.; Vaidyanathan, R.; Beauchamp, T.; Lin, R.; Farmer, P.J. *J. Org. Chem.* **1999**, 64, 6745.

²⁶⁷ Volodarsky, L.B.; Reznikov, V.A.; Ovcharenko, V.I. *Synthetic Chemistry of Stable Nitroxides*, CRC Press, Boca Raton, FL, **1994**; Keana, J.F.W. *Chem. Rev.* **1978**, 78, 37; Aurich, H.G. *Nitroxides. In Nitrones, Nitronates, Nitroxides*, Patai, S.; Rappoport, Z., Eds., Wiley, NY, **1989**; Chap. 4.

²⁶⁸ Neiman, M.B.; Rozantsev, E.G.; Mamedova, Yu.G. *Nature (London)* **1963**, 200, 256. See Breuer, E.; Aurich, H.G.; Nielsen, A. *Nitrones, Nitronates, and Nitroxides*, Wiley, NY, **1989**, pp. 313–399; Rozantsev, E.G.; Sholle, V.D. *Synthesis* **1971**, 190, 401.

²⁶⁹ See Ballester, M.; Veciana, J.; Riera, J.; Castañer, J.; Armet, O.; Rovira, C. *J. Chem. Soc. Chem. Commun.* **1983**, 982.

²⁷⁰ Adam, W.; Ortega Schulte, C. M. *J. Org. Chem.* **2002**, 67, 4569.

²⁷¹ Miura, Y.; Matsuba, N.; Tanaka, R.; Teki, Y.; Takui, T. *J. Org. Chem.* **2002**, 67, 8764. For another stable nitroxide radical, see Huang, W.-l.; Chiarelli, R.; Rassat, A. *Tetrahedron Lett.* **2000**, 41, 8787.

²⁷² Miura, Y.; Tomimura, T.; Matsuba, N.; Tanaka, R.; Nakatsuji, M.; Teki, Y. *J. Org. Chem.* **2001**, 66, 7456. See also, Miura, Y.; Muranaka, Y.; Teki, Y. *J. Org. Chem.* **2006**, 71, 4786; Miura, Y.; Mu, Y. *Chem. Lett.* **2005**, 34, 48

²⁷³ Janzen, E.G.; Chen, G.; Bray, T.M.; Reinke, L.A.; Poyer, J.L.; McCay, P.B. *J. Chem. Soc. Perkin Trans. 2.* **1993**, 1983.

²⁷⁴ Reznikov, V.A.; Volodarsky, L.B. *Tetrahedron Lett.* **1994**, 35, 2239.

²⁷⁵ Reznikov, V.A.; Pervukhina, N.V.; Ikorskii, V.N.; Ovcharenko, V.I.; Grand, A. *Chem. Commun.* **1999**, 539.

TABLE 5.4 The D_{298} Values for Some R—H Bonds^{a,b}

R	Reference	D_{298}	
		kcal mol ⁻¹	kJ mol ⁻¹
Ph [•]	279	111	464
CF ₃ [•]		107	446
CH ₂ =CH [•]		106	444
Cyclopropyl	280	106	444
Me [•]		105	438
Et [•]		100	419
Me ₃ CCH ₂ [•]		100	418
Pr [•]		100	417
Cl ₃ C [•]		96	401
Me ₂ CH [•]		96	401
Me ₃ C [•]	281	95.8	401
Cyclohexyl		95.5	400
PhCH ₂ [•]		88	368
HCO [•]		87	364
CH ₂ =CH—CH ₂ [•]		86	361

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^aSee Ref. 278.

^bFree radical stability is in the reverse order.

organic radical lacking resonance stabilization has been prepared (**48**), and its X-ray crystal structure was obtained.²⁷⁶ Dissociation energies (D values) of R—H bonds provide a measure of the relative inherent stability of free radicals R.²⁷⁷ Table 5.4 lists such values.^{278–281} The higher the D value, the less stable the radical. Bond-dissociation energies also have been reported for the C—H bond of alkenes and dienes²⁸² and for the C—H bond in radical precursors XYC—H, where X,Y can be H, alkyl, COOR, COR, SR, CN, NO₂, and so on.²⁸³ Bond dissociation energies for the C—O bond in hydroperoxide radicals (ROO[•]) have also been reported.²⁸⁴ However, note that basing radical

²⁷⁶ Apeloig, Y.; Bravo-Zhivotovskii, D.; Bendikov, M.; Danovich, D.; Botoshansky, M.; Vakulrskaya, T.; Voronkov, M.; Samoilova, R.; Zdravkova, M.; Igonin, V.; Shklover, V.; Struchkov, Y. *J. Am. Chem. Soc.* **1999**, *121*, 8118.

²⁷⁷ It has been claimed that relative D values do not provide such a measure: Nicholas, A.M. de P.; Arnold, D.R. *Can. J. Chem.* **1984**, *62*, 1850, 1860.

²⁷⁸ Except where noted, these values are from Lide, D.R. (Ed.), *Handbook of Chemistry and Physics*, 87th ed.; CRC Press: Boca Raton, FL, **2007**, pp. 9-60–9-61. For another list of D values, see McMillen, D.F.; Golden, D.M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493. See also, Holmes, J.L.; Lossing, F.P.; Maccoll, A. *J. Am. Chem. Soc.* **1988**, *110*, 7339; Holmes, J.L.; Lossing, F.P. *J. Am. Chem. Soc.* **1988**, *110*, 7343; Roginskii, V.A. *J. Org. Chem. USSR* **1989**, *25*, 403.

²⁷⁹ For the IR of a matrix-isolated phenyl radical, see Friderichsen, A. V.; Radziszewski, J. G.; Nimlos, M. R.; Winter, P. R.; Dayton, D. C.; David, D. E.; Ellison, G. B. *J. Am. Chem. Soc.* **2001**, *123*, 1977.

²⁸⁰ For a review of cyclopropyl radicals, see Walborsky, H.M. *Tetrahedron* **1981**, *37*, 1625. See also, Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, **1990**.

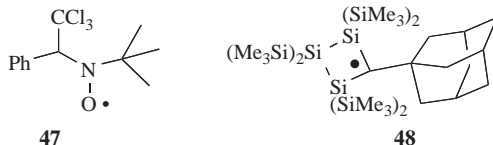
²⁸¹ This value is from Gutman, D. *Acc. Chem. Res.* **1990**, *23*, 375.

²⁸² Zhang, X.-M. *J. Org. Chem.* **1998**, *63*, 1872.

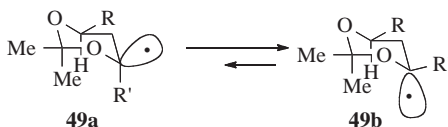
²⁸³ Brocks, J.J.; Beckhaus, H.-D.; Beckwith, A.L.J.; Rüchardt, C. *J. Org. Chem.* **1998**, *63*, 1935.

²⁸⁴ Pratt, D.A.; Porter, N.A. *Org. Lett.* **2003**, *5*, 387.

stabilization energy on the difference between the bond dissociation energy (BDE) of $\text{CH}_3\text{—H}$, as a reference point, and of R—H has been observed to have shortcomings.²⁸⁵ The problem is that these values are only applicable to carbon-centered radicals, and the stabilization energies are not transferable and cannot be used to estimate BDE of R—R' , R—R , or any R—X compounds.²⁸²



There are two possible structures for simple alkyl radicals.²⁸⁶ They might have sp^2 bonding, in which case the structure would be planar, with the odd electron in a p orbital, or the bonding might be sp^3 , which would make the structure pyramidal and place the odd electron in an sp^3 orbital. The ESR spectra of $\cdot\text{CH}_3$ and other simple alkyl radicals as well as other evidence indicate that these radicals have planar structures.²⁸⁷ This finding is in accord with the known loss of optical activity when a free radical is generated at a stereogenic carbon.²⁸⁸ In addition, electronic spectra of the CH_3 and CD_3 radicals (generated by flash photolysis) in the gas phase have definitely established that under these conditions the radicals are planar or near planar.²⁸⁹ The IR spectra of $\cdot\text{CH}_3$ trapped in solid argon led to a similar conclusion.²⁹⁰ Despite the usual loss of optical activity noted above, asymmetric radicals can be prepared in some cases. For example, asymmetric nitroxide radicals are known.²⁹¹ An anomeric effect was observed in alkoxy radical **49**, where the ratio of **49a**/**49b** was 1:1.78.²⁹²



Evidence from studies on bridgehead compounds shows that although a planar configuration is more stable, pyramidal structures are not impossible. In contrast to the situation with carbocations, free radicals have often been generated at bridgeheads, although studies have shown that bridgehead free radicals are less rapidly formed than the corresponding open-chain radicals.²⁹³ In sum, the available evidence indicates that

²⁸⁵ Zavitsas, A.A.; Rogers, D.W.; Matsunaga, N. *J. Org. Chem.* **2010**, 75, 5697.

²⁸⁶ For a review, see Kaplan, L. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, pp. 361–434.

²⁸⁷ See Giese, B.; Beckhaus, H. *Angew. Chem. Int. Ed.* **1978**, 17, 594; Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc.* **1978**, 100, 2556. See, however, Paddon-Row, M.N.; Houk, K.N. *J. Am. Chem. Soc.* **1981**, 103, 5047.

²⁸⁸ There are a few exceptions. See Section 14.A.iv.

²⁸⁹ Herzberg, G. *Proc. R. Soc. London, Ser. A* **1961**, 262, 291. See also, Tan, L.Y.; Winer, A.M.; Pimentel, G.C. *J. Chem. Phys.* **1972**, 57, 4028; Yamada, C.; Hirota, E.; Kawaguchi, K. *J. Chem. Phys.* **1981**, 75, 5256.

²⁹⁰ Andrews, L.; Pimentel, G.C. *J. Chem. Phys.* **1967**, 47, 3637; Milligan, D.E.; Jacox, M.E. *J. Chem. Phys.* **1967**, 47, 5146.

²⁹¹ Tamura, R.; Susuki, S.; Azuma, N.; Matsumoto, A.; Todda, F.; Ishii, Y. *J. Org. Chem.* **1995**, 60, 6820.

²⁹² Rychnovsky, S.D.; Powers, J.P.; LePage, T.J. *J. Am. Chem. Soc.* **1992**, 114, 8375.

²⁹³ Danen, W.C.; Tipton, T.J.; Saunders, D.G. *J. Am. Chem. Soc.* **1971**, 93, 5186; Fort, Jr., R.C.; Hiti, J. *J. Org. Chem.* **1977**, 42, 3968; Lomas, J.S. *J. Org. Chem.* **1987**, 52, 2627.

although simple alkyl free radicals prefer a planar, or near-planar shape, the energy difference between a planar and a pyramidal free radical is not great. However, free radicals in which the carbon is connected to atoms of high electronegativity (e.g., $\cdot\text{CF}_3$), prefer a pyramidal shape;²⁹⁴ increasing the electronegativity increases the deviation from planarity.²⁹⁵ Cyclopropyl radicals are also pyramidal.²⁹⁶ Free radicals with resonance are definitely planar, although triphenylmethyl-type radicals are propeller shaped,²⁹⁷ like the analogous carbocations (Sec. 5.A.i). Radicals possessing simple alkyl substituents attached to the radical carbon (C \cdot) that have C^{sp3}—C^{sp3} bonds, and rotation about those bonds is possible. The internal rotation barrier for the *tert*-butyl radical (Me₃C \cdot), for example, was estimated to be $\sim 1.4 \text{ kcal mol}^{-1}$ 6 kJ mol^{-1} .²⁹⁸

A number of diradicals (also called biradicals) are known,²⁹⁹ and the thermodynamic stability of diradicals has been examined.³⁰⁰ Orbital phase theory has been applied to the development of a theoretical model of localized 1,3-diradicals, and used to predict the substitution effects on the spin preference and S–T gaps, and to design stable localized carbon-centered 1,3-diradicals.³⁰¹ When the unpaired electrons of a diradical are widely separated, for example, as in $\cdot\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\cdot$, the species behaves spectrally like two doublets. When they are close enough for interaction or can interact through an unsaturated system (as in trimethylenemethane),³⁰² they can have total spin numbers of +1, 0, or -1, since each electron could be either $+\frac{1}{2}$ or $-\frac{1}{2}$. Spectroscopically they are called *triplets*,³⁰³ since each of the three possibilities is represented among the molecules and gives rise to its own spectral peak. In triplet molecules, the two unpaired electrons have the same spin. Not all diradicals have a triplet ground state. In 2,3-dimethylelecyclohexane-1,4-diyl (**50**), the singlet and triplet states were found to be almost degenerate.³⁰⁴ Diradicals (e.g., **51**) are very stable with a triplet ground state.³⁰⁵ Diradicals are generally short-lived species. The lifetime of **52** was measured to be $< 0.1 \text{ ns}$ and other diradicals were found to have lifetimes

²⁹⁴ Fessenden, R.W.; Schuler, R.H. *J. Chem. Phys.* **1965**, *43*, 2704; Rogers, M.T.; Kispert, L.D. *J. Chem. Phys.* **1967**, *46*, 3193; Pauling, L. *J. Chem. Phys.* **1969**, *51*, 2767.

²⁹⁵ See Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* **1974**, *96*, 2201. For a discussion, see Krusic, P.J.; Bingham, R.C. *J. Am. Chem. Soc.* **1976**, *98*, 230.

²⁹⁶ See Deycard, S.; Hughes, L.; Luszyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* **1987**, *109*, 4954.

²⁹⁷ Adrian, F.J. *J. Chem. Phys.* **1958**, *28*, 608; Andersen, P. *Acta Chem. Scand.* **1965**, *19*, 629.

²⁹⁸ Kubota, S.; Matsushita, M.; Shida, T.; Abu-Raqabah, A.; Symons, M.C.R.; Wyatt, J.L. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 140.

²⁹⁹ See Borden, W.T. *Diradicals*, Wiley, NY, **1982**; Johnston, L.J.; Scaiano, J.C. *Chem. Rev.* **1989**, *89*, 521; Doubleday Jr., C.; Turro, N.J.; Wang, J. *Acc. Chem. Res.* **1989**, *22*, 199; Scheffer, J.R.; Trotter, J. *Rev. Chem. Intermed.* **1988**, *9*, 271; Wilson, R.M. *Org. Photochem.* **1985**, *7*, 339; Borden, W.T. *React. Intermed. (Wiley)* **1985**, *3*, 151; **1981**, *2*, 175; Borden, W.T.; Davidson, E.R. *Acc. Chem. Res.* **1981**, *14*, 69. See also, Döhnert, D.; Koutecky, J. *J. Am. Chem. Soc.* **1980**, *102*, 1789. For a series of papers on diradicals, see *Tetrahedron* **1982**, *38*, 735. For a stable hydrocarbon diradical, see Rajca, A.; Shiraishi, K.; Vale, M.; Han, H.; Rajca, S. *J. Am. Chem. Soc.* **2005**, *127*, 9014.

³⁰⁰ Zhang, D. Y.; Borden, W. T. *J. Org. Chem.* **2002**, *67*, 3989.

³⁰¹ Ma, J.; Ding, Y.; Hattori, K.; Inagaki, S. *J. Org. Chem.* **2004**, *69*, 4245.

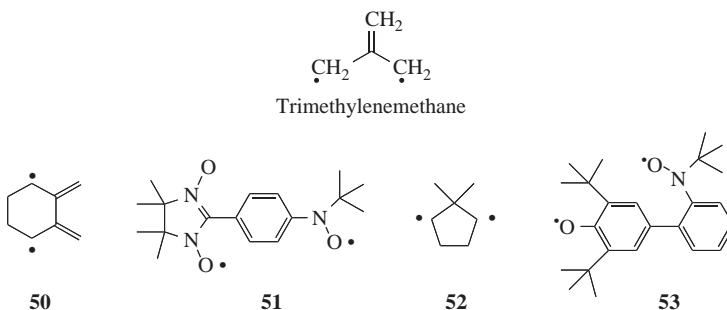
³⁰² For reviews of trimethylenemethane, see Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* **1979**, *30*, 125; Bergman, R.G. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, **1973**, pp. 141–149.

³⁰³ See Turro, N.J. *J. Chem. Educ.* **1969**, *46*, 2; Wasserman, E.; Hutton, R.S. *Acc. Chem. Res.* **1977**, *10*, 27; Ichinose, N.; Mizuno, K.; Otsuji, Y.; Caldwell, R.A.; Helms, A.M. *J. Org. Chem.* **1998**, *63*, 3176.

³⁰⁴ Matsuda, K.; Iwamura, H. *J. Chem. Soc. Perkin Trans. 2* **1998**, 1023. Also see, Roth, W.R.; Wollweber, D.; Offerhaus, R.; Rekowski, V.; Lenmartz, H.-W.; Sustmann, R.; Müller, W. *Chem. Ber.* **1993**, *126*, 2701.

³⁰⁵ Inoue, K.; Iwamura, H. *Angew. Chem. Int. Ed.* **1995**, *34*, 927. Also see, Ulrich, G.; Ziesel, R.; Luneau, D.; Rey, P. *Tetrahedron Lett.* **1994**, *35*, 1211.

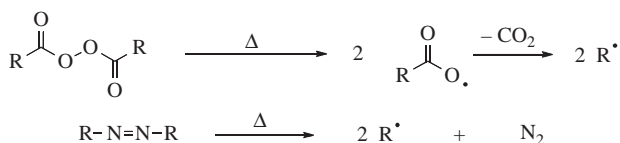
in the 4–316-ns range.³⁰⁶ Diradical **53** [3,5-di-*tert*-butyl-3'-(*N*-*tert*-butyl-*N*-aminoxyl)-4-oxybiphenyl] was found to have a lifetime of weeks even in the presence of oxygen, and survived brief heating in toluene up to ~60 °C.³⁰⁷ Radicals with both unpaired electrons on the same carbon are discussed under carbenes. 1,4-Biradicals are known, and α -carbonyl substituents increase the lifetime of the radical, and negative α -hyperconjugation (see Sec. 2.M) has been suggested as the cause.³⁰⁸



5.C.ii. The Generation and Fate of Free Radicals³⁰⁹

Free radicals are formed from molecules by breaking a bond so that each fragment keeps one electron.^{310,311} The energy necessary to break the bond is supplied in one of two ways.

1. *Thermal Cleavage.* Subjection of any organic molecule to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with *D* values or 20–40 kcal mol^{−1} (80–170 kJ mol^{−1}), cleavage can be caused in the liquid phase. Two common examples are cleavage of diacyl peroxides to acyl radicals that decompose to alkyl radicals³¹² and cleavage of azo compounds to alkyl radicals³¹³



³⁰⁶ Engel, P.S.; Lowe, K.L. *Tetrahedron Lett.* **1994**, 35, 2267.

³⁰⁷ Liao, Y.; Xie, C.; Lahti, P.M.; Weber, R.T.; Jiang, J.; Barr, D.P. *J. Org. Chem.* **1999**, 64, 5176.

³⁰⁸ Cai, X.; Cygon, P.; Goldfuss, B.; Griesbeck, A.G.; Heckroth, H.; Fujitsuka, M.; Majima, T. *Chemistry: European J.* **2006**, 12, 4662.

³⁰⁹ See Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, **1986**, pp. 267–281; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, **1980**, pp. 44–61.

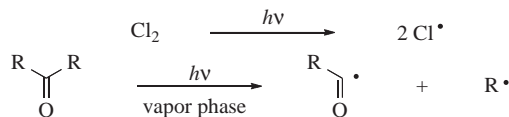
³¹⁰ See Harmony, J.A.K. *Methods Free-Radical Chem.* **1974**, 5, 101.

³¹¹ See Barker, P.J.; Winter, J.N. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, **1985**, pp. 151–218.

³¹² Matsuyama, K.; Sugiura, T.; Minoshima, Y. *J. Org. Chem.* **1995**, 60, 5520; Ryzhkov, L.R. *J. Org. Chem.* **1996**, 61, 2801. See Howard, J.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, **1983**, pp. 235–258; Batt, L.; Liu, M.T.H. in the same volume, pp. 685–710.

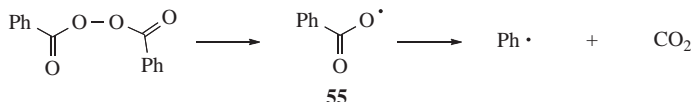
³¹³ See Engel, P.S. *Chem. Rev.* **1980**, 80, 99; Adams, J.S.; Burton, K.A.; Andrews, B.K.; Weisman, R.B.; Engel, P.S. *J. Am. Chem. Soc.* **1986**, 108, 7935; Schmittle, M.; Rüchardt, C. *J. Am. Chem. Soc.* **1987**, 109, 2750.

2. *Photochemical Cleavage* (see Sec. 7.A.v). Light energy of 600–300 nm is 48–96 kcal mol⁻¹ (200–400 kJ mol⁻¹), which is on the order of magnitude of covalent-bond energies. Typical examples are photochemical cleavage of alkyl halides in the presence of triethylamine,³¹⁴ alcohols in the presence of mercuric oxide and iodine,³¹⁵ alkyl 4-nitrobenzenesulfonates,³¹⁶ chlorine and of ketones:



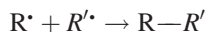
Photolytic decomposition of *N*-hydroxypyridin-2-thione is a method that generates hydroxyl radicals.³¹⁷ The photochemistry of radicals and biradicals has been reviewed.³¹⁸

Radicals are also formed from other radicals, either by the reaction between a radical and a molecule (which *must* give another radical, since the total number of electrons is odd) or by cleavage of a radical³¹⁹ to give another radical, for example, the decomposition of benzoyl peroxide to give the benzoyl radical:



Radicals can also be formed by oxidation or reduction, including electrolytic methods.

Reactions of free radicals either give nonradical products (termination reactions) or lead to other radicals, which themselves must usually react further (propagation reactions). The most common termination reactions are simple coupling of similar or different radicals:



Another termination process is disproportionation:³²⁰

A propagation reaction is one in which a radical reacts to give at least one radical product, which continues the radical reaction sequence. There are four principal propagation reactions, of which the first two are most common:



³¹⁴ Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* **1994**, 35, 8161.

³¹⁵ Courtneidge, J.L. *Tetrahedron Lett.* **1992**, 33, 3053.

³¹⁶ Pasto, D.J.; Cottard, F. *Tetrahedron Lett.* **1994**, 35, 4303.

³¹⁷ Halliwell, B.; Gutteridge, J.M.C. in *Free Radicals in Biology and Medicine*, Oxford University Press, Oxford, **1999**, pp 246–350; DeMatteo, M.P.; Poole, J.S.; Shi, X.; Sachdeva, R.; Hatcher, P.G.; Hadad, C.M.; Platz, M.S. *J. Am. Chem. Soc.* **2005**, 127, 7094.

³¹⁸ Johnston, L.J. *Chem. Rev.* **1993**, 93, 251.

³¹⁹ See Costentin, C.; Robert, M.; Saveant, J.-M. *J. Am. Chem. Soc.* **2003**, 125, 105.

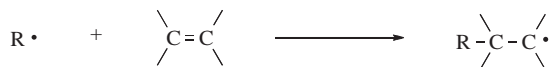
³²⁰ See Pilling, M.J. *Int. J. Chem. Kinet.* **1989**, 21, 267; Khudyakov, I.V.; Levin, P.P.; Kuz'min, V.A. *Russ. Chem. Rev.* **1980**, 49, 982; Gibian, M.J.; Corley, R.C. *Chem. Rev.* **1973**, 73, 441.

1. *Abstraction of Another Atom or Group, Usually a Hydrogen Atom (also see Chap 14).*



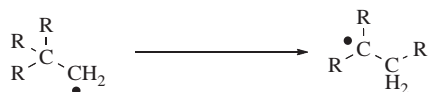
A radical may abstract hydrogen atoms from a second molecule, or by an intramolecular process. A bromine radical (Br^{\bullet}) reacts with an alkane, for example, to give HBr and a carbon radical. This type of reaction is known as hydrogen-atom transfer. Water is an excellent hydrogen atom source for many reactions involving metals.³²¹ The reduction of a carbon radical with Bu_3SnH is an example of a hydrogen-transfer reaction (see Sec. 14.A.i). Indeed, carbon radicals react as hydrogen-bond acceptors.³²² Other atoms may be removed by a radical via atom-transfer reactions. A halogen atom can be transferred in some cases, including the transfer of an iodine atom from an aryl iodide to give an aryl radical.³²³ Solvent effects play a role in hydrogen-atom transfer (hydrogen abstraction), and hydrogen-bonding plays a role.³²⁴

2. *Addition to a Multiple Bond (see Chap 15).*



The radical formed from an alkene may add to the double bond of a second equivalent of alkene, and so on. This is one of the chief mechanisms for vinyl polymerization.

3. *Decomposition.* This process can be illustrated by the decomposition of the benzyloxy radical (see 55).
4. *Rearrangement.*



This reaction is less common than rearrangement of carbocations, but it does occur (though not when R = alkyl or hydrogen; see Chapter 18). Perhaps the best-known rearrangement is that of cyclopropylcarbinyl radicals to a butenyl radical.³²⁵ The rate constant for this rapid ring opening has been measured in certain functionalized cyclopropylcarbinyl radicals by picosecond radical kinetics.³²⁶ Substituent effects on the kinetics of ring opening in substituted cyclopropylcarbinyl radicals have been studied.³²⁷ “The cyclopropylcarbinyl

³²¹ Cuerva, J.M.; Campaña, A.G.; Justicia, J.; Rosales, A.; Oller-López, J.L.; Robles, R.; Cárdenas, D.J.; Buñuel, E.; Oltra, J.E. *Angew. Chem. Int. Ed.* **2006**, 45, 5522.

³²² Hammerum, S. *J. Am. Chem. Soc.* **2009**, 131, 8627.

³²³ Dolenc, D.; Plesniar, B. *J. Org. Chem.* **2006**, 71, 8028.

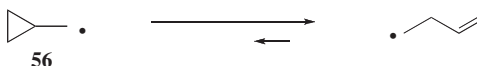
³²⁴ Bietti, M.; Salamone, M. *Org. Lett.* **2010**, 12, 3654.

³²⁵ See Stevenson, J. P.; Jackson, W. F.; Tanko, J. M. *J. Am. Chem. Soc.* **2002**, 124, 4271.

³²⁶ LeTadic-Biadatti, M.-H.; Newcomb, M. *J. Chem. Soc. Perkin Trans. 2* **1996**, 1467. See also, Choi, S.-Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **2000**, 65, 4447; Cooksy, A. L.; King, H. F.; Richardson, W. H. *J. Org. Chem.* **2003**, 68, 9441; Tian, F.; Dolbier, Jr., W.R. *Org. Lett.* **2000**, 2, 835.

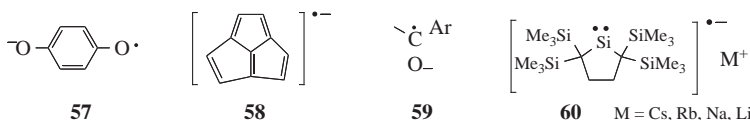
³²⁷ Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **2000**, 122, 2988.

radical (**56**) has found an important application as a radical clock.³²⁸ Various radical processes can be clocked by the competition of direct reaction with the cyclopropylcarbinyl radical (k_i) and opening of that radical to the 1-buten-4-yl radical (k_r) followed by trapping. Relative rates (k_i/k_r) can be determined from yields of 4-X-1-butene and cyclopropylcarbinyl products as a function of the radical trap³²⁹ (X—Y) concentration. Absolute rate constants have been determined for a number of radicals with various radical traps by laser flash photolysis methods.³³⁰ From these absolute rate constants, reasonably accurate values of k_i can be estimated, and with the relative rate (k_i/k_r), a value for k_r can be calculated. From the calibrated radical-clock reaction rate (k_r), rates (k_i) of other competing reactions can be determined from relative rate data (k_i/k_r).³²⁶ Other radical clocks are known.³³¹



Free radicals can also be oxidized to carbocations or reduced to carbanions.³³²

5.C.iii. Radical Ions³³³



Several types of radical anions are known with the unpaired electron or the charge or both on atoms other than carbon. Examples include semiquinones³³⁴ (**57**), acepentalenes (**58**),³³⁵ ketyls³³⁶ (**59**) and the radical anion of the isolable dialkylsilylene (**60**).³³⁷ Radical anions are formed by the reaction of carbene anions with chloromethanes.³³⁸ Reactions in

³²⁸ Newcomb, M.; Choi, S.-Y.; Toy, P. H. *Can. J. Chem.* **1999**, *77*, 1123; Nevill, S. M.; Pincock, J. A. *Can. J. Chem.* **1997**, *75*, 232.

³²⁹ See Barton, D.H.R.; Jacob, M.; Peralez, E. *Tetrahedron Lett.* **1999**, *40*, 9201.

³³⁰ Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* **2000**, *65*, 4447; Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Luszytk, J. *J. Org. Chem.* **1997**, *62*, 1210.

³³¹ See Leardini, R.; Lucarini, M.; Pedulli, G.F.; Valgimigli, L. *J. Org. Chem.* **1999**, *64*, 3726; Roschek, Jr., B.; Tallman, K.A.; Rector, C.L.; Gillmore, J.G.; Pratt, D.A.; Punta, C.; Porter, N.A. *J. Org. Chem.* **2006**, *71*, 3527.

³³² See Khudyakov, I.V.; Kuz'min, V.A. *Russ. Chem. Rev.* **1978**, *47*, 22.

³³³ See Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, **1968**; Gerson, F.; Huber, W. *Acc. Chem. Res.* **1987**, *20*, 85; Todres, Z.V. *Tetrahedron* **1985**, *41*, 2771; Holy, N.L.; Marcum, J.D. *Angew. Chem. Int. Ed.* **1971**, *10*, 115. See Chanon, M.; Rajzmann, M.; Chanon, F. *Tetrahedron* **1990**, *46*, 6193. For a series of papers on this subject, see *Tetrahedron* **1986**, *42*, 6097.

³³⁴ See Depew, M.C.; Wan, J.K.S. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, **1988**, pp. 963–1018; Huh, C.; Kang, C.H.; Lee, H.W.; Nakamura, H.; Mishima, M.; Tsuno, Y.; Yamataka, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1083.

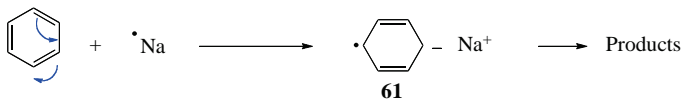
³³⁵ de Meijere, A.; Gerson, F.; Schreiner, P.R.; Merstetter, P.; Schüngel, F.-M. *Chem. Commun.* **1999**, 2189.

³³⁶ See Russell, G.A. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, **1989**, pp. 471–512. See Davies, A.G.; Neville, A.G. *J. Chem. Soc. Perkin Trans. 2* **1992**, 163, 171.

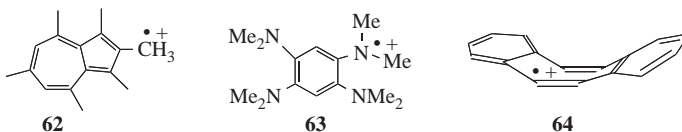
³³⁷ Ishida, S.; Iwamoto, T.; Kira, M. *J. Am. Chem. Soc.* **2003**, *125*, 3212; Sekiguchi, A.; Tanaka, T.; Ichinohe, M.; Akiyama, K.; Tero-Kubota, S. *J. Am. Chem. Soc.* **2003**, *125*, 4962; Inoue, S.; Ichinohe, M.; Sekiguchi, A. *J. Am. Chem. Soc.* **2007**, *129*, 6096.

³³⁸ Villano, S.M.; Eyet, N.; Lineberger, W.C.; Bierbaum, V.M. *J. Am. Chem. Soc.* **2008**, *130*, 7214.

which alkali metals are reducing agents often involve radical anion intermediates (*Birch reduction*, e.g., Reaction **15-13**) that proceed via radical anion **61**.



Several types of radical cation are also known.³³⁹ Typical examples include alkyl azulene cation radicals (**62**),³⁴⁰ trialkyl amine radical cations,³⁴¹ 1,2-bis(dialkylamino)benzenes radical cations (e.g., **63**),³⁴² dimethylsulfonium cation radicals ($\text{Me}_2\text{S}^{\bullet+}$),³⁴³ *N*-alkyl substituted imine cation radicals ($\text{Ph}_2\text{C}=\text{NEt}^{\bullet+}$),³⁴⁴ dibenzo[*a,e*]cyclooctene (**64**, a non-planar cation radical),³⁴⁵ and [*n.n*]paracyclophane cation radicals.³⁴⁶ A twisted radical cation derived from bicyclo[2.2.2]oct-2-ene has been reported.³⁴⁷



5.D. CARBENES

5.D.i. Stability and Structure³⁴⁸

Carbenes are highly reactive species, and practically all have lifetimes considerably < 1 s. With exceptions noted below (Sec. 5.D.ii), carbenes have been isolated only by entrapment in matrices at low temperatures (77 K or less).³⁴⁹ The parent species (CH_2) is usually called *methylene*, although derivatives are more often named by the carbene nomenclature. Thus CCl_2 is generally known as dichlorocarbene, although it can also be called dichloromethylene.

³³⁹ See Roth, H.D. *Acc. Chem. Res.* **1987**, 20, 343; Courtneidge, J.L.; Davies, A.G. *Acc. Chem. Res.* **1987**, 20, 90; Symons, M.C.R. *Chem. Soc. Rev.* **1984**, 13, 393; Marchetti, F.; Pinzino, C.; Zacchini, S.; Guido, G. *Angew. Chem. Int. Ed.* **2010**, 49, 5268.

³⁴⁰ Gerson, F.; Scholz, M.; Hansen, H.-J.; Uebelhart, P. *J. Chem. Soc. Perkin Trans. 2* **1995**, 215.

³⁴¹ de Meijere, A.; Chaplinski, V.; Gerson, F.; Merstetter, P.; Haselbach, E. *J. Org. Chem.* **1999**, 64, 6951.

³⁴² Neugebauer, F.A.; Funk, B.; Staab, H.A. *Tetrahedron Lett.* **1994**, 35, 4755. See Stickley, K.R.; Blackstock, S.C. *Tetrahedron Lett.* **1995**, 36, 1585.

³⁴³ Dauben, W.G.; Cogen, J.M.; Behar, V.; Schultz, A.G.; Geiss, W.; Taveras, A.G. *Tetrahedron Lett.* **1992**, 33, 1713.

³⁴⁴ Rhodes, C.J.; Agirbas H. *J. Chem. Soc. Perkin Trans. 2* **1992**, 397.

³⁴⁵ Gerson, F.; Felder, P.; Schmidlin, R.; Wong, H.N.C. *J. Chem. Soc. Chem. Commun.* **1994**, 1659.

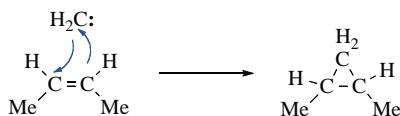
³⁴⁶ Wartini, A.R.; Valenzuela, J.; Staab, H.A.; Neugebauer, F.A. *Eur. J. Org. Chem.* **1998**, 139.

³⁴⁷ Nelson, S.F.; Reinhardt, L.A.; Tran, H.Q.; Clark, T.; Chen, G.-F.; Pappas, R.S.; Williams, F. *Chem. Eur. J.* **2002**, 8, 1074.

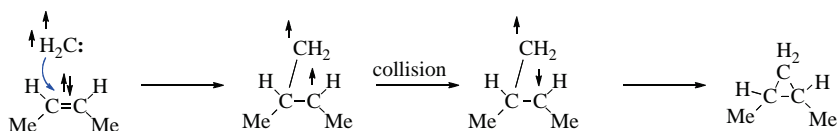
³⁴⁸ See Jones, Jr., M.; Moss, R.A. *Carbenes*, 2 Vols., Wiley, NY, **1973–1975**; Rees, C.W.; Gilchrist, T.L. *Carbenes, Nitrenes, and Arynes*, Nelson, London, **1969**; Minkin, V.I.; Simkin, B.Ya.; Glukhovtsev, M.N. *Russ. Chem. Rev.* **1989**, 58, 622; Moss, R.A.; Jones, Jr., M. *React. Intermed. (Wiley)* **1985**, 3, 45; Liebman, J.F.; Simons, J. *Mol. Struct. Energ.* **1986**, 1, 51.

³⁴⁹ See Nefedov, O.M.; Maltsev, A.K.; Mikaelyan, R.G. *Tetrahedron Lett.* **1971**, 4125; Wright, B.B. *Tetrahedron* **1985**, 41, 1517. For reviews, see Zuev, P.S.; Nefedov, O.M. *Russ. Chem. Rev.* **1989**, 58, 636; Sheridan, R.S. *Org. Photochem.* **1987**, 8, 159, pp. 196–216; Trozzolo, A.M. *Acc. Chem. Res.* **1968**, 1, 329.

The two nonbonded electrons of a carbene can be either paired or unpaired. If they are paired, the species is spectrally a *singlet*, while, as seen above (Sec. 5.C.i), two unpaired electrons appear as a *triplet*. An ingenious



method of distinguishing between the two possibilities was developed by Skell,³⁵⁰ based on the common reaction of addition of carbenes to double bonds to form cyclopropane derivatives (Reaction 15-51). If the singlet species adds to *cis*-2-butene, the resulting cyclopropane should be the *cis* isomer since the movements of the two pairs of electrons



should occur either simultaneously or with one rapidly succeeding another. However, if the attack is by a triplet species, the two unpaired electrons cannot both go into a new covalent bond, since by *Hund's rule* they have parallel spins. So one of the unpaired electrons will form a bond with the electron from the double bond that has the opposite spin, leaving two unpaired electrons that have the same spin and therefore cannot form a bond at once, but must wait until, by some collision process, one of the electrons can reverse its spin. During this time, there is free rotation about the C—C bond and a mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes should result.³⁵¹

The results of this type of experiment show that CH₂ itself is usually formed as a singlet species, which can decay to the triplet state, which consequently has a lower energy (MO calculations³⁵² and experimental determinations show that the difference in energy between singlet and triplet CH₂ is ~8–10 kcal mol⁻¹ or 33–42 kJ mol⁻¹)³⁵³. However, it is possible to prepare triplet CH₂ directly by a photosensitized decomposition of diazomethane.³⁵⁴ The CH₂ group is so reactive³⁵⁵ that it generally reacts as the singlet before it has a chance to decay to the triplet state.³⁵⁶ As to other carbenes, some react as triplets, some as singlets, and others as singlets or triplets, depending on how they are generated. There are, however, molecules that generate persistent triplet carbenes.³⁵⁷

³⁵⁰ Skell, P.S. *Tetrahedron* **1985**, 41, 1427.

³⁵¹ See Closs, G.L. *Top. Stereochem.* **1968**, 3, 193, pp. 203–210; Bethell, D. *Adv. Phys. Org. Chem.* **1969**, 7, 153, p. 194; Hoffmann, R. *J. Am. Chem. Soc.* **1968**, 90, 1475.

³⁵² Richards, Jr., C.A.; Kim, S.-J.; Yamaguchi, Y.; Schaefer, III, H.F. *J. Am. Chem. Soc.* **1995**, 117, 10104.

³⁵³ See Lengel, R.K.; Zare, R.N. *J. Am. Chem. Soc.* **1978**, 100, 7495; Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* **1979**, 30, 125, see pp. 128–134; Leopold, D.G.; Murray, K.K.; Lineberger, W.C. *J. Chem. Phys.* **1984**, 81, 1048.

³⁵⁴ Kopecky, K.R.; Hammond, G.S.; Leermakers, P.A. *J. Am. Chem. Soc.* **1961**, 83, 2397; **1962**, 84, 1015; Duncan, F.J.; Cvetanović, R.J. *J. Am. Chem. Soc.* **1962**, 84, 3593.

³⁵⁵ For a review of the kinetics of CH₂ reactions, see Laufer, A.H. *Rev. Chem. Intermed.* **1981**, 4, 225.

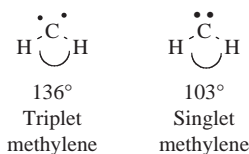
³⁵⁶ See Turro, N.J.; Cha, Y.; Gould, I.R. *J. Am. Chem. Soc.* **1987**, 109, 2101.

³⁵⁷ Tomioka, H. *Acc. Chem. Res.* **1997**, 30, 315; Kirmse, W. *Angew. Chem. Int. Ed.* **2003**, 42, 2117; Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, 109, 3275.

Indeed, remarkably stable diaryl triplet carbenes have been prepared,³⁵⁸ and protected diphenylcarbenes are particularly stable.³⁵⁹ There are also persistent singlet carbenes, although radical fragmentation is a problem.³⁶⁰

There is a limitation to the use of stereospecificity of addition as a diagnostic test for singlet or triplet carbenes.³⁶¹ When carbenes are generated by photolytic methods, they are often in a highly excited singlet state. When they add to the double bond, the addition is stereospecific; but the cyclopropane formed carries excess energy (i.e., it is in an excited state). It has been shown that under certain conditions (low pressures in the gas phase) the excited cyclopropane may undergo cis–trans isomerization *after* it is formed, so that triplet carbene may seem to be involved although in reality the singlet was present.³⁶²

Studies of the IR spectrum of CCl_2 trapped at low temperatures in solid argon indicate that the ground state for this species is the singlet.³⁶³ The geometrical structure of triplet methylene can be investigated by ESR measurements,³⁶⁴ since triplet species are diradicals. Such measurements made on triplet CH_2 trapped in matrices at very low temperatures (4 K) show that triplet CH_2 is a bent molecule, with an angle of $\sim 136^\circ$.³⁶⁵ The EPR measurements cannot be made on singlet species, but from electronic spectra of CH_2 formed in flash photolysis³⁶⁶ of diazomethane it was concluded that singlet CH_2 is also bent, with an angle of $\sim 103^\circ$.³⁶⁷ Singlet CCl_2 ³⁰⁰ and CBr_2 ³⁶⁸ are also bent, with angles of 100° and 114° , respectively. It has long been known that triplet aryl carbenes are bent.³⁶⁹



³⁵⁸ Woodcock, H.L.; Moran, D.; Schleyer, P.v.R.; Schaefer, III, H.F. *J. Am. Chem. Soc.* **2001**, 123, 4331.

³⁵⁹ Itoh, T.; Nakata, Y.; Hirai, K.; Tomioka, H. *J. Am. Chem. Soc.* **2006**, 128, 957.

³⁶⁰ Cattoën, X.; Miqueu, K.; Gornitzka, H.; Bourissou, D.; Bertrand, G. *J. Am. Chem. Soc.* **2005**, 127, 3292.

³⁶¹ For other methods of distinguishing singlet from triplet carbenes, see Hendrick, M.E.; Jones, Jr., M. *Tetrahedron Lett.* **1978**, 4249; Creary, X. *J. Am. Chem. Soc.* **1980**, 102, 1611.

³⁶² Rabinovitch, B.S.; Tschuikow-Roux, E.; Schlag, E.W. *J. Am. Chem. Soc.* **1959**, 81, 1081; Frey, H.M. *Proc. R. Soc. London, Ser. A* **1959**, 251, 575; Lambert, J.B.; Larson, E.G.; Bosch, R.J. *Tetrahedron Lett.* **1983**, 24, 3799.

³⁶³ Andrews, L. *J. Chem. Phys.* **1968**, 48, 979.

³⁶⁴ The technique of spin trapping (Sec. 5.C.i) has been applied to the detection of transient triplet carbenes: Forrester, A.R.; Sadd, J.S. *J. Chem. Soc. Perkin Trans. 2* **1982**, 1273.

³⁶⁵ Wasserman, E.; Kuck, V.J.; Hutton, R.S.; Anderson, E.D.; Yager, W.A. *J. Chem. Phys.* **1971**, 54, 4120; Bernheim, R.A.; Bernard, H.W.; Wang, P.S.; Wood, L.S.; Skell, P.S. *J. Chem. Phys.* **1971**, 54, 3223.

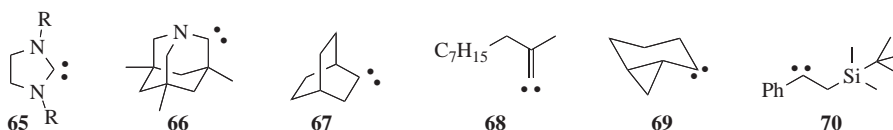
³⁶⁶ Hahn, F.E. *Angew. Chem. Int. Ed.* **2006**, 45, 1348. For imidazopyridine carbenes, see Moss, R.A.; Tian, J.; Sauers, R.R.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **2007**, 129, 10019.

³⁶⁷ Herzberg, G.; Johns, J.W.C. *J. Chem. Phys.* **1971**, 54, 2276 and cited references.

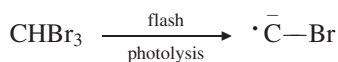
³⁶⁸ Ivey, R.C.; Schulze, P.D.; Leggett, T.L.; Kohl, D.A. *J. Chem. Phys.* **1974**, 60, 3174.

³⁶⁹ Senthilnathan, V.P.; Platz, M.S. *J. Am. Chem. Soc.* **1981**, 103, 5503; Gilbert, B.C.; Griller, D.; Nazran, A.S. *J. Org. Chem.* **1985**, 50, 4738.

The most common carbenes are :CH_2 and :CCl_2 ,³⁷⁰ but many others have been reported,³⁷¹ including heterocyclic carbenes³⁷² diboron carbenes,³⁷³ **65** (stabilized by the steric constraints of the ring geometry),³⁷⁴ **66** (an aminocarbene without π conjugation),³⁷⁵ bicyclo[2.2.2]octylidene, (**67**),³⁷⁶ alkylidene carbenes (e.g., **68**),³⁷⁷ conformationally restricted cyclopropylcarbenes, (e.g., **69**),³⁷⁸ β -silylcarbenes (e.g., **70**),³⁷⁹ α -keto carbenes,³⁸⁰ vinyl carbenes,³⁸¹ and chiral carbenoids.³⁸² Fluoro(phenoxy)carbene is stable for several days if it is generated within the cavity of a hemicarcerand (see Sec. 3.C.iii).³⁸³ In the case of **65** ($\text{R} = \text{Ph}$),³⁸⁴ the precursor is a tetraaminoethylene, and when potassium hydride is present to preclude electrophilic catalysis, starting tetraaminoethylenes are recovered unchanged.



Flash photolysis of CHBr_3 produced the intermediate CBr ,³⁸⁵ which is a *carbyne*.



The intermediates CF and CCl were generated similarly from CHFBr_2 and CHClBr_2 , respectively. Triplet acetylenes have been reported as equivalents for 1,2-bicarbenes.³⁸⁶

³⁷⁰ For reviews of halocarbenes, see Burton, D.J.; Hahnfeld, J.L. *Fluorine Chem. Rev.* **1977**, 8, 119; Margrave, J.L.; Sharp, K.G.; Wilson, P.W. *Fort. Chem. Forsch.* **1972**, 26, 1, pp. 3–13.

³⁷¹ See Stang, P.J. *Acc. Chem. Res.* **1982**, 15, 348; *Chem. Rev.* **1978**, 78, 383; Marchand, A.P.; Brockway, N.M. *Chem. Rev.* **1974**, 74, 431; Schuster, G.B. *Adv. Phys. Org. Chem.* **1986**, 22, 311. For a review of carbenes with neighboring hetero atoms, see Taylor, K.G. *Tetrahedron* **1982**, 38, 2751.

³⁷² Alcarazo, M.; Roseblade, S.J.; Cowley, A.R.; Fernández, R.; Brown, J.M.; Lassaletta, J.M. *J. Am. Chem. Soc.* **2005**, 127, 3290. See also, Kassae, M.Z.; Shakib, F.A.; Momeni, M.R.; Ghambarian, M.; Musavi, S.M. *J. Org. Chem.* **2010**, 75, 2539.

³⁷³ Krahulic, K.E.; Enright, G.D.; Parvez, M.; Roesler, R. *J. Am. Chem. Soc.* **2005**, 127, 4142.

³⁷⁴ Herrmann, W.A. *Angew. Chem. Int. Ed.* **2002**, 41, 1290.

³⁷⁵ Ye, Q.; Komarov, I. V.; Kirby, A. J.; Jones, Jr., M. *J. Org. Chem.* **2002**, 67, 9288.

³⁷⁶ Ye, Q.; Jones Jr., M.; Chen, T.; Shevlin, P.B. *Tetrahedron Lett.* **2001**, 42, 6979.

³⁷⁷ Ohira, S.; Yamasaki, K.; Nozaki, H.; Yamato, M.; Nakayama, M. *Tetrahedron Lett.* **1995**, 36, 8843. For dimethylvinylidene carbene see Reed, S.C.; Capitosti, G.J.; Zhu, Z.; Modarelli, D.A. *J. Org. Chem.* **2001**, 66, 287. For a review of alkylidenecarbenes, see Knorr, R. *Chem. Rev.* **2004**, 104, 3795.

³⁷⁸ Fernamberg, K.; Snoonian, J.R.; Platz, M.S. *Tetrahedron Lett.* **2001**, 42, 8761.

³⁷⁹ Creary, X.; Butchko, M.A. *J. Org. Chem.* **2002**, 67, 112.

³⁸⁰ Bonnichon, F.; Richard, C.; Grabner, G. *Chem. Commun.* **2001**, 73.

³⁸¹ Zuev, P. S.; Sheridan, R. S. *J. Am. Chem. Soc.* **2004**, 126, 12220.

³⁸² Topolski, M.; Duraisamy, M.; Rachoń, J.; Gawronski, J.; Gawronska, K.; Goedken, V.; Walborsky, H.M. *J. Org. Chem.* **1993**, 58, 546.

³⁸³ Kirmse, W. *Angew. Chem. Int. Ed.* **2005**, 44, 2476.

³⁸⁴ See Wanzlick, H.-W.; Schikora, E. *Angew. Chem.* **1960**, 72, 494.

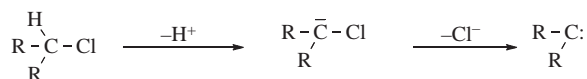
³⁸⁵ Ruzsicska, B.P.; Jodhan, A.; Choi, H.K.J.; Strausz, O.P. *J. Am. Chem. Soc.* **1983**, 105, 2489.

³⁸⁶ Zeidan, T.A.; Kovalenko, S.V.; Manoharan, M.; Clark, R.J.; Ghiviriga, I.; Alabugin, I.V. *J. Am. Chem. Soc.* **2005**, 127, 4270.

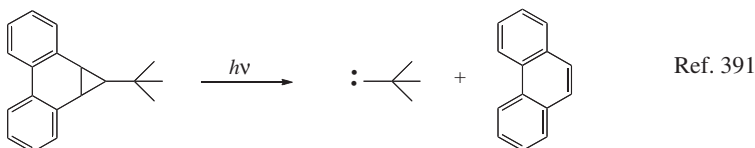
5.D.ii. The Generation and Fate of Carbenes³⁸⁷

There are two primary methods to form carbenes, although other pathways are also known.

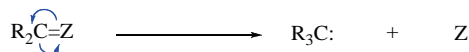
1. In α elimination, a carbon loses a group without its electron pair, usually a proton, and then a group with its pair, usually a halide ion:³⁸⁸



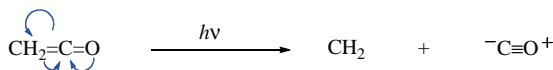
The most common example is formation of dichlorocarbene by treatment of chloroform with a base (see Reaction 10-3) and geminal alkyl dihalides with Me_3Sn^- ,³⁸⁹ but many other examples are known, such as



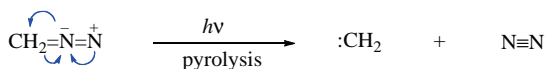
2. Disintegration of compounds containing certain types of double bonds:



The two most important ways of forming $:\text{CH}_2$ are examples: the photolysis of ketene



and the isoelectronic decomposition of diazomethane.³⁹²



³⁸⁷ See Jones, Jr., M. *Acc. Chem. Res.* **1974**, 7, 415; Kirmse, W. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9; Elsevier, NY, **1973**, pp. 373–415; Ref. 348; Petrosyan, V.E.; Niyazymbetov, M.E. *Russ. Chem. Rev.* **1989**, 58, 644.

³⁸⁸ For a review of formation of carbenes in this manner, see Kirmse, W. *Angew. Chem. Int. Ed.* **1965**, 4, 1.

³⁸⁹ Ashby, E.C.; Deshpande, A.K.; Doctorovich, F. *J. Org. Chem.* **1993**, 58, 4205. For a preparation from dichlorodiazirine, see Chu, G.; Moss, R.A.; Sauers, R.R. *J. Am. Chem. Soc.* **2005**, 127, 14206. Also see Moss, R.A.; Tian, J.; Sauers, R.R.; Ess, D.H.; Houk, K.N.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **2007**, 129, 5167.

³⁹⁰ Wagner, W.M. *Proc. Chem. Soc.* **1959**, 229.

³⁹¹ Glick, H.C.; Likhovtsov, I.R.; Jones, Jr., M. *Tetrahedron Lett.* **1995**, 36, 5715; Stang, P.J. *Acc. Chem. Res.* **1982**, 15, 348; *Chem. Rev.* **1978**, 78, 383.

³⁹² For a review, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, **1986**, pp. 170–184.

Some diazoalkanes decompose to the corresponding carbene.³⁹³ Diazirines³⁹⁴ (isomeric with diazoalkanes) give carbenes,³⁹⁵ but arylmethyl radicals have also been generated from diazirines.³⁹⁶ In a different study, thermolysis of diarylox-ydiazirines (**71**) gave the anticipated carbene products, but photolysis gave both carbenes and aryloxy radicals by α -scission.³⁹⁷



Because most carbenes are so reactive, it is often difficult to prove that they are actually present in a given reaction. The lifetime of formylcarbene was measured to be 0.15–0.73 ns by transient absorption and transient grating spectroscopy in dichloromethane.³⁹⁸ In many instances, where a carbene is *apparently* produced by an α elimination or by disintegration of a double-bond compound, there is evidence that no free carbene is actually involved. The neutral term *carbenoid* is used where it is known that a free carbene is not present or in cases where there is doubt. α -Halo organometallic compounds, (R_2CXM) are often called *carbenoids* because they readily give elimination reactions³⁹⁹ (e.g., see Reaction **12-39**).

The reactions of carbenes are more varied than those of the species previously discussed in this chapter.⁴⁰⁰ Solvent effects have been observed in carbene reactions. The selectivity of certain carbenes is influenced by the nature of the solvent.⁴⁰¹ The distribution of rearrangement products (see below) from *tert*-butylcarbene⁴⁰² are influenced by changes in solvent.⁴⁰³ It is known that singlet methylene forms a charge-transfer complex with benzene.⁴⁰⁴ Solvent interactions for chlorophenylcarbene and fluorophenylcarbene, however, are weak.⁴⁰⁵

1. Additions to carbon–carbon double bonds have already been mentioned. Carbenes also add to aromatic systems, but the immediate products rearrange, usually with ring enlargement (see Reaction **15-65**). Additions of carbenes to other double bonds [e.g., $\text{C}=\text{N}$ (Reactions **16-46** and **16-48**), and to triple bonds], have also been reported.
2. An unusual reaction of carbenes is that of insertion into $\text{C}-\text{H}$ bonds (Reaction **12-21**). Thus $:\text{CH}_2$ reacts with methane to give ethane and with propane

³⁹³ For example, see Mieusset, J.-L.; Brinker, U.H. *J. Org. Chem.* **2006**, *71*, 6975.

³⁹⁴ See Martinu, T.; Dailey, W.P. *J. Org. Chem.* **2004**, *69*, 7359.

³⁹⁵ Liu, M.T.H. *Chemistry of Diazirines*, 2 Vols, CRC Press, Boca Raton, FL, **1987**. For reviews, see Moss, R.A. *Acc. Chem. Res.* **2006**, *39*, 267; Liu, M.T.H. *Chem. Soc. Rev.* **1982**, *11*, 127.

³⁹⁶ Moss, R.A.; Fu, X. *Org. Lett.* **2004**, *6*, 3353.

³⁹⁷ Fede, J.-M.; Jockusch, S.; Lin, N.; Moss, R.A.; Turro, N.J. *Org. Lett.* **2003**, *5*, 5027.

³⁹⁸ Toscano, J.P.; Platz, M.S.; Nikolaev, V.; Cao, Y.; Zimmt, M.B. *J. Am. Chem. Soc.* **1996**, *118*, 3527.

³⁹⁹ For a review, see Nefedov, O.M.; D'yachenko, A.I.; Prokof'ev, A.K. *Russ. Chem. Rev.* **1977**, *46*, 941.

⁴⁰⁰ For a discussion of the nucleophilicity of dichlorocarbene, see Moss, R.A.; Zhang, M.; Krogh-Jespersen, K. *Org. Lett.* **2009**, *11*, 1947.

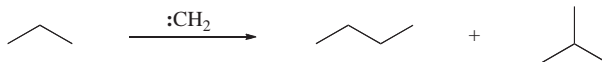
⁴⁰¹ Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* **1985**, *41*, 4987.

⁴⁰² Krogh-Jespersen, K.; Yan, S.; Moss, R.A. *J. Am. Chem. Soc.* **1999**, *121*, 6269.

⁴⁰³ Ruck, R. T.; Jones, Jr., M. *Tetrahedron Lett.* **1998**, *39*, 2277.

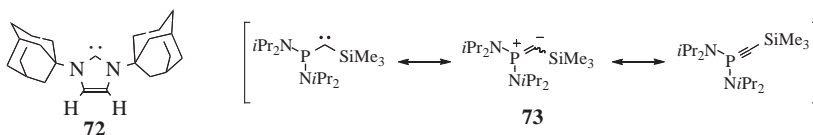
⁴⁰⁴ Khan, M. I.; Goodman, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 6635.

⁴⁰⁵ Sun, Y.; Tippmann, E. M.; Platz, M. S. *Org. Lett.* **2003**, *5*, 1305.

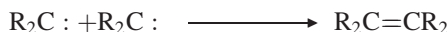


to give *n*-butane and isobutane, as shown. Elimination to give an alkene is a competing side reaction in polar solvents, but this is suppressed in nonpolar solvents.⁴⁰⁶ Simple alkyl carbenes, such as this, are not very useful for synthetic purposes, but do illustrate the extreme reactivity of carbene. However, carbenoids generated by rhodium-catalyzed decomposition of diazoalkanes are very useful (see Reaction 12-23) and have been used in a variety of syntheses. Treatment in the liquid phase of an alkane (e.g., pentane) with carbene formed from the photolysis of diazomethane, gives the three possible products in statistical ratios⁴⁰⁷ demonstrating that carbene is displaying no selectivity. For many years, it was a generally accepted principle that the lower the selectivity the greater the reactivity; however, this principle is no longer regarded as general because many exceptions have been found.⁴⁰⁸ Singlet CH_2 generated by photolysis of diazomethane is probably the most reactive organic species known, but triplet CH_2 is somewhat less reactive, and other carbenes are still less reactive. The following series of carbenes of decreasing reactivity has been proposed on the basis of discrimination between insertion and addition reactions: $\text{CH}_2 > \text{HCCOOR} > \text{PhCH} > \text{BrCH} \sim \text{ClCH}$.⁴⁰⁹ Dihalocarbenes generally do not give insertion reactions at all. Insertion of carbenes into other bonds has also been demonstrated, although not insertion into C—C bonds.⁴¹⁰

Two carbenes that are stable at room temperature have been reported:⁴¹¹ **72** and **73**. In the absence of oxygen and moisture, **72** exists as stable crystals with a melting point of 240–241 °C.⁴¹² This structure was proved by X-ray crystallography.



3. It would seem that dimerization to form an alkene should be an important reaction of carbenes, but it is not.



⁴⁰⁶ Ruck, R.T.; Jones, Jr., M. *Tetrahedron Lett.* **1998**, 39, 2277.

⁴⁰⁷ See Halberstadt, M.L.; McNesby, J.R. *J. Am. Chem. Soc.* **1967**, 89, 3417.

⁴⁰⁸ See Buncel, E.; Wilson, H. *J. Chem. Educ.* **1987**, 64, 475; Johnson, C.D. *Tetrahedron* **1980**, 36, 3461; *Chem. Rev.* **1975**, 75, 755; Giese, B. *Angew. Chem. Int. Ed.* **1977**, 16, 125; Pross, A. *Adv. Phys. Org. Chem.* **1977**, 14, 69. See also, Srinivasan, C.; Shunmugasundaram, A.; Arumugam, N. *J. Chem. Soc. Perkin Trans. 2* **1985**, 17; Bordwell, F.G.; Branca, J.C.; Cripe, T.A. *Isr. J. Chem.* **1985**, 26, 357; Formosinho, S.J. *J. Chem. Soc. Perkin Trans. 2* **1988**, 839; Johnson, C.D.; Stratton, B. *J. Chem. Soc. Perkin Trans. 2* **1988**, 1903. For a group of papers on this subject, see *Isr. J. Chem.* **1985**, 26, 303.

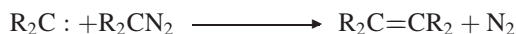
⁴⁰⁹ Closs, G.L.; Coyle, J.J. *J. Am. Chem. Soc.* **1965**, 87, 4270.

⁴¹⁰ See Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* **1985**, 41, 4987; Frey, H.M.; Walsh, R.; Watts, I.M. *J. Chem. Soc. Chem. Commun.* **1989**, 284.

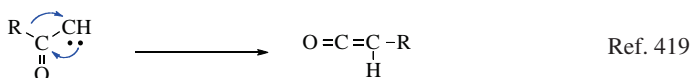
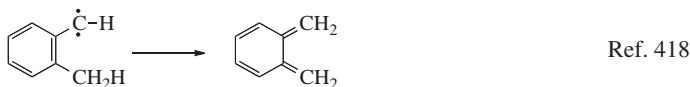
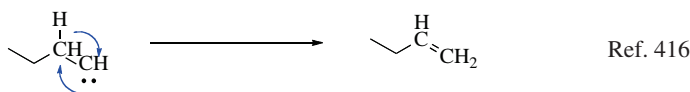
⁴¹¹ For a discussion, see Regitz, M. *Angew. Chem. Int. Ed.* **1991**, 30, 674.

⁴¹² Arduengo, III, A.J.; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* **1991**, 113, 361.

Generally, the reactivity is so great that the carbene species do not have time to find each other and because the dimer generally has so much energy that it dissociates again. Apparent dimerization has been observed, but it is likely that the products in many reported instances of “dimerization” do not arise from an actual dimerization of two carbenes, but come from attack by a carbene on a molecule of a carbene precursor, for example,



4. Alkylcarbenes can undergo rearrangement, with migration of alkyl or hydrogen.⁴¹³ Indeed these rearrangements are generally so rapid⁴¹⁴ that additions to multiple bonds and insertion reactions, which are so common for CH_2 , are seldom encountered with alkyl or dialkyl carbenes. Unlike rearrangement of the species previously encountered in this chapter, most rearrangements of carbenes directly give stable molecules. A carbene intermediate has been suggested for the isomerization of cyclopropane.⁴¹⁵ Some examples of carbene rearrangement are



The rearrangement of acylcarbenes to ketenes is called the *Wolff rearrangement* (Reaction 18-8). A few rearrangements in which carbenes rearrange to other

⁴¹³ See Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* **2001**, *123*, 1658; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, **1980**, pp. 115–163; Wentrup, C. *Adv. Heterocycl. Chem.*, **1981**, *28*, 231; Jones, W.M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, **1980**, pp. 95–160; Schaefer, III, H.F. *Acc. Chem. Res.* **1979**, *12*, 288; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, **1971**, pp. 457–496.

⁴¹⁴ The activation energy for the 1,2-hydrogen shift has been estimated at 1.1 kcal mol⁻¹ (4.5 kJ mol⁻¹), an exceedingly low value: Stevens, I.D.R.; Liu, M.T.H.; Soundararajan, N.; Paik, N. *Tetrahedron Lett.* **1989**, *30*, 481. Also see, Pezacki, J. P.; Couture, P.; Dunn, J. A.; Warkentin, J.; Wood, P. D.; Luszyk, J.; Ford, F.; Platz, M. S. *J. Org. Chem.* **1999**, *64*, 4456.

⁴¹⁵ Bettinger, H.F.; Rienstra-Kiracofe, J.C.; Hoffman, B.C.; Schaefer, III, H.F.; Baldwin, J.E.; Schleyer, P.v.R. *Chem. Commun.* **1999**, 1515.

⁴¹⁶ Liu, M.T.H.; Bonneau, R. *J. Am. Chem. Soc.* **1989**, *111*, 6873; Jackson, J.E.; Soundararajan, N.; White, W.; Liu, M.T.H.; Bonneau, R.; Platz, M.S. *J. Am. Chem. Soc.* **1989**, *111*, 6874; Ho, G.; Krogh-Jespersen, K.; Moss, R. A.; Shen, S.; Sheridan, R.S.; Subramanian, R. *J. Am. Chem. Soc.* **1989**, *111*, 6875; LaVilla, J.A.; Goodman, J.L. *J. Am. Chem. Soc.* **1989**, *111*, 6877.

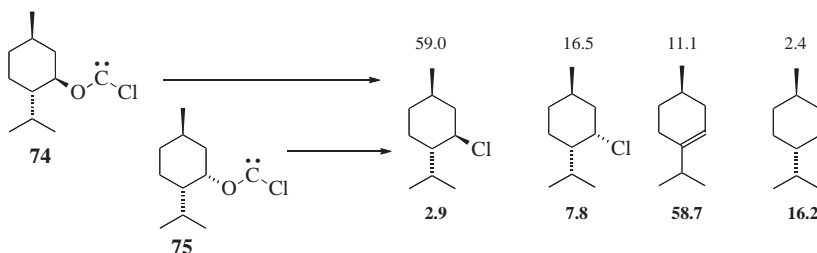
⁴¹⁷ Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1960**, *82*, 1002.

⁴¹⁸ McMahon, R.J.; Chapman, O.L. *J. Am. Chem. Soc.* **1987**, *109*, 683.

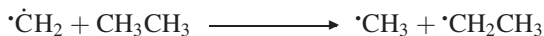
⁴¹⁹ Friedman, L.; Berger, J.G. *J. Am. Chem. Soc.* **1961**, *83*, 492, 500.

carbenes are also known.⁴²⁰ Of course, the new carbene must stabilize itself in one of the ways mentioned.

5. The fragmentation reactions of alicyclic oxychlorocarbenes (e.g., **74** and **75**)⁴²¹ give substitution and elimination products. Menthylloxylchlorocarbene (**74**) gave primarily the substitution product, whereas neomenthylloxylchlorocarbene (**75**) gave primarily the elimination product, as shown. In this case, the substitution product is likely due to rearrangement of the chlorocarbene.⁴²² It is known that fragmentation of nortricycloxychlorocarbene in pentane occurs by an S_Ni-like process to give nortricycyl chloride.⁴²³ In more polar solvents, fragmentation leads to nortricycyl cation–chloride anion pair that gives nortricycyl chloride and a small amount of *exo*-2-norbornenyl chloride. Fragmentation can also lead to radicals.⁴²⁴



6. Triplet carbenes can abstract hydrogen or other atoms to give free radicals, for example,



This is not surprising, since triplet carbenes are free radicals. But singlet carbenes⁴²⁵ can also give this reaction, although in this case only halogen atoms are abstracted, not hydrogen.⁴²⁶

5.E. NITRENES

Nitrenes (R—N),⁴²⁷ are the nitrogen analogues of carbenes, and most of the comments about carbenes also applies to them. Nitrenes are too reactive for isolation under ordinary

⁴²⁰ For a review, see Jones, W.M. *Acc. Chem. Res.* **1977**, *10*, 353.

⁴²¹ Moss, R.A.; Johnson, L.A.; Kacprzynski, M.; Sauers, R.R. *J. Org. Chem.* **2003**, *68*, 5114.

⁴²² See Yao, G.; Rempala, P.; Bashore, C.; Sheridan, R.S. *Tetrahedron Lett.* **1999**, *40*, 17.

⁴²³ Moss, R. A.; Ma, Y.; Sauers, R. R.; Madni, M. *J. Org. Chem.* **2004**, *69*, 3628.

⁴²⁴ Mekley, N.; El-Saidi, M.; Warkentin, J. *Can. J. Chem.* **2000**, *78*, 356.

⁴²⁵ Vignolle, J.; Catton, X.; Bourissou, D. *Chem. Rev.* **2009**, *109*, 3333.

⁴²⁶ Roth, H.D. *J. Am. Chem. Soc.* **1971**, *93*, 1527, 4935, *Acc. Chem. Res.* **1977**, *10*, 85.

⁴²⁷ See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, **1984**; Lwowski, W. *React. Intermed. (Wiley)* **1985**, *3*, 305; **1981**, *2*, 315; **1978**, *1*, 197; Abramovitch, R.A. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, **1973**, pp. 127–192; Kuznetsov, M.A.; Ioffe, B.V. *Russ. Chem. Rev.* **1989**, *58*, 732 (*N*- and *O*-nitrenes); Meth-Cohn, O. *Acc. Chem. Res.* **1987**, *20*, 18 (oxycarbonylnitrenes); Abramovitch, R.A.; Sutherland, R.G. *Fortsch. Chem. Forsch.* **1970**, *16*, 1 (sulfonyl nitrenes); Ioffe, B.V.; Kuznetsov, M.A. *Russ. Chem. Rev.* **1972**, *41*, 131 (*N*-nitrenes).

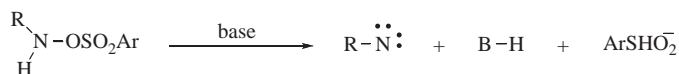
conditions,⁴²⁸ although *ab initio* calculations show that nitrenes are more stable than carbenes with an enthalpy difference of 25–26 kcal mol⁻¹ (104.7–108.8 kJ mol⁻¹).⁴²⁹



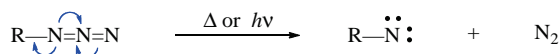
Alkyl nitrenes have been isolated by trapping in matrices at 4 K,⁴³⁰ while aryl nitrenes, which are less reactive, can be trapped at 77 K.⁴³¹ The ground state of NH, and probably of most nitrenes,⁴³² is a triplet, although nitrenes can be generated in both triplet⁴³³ and singlet states. A quartet ground-state nitreno radical has been reported.⁴³⁴ In additions of EtOOC—N to C=C double bonds two species are involved, one of which adds in a stereospecific manner and the other not. By analogy with Skell's proposal involving carbenes (Sec. 5.D.i) these are taken to be the singlet and triplet species, respectively.⁴³⁵

The two principal means of generating nitrenes are analogous to those used to form carbenes.

1. *Elimination.* An example is



2. *Breakdown of Certain Double-Bond Compounds.* The most common method of forming nitrenes is photolytic or thermal decomposition of azides,⁴³⁶



The unsubstituted nitrene (NH) has been generated by photolysis of electric discharge through NH₃, N₂H₄, or HN₃.

The reactions of nitrenes are also similar to those of carbenes.⁴³⁷ As in that case, many reactions in which nitrene intermediates are suspected probably do not involve free nitrenes. It is often very difficult to obtain proof in any given case that a free nitrene is or is not an intermediate.

⁴²⁸ McClelland, R.A. *Tetrahedron* **1996**, 52, 6823.

⁴²⁹ Kemnitz, C.R.; Karney, W.L.; Borden, W.T. *J. Am. Chem. Soc.* **1998**, 120, 3499.

⁴³⁰ Wasserman, E.; Smolinsky, G.; Yager, W.A. *J. Am. Chem. Soc.* **1964**, 86, 3166. See Carrick, P.G.; Brazier, C. R.; Bernath, P.F.; Engelking, P.C. *J. Am. Chem. Soc.* **1987**, 109, 5100.

⁴³¹ Smolinsky, G.; Wasserman, E.; Yager, W.A. *J. Am. Chem. Soc.* **1962**, 84, 3220. For a review, see Sheridan, R.S. *Org. Photochem.* **1987**, 8, 159, pp. 159–248.

⁴³² See Sigman, M.E.; Autrey, T.; Schuster, G.B. *J. Am. Chem. Soc.* **1988**, 110, 4297.

⁴³³ See Singh, P.N.D.; Mandel, S.M.; Robinson, R.M.; Zhu, Z.; Franz, R.; Ault, B.S.; Gudmundsdottir, A.D. *J. Org. Chem.* **2003**, 68, 7951.

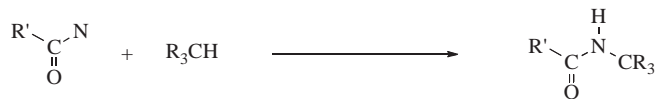
⁴³⁴ Sander, W.; Grote, D.; Kossmann, S.; Neese, F. *J. Am. Chem. Soc.* **2008**, 130, 4396.

⁴³⁵ McConaghy, Jr., J.S.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, 89, 2357, 4450; Mishra, A.; Rice, S.N.; Lwowski, W. *J. Org. Chem.* **1968**, 33, 481.

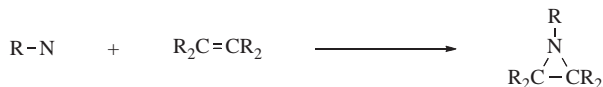
⁴³⁶ See Dyall, L.K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, **1983**, pp. 287–320; Dürr, H.; Kober, H. *Top. Curr. Chem.* **1976**, 66, 89; L'Abbé, G. *Chem. Rev.* **1969**, 69, 345.

⁴³⁷ See Subbaraj, A.; Subba Rao, O.; Lwowski, W. *J. Org. Chem.* **1989**, 54, 3945.

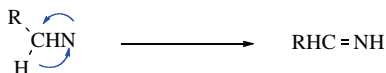
1. *Insertion (see Reaction 12-13).* Nitrenes, especially acyl nitrenes and sulfonyl nitrenes, can insert into C—H and certain other bonds, for example,



2. *Addition to C=C bonds (see Reaction 15-54):*

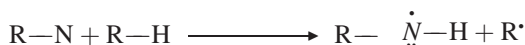


3. *Rearrangements.*⁴¹³ Alkyl nitrenes do not generally give either of the two preceding reactions because rearrangement is more rapid, for example,



Such rearrangements are so rapid that it is usually difficult to exclude the possibility that a free nitrene was never present at all; that is, that migration takes place at the same time the nitrene is formed⁴³⁸ (see Reaction 18-12). However, the rearrangement of naphthyl nitrenes to novel bond-shift isomers has been reported.⁴³⁹

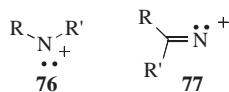
4. *Abstraction.* For example,



5. *Dimerization.* One of the principal reactions of NH is dimerization to diimide (N_2H_2). Azobenzenes are often obtained in reactions where aryl nitrenes are implicated:⁴⁴⁰



It would thus seem that dimerization is more important for nitrenes than it is for carbenes, but again it has not been proven that free nitrenes are actually involved.



At least two types of *nitrenium ions*,⁴⁴¹ the nitrogen analogues of carbocations, can exist as intermediates, although much less work has been done in this area

⁴³⁸ See Abramovitch, R.A.; Kyba, E.P. *J. Am. Chem. Soc.* **1971**, 93, 1537.

⁴³⁹ Maltsev, A.; Bally, T.; Tsao, M.-L.; Platz, M. S.; Kuhn, A.; Vosswinkel, M.; Wentrup, C. *J. Am. Chem. Soc.* **2004**, 126, 237.

⁴⁴⁰ See, for example, Leyva, E.; Platz, M.S.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* **1986**, 108, 3783.

⁴⁴¹ Novak, M.; Rajagopal, S. *Adv. Phys. Org. Chem.* **2001**, 36, 167; Falvey, D. E. in Moss, R. A.; Platz, M. S.; Jones, Jr., M. *Reactive Intermediate Chemistry*, Wiley-Interscience, Hoboken, NJ, **2004**, Vol. 1, pp 593–650.

than on carbocations. In one type (**76**), the nitrogen is bonded to two atoms (R or R' can be H),⁴⁴² and in the other (**77**) to only one atom.⁴⁴³ When R = H in **76** the species is a protonated nitrene. Like carbenes and nitrenes, nitrenium ions can exist in singlet or triplet states.⁴⁴⁴

⁴⁴² Winter, A.H.; Falvey, D.E.; Cramer, C.J. *J. Am. Chem. Soc.*, **2004**, *126*, 9661.

⁴⁴³ See Abramovitch, R.A.; Jeyaraman, R. in Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, **1984**, pp. 297–357; Gassman, P.G. *Acc. Chem. Res.* **1970**, *3*, 26; Lansbury, P.T. in Lwowski, W. *Nitrenes*, Wiley, NY, **1970**, pp. 405–419.

⁴⁴⁴ Gassman, P.G.; Cryberg, R.L. *J. Am. Chem. Soc.* **1969**, *91*, 5176.

Mechanisms and Methods of Determining Them

A mechanism is the actual process by which a reaction takes place: which bonds are broken, in what order, how many steps are involved, the relative rate of each step, and so on. In order to state a mechanism completely, the positions of all atoms should be specified, including those in solvent molecules, and the energy of the system, at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course is that the gross features of a mechanism are the first to be known and then increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms can be written today with a good degree of assurance, no mechanism is known completely.¹ There is much about the fine details that is still puzzling, and for some reactions even the gross mechanism is not yet clear. The problems involved are difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In some cases, there are several proposed mechanisms, each of which completely explains all the data.

6.A. TYPES OF MECHANISM

In most reactions of organic compounds, one or more covalent bonds are broken. Organic mechanisms may be divided into three basic types, depending on how the bonds break.

1. If a bond breaks in such a way that both electrons remain with one fragment, the mechanism is called *heterolytic*. Such reactions do not necessarily involve ionic intermediates, although they often do. The important thing is that the electrons are never unpaired. For most reactions, it is convenient to call one reactant the *attacking reagent* and the other the *substrate*. In this book, the substrate is always designated as that molecule that supplies carbon to the new bond. When carbon–carbon bonds are formed via heterolytic reactions, the reagent generally brings a pair of electrons

¹ *Perspectives on Structure and Mechanism in Organic Chemistry*, Carroll, F.A., Wiley, **2010**; *Arrow-Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms*, Levy, D.E., Wiley–Interscience, **2008**; *Guidebook to Mechanism in Organic Chemistry*, 6th Edition, Sykes, P., Prentice Hall, **1996**.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.

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to the substrate or takes a pair of electrons from it. A reagent that brings an electron pair is called a *nucleophile* and the reaction is *nucleophilic*. A reagent that takes an electron pair is called an *electrophile* and the reaction is *electrophilic*. For a reaction in which the substrate molecule becomes cleaved, part of it (the part not containing the carbon) is usually called the *leaving group*. A leaving group that carries away an electron pair is called a *nucleofuge*. If it comes away without the electron pair, it is called an *electrofuge*.

2. If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to take place by *homolytic* or *free radical mechanisms*.
3. It would seem that all bonds must break in one of the two ways previously noted. But there is a third type of mechanism in which electrons (usually six, but sometimes some other number) move in a closed ring. There are no intermediates, ions or free radicals, and it is impossible to say whether the electrons are paired or unpaired. Reactions with this type of mechanism are called *pericyclic*² (see Reactions **15-58-15-61** and **18-29-18-33**).

Examples of all three types of mechanisms are given in Section 6.B.

6.B. TYPES OF REACTION

The number and range of organic reactions is so great as to seem bewildering, but actually almost all of them can be fitted into just six categories. In the description of the six types that follows, the immediate products are shown, although in many cases they then react with something else. All the species are shown without charges, since differently charged reactants can undergo analogous changes. The descriptions given here are purely for the purpose of classification and comparison. All are discussed in detail in Part II.

1. *Substitutions*. If heterolytic, these reactions can be classified as nucleophilic or electrophilic depending on which reactant is designated as the substrate and which as the attacking reagent (very often Y must first be formed by a previous bond cleavage).

- a. Nucleophilic substitution (Chaps 10 and 13).



- b. Electrophilic substitution (Chaps 11 and 12).



- c. Free radical substitution (Chap 14).

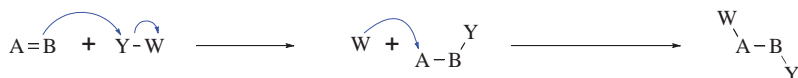


² For a classification of pericyclic reactions, see Hendrickson, J.B. *Angew. Chem. Int. Ed.* **1974**, 13, 47. Also see, Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, **1999**.

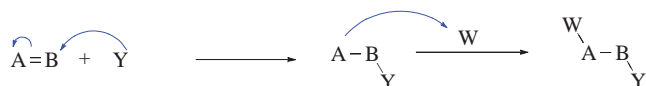
In free radical substitution, Y^\bullet is usually produced by a previous free radical cleavage, and X^\bullet goes on to react further.

2. *Additions to Double or Triple Bonds (Chaps 15 and 16).* These reactions can take place by all three of the mechanistic possibilities.

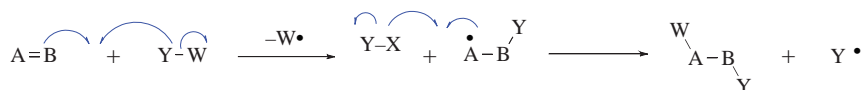
a. Electrophilic addition (heterolytic).



b. Nucleophilic addition (heterolytic).



c. Free-radical addition (homolytic).



d. Simultaneous addition (pericyclic).



The examples show Y and W coming from the same molecule, but very often (except in simultaneous addition) they come from different molecules, as illustrated by (b). Cleavage of the Y—W bond may occur at the same time that Y is bonding to B, but the cleavage may also occur earlier.

3. β Elimination (*Chap 17*).



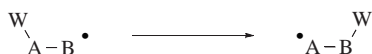
These reactions can take place by either heterolytic or pericyclic mechanisms. Examples of the latter are shown in Section 17.C.i. Free radical β eliminations are extremely rare. In heterolytic eliminations, W and X may or may not leave simultaneously and may or may not combine afterwards.

4. *Rearrangement (Chap 18).* Many rearrangements involve migration of an atom or group from one atom to another. There are three types, depending on how many electrons the migrating atom or group carries with it.

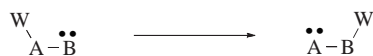
a. Migration with electron pair (nucleophilic; common).



b. Migration with one electron (free radical; rare).



c. Migration without electrons (electrophilic; rare).



The generic examples show 1,2 rearrangements, in which the migrating group moves to the adjacent atom. These are the most common, although longer rearrangements are also possible. There are also some rearrangements that do not involve simple migration at all, but rather migration across a π -framework (see Chap 18). Some of the latter involve pericyclic mechanisms.

5. *Oxidation and Reduction (Chap 19)*. Many oxidation and reduction reactions fall naturally into one of the four types mentioned above, but many others do not. For a description of oxidation–reduction mechanistic types, see Section 19.A.
6. *Combinations of the Above*. Note that arrows are used to show movement of *electrons*. An arrow always follows the motion of electrons and never of a nucleus or anything else (it is understood that the rest of the molecule follows the electrons). Ordinary arrows (double-headed) follow electron pairs, while single-headed arrows follow unpaired electrons. Double-headed arrows are also used in pericyclic reactions for convenience, but in these reactions how or in which direction the electrons are moving is usually unknown.

While not mentioned here as a distinct category, it must be said that many reactions, including some examples of 1–6 are actually acid–base reactions. In other cases, an acid–base reaction initiates the process or sometimes ends the process. In 2a, for example, $\text{Y} = \text{H}$ and this is an acid–base reaction in which the π bond is the base and the proton is the acid. If $\text{W} = \text{H}$ in 3a, then the elimination process begins with an acid–base reaction in which a base donates two electrons to $\text{H} (= \text{W})$. In 2b, if A donates electrons to W and $\text{W} = \text{H}$, this is another example of an acid–base reaction. Always be mindful of the acid–base properties of reactions.

Many, if not most of the reactions, noted above are subject to modification of the reactivity by the introduction of π bonds. Most reactions involve the transfer of two electrons to make or break a bond. The presence of two electrons in a π bond allows this two- electron-transfer process to proceed through the intervening atoms. In effect, the reactivity of a given center is extended by the presence of π bonds. This is the concept of *vinylology*: the extension of points of reactivity by intervening π bonds. In other words, if a system $\text{X}-\text{C}-1-\text{C}-2$ undergoes a reaction at C-2 with loss of X from C-1, $\text{X}-\text{C}-1-\text{C}-2=\text{C}-3-\text{C}-4$ may undergo reaction at C-4. Reaction at C-4 initiates electron transfer via the π bond that is extended to C-1 for loss of X. Several examples of this type of reaction will be presented in later chapters.

6.C. THERMODYNAMIC REQUIREMENTS FOR REACTION

In order for a reaction to take place spontaneously, the free energy of the products must be lower than the free energy of the reactants (i.e., ΔG must be negative). Reactions can go the other way, of course, but only if free energy is added. Like water on the surface of the earth, which naturally flows only downhill and never uphill, molecules seek the lowest possible potential energy. Free energy is made up of two components, enthalpy (H) and entropy (S).

These quantities are related by the equation

$$\Delta G = \Delta H - T\Delta S$$

The enthalpy change in a reaction is essentially the difference in bond energies (including resonance, strain,³ and solvation energies) between the reactants and the products. The enthalpy change can be calculated by totaling the bond energies of all the bonds broken, subtracting from this the total of the bond energies of all the bonds formed, and adding any changes in resonance, strain, or solvation energies. Entropy changes are quite different, and refer to the disorder or randomness of the system. The lower the order in a system, the greater the entropy. The preferred conditions in Nature are *low* enthalpy and *high* entropy, and in reacting systems, enthalpy spontaneously decreases while entropy spontaneously increases.

For many reactions, entropy effects are small and it is the enthalpy that mainly determines whether the reaction can take place spontaneously. However, in certain processes entropy is important and can sometimes dominate enthalpy. Several examples will be discussed.

1. In general, liquids have lower entropies than gases, since the molecules of gas have much more freedom and randomness. Solids, of course, have still lower entropies. Any reaction in which the reactants are all liquids and one or more of the products is a gas is therefore thermodynamically favored by the increased entropy; the equilibrium constant for that reaction will be higher than it would otherwise be. Similarly, the entropy of a gaseous substance is higher than that of the same substance dissolved in a solvent.
2. In a reaction in which the number of product molecules is equal to the number of reactant molecules (e.g., $A + B \rightarrow C + D$), entropy effects are usually small, but if the number of molecules is increased, (e.g., $A \rightarrow B + C$), there is a gain in entropy because more arrangements in space are possible when more molecules are present. Reactions in which a molecule is cleaved into two or more parts are likely to be thermodynamically favored by the entropy factor. Conversely, reactions in which the number of product molecules is less than the number of reactant molecules show entropy decreases, and in such cases there must be a sizable decrease in enthalpy to overcome the unfavorable entropy change.
3. Although reactions in which molecules are cleaved into two or more pieces have favorable entropy effects, many potential cleavages do not take place because of large increases in enthalpy.⁴ An example is cleavage of ethane into two methyl radicals. In this case, a bond of $\sim 79 \text{ kcal mol}^{-1}$ (330 kJ mol^{-1}) is broken, and no new bond is formed to compensate for this enthalpy increase. However, ethane can be cleaved at very high temperatures, which illustrates the principle that *entropy becomes more important as the temperature increases*, as is obvious from the equation $\Delta G = \Delta H - T\Delta S$. The enthalpy term is independent of temperature, while the entropy term is directly proportional to the absolute temperature.

³ For a discussion of the activation strain model of chemical reactivity, see van Zeist, W.-J.; Bickelhaupt, F.M. *Org. Biomol. Chem.*, **2010**, 8, 3118.

⁴ For calculations of long-chain alkane energies see Song, J.-W.; Tsuneda, T.; Sato, T.; Hirao, K. *Org. Lett.* **2010**, 12, 1440.

4. An acyclic molecule has more entropy than a similar cyclic molecule because there are more conformations (cf. hexane and cyclohexane). Ring opening therefore correlates with a gain in entropy and ring closing a loss.

6.D. KINETIC REQUIREMENTS FOR REACTION

Just because a reaction has a negative ΔG does not necessarily mean that it will take place in a reasonable period of time. A negative ΔG is a *necessary*, but not a *sufficient*, condition for a reaction to occur spontaneously. For example, the reaction between H_2 and O_2 to give H_2O has a large negative ΔG , but mixtures of H_2 and O_2 can be kept at room temperature for many centuries without reacting to any significant extent. In order for a reaction to take place, *free energy of activation* (ΔG^\ddagger) must be added.⁵ This situation is illustrated in Fig. 6.1,⁶ which is an energy profile for a one-step reaction without an intermediate. In this type of diagram, the horizontal axis (called the *reaction coordinate*)⁷ signifies the progression of the reaction. The parameter ΔG_f^\ddagger is the free energy of activation for the forward reaction. If the reaction shown in Fig. 6.1 is reversible, ΔG_r^\ddagger must be $> \Delta G_f^\ddagger$, since it is the sum of ΔG and ΔG_f^\ddagger .

When a reaction between two or more molecules has progressed to the point corresponding to the top of the curve, the term *transition state* is applied to the positions of the nuclei and electrons. The transition state possesses a definite geometry and charge distribution, but has no finite existence; the system passes through it. The system at this point is called an *activated complex*.⁸

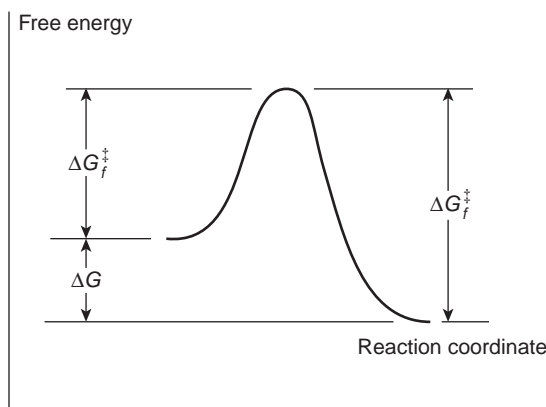


FIG. 6.1. Free energy profile of a reaction without an intermediate where the products have a lower free energy than the reactants.

⁵ To initiate a reaction of a mixture of H_2 and O_2 , energy must be added such as by striking a match.

⁶ Strictly speaking, this is an energy profile for a reaction of the type $\text{XY} + \text{Z} \rightarrow \text{X} + \text{YZ}$. However, it may be applied, in an approximate way, to other reactions.

⁷ For a review of reaction coordinates and structure–energy relationships, see Grunwald, E. *Prog. Phys. Org. Chem.* **1990**, 17, 55.

⁸ For a discussion of transition states, see Laidler, K.J. *J. Chem. Educ.* **1988**, 65, 540.

In *transition-state theory*,⁹ the starting materials and the activated complex are taken to be in equilibrium, the equilibrium constant being designated K^\ddagger . According to the theory, all activated complexes go on to product at the same rate (which, although at first sight is surprising, is not unreasonable since they are all “falling downhill”) so that the rate constant (see Sec. 6.J.vi) of the reaction depends only on the position of the equilibrium between the starting materials and the activated complex, (i.e., on the value of K^\ddagger). The parameter ΔG^\ddagger is related to K^\ddagger by

$$\Delta G^\ddagger = -2.3 RT \log K^\ddagger$$

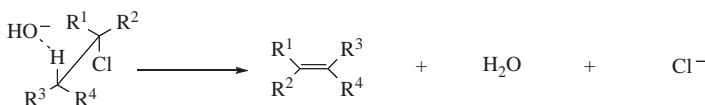
so that a higher value of ΔG^\ddagger is associated with a smaller rate constant. The rates of nearly all reactions increase with increasing temperature because the additional energy thus supplied helps the molecules to overcome the activation energy barrier.¹⁰ Some reactions have no free energy of activation at all, meaning that K^\ddagger is essentially infinite and that virtually all collisions lead to reaction. Such processes are said to be *diffusion controlled*.¹¹

Like ΔG , ΔG^\ddagger is made up of enthalpy and entropy components

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

ΔH^\ddagger , the *enthalpy of activation*, is the difference in bond energies, including strain, resonance, and solvation energies, between the starting compounds and the *transition state*. In many reactions, bonds have been broken or partially broken by the time the transition state is reached; the energy necessary for this is ΔH^\ddagger . It is true that additional energy will be supplied by the formation of new bonds, but if this occurs after the transition state, it can affect only ΔH and not ΔH^\ddagger .

Entropy of activation, (ΔS^\ddagger), which is the difference in entropy between the starting compounds and the transition state, becomes important when two reacting molecules must approach each other in a specific orientation in order for the reaction to take place. For example, the reaction between a simple non-cyclic alkyl chloride and hydroxide ion to give an alkene (Reaction 17-13) takes place only if, in the transition state, the reactants are oriented as shown. This is an acid–base reaction because the proton on the carbon β to the chlorine is polarized δ^+ , and is a weak acid. Removal of that proton initiates loss of the chlorine atom and formation of the alkene. The electrons in the C—H bond (the acidic proton) must align anti to the leaving groups (Cl) for the reaction to proceed.¹²



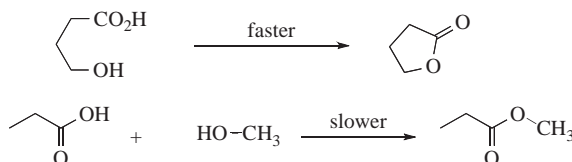
⁹ See Kreevoy, M.M.; Truhlar, D.G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, **1986**, pp. 13–95; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed., Wiley, NY, **1981**, pp. 137–181; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, **1982**; pp. 227–378. See Zevatskii, Y.E.; Samoilov, D.V. *Russ. J. Org. Chem.* **2007**, *43*, 483.

¹⁰ See Donahue, N.M. *Chem. Rev.* **2003**, *103*, 4593.

¹¹ For a monograph on diffusion-controlled reactions, see Rice, S.A. *Comprehensive Chemical Kinetics*, Vol. 25 (edited by Bamford, C.H.; Tipper, C.F.H.; Compton, R.G.); Elsevier: NY, **1985**.

¹² As will be seen in Chapter 17, elimination is also possible with some molecules if the hydrogen is oriented syn, instead of anti, to the chlorine atom. Of course, this orientation also requires a considerable loss of entropy.

When the two reacting molecules collide, if the ^-OH should approach the molecule, the chlorine atom, or near R^1 or R^2 , no reaction can take place. In order for a reaction to occur, the molecules must surrender the freedom they normally have to assume many possible arrangements in space because only one leads to reaction. Thus, a considerable loss in entropy is involved, (i.e., ΔS^\ddagger is negative).



Entropy of activation is also responsible for the difficulty in closing rings¹³ larger than six members. Consider a ring-closing reaction in which the two groups that must interact are situated on the ends of a 10-carbon chain. In order for reaction to take place, the groups must encounter each other. But a 10-carbon chain has many conformations, and in only a few of these are the ends of the chain near each other. Thus, forming the transition state requires a great loss of entropy.¹⁴ This factor is also present, although less so, in closing rings of six members or less (except three-membered rings), but with rings of this size the entropy loss is less than that of bringing two individual molecules together. For example, a reaction between an OH group and a COOH group in the same molecule to form a lactone with a five- or six-membered ring takes place much faster than the same reaction between a molecule containing an OH group and another containing a COOH group. Although ΔH^\ddagger is about the same, ΔS^\ddagger is much less for the cyclic case. However, if the ring to be closed has three or four members, small-angle strain is introduced and the favorable ΔS^\ddagger may not be sufficient to overcome the unfavorable ΔH^\ddagger change. Table 6.1 shows the relative rate constants for the closing of rings of 3–23 members all by the same reaction.¹⁵ Reactions in which the transition state has more disorder than the starting compounds, for example, the pyrolytic conversion of cyclopropane to propene, have positive ΔS^\ddagger values and are thus favored by the entropy effect.

Reactions with intermediates are two-step (or more) processes. In these reactions, there is an energy “well”. There are two transition states, each with an energy higher than the intermediate (Fig. 6.2). The deeper the well, the more stable the intermediate. In Fig. 6.2a, the second peak is higher than the first. The opposite situation is shown in Fig. 6.2b. Note that in reactions in which the second peak is higher than the first, the overall ΔG^\ddagger is less than the sum of the ΔG^\ddagger values for the two steps. Minima in free energy profile diagrams (*intermediates*) correspond to real species that have a finite though usually short existence.

¹³ See De Tar, D.F.; Luthra, N.P.J. *Am. Chem. Soc.* **1980**, 102, 4505; Mandolini, L. *Bull. Soc. Chim. Fr.* **1988**, 173. For a related discussion, see Menger, F.M. *Acc. Chem. Res.* **1985**, 18, 128.

¹⁴ See Nakagaki, R.; Sakuragi, H.; Mutai, K. *J. Phys. Org. Chem.* **1989**, 2, 187; Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, 22, 1; Winnik, M.A. *Chem. Rev.* **1981**, 81, 491; Valters, R. *Russ. Chem. Rev.* **1982**, 51, 788.

¹⁵ The values for ring sizes 4, 5, and 6 are from Mandolini, L. *J. Am. Chem. Soc.* **1978**, 100, 550; the others are from Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, 99, 2591. See also, Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, 14, 95. See, however, Benedetti, F.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* **1986**, 605.

TABLE 6.1¹⁵ Relative Rate Constants at 50 °C^a

$\text{Br}(\text{CH}_2)_{n-2}\text{CO}_2^- \longrightarrow (\text{CH}_2)_{n-2} \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{C} \end{array}$ where $n = \text{the ring size}$.	
Ring Size	Relative Rate
3	21.7
4	5.4×10^3
5	1.5×10^6
6	1.7×10^4
7	97.3
8	1.00
9	1.12
10	3.35
11	8.51
12	10.6
13	32.2
14	41.9
15	45.1
16	52.0
18	51.2
23	60.4

^aThe rate for an eight-membered ring = 1 for the reaction.

Reprinted with permission from Mandolini, L. *J. Am. Chem. Soc.* **1978**, 100, 550. Copyright © 1978 American Chemical Society. Reprinted with permission from Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, 99, 2591. Copyright © 1977 American Chemical Society.

These may be the carbocations, carbanions, free radicals, and so on., discussed in Chapter 5 or molecules in which all the atoms have their normal valences. In either case, under the reaction conditions they do not live long (because ΔG_2^\ddagger is small), but rapidly go on to products. Maxima in these curves, however, do not correspond to actual species, but only to

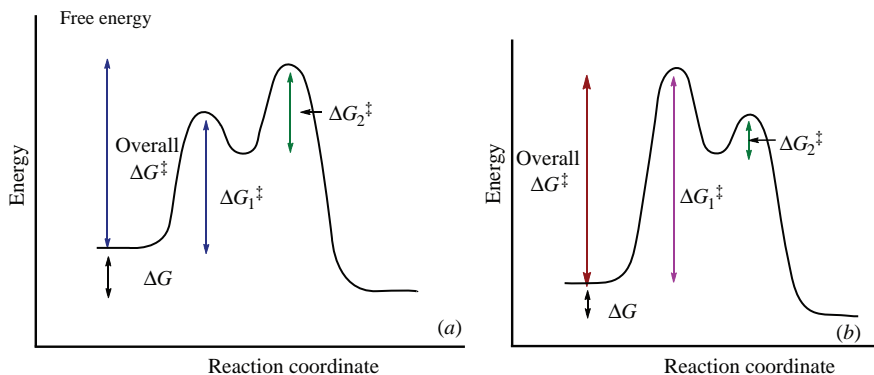
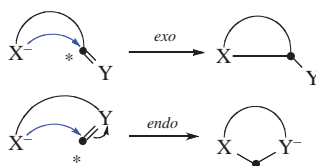


FIG. 6.2. (a) Free energy profile for a reaction with an intermediate ΔG_1^\ddagger and ΔG_2^\ddagger are the free energy of activation for the first and second stages, respectively. (b) Free energy profile for a reaction with an intermediate in which the first peak is higher than the second

transition states in which bond breaking and/or bond making have partially taken place. Transition states have only a transient existence with an essentially zero lifetime.¹⁶

6.E. THE BALDWIN RULES FOR RING CLOSURE¹⁷

In previous sections, the kinetic and thermodynamic aspects of ring-closure reactions were discussed in a general way. J.E. Baldwin¹⁸ supplied a more specific set of rules for certain closings of three seven-membered rings. These rules distinguish two types of ring closure, called *exo* and *endo*, and three kinds of atoms at the starred positions: *Tet* for sp^3 , *Trig* for sp^2 , and *Dig* for sp . The following are *Baldwin's rules* for closing rings of 3–7 members.



Rule 1. Tetrahedral systems

- a. 3-7-*Exo-Tet* are all favored processes
- b. 5-6-*Endo-Tet* are disfavored

Rule 2. Trigonal systems

- a. 3-7-*Exo-Trig* are favored
- b. 3-5-*Endo-Trig* are disfavored¹⁹
- c. 6-7-*Endo-Trig* are favored

Rule 3. Digonal systems

- a. 3-4-*Exo-Dig* are disfavored
- b. 5-7-*Exo-Dig* are favored
- c. 3-7-*Endo-Dig* are favored

“Disfavored” does not mean it cannot be done, only that it is more difficult than the favored cases. These rules are empirical and have a stereochemical basis. The favored pathways are those in which the length and nature of the linking chain will enable the terminal atoms to achieve the proper geometries for reaction. The disfavored cases require severe distortion of bond angles and distances. Many cases in the literature are in

¹⁶ See laser femtochemistry: Zewall, A.H.; Bernstein, R.B. *Chem. Eng. News* **1988**, 66, No. 45 (Nov. 7), 24–43. For another method, see Collings, B.A.; Polanyi, J.C.; Smith, M.A.; Stolow, A.; Tarr, A.W. *Phys. Rev. Lett.* **1987**, 59, 2551.

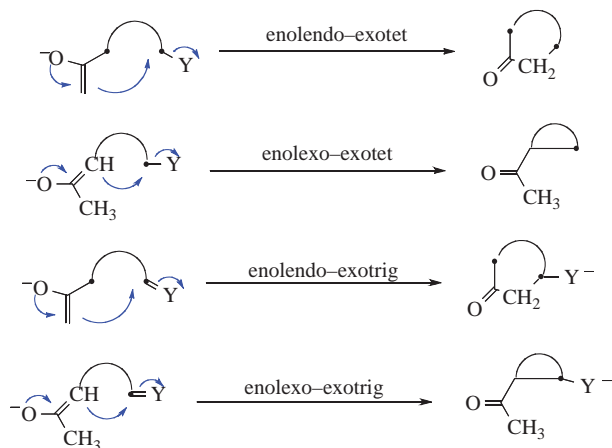
¹⁷ See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 564–572.

¹⁸ Baldwin, J.E. *J. Chem. Soc. Chem. Commun.* **1976**, 734; Baldwin, J.E. in *Further Perspectives in Organic Chemistry (Ciba Foundation Symposium 53)*, Elsevier, Amsterdam, The Netherlands, **1979**, pp. 85–99. See also, Baldwin, J.E.; Thomas, R.C.; Kruse, L.I.; Silberman, L. *J. Org. Chem.* **1977**, 42, 3846; Baldwin, J.E.; Lusch, M.J. *Tetrahedron* **1982**, 38, 2939; Fountain, K.R.; Gerhardt, G. *Tetrahedron Lett.* **1978**, 3985.

¹⁹ For some exceptions to the rule in this case, see Trost, B.M.; Bonk, P.J. *J. Am. Chem. Soc.* **1985**, 107, 1778; Torres, L.E.; Larson, G.L. *Tetrahedron Lett.* **1986**, 27, 2223.

substantial accord with these rules, and they are important in the formation of five- and six-membered rings.²⁰

Although Baldwin's rules can be applied to ketone enolates,²¹ additional rules were added to make the terminology more specific.²² The orientation of the orbital as it approaches the reactive center must be considered for determining the correct angle of approach. Diagrams that illustrate the enolate rules are shown.



The rules are

- 6-7 enolendo-exo-tet reactions are favored
- 3-5 enolendo-exo-tet reactions are disfavored
- 3-7 enolexo-exo-tet reactions are favored
- 3-7 enolexo-exo-trig reactions are favored
- 6-7 enolendo-exo-trig reactions are favored
- 3-5 enolendo-exo-trig reactions are disfavored

6.F. KINETIC AND THERMODYNAMIC CONTROL



There are many cases in which a compound under a given set of reaction conditions can undergo competing reactions to give different products. Starting material **A** may give either **B** or **C**, for example. Figure 6.3 shows a free energy profile for a reaction in which **B** is thermodynamically more stable than **C** (ΔG_{B} is $> \Delta G_{\text{C}}$), but **C** is formed faster (lower ΔG^{\ddagger}). If neither reaction is reversible, **C** will be formed in a larger amount because it is formed faster. The product is said to be *kinetically controlled*. However, if the reactions are reversible, this will not necessarily be the case. If such a process is stopped well before the

²⁰ Johnson, C.D. *Accts. Chem. Res.* **1997**, 26, 476.

²¹ Baldwin, J.E.; Kruse, L.I. *J. Chem. Soc. Chem. Commun.* **1977**, 233.

²² Baldwin, J.E.; Luschny, M.J. *Tetrahedron* **1982**, 38, 2939.

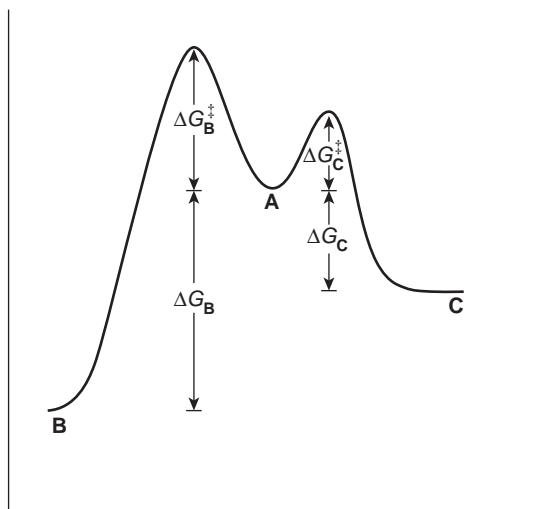


FIG. 6.3. Free energy profile illustrating kinetic versus thermodynamic control of products. The starting compounds (**A**) can react to give either **B** or **C**.

equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present. However, if the reaction is permitted to approach equilibrium, the predominant or even exclusive product will be **B**. Under these conditions the **C** that is first formed reverts to **A**, while the more stable **B** does so much less. We say the product is *thermodynamically controlled*.²³ Of course, Fig. 6.3 does not describe all reactions in which a compound **A** can give two different products. In many cases the more stable product is also the one that is formed faster. In such cases, the product of kinetic control is also the product of thermodynamic control.

6.G. THE HAMMOND POSTULATE

Transition states are not detectable and have zero lifetimes, so it is impossible to observe them directly. Information about their geometries must be obtained from inference and modeling. In some cases, the inferences can be very strong. For example, in the S_N2 reaction (Sec. 10.A.i) between CH_3I and I^- (a reaction in which the product is identical to the starting compound), the transition state should be perfectly symmetrical. In most cases, however, it is not possible to reach such easy conclusions, and conclusions are greatly aided by the *Hammond postulate*,²⁴ which states that for any single reaction step, *the geometry of the transition state for that step resembles the side to which it is closer in free energy*. Thus, for an exothermic reaction like that shown in Fig. 6.1, the transition state resembles the reactants more than the products, although not much more because there is a substantial ΔG^\ddagger on both sides.

The postulate is most useful in dealing with reactions with intermediates. In the reaction illustrated in Fig. 6.2a, the first transition state lies much closer in energy to the

²³ See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, **1982**, pp. 36–89.

²⁴ Hammond, G.S. *J. Am. Chem. Soc.* **1955**, 77, 334. For a discussion, see Farcasiu, D. *J. Chem. Educ.* **1975**, 52, 76.

intermediate than to the reactants, and it is possible to predict that the geometry of the transition state resembles that of the intermediate more than it does that of the reactants. Likewise, the second transition state also has a free energy much closer to that of the intermediate than to the products, so that both transition states resemble the intermediate more than they do the products or reactants. This is generally the case in reactions that involve very reactive intermediates. More is usually known about the structure of intermediates than of transition states, so a knowledge of intermediates is used to draw conclusions about the transition states (e.g., see Sec. 10.G.i and 15.B.i).

6.H. MICROSCOPIC REVERSIBILITY

In the course of a reaction, the nuclei and electrons assume positions that at each point correspond to the lowest free energies possible. If the reaction is reversible, these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the *principle of microscopic reversibility*. For example, if in a reaction $\mathbf{A} \rightarrow \mathbf{B}$ there is an intermediate \mathbf{C} , then \mathbf{C} must also be an intermediate in the reaction $\mathbf{B} \rightarrow \mathbf{A}$. This is a useful principle since it enables one to know the mechanism of reactions in which the equilibrium lies far over to one side. Reversible photochemical reactions are an exception, since a molecule that has been excited photochemically does not have to lose its energy in the same way (Chap 7).

6.I. MARCUS THEORY

It is often useful to compare the reactivity of one compound with that of similar compounds. The real goal is to find out how a reaction coordinate (and in particular the transition state) changes when one reactant molecule is replaced by a similar molecule. *Marcus theory* is a method for doing this.²⁵

In this theory, the activation energy (ΔG^\ddagger) is thought of as consisting of two parts.

1. An *intrinsic* free energy of activation, which would exist if the reactants and products had the same ΔG° .²⁶

This is a kinetic part, called the *intrinsic barrier* ($\Delta G_{\text{int}}^\ddagger$).

2. A thermodynamic part, which arises from the ΔG° for the reaction.

The Marcus equation says that the overall ΔG^\ddagger for a one-step reaction is²⁷

$$\Delta G^\ddagger = \Delta G_{\text{int}}^\ddagger + \frac{1}{2} \Delta G^\Delta + \frac{(\Delta G^\Delta)^2}{16(\Delta G_{\text{int}}^\ddagger - w^R)}$$

²⁵ See Albery, W.J. *Annu. Rev. Phys. Chem.* **1980**, *31*, 227; Kreevoy, M.M.; Truhlar, D.G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, **1986**, pp. 13–95.

²⁶ The parameter ΔG° is the standard free energy; that is, ΔG at atmospheric pressure.

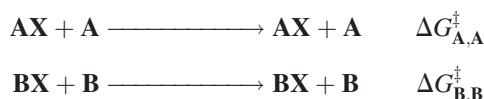
²⁷ Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* **1978**, *16*, 87, pp. 98–99.

where the term ΔG^Δ stands for

$$\Delta G^\Delta = \Delta G^\circ - w^R + w^P$$

w^R , a work term, is the free energy required to bring the reactants together and w^P is the work required to form the successor configuration from the products.

For a reaction of the type $\mathbf{AX} + \mathbf{B} \rightarrow \mathbf{BX}$, the intrinsic barrier²⁸ $\Delta G_{\text{int}}^\ddagger$ is taken to be the average ΔG^\ddagger for the two symmetrical reactions



so that

$$\Delta G_{\text{int}}^\ddagger + \frac{1}{2}(\Delta G_{\mathbf{A},\mathbf{A}}^\ddagger + \Delta G_{\mathbf{B},\mathbf{B}}^\ddagger)$$

One type of process that can successfully be treated by the Marcus equation is the S_N2 mechanism (Sec. 10.A.i).



When R is CH_3 the process is called *methyl transfer*.²⁹ For such reactions, the work terms w^R and w^P are assumed to be very small compared to ΔG° , and can be neglected, so that the Marcus equation simplifies to

$$\Delta G^\ddagger = \Delta G_{\text{int}}^\ddagger + \frac{1}{2} \Delta G^\circ + \frac{(\Delta G)^\circ^2}{16 \Delta G_{\text{int}}^\ddagger}$$

The Marcus equation allows ΔG^\ddagger for $\mathbf{RX} + \mathbf{Y} \rightarrow \mathbf{RY} + \mathbf{X}$ to be calculated from the barriers of the two symmetrical reactions $\mathbf{RX} + \mathbf{X} \rightarrow \mathbf{RX} + \mathbf{X}$ and $\mathbf{RY} + \mathbf{Y} \rightarrow \mathbf{RY} + \mathbf{Y}$. The results of such calculations are generally in agreement with the *Hammond postulate*.

Marcus theory can be applied to any single-step process where something is transferred from one particle to another. It was originally derived for electron transfers,³⁰ and then extended to transfers of H^+ (see Sec. 8.D), H^- ,³¹ and H^\bullet ,³² as well as methyl transfers.

²⁸ See Lee, I. *J. Chem. Soc. Perkin Trans. 2* **1989**, 943, *Chem. Soc. Rev.* **1990**, 19, 133.

²⁹ See Alberty, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* **1978**, 16, 87. See also, Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1989**, 943; Lewis, E.S.; McLaughlin, M.L.; Douglas, T.A. *J. Am. Chem. Soc.* **1985**, 107, 6668; Lewis, E.S. *Bull. Soc. Chim. Fr.* **1988**, 259.

³⁰ Marcus, R.A. *J. Phys. Chem.* **1963**, 67, 853, *Annu. Rev. Phys. Chem.* **1964**, 15, 155; Ebersson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer: NY, **1987**.

³¹ Kim, D.; Lee, I.H.; Kreevoy, M.M. *J. Am. Chem. Soc.* **1990**, 112, 1889 and references cited therein.

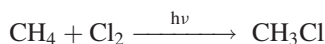
³² See, for example, Dneprovskii, A.S.; Eliseenkov, E.V. *J. Org. Chem. USSR* **1988**, 24, 243.

6.J. METHODS OF DETERMINING MECHANISMS³³

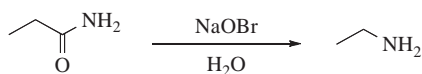
There are a number of commonly used methods for determining mechanisms.³⁴ In most cases, one method is not sufficient, and the problem is generally approached from several directions.

6.J.i. Identification of Products

Obviously any mechanism proposed for a reaction must account for all the products obtained and for their relative proportions, including products formed by side reactions. Incorrect mechanisms for the *von Richter reaction* (Reaction **13-30**) were accepted for many years because it was not realized that nitrogen was a major product. A proposed mechanism cannot be correct if it fails to predict the products in approximately the observed proportions. For example, any mechanism for the reaction



that fails to account for the formation of a small amount of ethane cannot be correct (see Reaction **14-1**), and any mechanism proposed for the *Hofmann rearrangement* (Reaction **18-13**):



must account for the fact that the carbonyl carbon is lost as CO_2 .

6.J.ii. Determination of the Presence of an Intermediate

Intermediates are postulated in many mechanisms, and the presence or absence of an intermediate is essential information. There are several methods, none of them foolproof,³⁵ for attempting to learn whether or not an intermediate is present and, if so, its structure. All methods are experimental, and an intermediate must be detected in one way or another, often by isolation or trapping.

1. *Isolation of an Intermediate.* It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. For example, in the *Neber rearrangement* (Reaction **18-12**) the intermediate **1** (an azirene)³⁶ has been isolated. If it can be shown that the isolated compound gives the same product when subjected to the reaction conditions, and at a rate no slower than the starting compound, this constitutes strong evidence that the reaction involves that intermediate, although it is not conclusive,

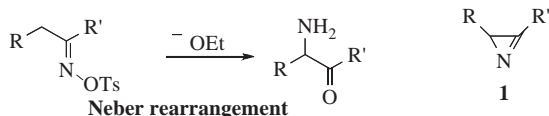
³³ *The Investigation of Organic Reactions and their Mechanisms* Maskill, H. (Ed.), Blackwell, Oxford, **2006**.

³⁴ See Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 2 pts., Wiley: NY, **1986**; Carpenter, B.K. *Determination of Organic Reaction Mechanisms*, Wiley: NY, **1984**.

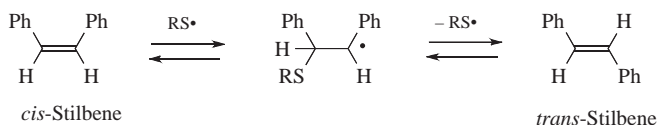
³⁵ For a discussion, see Martin, R.B. *J. Chem. Educ.* **1985**, 62, 789.

³⁶ See Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, 36, 4665.

since the compound may arise by an alternate path and by coincidence give the same product.



2. *Detection of an Intermediate.* In many cases an intermediate cannot be isolated, but can be detected by normal IR, ReactIR,³⁷ NMR, or other spectra.³⁸ The detection by Raman spectra of NO_2^+ was regarded as strong evidence that this is an intermediate in the nitration of benzene (see Reaction 11-2). Free radical and triplet intermediates can often be detected by ESR and by CIDNP (see Chap 5). Free radicals (as well as radical ions and EDA complexes) can also be detected by a method that does not rely on spectra. In this method, a double-bond compound is added to the reaction mixture, and its fate traced.³⁹ One possible result is cis–trans conversion. For example, *cis*-stilbene is isomerized to the *trans* isomer in the presence of RS^\bullet radicals, by this mechanism:



Since the *trans* isomer is more stable than the *cis*, the reaction does not go the other way, and the detection of the isomerized product is evidence for the presence of the RS^\bullet radicals.

3. *Trapping of an Intermediate.* In some cases, the suspected intermediate is known to be one that reacts in a given way with a certain compound. The intermediate can then be trapped by running the reaction in the presence of that compound. For example, benzyne (Sec. 13.A.iii) react with dienes in the *Diels–Alder reaction* (15-60). In any reaction where a benzyne is a suspected intermediate, the addition of a diene and the detection of the *Diels–Alder* adduct indicate that the benzyne was probably present.
4. *Addition of a Suspected Intermediate.* If a certain intermediate is suspected, and if it can be obtained by other means, then under the same reaction conditions it should give the same products. This kind of experiment can provide conclusive negative evidence: if the correct products are not obtained, the suspected compound is not an intermediate. However, if the correct products are obtained, this is not conclusive since they may arise by coincidence. The *von Richter reaction* (Reaction 13-30) provides a good example here too. For many years, it had been assumed that an aryl cyanide was an intermediate, since cyanides are easily hydrolyzed to carboxylic acids (Reaction 16-4). Indeed, *p*-chlorobenzonitrile was shown to

³⁷ ReactIR uses mid-range IR spectroscopy for the identification and monitoring of critical reaction species and follows the changes in the reaction on a second-by-second basis. For applications, see Stead, D.; Carbone, G.; O'Brien, P.; Campos, K.R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010**, *132*, 7260; Pippel, D.J.; Weisenburger, G.A.; Faibish, N.C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919.; Rutherford, J.L.; Hoffmann, D.; Collum, D.B. *J. Am. Chem. Soc.* **2002**, *124*, 264.

³⁸ See Parker, V.D. *Adv. Phys. Org. Chem.* **1983**, *19*, 131; Sheridan, R.S. *Org. Photochem.* **1987**, *8*, 159.

³⁹ For a review, see Todres, Z.V. *Tetrahedron* **1987**, *43*, 3839.

give *p*-chlorobenzoic acid under normal *von Richter* conditions.⁴⁰ However, when the experiment was repeated with 1-cyanonaphthalene, no 1-naphthoic acid was obtained, although 2-nitronaphthalene gave 13% 1-naphthoic acid under the same conditions.⁴¹ This proved that 2-nitronaphthalene must have been converted to 1-naphthoic acid by a route that does not involve 1-cyanonaphthalene. It also showed that even the conclusion that *p*-chlorobenzonitrile was an intermediate in the conversion of *m*-nitrochlorobenzene to *p*-chlorobenzoic acid must now be suspect, since it is not likely that the mechanism would substantially change in going from the naphthalene to the benzene system.

6.J.iii. The Study of Catalysis⁴²

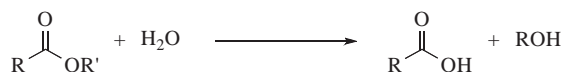
Many organic reactions are slow in the absence of a catalyst. Acid-catalyzed reactions are prevalent for example. Once it is known that a reaction is subject to catalysis, much information about the mechanism of a reaction can be obtained from a knowledge of which substances catalyze the reaction, which inhibit it, and which do neither. Of course, just as a mechanism must be compatible with the products, so must it be compatible with its catalysts. In general, *catalysts perform their actions by providing an alternate pathway for the reaction* in which ΔG^\ddagger is less than it would be without the catalyst. Catalysts do not change ΔG .

6.J.iv. Isotopic Labeling⁴³

Molecules that have been isotopically labeled can be used to trace the path of the reaction, which may provide much useful mechanistic information. For example, in the reaction



does the CN group in the product come from the CN in the BrCN? The use of ¹⁴C supplied the answer, since $R^{14}CO_2^-$ gave *radioactive* RCN.⁴⁴ This surprising result saved a lot of labor, since it ruled out a mechanism involving the replacement of CO₂ by CN (see Reaction 16-94). Other radioactive isotopes are also frequently used as tracers, but even stable isotopes can be used. An example is the hydrolysis of esters



Which bond of the ester is broken, the acyl–O or the alkyl–O bond? The answer is found by the use of H₂¹⁸O. If the acyl–O bond breaks, the labeled oxygen will appear in the acid;

⁴⁰ Bunnett, J.F.; Rauhut, M.M.; Knutson, D.; Bussell, G.E. *J. Am. Chem. Soc.* **1954**, 76, 5755.

⁴¹ Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* **1956**, 21, 944.

⁴² See Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, **1969**; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, **1971**; Coenen, J.W.E. *Recl. Trav. Chim. Pays-Bas*, **1983**, 102, 57; and in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, **1986**, the articles by Keeffe, J.R.; Kresge, A.J. pp. 747–790; Haller, G.L.; Delgass, W.N. pp. 951–979.

⁴³ See Wentrup, C. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, **1986**, pp. 613–661; Collins, C.J. *Adv. Phys. Org. Chem.* **1964**, 2, 3. See also, the series *Isotopes in Organic Chemistry*.

⁴⁴ Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* **1958**, 36, 1256.

otherwise it will be in the alcohol (see Reaction **16-59**). Although neither compound is radioactive, the one that contains ^{18}O can be determined by submitting both to mass spectrometry. In a similar way, deuterium can be used as a label for hydrogen. In this case, mass spectrometry is not the only option since IR and ^1H and ^{13}C NMR⁴⁵ spectra can be used to determine when deuterium has been substituted for hydrogen.

In the labeling technique, it is not generally necessary to use completely labeled compounds. Partially labeled material is usually sufficient.

6.J.v. Stereochemical Evidence⁴⁶

If the products of a reaction are capable of existing in more than one stereoisomeric form, the form that is obtained may give information about the mechanism.⁴⁷ For example, Walden⁴⁸ discovered that (+)-malic acid gives (–)-chlorosuccinic acid when treated with PCl_5 and the (+) enantiomer when treated with SOCl_2 , showing that the mechanisms of these apparently similar conversions could not be the same (see Sec. 10.A.i and 10.D). Much useful information has been obtained about nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment. The isomers involved need not be enantiomers. Thus, the fact that *cis*-2-butene treated with KMnO_4 gives *meso*-2,3-butanediol and not the racemic mixture is evidence that the two OH groups attack the double bond from the same side (see Reaction **15-48**).

6.J.vi. Kinetic Evidence⁴⁹

The rate of a homogeneous reaction⁵⁰ is the rate of disappearance of a reactant or appearance of a product. The rate nearly always changes with time, since it is usually proportional to concentration and the concentration of reactants decreases with time. However, the rate is not always proportional to the concentration of all reactants. In some cases, a change in the concentration of a reactant produces no change at all in the rate, while in other cases the rate may be proportional to the concentration of a substance (a catalyst) that does not even appear in the stoichiometric equation. A study of which reactants affect the rate often tells a good deal about the mechanism.

If the rate is proportional to the change in concentration of only one reactant (**A**), the *rate law* (the rate of change of concentration of **A** with time *t*) is

$$\text{Rate} = \frac{-d[\text{A}]}{dt} = k[\text{A}]$$

⁴⁵ For a review, see Hinton, J.; Oka, M.; Fry, A. *Isot. Org. Chem.* **1977**, 3, 41.

⁴⁶ See Billups, W.E.; Houk, K.N.; Stevens, R.V. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, **1986**, pp. 663–746; Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, **1962**; Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, **1956**.

⁴⁷ Bonnet, L.; Larrégaray, P.; Duguay, B.; Rayez, J.-C.; Che, D.C.; Kasai, T. *Bull. Chem. Soc. Jpn.* **2007**, 80, 707.

⁴⁸ Walden, P. *Ber.* **1896**, 29, 136; **1897**, 30, 3149; **1899**, 32, 1833.

⁴⁹ See Connors, K.A. *Chemical Kinetics*, VCH, NY, **1990**; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, **1984**; Drenth, W.; Kwart, H. *Kinetics Applied to Organic Reactions*, Marcel Dekker, NY, **1980**; Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, **1970**, pp. 53–100; Gardiner Jr., W.C. *Rates and Mechanisms of Chemical Reactions*, W.A. Benjamin, NY, **1969**; Leffler, J.E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*, Wiley, NY, **1963**; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, **1969**, pp. 555–614.

⁵⁰ A homogeneous reaction occurs in one phase. Heterogeneous kinetics have been studied much less.

where k is the *rate constant* for the reaction.⁵¹ There is a minus sign because the concentration of **A** decreases with time. A reaction that follows such a rate law is called a *first-order reaction*. The units of k for a first-order reaction are reciprocal second (s^{-1}). The rate of a *second-order reaction* is proportional to the concentration of two reactants, or to the square of the concentration of one:

$$\text{Rate} = \frac{-d[\text{A}]}{dt} = k [\text{A}][\text{B}] \quad \text{or} \quad \text{Rate} = \frac{-d[\text{A}]}{dt} = k [\text{A}]^2$$

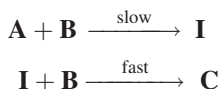
For a second-order reaction, the units are $\text{L mol}^{-1} \text{s}^{-1}$ or some other units expressing the reciprocal of concentration or pressure per unit time interval.

Similar expressions can be written for third-order reactions. A reaction whose rate is proportional to $[\text{A}]$ and to $[\text{B}]$ is said to be first order in **A** and in **B**, second order overall. A reaction rate can be measured in terms of any reactant or product, but the rates so determined are not necessarily the same. For example, if the stoichiometry of a reaction is $2\text{A} + \text{B} \rightarrow \text{C} + \text{D}$ then, on a molar basis, **A** must disappear twice as fast as **B**, so that $-d[\text{A}]/dt$ and $-d[\text{B}]/dt$ are not equal but the former is twice as large as the latter.

The rate law of a reaction is an experimentally determined fact. The rate law leads to an understanding of the *molecularity*, which may be defined as the number of molecules that come together to form the activated complex. It is obvious that if it is known how many (and which) molecules take part in the activated complex, a good deal is known about the mechanism. The experimentally determined rate order is not necessarily the same as the molecularity. Any reaction, no matter how many steps are involved, has only one rate law, but each step of the mechanism has its own molecularity. For reactions that take place in one step (reactions without an intermediate), the order is the same as the molecularity. A first-order, one-step reaction is always unimolecular; a one-step reaction that is second order in **A** always involves two molecules of **A**; if it is first order in **A** and in **B**, then a molecule of **A** reacts with one of **B**, and so on. For reactions that take place in more than one step, the order *for each step* is the same as the molecularity *for that step*. This fact enables us to predict the rate law for any proposed mechanism, although the calculations may get lengthy at times.⁵² If any one step of a mechanism is considerably slower than all the others (this is usually the case), the rate of the overall reaction is essentially the same as that of the slow step, which is consequently called the *rate-determining step*.⁵³

For reactions that take place in two or more steps, two broad cases can be distinguished:

1. The first step is slower than any subsequent step and is consequently rate determining. In such cases, the rate law simply includes the reactants that participate in the slow step. For example, if the reaction $\text{A} + 2\text{B} \rightarrow \text{C}$ has the mechanism



⁵¹ Colins, C.C.; Cronin, M.F.; Moynihan, H.A.; McCarthy, D.G. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1267.

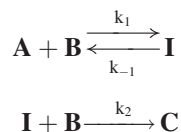
⁵² For a discussion of how order is related to *molecularity* in many complex situations, see Szabó, Z.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol.2, Elsevier, NY, **1969**, pp. 1–80.

⁵³ Many chemists prefer to use the term *rate-limiting step* or *rate-controlling step* for the slow step, rather than *rate-determining step*. See the definitions in Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *IUPAC Compendium of Chemical Terminology*, Blackwell Scientific Publications, Oxford, **1987**, p. 337. For a discussion of rate-determining steps, see Laidler, K.J. *J. Chem. Educ.* **1988**, 65, 250.

where **I** is an intermediate, the reaction is second order, with the rate law

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k [\mathbf{A}][\mathbf{B}]$$

2. When the first step is not rate determining, determination of the rate law is usually much more complicated. For example, consider the mechanism



where the first step is a rapid attainment of equilibrium, followed by a slow reaction to give **C**. The rate of disappearance of **A** is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k_1 [\mathbf{A}][\mathbf{B}] - k_{-1} [\mathbf{I}]$$

Both terms must be included because **A** is being formed by the reverse reaction, as well as being used up by the forward reaction. This equation is of very little help as it stands since the concentration of the intermediate cannot be measured. However, the combined rate law for the formation and disappearance of **I** is

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k_1 [\mathbf{A}][\mathbf{B}] - k_{-1} [\mathbf{I}] - k_2 [\mathbf{I}][\mathbf{B}]$$

This equation is of little help unless the assumption is made that *the concentration of I does not change with time*, since it is an intermediate that is used up (going either to **A** + **B** or to **C**) as fast as it is formed. This assumption, called the assumption of the *steady state*,⁵⁴ enables $d[\mathbf{I}]/dt$ to be set equal to zero, and hence to solve for **[I]** in terms of the measurable quantities **[A]** and **[B]**:

$$[\mathbf{I}] = \frac{k_1 [\mathbf{A}][\mathbf{B}]}{k_2 [\mathbf{B}] + k_{-1}}$$

Inserting this value for **[I]** into the original rate expression gives

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2 [\mathbf{A}][\mathbf{B}]^2}{k_2 [\mathbf{B}] + k_{-1}}$$

Note that this rate law is valid whatever the values of k_1 , k_{-1} , and k_2 . However, our original hypothesis was that the first step was faster than the second, or that

$$k_1 [\mathbf{A}][\mathbf{B}] \gg k_2 [\mathbf{I}][\mathbf{B}]$$

⁵⁴ For a discussion, see Raines, R.T.; Hansen, D.E. *J. Chem. Educ.* **1988**, 65, 757.

Since the first step is an equilibrium

$$k_1[\mathbf{A}][\mathbf{B}] = k_{-1}[\mathbf{I}]$$

this gives

$$k_{-1}[\mathbf{I}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Canceling $[\mathbf{I}]$ gives

$$k_{-1} \gg k_2[\mathbf{B}]$$

Neglecting $k_2[\mathbf{B}]$ in comparison with k_{-1} gives

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2}{k_{-1}} [\mathbf{A}][\mathbf{B}]^2$$

The overall rate is thus third order: first order in \mathbf{A} and second order in \mathbf{B} . Incidentally, if the first step is rate determining (as was the case in the preceding paragraph), then

$$k_2[\mathbf{B}] \gg k_{-1} \quad \text{and} \quad \frac{-d[\mathbf{A}]}{dt} = k_1 [\mathbf{A}][\mathbf{B}]$$

which is the same rate law deduced from the rule that where the first step is rate determining, the rate law includes the reactants that participate in that step.

It is possible for a reaction to involve \mathbf{A} and \mathbf{B} in the rate-determining step, although only $[\mathbf{A}]$ appears in the rate law. This occurs when a large excess of \mathbf{B} is present, say 100 times the molar quantity of \mathbf{A} . In this case, the complete reaction of \mathbf{A} uses up only 1 equiv of \mathbf{B} , leaving 99 equiv. It is not easy to measure the change in concentration of \mathbf{B} with time in such a case, and it is seldom attempted, especially when \mathbf{B} is also the solvent. Since $[\mathbf{B}]$, for practical purposes, does not change with time, the reaction appears to be first order in \mathbf{A} although actually both \mathbf{A} and \mathbf{B} are involved in the rate-determining step. This is often referred to as a *pseudo-first-order* reaction. Pseudo-order reactions can also come about when one reactant is a catalyst whose concentration does not change with time because it is replenished as fast as it is used up and when a reaction is conducted in a medium that keeps the concentration of a reactant constant, for example, in a buffer solution where H^+ or OH^- is a reactant. Pseudo-first-order conditions are frequently used in kinetic investigations for convenience in experimentation and calculations.

What is actually being measured is the change in concentration of a product or a reactant with time. Many methods have been used to make such measurements.⁵⁵ The choice of a method depends on its convenience and its applicability to the reaction being studied. Among the most common methods are the following:

1. *Periodic or Continuous Spectral Readings.* In many cases, the reaction can be carried out in the cell while it is in the instrument. Then all that is necessary is that

⁵⁵ See Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, **1984**. See Batt, L. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 1, Elsevier, NY, **1969**, pp. 1–111.

the instrument be read, periodically or continuously. Among the methods used are IR and UV spectroscopy, polarimetry, NMR, and ESR.⁵⁶

2. *Quenching and Analyzing.* A series of reactions can be set up and each stopped in some way (perhaps by suddenly lowering the temperature or adding an inhibitor) after a different amount of time has elapsed. The materials are then analyzed by spectral readings, titrations, chromatography, polarimetry, or any other method.
3. *Removal of Aliquots at Intervals.* Each aliquot is then analyzed as in method 2.
4. *Measurement of Changes in Total Pressure, for Gas-Phase Reactions.*⁵⁷
5. *Calorimetric Methods.* The output or absorption of heat can be measured at time intervals.

Special methods exist for kinetic measurements of very fast reactions.⁵⁸

A graph is usually obtained that shows the change in concentration with time. Interpretation⁵⁹ is required to obtain a rate law and a value of k . If a reaction obeys simple first- or second-order kinetics, the interpretation is generally not difficult. For example, for a concentration at the start = A_0 , the first-order rate law

$$\frac{-d[A]}{dt} = k[A] \quad \text{or} \quad \frac{-d[A]}{[A]} = k dt$$

can be integrated between the limits $t=0$ and $t=t$ to give

$$-\ln \frac{[A]}{A_0} = kt \quad \text{or} \quad \ln [A] = -kt + \ln A_0$$

Therefore, if a plot of $\ln [A]$ against t is linear, the reaction is first order and k can be obtained from the slope. For first-order reactions, it is customary to express the rate not only by the rate constant k , but also by the *half-life*, which is the time required for one-half of any given quantity of a reactant to be used up. Since the half-life $t_{1/2}$ is the time required for $[A]$ to reach $A_0/2$:

$$\ln \frac{A_0}{2} = kt_{1/2} + \ln A_0$$

⁵⁶ For a review of ESR to measure kinetics, see Norman, R.O.C. *Chem. Soc. Rev.* **1979**, 8, 1.

⁵⁷ See le Noble, W.J. *Prog. Phys. Org. Chem.* **1967**, 5, 207; Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1; Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999.

⁵⁸ See Connors, K.A. *Chemical Kinetics*, VCH, NY, **1990**, pp. 133–186; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, **1984**, pp. 247–327; Krüger, H. *Chem. Soc. Rev.* **1982**, 11, 227; Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, **1986**. See also, Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 24, Elsevier, NY, **1983**.

⁵⁹ See Connors, K.A. *Chemical Kinetics*, VCH, NY, **1990**, pp. 17–131; Ritchie, C.D. *Physical Organic Chemistry*, 2nd ed., Marcel Dekker, NY, **1990**, pp. 1–35; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, **1984**; Margerison, D. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 1, Elsevier, NY, **1969**, pp. 343–421; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed., Wiley, NY, **1981**, pp. 12–82; in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, **1986**, the articles by Bunnett, J.F. pp. 251–372, Noyes Pub., pp. 373–423, Bernasconi, C.F. pp. 425–485, Wiberg, K.B. pp. 981–1019.

so that

$$t_{1/2} = \frac{\ln \left[\frac{A_0}{A_0/2} \right]}{k} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

For the general case of a reaction first order in **A** and first order in **B**, second order overall, integration is complicated, but it can be simplified if equimolar amounts of **A** and **B** are used, so that $A_0 = B_0$. In this case,

$$\frac{-d[A]}{dt} = k [A][B]$$

is equivalent to

$$\frac{-d[A]}{dt} = k [A]^2 \quad \text{or} \quad \frac{-d[A]}{[A]^2} = k dt$$

Integrating as before gives

$$\frac{1}{[A]} - \frac{1}{A_0} = kt$$

Thus, under equimolar conditions, if a plot of $1/[A]$ against t is linear, the reaction is second order with a slope of k . It is obvious that the same will hold true for a reaction second order in **A**.⁶⁰

Although many reaction-rate studies do give linear plots, which are easily interpreted, the results in many other studies are not so simple. In some cases, a reaction may be first order at low concentrations but second order at higher concentrations. In other cases, fractional orders are obtained, and even negative orders. The interpretation of complex kinetics often requires much skill and effort. Even where the kinetic data are relatively simple, there is often a problem in interpreting the data because of the difficulty of obtaining sufficiently precise measurements.⁶¹

Nuclear magnetic resonance spectra can be used to obtain kinetic information in a completely different manner from that mentioned above. This method, which involves the study of NMR line shapes,⁶² depends on the fact that NMR spectra have an inherent time factor: If a proton changes its environment less rapidly than $\sim 10^3$ times s^{-1} , an NMR spectrum shows a separate peak for each position the proton assumes. For example, if the rate of rotation around the C—N bond of N,N-dimethylacetamide is slower than 10^3 rotations per second, the two N-methyl groups appear as a separate signal with different chemical shifts indicating that they are not equivalent, one being *cis* to the oxygen and the other *trans* to the acyl methyl group. However, if the environmental change takes place more rapidly than $\sim 10^3$ times per second, only one signal is found, at a chemical shift that is the weighted average of the two individual positions. In many cases, two or more signals

⁶⁰ See Margerison, D. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 1, Elsevier, NY, **1969**, p. 361.

⁶¹ See Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, **1970**, pp. 62–70.

⁶² See Ōki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, **1985**; Fraenkel, G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, **1986**, pp. 547–604; Roberts, J.D. *Pure Appl. Chem.* **1979**, 51, 1037; Binsch, G. *Top. Stereochem.* **1968**, 3, 97.

are found at low temperatures, but as the temperature is increased, the lines coalesce because the interconversion rate increases with temperature and passes the 10^3 per second mark. From studies of the way line shapes change with temperature it is often possible to calculate rates of reactions and of conformational changes. This method is not limited to changes in proton line shapes, but can also be used for other atoms that give NMR and ESR spectra (Sec. 5.C.i).

Several types of mechanistic information can be obtained from kinetic studies.

1. Information can be obtained from the order of a reaction. Which molecules and how many take part in the rate-determining step may be determined. Such knowledge is very useful and often essential in elucidating a mechanism. For any mechanism that can be proposed for a given reaction, a corresponding rate law can be calculated by the methods discussed in the beginning of this section. If the experimentally obtained rate law fails to agree with this, the proposed mechanism is wrong. However, it is often difficult to relate the order of a reaction to the mechanism, especially when the order is fractional or negative. It is frequently the case that two or more proposed mechanisms for a reaction are kinetically indistinguishable, that is, they predict the same rate law.
2. Probably the most useful data obtained kinetically are the rate constants themselves. They are important since they can relate the effect on the rate of a reaction of changes in the structure of the reactants (see Chapter 9), the solvent,⁶³ the ionic strength, the addition of catalysts, and so on.
3. If the rate is measured at several temperatures, in most cases a plot of $\ln k$ against $1/T$ (T stands for absolute temperature) is nearly linear⁶⁴ with a negative slope, and fits the equation

$$\ln k = \frac{-E_a}{RT} + \ln A$$

where R is the gas constant and A is a constant called the *frequency factor*. This permits the calculation of E_a , which is the *Arrhenius activation energy* of the reaction. Now ΔH^\ddagger can then be obtained by

$$E_a = \Delta H^\ddagger + RT$$

It is also possible to use these data to calculate ΔS^\ddagger by the formula⁶⁵

$$\frac{\Delta S^\ddagger}{4.576} = \log k - 10.753 - \log T + \frac{E_a}{4.576T}$$

for energies in calorie units. For joule units, the formula is

$$\frac{\Delta S^\ddagger}{19.15} = \log k - 10.753 - \log T + \frac{E_a}{19.15T}$$

One then obtains ΔG^\ddagger from $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$.

⁶³ For a discussion of organic reaction rate acceleration by immediate solvent evaporation, see Orita, A.; Uehara, G.; Miwa, K.; Otera, J. *Chem. Commun.* **2006**, 4729.

⁶⁴ See Blandamer, M.J.; Burgess, J.; Robertson, R.E.; Scott, J.M.W. *Chem. Rev.* **1982**, 82, 259.

⁶⁵ See Bunnett, J.F. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, **1986**, p. 287.

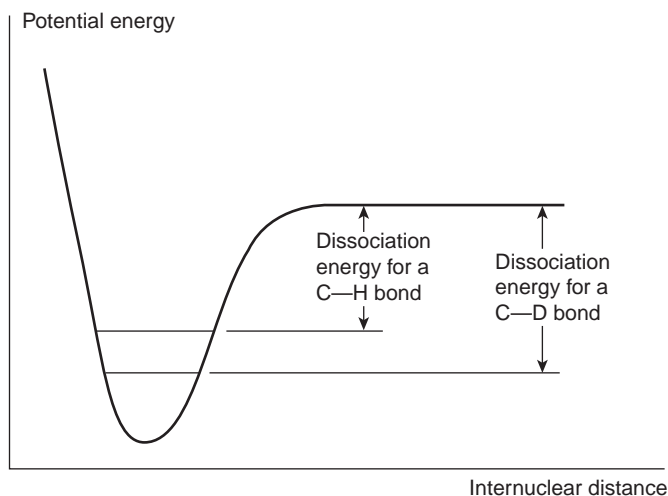


FIG. 6.4. A C—D bond has a lower zero point than a corresponding C—H bond; thus the dissociation energy is higher.

6.J.vii. Isotope Effects

When a hydrogen atom in a reactant molecule is replaced by deuterium, there is often a change in the rate. Such changes are known as *deuterium isotope effects*⁶⁶ and are expressed by the ratio $k_{\text{H}}/k_{\text{D}}$. The ground-state vibrational energy (called the zero-point vibrational energy) of a bond depends on the mass of the atoms and is lower when the reduced mass is higher.⁶⁷ Therefore, D—C, D—O, D—N bonds, and so on, have lower energies in the ground state than the corresponding H—C, H—O, H—N bonds, and so on. Complete dissociation of a deuterium bond consequently requires more energy than that for a corresponding hydrogen bond in the same environment (Fig. 6.4). If a H—C, H—O, or H—N bond is not broken at all in a reaction or is broken in a non-rate-determining step, substitution of deuterium for hydrogen causes no change in the rate (see below for an exception to this statement), but if the bond is broken in the rate-determining step, the rate must be lowered by the substitution.

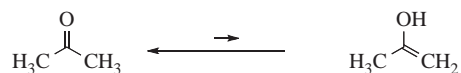


This provides a valuable diagnostic tool for determination of mechanism. For example, in the bromination of acetone (Reaction 12-4) the fact that the rate is independent of the bromine concentration led to the postulate that the rate-determining step was prior to

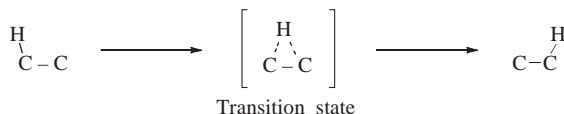
⁶⁶ See Melander, L.; Saunders, Jr., W.H. *Reaction Rates of Isotopic Molecules*, Wiley, NY, 1980. For reviews, see Isaacs, N.S. *Physical Organic Chemistry*, Longman Scientific and Technical, Essex, 1987, pp. 255–281; Lewis, E.S. *Top. Curr. Chem.* 1978, 74, 31; Saunders, Jr., W.H. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, 1986, pp. 565–611; Bell, R.P. *Chem. Soc. Rev.* 1974, 3, 513; Bigeleisen, J.; Lee, M.W.; Mandel, F. *Annu. Rev. Phys. Chem.* 1973, 24, 407; Wolfsberg, M. *Annu. Rev. Phys. Chem.* 1969, 20, 449. Also see Kwart, H. *Acc. Chem. Res.* 1982, 15, 401; Isaacs, E.S. *Isot. Org. Chem.* 1984, 6, 67; Thibblin, A.; Ahlberg, P. *Chem. Soc. Rev.* 1989, 18, 209. See also, the series *Isotopes in Organic Chemistry*.

⁶⁷ The reduced mass μ of two atoms connected by a covalent bond is $\mu = m_1 m_2 / (m_1 + m_2)$.

tautomerization of the acetone:

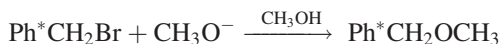


In turn, the rate-determining step of the tautomerization involves cleavage of a C—H bond (see Reaction 12-3). Thus there should be a substantial isotope effect if deuterated acetone is brominated. In fact, $k_{\text{H}}/k_{\text{D}}$ was found to be ~ 7 .⁶⁸ Deuterium isotope effects usually range from 1 (no isotope effect at all) to ~ 7 or 8, although in a few cases, larger⁶⁹ or smaller values have been reported.⁷⁰ Values of $k_{\text{H}}/k_{\text{D}} < 1$ are called *inverse isotope effects*. Isotope effects are greatest when, in the transition state, the hydrogen is symmetrically bonded to the atoms between which it is being transferred.⁷¹ Also, calculations show that isotope effects are at a maximum when the hydrogen atom in the transition state is on the straight line connecting the two atoms between which it is being transferred, and that for sufficiently nonlinear configurations, they decrease to $k_{\text{H}}/k_{\text{D}} = 1$.⁷² Of course, in open systems there is no reason for the transition state to be nonlinear, but this is not the case in many intramolecular mechanisms, (e.g., in a 1,2-migration of a hydrogen)



To measure isotope effects, it is not always necessary to prepare deuterium-enriched starting compounds. It can also be done by measuring the change in deuterium concentration at specific sites between a compound containing deuterium in natural abundance and the reaction product, using a high field NMR instrument.⁷³

The substitution of tritium for hydrogen gives isotope effects that are numerically larger. Isotope effects have also been observed with other elements, but they are much smaller, ~ 1.02 – 1.10 . For example, $k_{12\text{C}}/k_{13\text{C}}$ for the reaction of methoxide with benzyl bromide is 1.053 .⁷⁴ Although they are small, heavy-atom isotope effects can be measured quite accurately and are often very useful.⁷⁵



⁶⁸ Reitz, O.; Kopp, J. Z. *Phys. Chem. Abt. A* **1939**, 184, 429.

⁶⁹ For an example of a reaction with a deuterium isotope effect of 24.2, see Lewis, E.S.; Funderburk, L.H. *J. Am. Chem. Soc.* **1967**, 89, 2322. The high isotope effect in this case has been ascribed to *tunneling* of the proton: See Lewis, E.S.; Robinson, J.K. *J. Am. Chem. Soc.* **1968**, 90, 4337; Kresge, A.J.; Powell, M.F. *J. Am. Chem. Soc.* **1981**, 103, 201; Caldin, E.F.; Mateo, S.; Warrick, P. *J. Am. Chem. Soc.* **1981**, 103, 202. For arguments that high isotope effects can be caused by factors other than tunneling, see Thibblin, A. *J. Phys. Org. Chem.* **1988**, 1, 161; Kresge, A.J.; Powell, M.F. *J. Phys. Org. Chem.* **1990**, 3, 55.

⁷⁰ See Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* **1984**, 6, 161.

⁷¹ Bethell, D.; Hare, G.J.; Kearney, P.A. *J. Chem. Soc. Perkin Trans. 2* **1981**, 684, and references cited therein. See, however, Motell, E.L.; Boone, A.W.; Fink, W.H. *Tetrahedron* **1978**, 34, 1619.

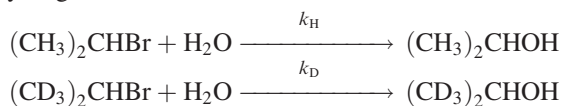
⁷² More O'Ferrall, R.A. *J. Chem. Soc. B* **1970**, 785, and references cited therein.

⁷³ Pascal, R.A.; Baum, M.W.; Wagner, C.K.; Rodgers, L.R.; Huang, D. *J. Am. Chem. Soc.* **1986**, 108, 6477.

⁷⁴ Stothers, J.B.; Bourns, A.N. *Can. J. Chem.* **1962**, 40, 2007. See also, Ando, T.; Yamataka, H.; Tamura, S.; Hanafusa, T. *J. Am. Chem. Soc.* **1982**, 104, 5493.

⁷⁵ For a review of carbon isotope effects, see Willi, A.V. *Isot. Org. Chem.* **1977**, 3, 237.

Deuterium isotope effects have been found even where it is certain that the C—H bond does not break at all in the reaction. Such effects are called *secondary isotope effects*,⁷⁶ the term *primary isotope effect* being reserved for the type discussed previously. Secondary isotope effects can be divided into α and β effects. In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond breaking slows the reaction. An example is solvolysis of 2-bromopropane to 2-propanol, where k_H/k_D was found to be 1.34.⁷⁷ The cause of β isotope effects has been a matter of much controversy, but they are most likely due to hyperconjugation effects in the transition state. The effects are greatest when the transition state has considerable carbocation character.⁷⁸ Although the C—H bond in question is not broken in the transition state, the carbocation is stabilized by hyperconjugation (Sec. 2.M) involving this bond. Because of hyperconjugation, the difference in vibrational energy between the C—H bond and the C—D bond in the transition state is less than it is in the ground state, so the reaction is slowed by substitution of deuterium for hydrogen.



Support for hyperconjugation as the major cause of β isotope effects is the fact that the effect is greatest when D is anti to the leaving group⁷⁹ (because of the requirement that all atoms in a resonance system be coplanar, planarity of the D—C—C—X system would most greatly increase the hyperconjugation), and the fact that secondary isotope effects can be transmitted through unsaturated systems.⁸⁰ There is evidence that at least some β isotope effects are steric in origin⁸¹ (e.g., a CD_3 group has a smaller steric requirement than a CH_3 group) and a field-effect explanation has also been suggested (CD_3 is apparently a better electron donor than CH_3 ⁸²), but hyperconjugation is the most probable cause in most instances.⁸³ Part of the difficulty in attempting to explain these effects is their small size, ranging only as high as ~ 1.5 .⁸⁴ Another complicating factor is that they can change with temperature. In one case,⁸⁵ k_H/k_D was 1.00 ± 0.01 at 0°C , 0.90 ± 0.01 at 25°C , and 1.15 ± 0.09 at 65°C . Whatever the cause, there seems to be a good correlation between β secondary isotope effects and carbocation character in the transition state. They are thus a useful tool for probing mechanisms.

The other type of secondary isotope effect results from a replacement of hydrogen by deuterium at the carbon containing the leaving group. These so-called *secondary isotope*

⁷⁶ See Westaway, K.C. *Isot. Org. Chem.* **1987**, 7, 275; Sunko, D.E.; Hehre, W.J. *Prog. Phys. Org. Chem.* **1983**, 14, 205; Halevi, E.A. *Prog. Phys. Org. Chem.* **1963**, 1, 109. See McLennan, D.J. *Isot. Org. Chem.* **1987**, 7, 393. See also, Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* **1984**, 6, 161.

⁷⁷ Leffek, K.T.; Llewellyn, J.A.; Robertson, R.E. *Can. J. Chem.* **1960**, 38, 2171.

⁷⁸ Bender, M.L.; Feng, M.S. *J. Am. Chem. Soc.* **1960**, 82, 6318; Jones, J.M.; Bender, M.L. *J. Am. Chem. Soc.* **1960**, 82, 6322.

⁷⁹ DeFrees, D.J.; Hehre, W.J.; Sunko, D.E. *J. Am. Chem. Soc.* **1979**, 101, 2323. See also, Siehl, H.; Walter, H. *J. Chem. Soc. Chem. Commun.* **1985**, 76.

⁸⁰ Shiner, Jr., V.J.; Kriz, Jr., G.S. *J. Am. Chem. Soc.* **1964**, 86, 2643.

⁸¹ Carter, R.E.; Dahlgren, L. *Acta Chem. Scand.* **1970**, 24, 633; Leffek, K.T.; Matheson, A.F. *Can. J. Chem.* **1971**, 49, 439; Sherrod, S.A.; Boekelheide, V. *J. Am. Chem. Soc.* **1972**, 94, 5513.

⁸² Halevi, E.A.; Nussim, M.; Ron, M. *J. Chem. Soc.* **1963**, 866; Halevi, E.A.; Nussim, M. *J. Chem. Soc.* **1963**, 876.

⁸³ Sunko, D.E.; Szele, I.; Hehre, W.J. *J. Am. Chem. Soc.* **1977**, 99, 5000; Kluger, R.; Brandl, M. *J. Org. Chem.* **1986**, 51, 3964.

⁸⁴ Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* **1964**, 174. A value for $k_{\text{CH}_3}/k_{\text{CD}_3}$ of 2.13 was reported for one case: Liu, K.; Wu, Y.W. *Tetrahedron Lett.* **1986**, 27, 3623.

⁸⁵ Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* **1964**, 174.

effects are varied, with values so far reported⁸⁶ ranging from 0.87 to 1.26.⁸⁷ These effects are also correlated with carbocation character. Nucleophilic substitutions that do not proceed through carbocation intermediates (S_N2 reactions) have an isotope effect near unity.⁸⁸ Those that do involve carbocations (S_N1 reactions) have higher isotope effects, which depend on the nature of the leaving group.⁸⁹ The accepted explanation for a isotope effects is that one of the bending C—H vibrations is affected by the substitution of D for H more or less strongly in the transition state than in the ground state.⁹⁰ Depending on the nature of the transition state, this may increase or decrease the rate of the reaction. The α isotope effects on S_N2 reactions can vary with concentration,⁹¹ an effect attributed to a change from a free nucleophile to one that is part of an ion pair⁹² (see Sec. 10.G.ii). This illustrates the use of secondary isotope effects as a means of studying transition state structure. The γ secondary isotope effects have also been reported.⁹³

Another kind of isotope effect is the *solvent isotope effect*.⁹⁴ Reaction rates often change when the solvent is changed from H_2O to D_2O or from ROH to ROD. These changes may be due to any of three factors or a combination of all of them.

1. The solvent may be a reactant. If an O—H bond of the solvent is broken in the rate-determining step, there will be a primary isotope effect. If the molecules involved are D_2O or D_3O^+ there may also be a secondary effect caused by the O—D bonds that are not breaking.
2. The substrate molecules may become labeled with deuterium by rapid hydrogen exchange, and then the newly labeled molecule may become cleaved in the rate-determining step.
3. The extent or nature of solvent–solute interactions may be different in the deuterated and non-deuterated solvents; this may change the energies of the transition state, and hence the activation energy of the reaction. These are secondary isotope effects. Two physical models for this third factor have been constructed.⁹⁵

It is obvious that in many cases the first and third factors at least, and often the second, are working simultaneously. Attempts have been made to separate them.⁹⁶

The methods described in this chapter are not the only means of determining mechanisms. A detailed examination of the literature, coupled with well-planned experiments is the best way to devise an approach to the mechanism of a given reaction.

⁸⁶ See Caldwell, R.A.; Misawa, H.; Healy, E.F.; Dewar, M.J.S. *J. Am. Chem. Soc.* **1987**, *109*, 6869.

⁸⁷ See Harris, J.M.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1971**, *93*, 2551.

⁸⁸ For reported exceptions, see Tanaka, N.; Kaji, A.; Hayami, J. *Chem. Lett.* **1972**, 1223; Westaway, K.C. *Tetrahedron Lett.* **1975**, 4229.

⁸⁹ Shiner, Jr., V.J.; Neumann, A.; Fisher, R.D. *J. Am. Chem. Soc.* **1982**, *104*, 354 and references cited therein.

⁹⁰ Streitwieser, Jr., A.; Jagow, R.H.; Fahey, R.C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, *80*, 2326.

⁹¹ Westaway, K.C.; Waszczylo, Z.; Smith, P.J.; Rangappa, K.S. *Tetrahedron Lett.* **1985**, *26*, 25.

⁹² Westaway, K.C.; Lai, Z. *Can. J. Chem.* **1988**, *66*, 1263.

⁹³ Werstiuk, N.H.; Timmins, G.; Cappelli, F.P. *Can. J. Chem.* **1980**, *58*, 1738.

⁹⁴ See Alvarez, F.J.; Schowen, R.L. *Isot. Org. Chem.* **1987**, *7*, 1; Kresge, A.J.; More O'Ferrall, R.A.; Powell, M.F. *Isot. Org. Chem.* **1987**, *7*, 177; Schowen, R.L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275; See Arnett, E.M.; McKelvey, D.R. in Coetzee, J.F.; Ritchie, C.D. cited above, pp. 343–398.

⁹⁵ Bunton, C.A.; Shiner, Jr., V.J. *J. Am. Chem. Soc.* **1961**, *83*, 42, 3207, 3214; Swain, C.G.; Thornton, E.R. *J. Am. Chem. Soc.* **1961**, *83*, 3884, 3890. See also, Mitton, C.G.; Gresser, M.; Schowen, R.L. *J. Am. Chem. Soc.* **1969**, *91*, 2045.

⁹⁶ More O'Ferrall, R.A.; Koepl, G.W.; Kresge, A.J. *J. Am. Chem. Soc.* **1971**, *93*, 9.

Irradiation Processes in Organic Chemistry

Most reactions carried out in organic chemistry laboratories take place between molecules, all of which are in their ground electronic states. In a *photochemical reaction*,¹ however, a reacting molecule has been previously promoted to an electronically excited state by absorption of light. A molecule in an excited state must lose its extra energy in some manner; it cannot remain in the excited state for long. The subject of electronic spectra is closely related to photochemistry. A chemical reaction is not the only possible means of relinquishing the extra energy in a photochemical process. In this chapter, electronically excited states and the processes of promotion to these states will be discussed. Reactions of such molecules are called photoreactions. There are enantioselective organocatalytic photoreactions, but they will not be discussed here.² Two other methods are available to facilitate chemical reactions: sonochemistry and microwave chemistry. Although the physical processes involved are not the same excitation processes observed in photochemistry, irradiation with ultrasound or with microwaves have a significant influence on chemical reactivity, and both are widely used. For that reason, they are included in this chapter.

7.A. PHOTOCHEMISTRY³

7.A.i. Excited States and the Ground State

Electrons can move from the ground-state energy level of a molecule to a higher level (i.e., an unoccupied orbital of higher energy) if outside energy is supplied. In a photochemical

¹ See Michl, J.; Bonačić-Koutecký, V. *Electronic Aspects of Organic Photochemistry*, Wiley, NY, **1990**; Scaiano, J.C. *Handbook of Organic Photochemistry*, 2 vols., CRC Press, Boca Raton, FL, **1989**; Coxon, J.M.; Halton, B. *Organic Photochemistry*, 2nd ed., Cambridge University Press, Cambridge, **1987**; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, **1986**; *Introduction to Organic Photochemistry*, Wiley, NY, **1986**; Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, **1984**; Margaretha, P. *Preparative Organic Photochemistry*, *Top. Curr. Chem.* **1982**, 103; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, **1978**; Rohatgi-Mukherjee, K.K. *Fundamentals of Photochemistry*, Wiley, NY, **1978**; Barltrop, J.A.; Coyle, J.D. *Principles of Photochemistry*, Wiley, NY, **1978**; Scaiano, J.; Johnston, L.J. *Org. Photochem.* **1989**, 10, 309. For a history of photochemistry, see Roth, H.D. *Angew. Chem. Int. Ed.* **1989**, 28, 1193; Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* **1988**, 60, 1055. See also, the series, *Advances in Photochemistry*, *Organic Photochemistry*, and *Excited States*.

² Wessig, P. *Angew. Chem. Int. Ed.* **2006**, 45, 2168.

³ Zimmerman, H.E. *Pure Appl. Chem.* **2006**, 78, 2193.

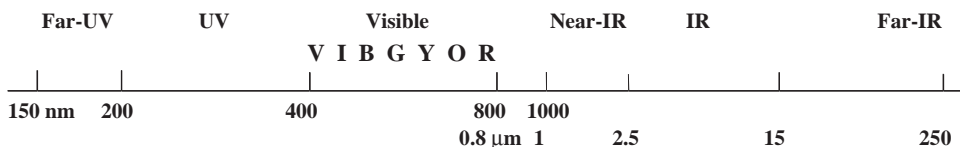


FIG. 7.1. The UV, vis, and IR portions of the electromagnetic spectrum.

process, this energy is in the form of light. Light of any wavelength has an energy value associated with it given by $E = h\nu$, where ν is the frequency of the light ($\nu = \text{velocity of light } c \text{ divided by the wavelength } \lambda$), and h is Planck's constant. Since the energy levels of a molecule are quantized, the amount of energy required to raise an electron in a given molecule from one level to a higher one is a fixed quantity. Only light with exactly the frequency corresponding to this amount of energy will cause the electron to move to the higher level. If light of another frequency (too high or too low) is sent through a sample, it will pass out without a loss in intensity, since the molecules will not absorb it. However, if light of the correct frequency is passed into a sample, molecules will use that energy for electron promotion, and the light that leaves the sample will be diminished in intensity or altogether gone. A *spectrophotometer* is an instrument that allows light of a given frequency to pass through a sample and that detects (by means of a phototube) the amount of light that has been transmitted, that is, not absorbed. A spectrophotometer compares the intensity of the transmitted light with that of the incident light. Automatic instruments gradually and continuously change the frequency, and an automatic recorder plots a graph of absorption versus frequency or wavelength.

The energy of electronic transitions corresponds to light in the vis, UV, and far-UV regions of the spectrum (Fig. 7.1). Absorption positions are normally expressed in wavelength units, usually nanometers (nm).⁴ If a compound absorbs in the visible, it is colored, possessing a color complementary to that absorbed.⁵ Thus a compound absorbing in the violet has a yellow color. Organic chemists study the far-UV region less often than the vis or ordinary UV regions because special vacuum instruments are required, owing to the fact that oxygen and nitrogen absorb in these regions.

From these considerations it would seem that an electronic spectrum should consist of one or more sharp peaks, each corresponding to the transfer of an electron from one electronic level to another. Under ordinary conditions the peaks are seldom sharp. In order to understand why, it is necessary to realize that molecules are constantly vibrating and rotating and that these motions are also quantized. A molecule at any time is not only in a given electronic state, but also in a given vibrational and rotational state. The difference between two adjacent vibrational levels is much smaller than the difference between adjacent electronic levels, and the difference between adjacent rotational levels is smaller still. A typical situation is shown in Fig. 7.2. When an electron moves from one electronic level to another, it moves from a given vibrational and rotational level within that electronic level to some vibrational and rotational level at the next electronic level. A given sample contains a large number of molecules, and even if all of them are in the ground electronic state, they are still distributed

⁴ Formerly, millimicrons (mμ) were frequently used; numerically they are the same as nanometers.

⁵ For monographs, see Zollinger, H. *Color Chemistry*, VCH, NY, 1987; Gordon, P.F.; Gregory, P. *Organic Chemistry in Colour*, Springer, NY, 1983; Griffiths, J. *Colour and Constitution of Organic Molecules*, Academic Press, NY, 1976. See also, Fabian, J.; Zahradník, R. *Angew. Chem. Int. Ed.* 1989, 28, 677.

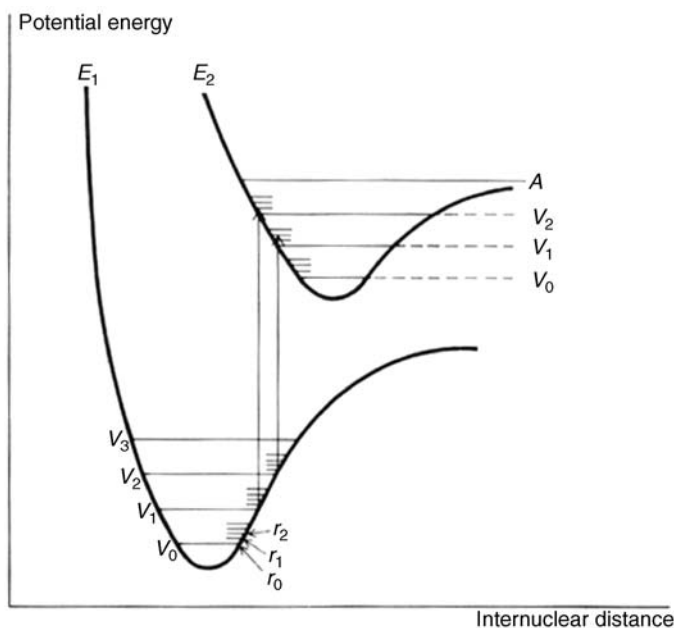


FIG. 7.2. Energy curves for a diatomic molecule. Two possible transitions are shown. When an electron has been excited to the point marked A, the molecule may cleave (Sec. 7.A.v).

among the vibrational and rotational states (though the ground vibrational state, V_0 , is most heavily populated). This means that not just one wavelength of light will be absorbed, but a number of them close together, with the most probable transition causing the most intense peak. But in molecules containing more than a few atoms, there are so many possible transitions, and these are so close together that what is observed is a relatively broad band. The height of the peak depends on the number of molecules making the transition and is proportional to $\log \epsilon$, where ϵ is the *extinction coefficient*. The extinction coefficient can be expressed by $\epsilon = E/cl$, where c is the concentration in moles per liter, l is the cell length in centimeters, and $E = \log I_0/I$, where I_0 is the intensity of the incident light and I of the transmitted light. The wavelength is usually reported as λ_{\max} , meaning that this is the top of the peak. Purely vibrational transitions (e.g., between V_0 and V_1 of E_1), which require much less energy, are found in the IR region and are the basis of IR spectra. Purely rotational transitions are found in the far-IR and microwave (beyond the far-IR) regions.

A UV or vis absorption peak is caused by the promotion of an electron in one orbital (usually ground-state) to a higher orbital. Normally, the amount of energy necessary to make this transition depends mostly on the nature of the two orbitals involved and much less on the rest of the molecule. Therefore, a simple functional group (e.g., the C=C double bond) always causes absorption in the same general area. A group that causes absorption is called a *chromophore*.

7.A.ii. Singlet and Triplet States: "Forbidden" Transitions

In most organic molecules, all electrons in the ground state are paired, with each member of a pair possessing opposite spin, as demanded by the *Pauli principle*. When one of a pair of electrons is promoted to an orbital of higher energy, the two electrons no longer share an

orbital, and the promoted electron may, in principle, have the same spin as its former partner or the opposite spin. As seen in Chapter 5, a molecule in which two unpaired electrons have the same spin is called a *triplet*,⁶ while one in which all spins are paired is a *singlet*. Thus, at least in principle, for every excited singlet state there is a corresponding triplet state. In most cases, the triplet state has a lower energy than the corresponding singlet, which is in accord with *Hund's rule*. Therefore, a different amount of energy, and hence a different wavelength, is required to promote an electron from the ground state (which is almost always a singlet) to an excited singlet than to the corresponding triplet state.

It would thus seem that promotion of a given electron in a molecule could result either in a singlet or a triplet excited state depending on the amount of energy added. However, this is often not the case because transitions between energy levels are governed by selection rules, which state that certain transitions are “forbidden”. There are several types of “forbidden” transitions, two of which are more important than the others.

1. *Spin-Forbidden Transitions*. If the spin of an electron changes, transitions are not allowed, because a change from one spin to the opposite involves a change in angular momentum. Such a change would violate the law of conservation of angular momentum. Therefore, singlet–triplet and triplet–singlet transitions are forbidden, whereas singlet–singlet and triplet–triplet transitions are allowed.
2. *Symmetry-Forbidden Transitions*. Among the transitions in this class are those in which a molecule has a center of symmetry. In such cases, a $g \rightarrow g$ or $u \rightarrow u$ transition (see Sec. 1.A.) is “forbidden”, while a $g \rightarrow u$ or $u \rightarrow g$ transition is allowed.

The word “forbidden” is in quotation marks because these transitions are not actually forbidden, but only highly improbable. In most cases, promotions from a singlet ground state to a triplet excited state are so improbable that they cannot be observed, and it is safe to state that in most molecules only singlet–singlet promotions take place. However, this rule does break down in certain cases, most often when a heavy atom (e.g., iodine) is present in the molecule, in which cases it can be shown from spectra that singlet–triplet promotions are occurring.⁷ Symmetry-forbidden transitions can frequently be observed, though usually with low intensity.

7.A.iii. Types of Excitation

When an electron in a molecule is promoted (normally only one electron in any molecule), it usually goes into the lowest available vacant orbital, though promotion to higher orbitals is also possible. For most organic molecules, there are consequently four types of electronic excitation:

1. $\sigma \rightarrow \sigma^*$. Alkanes, which have no n or π electrons, can be excited only in this way.⁸
2. $n \rightarrow \sigma^*$. Alcohols, amines,⁹ ethers, and so on can also be excited in this manner.

⁶ See Kurreck, H. *Angew. Chem. Int. Ed.* **1993**, 32, 1409.

⁷ See Koziar, J.C.; Cowan, D.O. *Acc. Chem. Res.* **1978**, 11, 334.

⁸ An n electron is one in an unshared pair.

⁹ See Malkin, Yu.N.; Kuz'min, V.A. *Russ. Chem. Rev.* **1985**, 54, 1041.

TABLE 7.1 Ultraviolet Absorption¹⁰ of $\text{CH}_3-(\text{CH}=\text{CH})_n-\text{CH}_3$ for Some Values of n

n	nm
2	227
3	263
6	352
9	413

3. $\pi \rightarrow \pi^*$. This pathway is open to alkenes as well as to aldehydes, carboxylic esters, and so on.
4. $n \rightarrow \pi^*$. Aldehydes, ketones, carboxylic esters, and so on can undergo this promotion, as well as the other three.

The four excitation types above are listed in what is normally the order of decreasing energy. Thus light of the highest energy (in the far-UV) is necessary for $\sigma \rightarrow \sigma^*$ excitation, while $n \rightarrow \pi^*$ promotions are caused by ordinary UV light. However, the order may sometimes be altered in some solvents.

In 1,3-butadiene (and other compounds with two conjugated double bonds), there are two π and two π^* orbitals (Sec. 2.C). The energy difference between the higher π (χ_2) and the lower π^* (χ_3) orbital is less than the difference between the π and π^* orbitals of ethylene. Therefore 1,3-butadiene requires less energy than ethylene, and thus light of a higher wavelength, to promote an electron. This is a general phenomenon, and it may be stated that, in general, *the more conjugation in a molecule, the more the absorption is displaced toward higher wavelengths* (see Table 7.1).¹⁰ When a chromophore absorbs at a certain wavelength and the substitution of one group for another causes absorption at a longer wavelength, a *bathochromic shift* is said to have occurred. The opposite kind of shift is called *hypsochromic*.

Of the four excitation types listed above, the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ are far more important in organic photochemistry than the other two. Compounds containing C=O groups can be excited in both ways, giving rise to at least two peaks in the UV.

As seen above, a *chromophore* is a group that causes a molecule to absorb light. Examples of chromophores in the vis or UV are C=O, N=N,¹¹ Ph, and NO₂. Some chromophores in the far-UV (beyond 200 nm) are C=C, C≡C, Cl, and OH. An *auxochrome* is a group that displaces (through resonance) and usually intensifies the absorption of a chromophore present in the same molecule. Groups (e.g., Cl, OH, and NH₂) are generally regarded as auxochromes since they shift (usually bathochromically) the UV and vis bands of chromophores (e.g., Ph or C=O; see Table 7.2).¹² Since auxochromes are themselves chromophores (to be sure, generally in the far-UV), it is sometimes difficult to decide which group in a molecule is an auxochrome and which is a chromophore. For

¹⁰ Bohlmann, F.; Mannhardt, H. *Chem. Ber.* **1956**, 89, 1307.

¹¹ For a review of the azo group as a chromophore, see Rau, H. *Angew. Chem. Int. Ed.* **1973**, 12, 224.

¹² These values are from Silverstein, R.M.; Bassler, G.C. *Spectrometric Identification of Organic Compounds*, 2nd ed., John Wiley, NY, **1967**, pp. 164–165. Also see Jaffé, H.H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*, Wiley, NY, **1962**, p. 257.

TABLE 7.2 Some UV Peaks of Substituted Benzenes^a

	Primary Band		Secondary Band	
	λ_{\max} (nm)	ϵ_{\max}	λ_{\max} (nm)	ϵ_{\max}
PhH (hexane) ^b	204	7,900	256	200
PhCl	210	7,600	265	240
PhOH	210.5	6,200	270	1,450
PhOMe	217	6,400	269	1,480
PhCN	224	13,000	271	1,000
PhCOOH	230	10,000	270	800
PhNH ₂	230	8600	280	1,430
PhO ⁻	235	9,400	287	2,600
PhAc	240	13,000	278	1,100
PhCHO	244	15,000	280	1,500
PhNO ₂	252	10,000	280	1,000

^aNote how auxochromes shift and usually intensify the peaks. See Ref. 12.

^bThe solvent is in parentheses.

[Reprinted with permission from Silverstein, R.M.; Bassler, G.C. *Spectrometric Identification of Organic Compounds*, 2nd ed., John Wiley, NY, **1967**, pp. 164–165, Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © **1967** by Wiley–VCH Verlag]

example, in acetophenone (PhCOMe) is the chromophore Ph or C=O? In such cases, the distinction becomes practically meaningless.

7.A.iv. Nomenclature and Properties of Excited States

An excited state of a molecule can be regarded as a distinct chemical species, different from the ground state of the same molecule and from other excited states. It is obvious that some method of naming excited states is required. Unfortunately, there are several methods in use, depending on whether one is primarily interested in photochemistry, spectroscopy, or MO theory.¹³ One of the most common methods simply designates the original and newly occupied orbitals, with or without a superscript to indicate singlet or triplet. Thus the singlet state arising from promotion of a π to a π^* orbital in ethylene would be the $^1(\pi, \pi^*)$ state or the π, π^* singlet state. Another very common method can be used even in cases where one is not certain which orbitals are involved. The lowest-energy excited state is called S_1 , the next is S_2 , and so on. Triplet states are similarly labeled T_1 , T_2 , T_3 , and so on. In this notation, the ground state is S_0 . Other notational systems exist, but this text shall discuss only the two types just mentioned.

The properties of excited states are not easy to measure because of their generally short lifetimes and low concentrations, but enough work has been done for us to know that they often differ from the ground state in geometry, dipole moment, and acid or base strength.¹⁴

¹³ See Pitts, Jr., J.N.; Wilkinson, F.; Hammond, G.S. *Adv. Photochem.* **1963**, *1*, 1; Porter, G.B.; Balzani, V.; Moggi, L. *Adv. Photochem.* **1974**, *9*, 147; Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* **1988**, *60*, 1055.

¹⁴ For reviews of the structures of excited states, see Zink, J.I.; Shin, K.K. *Adv. Photochem.* **1991**, *16*, 119; Innes, K.K. *Excited States* **1975**, *2*, 1; Hirakawa, A.Y.; Masamichi, T. *Vib. Spectra Struct.* **1983**, *12*, 145.

TABLE 7.3 Typical Energies for Some Covalent Single Bonds^a and the Corresponding Approximate Wavelengths

Bond	<i>E</i>		nm
	kcal mol ⁻¹	kJ mol ⁻¹	
C—H	95	397	300
C—O	88	368	325
C—C	83	347	345
Cl—Cl	58	243	495
C—O	35	146	820

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^aSee Table 1.7.

For example, acetylene, which is linear in the ground state, has a trans geometry in the excited state with $\sim sp^2$ carbons in the $^1(\pi, \pi^*)$ state.¹⁵ Similarly, the $^1(\pi, \pi^*)$ and the $^3(\pi, \pi^*)$ states of ethylene have a perpendicular and not a planar geometry,¹⁶ and the $^1(n, \pi^*)$ and $^3(n, \pi^*)$ states of formaldehyde are both pyramidal.¹⁷ Triplet species tend to stabilize themselves by distortion, which relieves interaction between the unpaired electrons. Obviously, if the geometry is different, the dipole moment will probably differ also and the change in geometry and electron distribution often results in a change in acid or base strength.¹⁸ For example, the S_1 state of 2-naphthol is a much stronger acid ($pK = 3.1$) than the ground state (S_0) of the same molecule ($pK = 9.5$).¹⁹

7.A.v. Photolytic Cleavage

As stated above, when a molecule absorbs a quantum of light it is promoted to an excited state. Actually, that is not the only possible outcome. Because the energy of vis and UV light is of the same order of magnitude as that of covalent bonds (Table 7.3), another possibility is that the molecule may cleave into two parts, a process known as *photolysis*. There are three situations that can lead to cleavage:

1. The promotion may bring the molecule to a vibrational level so high that it lies above the right-hand portion of the E_2 curve (line A in Fig. 7.2). In such a case, the excited molecule cleaves at its first vibration.
2. Even where the promotion is to a lower vibrational level, one that lies wholly within the E_2 curve (e.g., V_1 or V_2), the molecule may still cleave. As shown in Fig. 7.2, equilibrium distances are greater in excited states than in the ground state. The

¹⁵ Ingold, C.K.; King, G.W. *J. Chem. Soc.* **1953**, 2702, 2704, 2708, 2725, 2745. For a review of acetylene photochemistry, see Coyle, J.D. *Org. Photochem.* **1985**, 7, 1.

¹⁶ Merer, A.J.; Mulliken, R.S. *Chem. Rev.* **1969**, 69, 639.

¹⁷ Garrison, B.J.; Schaefer III, H.F.; Lester Jr., W.A. *J. Chem. Phys.* **1974**, 61, 3039; Streitwieser Jr., A.; Kohler, B. *J. Am. Chem. Soc.* **1988**, 110, 3769. For reviews of excited states of formaldehyde, see Buck, H.M. *Recl. Trav. Chim. Pays-Bas* **1982**, 101, 193, 225; Moule, D.C.; Walsh, A.D. *Chem. Rev.* **1975**, 75, 67.

¹⁸ See Ireland, J.F.; Wyatt, P.A.H. *Adv. Phys. Org. Chem.* **1976**, 12, 131.

¹⁹ Weller, A. *Z. Phys. Chem. (Frankfurt am Main)* **1955**, 3, 238, *Discuss. Faraday Soc.* **1959**, 27, 28.

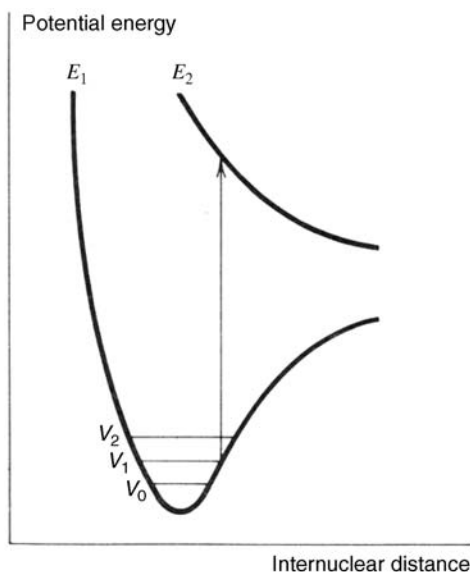


FIG. 7.3. Promotion to a dissociative state results in bond cleavage.

Franck–Condon principle states that promotion of an electron takes place much faster than a single vibration (the promotion takes $\sim 10^{-15}$ s; a vibration $\sim 10^{-12}$ s). Therefore, when an electron is suddenly promoted, even to a low vibrational level, the distance between the atoms is essentially unchanged and the bond finds itself in a compressed condition like a pressed-in spring; this condition may be relieved by an outward surge that is sufficient to break the bond.

3. In some cases, the excited state is entirely dissociative (Fig. 7.3); that is, there is no distance where attraction outweighs repulsion, and the bond must cleave. An example is the hydrogen molecule, where a $\sigma \rightarrow \sigma^*$ promotion always results in cleavage.

A photolytic cleavage can break the molecule into two smaller molecules or into two free radicals (see Sec. 7.A.vii). Cleavage into two ions, though known, is rare. Once free radicals are produced by a photolysis, they behave like free radicals produced in any other way (Chap 5) except that they may be in excited states, and this can cause differences in behavior.²⁰

7.A.vi. The Fate of the Excited Molecule: Physical Processes

When a molecule has been photochemically promoted to an excited state, it does not remain in the excited state for long. Most promotions are from the S_0 to the S_1 state. As seen previously, promotions from S_0 to triplet states are “forbidden”. Promotions to S_2 and higher singlet states take place, but in liquids and solids these higher states usually drop very rapidly to the S_1 state ($\sim 10^{-13}$ to $\sim 10^{-11}$ s). The energy lost when an S_2 or S_3

²⁰ Lubitz, W.; Lendzian, F.; Bittl, R. *Acc. Chem. Res.* **2002**, *35*, 313.

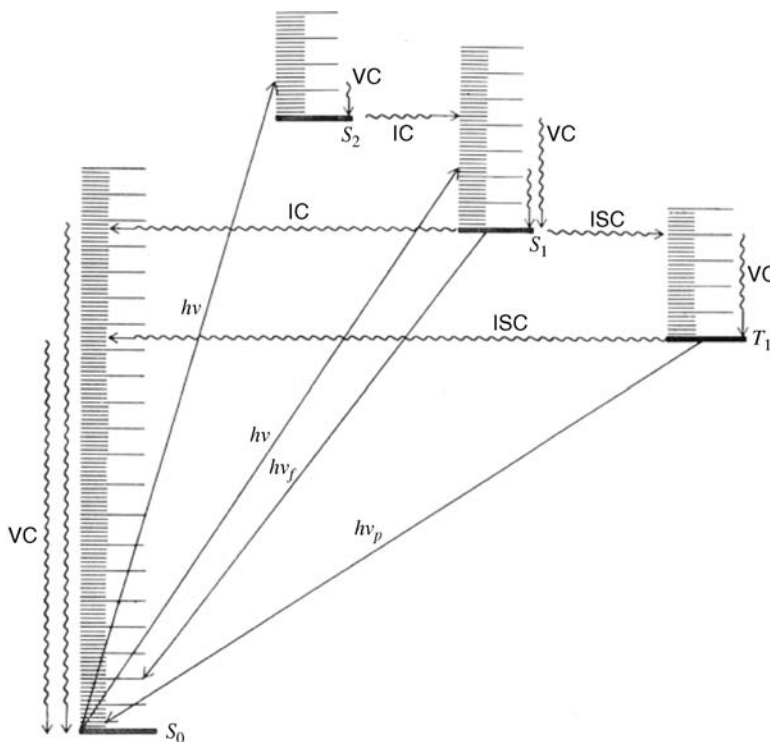


FIG. 7.4. Modified Jablonski diagram showing transitions between the excited and the ground state. Radiative processes are shown by straight lines, radiationless processes by wavy lines. vc = vibrational cascade; $h\nu_f$ = fluorescence; $h\nu_p$ = phosphorescence.

molecule drops to S_1 is given up in small increments to the environment by collisions with neighboring molecules. Such a process is called an *energy cascade*. In a similar manner, the initial excitation and the decay from higher singlet states initially populate many of the vibrational levels of S_1 , but these also cascade, down to the lowest vibrational level of S_1 . Therefore, in most cases, the lowest vibrational level of the S_1 state is the only important excited singlet state.²¹ This state can undergo various physical and chemical processes. In the following list, we describe the physical pathways open to molecules in the S_1 and excited triplet states. These pathways are also shown in a modified *Jablonski diagram* (Fig. 7.4) and in Table 7.4.

1. A molecule in the S_1 state can cascade down through the vibrational levels of the S_0 state and thus return to the ground state by giving up its energy in small increments to the environment. This process is generally quite slow because the amount of energy is large and is called *internal conversion* (IC, see Fig. 7.4). Because it is slow, most molecules in the S_1 state adopt other pathways.²²

²¹ See Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* **1978**, 78, 125.

²² See Lin, S.H. *Radiationless Transitions*, Academic Press, NY, **1980**. For reviews, see Kommandeur, J. *Recl. Trav. Chim. Pays-Bas* **1983**, 102, 421; Freed, K.F. *Acc. Chem. Res.* **1978**, 11, 74.

TABLE 7.4 Physical Processes Undergone by Excited Molecules^a

$S_0 + h\nu \rightarrow S_1^v$	Excitation
S_1^v	$\rightsquigarrow S_1 + \Delta$ Vibrational relaxation
$S_1 \rightarrow S_0 + h\nu$	Fluorescence
S_1	$\rightsquigarrow S_0 + \Delta$ Internal conversion
$S_1 \rightsquigarrow T_1^v$	Intersystem crossing
T_1^v	$\rightsquigarrow T_1 + \Delta$ Vibrational relaxation
$T_1^v \rightarrow S_0 + h\nu$	Phosphorescence
T_1	$\rightsquigarrow S_0 + \Delta$ Intersystem crossing
$S_1 + A_{(S_0)} \rightarrow S_0 + A_{(S_1)}$	Singlet–singlet transfer (photosensitization)
$T_1 + A_{(S_0)} \rightarrow S_0 + A_{(T_1)}$	Triplet–triplet transfer (photosensitization)

^aThe superscript *v* indicates vibrationally excited state; excited states higher than S_1 or T_1 are omitted.

2. A molecule in the S_1 state can drop to some low vibrational level of the S_0 state all at once by giving off the energy in the form of light. This process, which generally happens within 10^{-9} s, is called *fluorescence*. This pathway is not very common either (because it is relatively slow), except for small molecules (e.g., diatomic) and rigid molecules (e.g., aromatic). For most other compounds, fluorescence is very weak or undetectable. For compounds that do fluoresce, the fluorescence emission spectra are usually the approximate mirror images of the absorption spectra. This comes about because the fluorescing molecules all drop from the lowest vibrational level of the S_1 state to various vibrational levels of S_0 , while excitation is from the lowest vibrational level of S_0 to various levels of S_1 (Fig. 7.5). The only peak in common is the one that results from transitions between the lowest vibrational levels of the two states (called the 0–0 peak). In solution, even the 0–0 peak may be noncoincident because the two states are solvated differently. Fluorescence nearly always arises from a $S_1 \rightarrow S_0$ transition, although azulene (Sec. 2.I.iii) and its simple derivatives are exceptions,²³ emitting fluorescence from $S_2 \rightarrow S_0$ transitions.

Because of the possibility of fluorescence, any chemical reactions of the S_1 state must take place very fast, or fluorescence will occur before they can happen.

3. Most molecules (but by no means all) in the S_1 state can undergo an *intersystem crossing* (ISC, see Fig. 7.4) to the lowest triplet state T_1 .²⁴ An important example is benzophenone, of which 100% of the molecules that are excited to the S_1 state cross over to the T_1 .²⁵ Intersystem crossing from singlet to triplet is of course a “forbidden” pathway, since the angular-momentum problem (Sec. 7.A.ii) must

²³ For other exceptions, see Sugihara, Y.; Wakabayashi, S.; Murata, I.; Jinguji, M.; Nakazawa, T.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* **1985**, *107*, 5894, and references cited therein. See also, Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* **1978**, *78*, 125, see pp. 126–129.

²⁴ Also see Li, R.; Lim, E.C. *Chem. Phys.* **1972**, *57*, 605; Sharf, B.; Silbey, R. *Chem. Phys. Lett.* **1970**, *5*, 314; Schlag, E.W.; Schneider, S.; Fischer, S.F. *Annu. Rev. Phys. Chem.* **1971**, *22*, 465, pp. 490. There is evidence that ISC can also occur from the S_2 state of some molecules: Samanta, A. *J. Am. Chem. Soc.* **1991**, *113*, 7427; Ohsaku, M.; Koga, N.; Morokuma, K. *J. Chem. Soc. Perkin Trans. 2* **1993**, 71.

²⁵ Moore, W.M.; Hammond, G.S.; Foss, R.P. *J. Am. Chem. Soc.* **1961**, *83*, 2789.

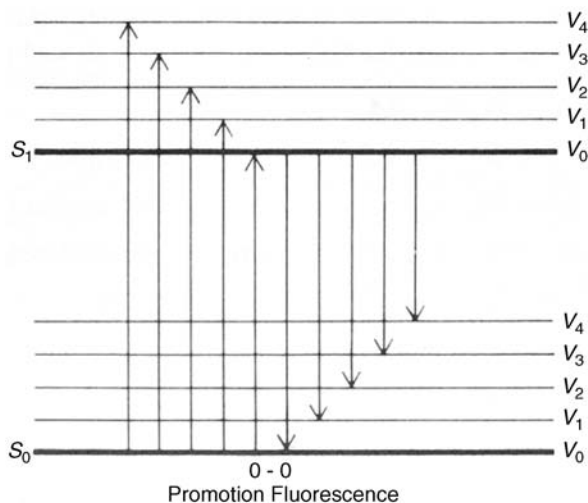


FIG. 7.5. Promotion and fluorescence between S_1 and S_0 states.

be taken care of, but this often takes place by compensations elsewhere in the system. Intersystem crossings take place without loss of energy. Since a singlet state usually has a higher energy than the corresponding triplet, this means that energy must be given up. One way for this to happen is for the S_1 molecule to cross to a T_1 state at a high vibrational level and then for the T_1 to cascade down to its lowest vibrational level (see Fig. 7.4). This cascade is very rapid (10^{-12} s). When T_2 or higher states are populated, they too rapidly cascade to the lowest vibrational level of the T_1 state.

4. A molecule in the T_1 state may return to the S_0 state by giving up heat (ISC) or light (this is called *phosphorescence*).²⁶ Of course, the angular momentum difficulty exists here, so that both ISC and phosphorescence are very slow ($\sim 10^{-3}$ – 10^1 s). This means that T_1 states generally have much longer lifetimes than S_1 states. When they occur in the same molecule, phosphorescence is found at lower frequencies than fluorescence (because of the higher difference in energy between S_1 and S_0 than between T_1 and S_0) and is longer-lived (because of the longer lifetime of the T_1 state).
5. If nothing else happens to it first, a molecule in an excited state (S_1 or T_1) may transfer its excess energy all at once to another molecule in the environment, in a process called *photosensitization*.²⁷ The excited molecule, which we will call D for donor, thus drops to S_0 while the other molecule (A for acceptor) becomes excited:

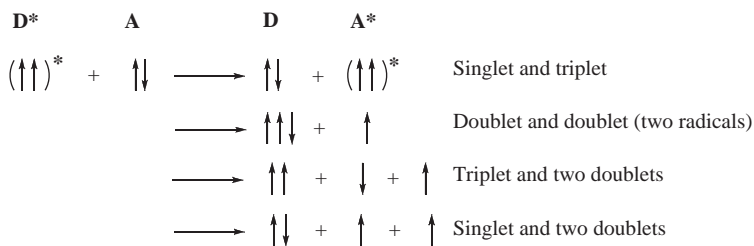


²⁶ See Lower, S.K.; El-Sayed, M.A. *Chem. Rev.* **1966**, 66, 199. For a review of physical and chemical processes of triplet states see Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* **1968**, 5, 21.

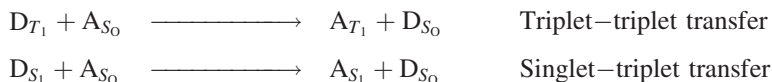
²⁷ See Albini, A. *Synthesis*, **1981**, 249; Turro, N.J.; Dalton, J.C.; Weiss, D.S. *Org. Photochem.* **1969**, 2, 1. Ionic liquids may be soluble photosensitizers. See Hubbard, S.C.; Jones, P.B. *Tetrahedron* **2005**, 61, 7425.

Thus there are *two* ways for a molecule to reach an excited state: by absorption of a quantum of light or by transfer from a previously excited molecule.²⁸ The donor D is also called a *photosensitizer*. This energy transfer is subject to the *Wigner spin-conservation rule*, which is actually a special case of the law of conservation of momentum we encountered previously. According to the Wigner rule, the total electron spin does not change after the energy transfer. For example, when a triplet species interacts with a singlet these are some allowed possibilities:²⁹

In all these cases, the products have three electrons spinning “up” and the fourth “down” (as do the starting molecules). However, formation of, say, two triplets ($\uparrow\downarrow + \uparrow\downarrow$) or two singlets ($\uparrow\downarrow + \uparrow\downarrow$), whether ground states or excited, would violate the rule.



In the two most important types of photosensitization, both of which are in accord with the Wigner rule, a triplet excited state generates another triplet and a singlet generates a singlet:



Singlet–singlet transfer can take place over relatively long distances (e.g., 40 Å), but triplet transfer normally requires a collision between the molecules.³⁰ Both types of photosensitization can be useful for creating excited states when they are difficult to achieve by direct irradiation. Photosensitization is therefore an important method for carrying out photochemical reactions when a molecule cannot be brought to the desired excited state by direct absorption of light. Triplet–triplet transfer is especially important because triplet states are usually much more difficult to prepare by direct irradiation than singlet states (often impossible) and because triplet states, having longer lifetimes, are much more likely than singlets to transfer energy by photosensitization. Photosensitization can also be accomplished by electron transfer.³¹

In choosing a photosensitizer,³² one should avoid a compound that absorbs in the same region as the acceptor because the latter will then compete for the light.³³ For

²⁸ In certain cases excited states can be produced directly in ordinary reactions. See White, E.H.; Miano, J.D.; Watkins, C.J.; Breaux, E.J. *Angew. Chem. Int. Ed.* **1974**, 13, 229.

²⁹ For another table of this kind, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, **1966**, p. 89.

³⁰ See Bennett, R.G.; Schwenker, R.P.; Kellogg, R.E. *J. Chem. Phys.* **1964**, 41, 3040; Ermolaev, V.L.; Sveshnikova, E.B. *Opt. Spectrosc. (USSR)* **1964**, 16, 320.

³¹ See Kavarno, G.J.; Turro, N.J. *Chem. Rev.* **1986**, 86, 401; Mariano, P.S. *Org. Photochem.* **1987**, 9, 1.

³² For a discussion of pyrylogens as an electron-transfer sensitizer, see Clennan, E.L.; Liao, C.; Ayokosok, E. *J. Am. Chem. Soc.* **2008**, 130, 7552.

³³ See Engel, P.S.; Monroe, B.M. *Adv. Photochem.* **1971**, 8, 245.

examples of the use of photosensitization to accomplish reactions, see Reactions **15-62** and **15-63**.

6. An excited species can be quenched. Quenching is the deactivation of an excited molecular entity intermolecularly by an external environmental influence (e.g., a quencher), or intramolecularly by a substituent through a nonradiative process.³⁴ When the external environmental influence (quencher) interferes with the behavior of the excited state after its formation, the process is referred to as dynamic quenching. Common mechanisms include energy transfer, charge transfer, and so on. When the environmental influence inhibits the excited state formation, the process is referred to as static quenching. A quencher is defined as a molecular entity that deactivates (quenches) an excited state of another molecular entity, either by energy transfer, electron transfer, or by a chemical mechanism.³⁴

An example is the rapid triplet quenching of aromatic ketone triplets³⁵ by amines, which is well known.³⁶ Alkyl and aryl thiols and thioethers also serve as quenchers in this system.³⁷ In this latter case, the mechanism involves electron transfer from the sulfur atom to the triplet ketone, and this is supported by theoretical calculations.³⁸ Aromatic ketone triplets are quenched by phenols, and the photochemical reaction between aromatic ketones and phenols is efficient only in the presence of an acid catalyst.³⁹ Indirect evidence has been provided for involvement of the hydrogen-bonded triplet exciplex and for the role of electron transfer in this reaction.⁴⁰

7.A.vii. The Fate of the Excited Molecule: Chemical Processes

Although both excited singlet and triplet species can undergo chemical reactions, they are much more common for triplets, simply because these generally have much longer lifetimes. Excited singlet species, in most cases, have a lifetime of $<10^{-10}$ s and undergo one of the physical processes already discussed before they have a chance to react chemically. Therefore, photochemistry is largely the chemistry of triplet states.⁴¹ Table 7.5⁴² lists many of the possible chemical pathways that can be taken by an excited molecule.⁴³ The first four of these are unimolecular reactions; the others are bimolecular. In

³⁴ Verhoeven, J.W. *Pure Appl. Chem.* **1996**, 68, 2223 (see p. 2268).

³⁵ See Samanta, S.; Mishra, B.K.; Pace, T.C.S.; Sathyamurthy, N.; Bohne, C.; Moorthy, J.N. *J. Org. Chem.* **2006**, 71, 4453.

³⁶ See Aspari, P.; Ghoneim, N.; Haselbach, E.; von Raumer, M.; Suppan, P.; Vauthey, E. *J. Chem. Soc., Faraday Trans.* **1996**, 92, 1689; Cohen, S.G.; Parola, A.; Parsons, Jr., G.H. *Chem. Rev.* **1973**, 73, 141; von Raumer, M.; Suppan, P.; Haselbach, E. *Helv. Chim. Acta* **1997**, 80, 719.

³⁷ Inbar, S.; Linschitz, H.; Cohen, S.G. *J. Am. Chem. Soc.* **1982**, 104, 1679; Bobrowski, K.; Marciniak, B.; Hug, G.L. *J. Photochem. Photobiol. A: Chem.* **1994**, 81, 159; Wakasa, M.; Hayashi, H. *J. Phys. Chem.* **1996**, 100, 15640.

³⁸ Marciniak, B.; Bobrowski, K.; Hug, G.L. *J. Phys. Chem.* **1993**, 97, 11937.

³⁹ Becker, H.-D. *J. Org. Chem.* **1967**, 32, 2115; 2124; 2140.

⁴⁰ Lathioor, E.C.; Leigh, W.J.; St. Pierre, M.J. *J. Am. Chem. Soc.* **1999**, 121, 11984.

⁴¹ See Wagner, P.J.; Hammond, G.S.; Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* **1968**, 5, 21. For other reviews of triplet states, see *Top. Curr. Chem.* **1975**, Vols. 54 and 55.

⁴² Adapted from Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, **1966**, p. 367.

⁴³ For a different kind of classification of photochemical reactions, see Dauben, W.G.; Salem, L.; Turro, N.J. *Acc. Chem. Res.* **1975**, 8, 41. For reviews of photochemical reactions where the molecules are geometrically constrained, see Ramamurthy, V. *Tetrahedron* **1986**, 42, 5753; Ramamurthy, V.; Eaton, D.F. *Acc. Chem. Res.* **1988**, 21, 300; Turro, N.J.; Cox, G.S.; Paczkowski, M.A. *Top. Curr. Chem.* **1985**, 129, 57.

TABLE 7.5 Primary Photochemical Reactions^a of an Excited Molecule A—B—C^b

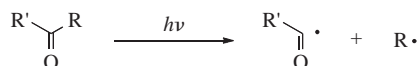
Reactions	Reaction Type	Example Number
(A—B—C) → A—B• + C•	Simple cleavage into radicals ⁴⁶	(1)
(A—B—C) → E + F	Decomposition into molecules	(2)
(A—B—C) → A—C—B	Intramolecular rearrangement	(3)
(A—B—C) → A—B—C'	Photoisomerization	(4)
(A—B—C) + RH → A—B—C—H + R•	Hydrogen-atom abstraction	(5)
(A—B—C) → (ABD) ₂	Photodimerization	(6)
(A—B—C) + A → ABX + A*	Photosensitization	(7)

^aExamples are given in the text; the most common are (1), (2), and, in the presence of a suitable acceptor molecule (7).

^bSee Ref. 42.

the case of bimolecular reactions, it is rare for two excited molecules to react with each other (because the concentration of excited molecules at any one time is generally low); reactions are between an excited molecule and an unexcited molecule of either the same or another species. The reactions listed in Table 7.5 are primary processes. Secondary reactions often follow, since the primary products are frequently radicals or carbenes; even if they are ordinary molecules, they are often in upper vibrational levels and so have excess energy. In almost all cases, the primary products of photochemical reactions are in their ground states, though exceptions are known.⁴⁴ Of the reactions listed in Table 7.5, the most common are cleavage into radicals (1), decomposition into molecules (2), and (in the presence of a suitable acceptor molecule) photosensitization (7), which we have already discussed. The following are some specific examples of reaction categories (1)–(6). Other examples are discussed in Part II.^{45,46}

*Category 1. Simple Cleavage into Radicals.*⁴⁷ Aldehydes and ketones absorb in the 230–330-nm region. This is assumed to result from an $n \rightarrow \pi^*$ singlet–singlet transition. The excited aldehyde or ketone can then cleave.⁴⁸



⁴⁴ Turro, N.J.; Lechtken, P.; Lyons, A.; Hautala, R.T.; Carnahan, E.; Katz, T.J. *J. Am. Chem. Soc.* **1973**, *95*, 2035.

⁴⁵ See Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, **1989**; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, **1986**; Schönberg, A. *Preparative Organic Photochemistry*, Springer, Berlin, **1968**.

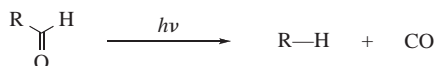
⁴⁶ See DeLuca, L.; Giacomelli, G.; Porcu, G.; Taddei, M. *Org. Lett.* **2001**, *3*, 855.

⁴⁷ For reviews, see Jackson, W.M.; Okabe, H. *Adv. Photochem.* **1986**, *13*, 1; Kresin, V.Z.; Lester, Jr., W.A. *Adv. Photochem.* **1986**, *13*, 95.

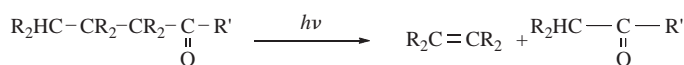
⁴⁸ See Formosinho, S.J.; Arnaut, L.G. *Adv. Photochem.* **1991**, *16*, 67; Newton, R.F. in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, **1986**, pp. 39–60; Lee, E.K.C.; Lewis, R.S. *Adv. Photochem.* **1980**, *12*, 1; Coyle, J.D.; Carless, H.A.J. *Chem. Soc. Rev.* **1972**, *1*, 465; Bérces, T. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5; Elsevier, NY, **1972**, pp. 277–380; Turro, N.J.; Dalton, J.C.; Dawes, K.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Shore, N. *Acc. Chem. Res.* **1972**, *5*, 92; Wagner, P.J. *Top. Curr. Chem.* **1976**, *66*, 1. Also see Weiss, D.S. *Org. Photochem.* **1981**, *5*, 347; Rubin, M.B. *Top. Curr. Chem.* **1985**, *129*, 1; **1969**, *13*, 251; Childs, R.F. *Rev. Chem. Intermed.* **1980**, *3*, 285. C=S compounds, see Coyle, J.D. *Tetrahedron* **1985**, *41*, 5393; Ramamurthy, V. *Org. Photochem.* **1985**, *7*, 231. C=N compounds, see Mariano, P.S. *Org. Photochem.* **1987**, *9*, 1.

When applied to ketones, this is called *Norrish Type I cleavage* or often just *Type I cleavage*. In a secondary process, the acyl radical ($R'-CO\bullet$) can then lose CO to give $R'\bullet$ radicals. Another example of a category 1 process is cleavage of Cl_2 to give two Cl atoms. Other bonds that are easily cleaved by photolysis are the O—O bonds of peroxy compounds and the C—N bonds of aliphatic azo compounds ($R-N=N-R$).⁴⁹ The latter is an important source of radicals $R\bullet$, since the other product is the very stable N_2 .

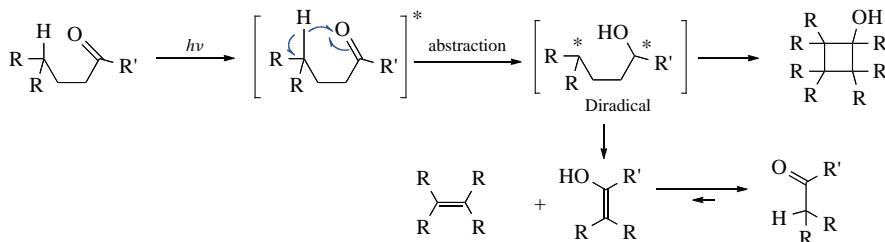
Category 2. Decomposition into Molecules. Aldehydes (though not generally ketones) can also cleave in this manner:



This is an extrusion reaction (see Chapter 17). In another example of a process in category 2, aldehydes and ketones with an γ hydrogen can cleave in still another way (a β -elimination, see Chap 17):



This reaction, called *Norrish Type II cleavage*,⁵⁰ involves intramolecular abstraction of the γ hydrogen followed by cleavage of the resulting diradical⁵¹ (a secondary reaction) to give an enol that tautomerizes to the aldehyde or ketone product.⁵²



Both singlet and triplet n,π^* states undergo the reaction.⁵³ The intermediate diradical can also cyclize to a cyclobutanone, which is often a side product. Carboxylic esters, anhydrides, and other carbonyl compounds can also give this reaction.⁵⁴ The

⁴⁹ See Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* **1986**, 25, 661; Dürr, H.; Ruge, B. *Top. Curr. Chem.* **1976**, 66, 53; Drewier, R.J. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, **1975**, pp. 935–1015.

⁵⁰ See Wagner, P.J. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, **1980**, pp. 381–444; *Acc. Chem. Res.* **1971**, 4, 168. See Niu, Y.; Christophy, E.; Hossenlopp, J.M. *J. Am. Chem. Soc.* **1996**, 118, 4188 for a new view of Norrish Type II elimination.

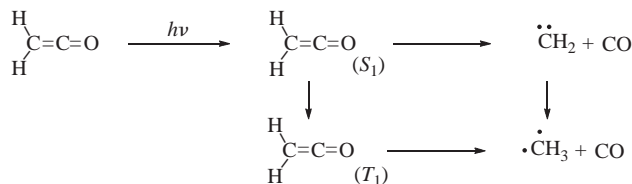
⁵¹ See Wilson, R.M. *Org. Photochem.* **1985**, 7, 339, pp. 349–373; Scaiano, J.C.; Lissi, E.A.; Encina, M.V. *Rev. Chem. Intermed.* **1978**, 2, 139. Also see Wagner, P.J. *Acc. Chem. Res.* **1989**, 22, 83.

⁵² This mechanism was proposed by Yang, N.C.; Yang, D.H. *J. Am. Chem. Soc.* **1958**, 80, 2913. The diradical intermediate has been trapped: Wagner, P.J.; Zepp, R.G. *J. Am. Chem. Soc.* **1972**, 94, 287; Wagner, P.J.; Kelso, P.A.; Zepp, R.G. *J. Am. Chem. Soc.* **1972**, 94, 7480; Adam, W.; Grabowski, S.; Wilson, R.M. *Chem. Ber.* **1989**, 122, 561. See also, Caldwell, R.A.; Dhawan, S.N.; Moore, D.E. *J. Am. Chem. Soc.* **1985**, 107, 5163.

⁵³ See Casey, C.P.; Boggs, R.A. *J. Am. Chem. Soc.* **1972**, 94, 6457.

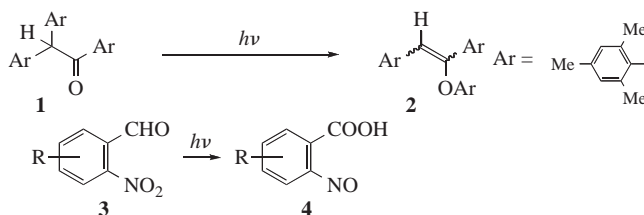
⁵⁴ For a review of the photochemistry of carboxylic acids and acid derivatives, see Givens, R.S.; Levi, N. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1; Wiley, NY, **1979**, pp. 641–753.

photolysis of ketene to CH_2 (Sec. 5.D.ii) is still another example of a reaction in category 2. Both singlet and triplet CH_2 are generated, the latter in two ways:

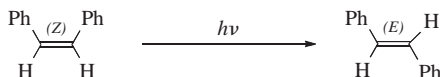


Reactions are known where *both* Norrish Type I and Type II reactions compete, and the substituents on and nature of the substrate will determine which leads to the major product.⁵⁵

Category 3. Intramolecular Rearrangement. Two examples are the rearrangement of the trimesityl compound **1** to the enol ether (**2**),⁵⁶ and irradiation of *o*-nitrobenzaldehydes (**3**) to give *o*-nitrosobenzoic acids (**4**).⁵⁷



Category 4. Photoisomerization. The most common reaction in this category is photochemical *cis*–*trans* isomerization.⁵⁸ For example, *cis*-stilbene can be converted to the *trans* isomer,⁵⁹ and the photoisomerization of *O*-methyl oximes is known.⁶⁰



The isomerization takes place because the excited states, both S_1 and T_1 , of many alkenes have a perpendicular instead of a planar geometry (Sec. 7.A.iv), so *cis*–*trans* isomerism disappears upon excitation. When the excited molecule drops back to the S_0 state, either isomer can be formed. A useful example is the photochemical

⁵⁵ See Hwu, J.R.; Chen, B.-L.; Huang, L.W.; Yang, T.-H. *J. Chem. Soc. Chem. Commun.* **1995**, 299.

⁵⁶ Wagner, P.J.; Zhou, B. *J. Am. Chem. Soc.* **1988**, 110, 611.

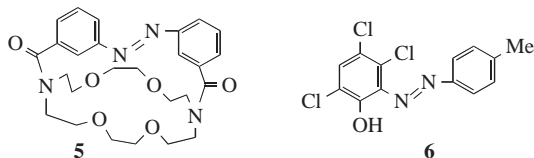
⁵⁷ See Morrison, H.A. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, **1969**, pp. 165–213, 185–191; Kaupp, G. *Angew. Chem. Int. Ed.* **1980**, 19, 243. See also, Yip, R.W.; Sharma, D.K. *Res. Chem. Intermed.* **1989**, 11, 109.

⁵⁸ See Sonnet, P.E. *Tetrahedron* **1980**, 36, 557; Schulte-Frohlinde, D.; Görner, H. *Pure Appl. Chem.* **1979**, 51, 279; Saltiel, J.; Charlton, J.L. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, **1980**, pp. 25–89; Saltiel, J.; Chang, D.W.L.; Megarity, E.D.; Rousseau, A.D.; Shannon, P.T.; Thomas, B.; Uriarte, A.K. *Pure Appl. Chem.* **1975**, 41, 559; Saltiel, J.; D'Agostino, J.; Megarity, E.D.; Metts, L.; Neuberger, K.R.; Wrighton, M.; Zafiriou, O.C. *Org. Photochem.* **1979**, 3, 1. Also see Leigh, W.J.; Srinivasan, R. *Acc. Chem. Res.* **1987**, 20, 107; Steinmetz, M.G. *Org. Photochem.* **1987**, 8, 67; Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* **1986**, 25, 661; Johnson, R.P. *Org. Photochem.* **1985**, 7, 75.

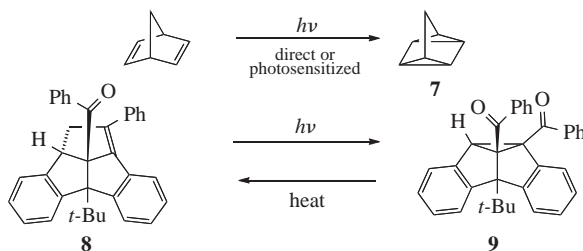
⁵⁹ For a review of the photoisomerization of stilbenes, see Waldeck, D.H. *Chem. Rev.* **1991**, 91, 415.

⁶⁰ Kawamura, Y.; Takayama, R.; Nishiuchi, M.; Tsukayama, M. *Tetrahedron Lett.* **2000**, 41, 8101.

conversion of *cis*-cyclooctene to the much less stable *trans* isomer.⁶¹ Another interesting example of this isomerization involves azo crown ethers. The crown ether **5**, in which the N=N bond is *anti*, preferentially binds NH_4^+ , Li^+ , and Na^+ , but the *syn* isomer preferentially binds K^+ and Rb^+ (see Sec. 3.C.ii). Thus, ions can be selectively put in or taken out of solution merely by turning a light source on or off.⁶²



In another example, the *trans* azo compound (**6**) is converted to its *cis* isomer when exposed to light. In this case⁶³ the *cis* isomer is a stronger acid than the *trans*. The *trans* isomer is dissolved in a system containing a base, wherein a liquid membrane separates two sides, one of which is illuminated, the other kept dark. On the illuminated side, the light converts the *trans* isomer to the *cis*. The *cis* isomer, being a stronger acid, donates its proton to the base, converting *cis*-ArOH to *cis*-ArO[−]. This ion migrates to the dark side, where it rapidly reverts to the *trans* ion, which reacquires a proton. Because each cycle forms one H_3O^+ ion in the illuminated compartment and one [−]OH ion in the dark compartment, the process reverses the normal reaction whereby these ions neutralize each other.⁶⁴ Thus the energy of light is used to do chemical work.⁶⁵ Another example of a category 4 reaction is the conversion of bicyclo[2.2.1]hept-2,5-diene to **7**.⁵⁸ The thermal isomerization of dibenzosubvalene (**9**) to the corresponding dibenzodihydropentalenofuran (**8**) in quantitative yield was known,⁶⁶ but in another example of a category 4 reaction the photochemical isomerization of **8** to **9** has now been reported.⁶⁷



These examples illustrate that the use of photochemical reactions can make it very easy to obtain compounds that would be difficult to get in other ways. Reactions similar to these are discussed in Reaction 15-63.

⁶¹ Deyrup, J.A.; Betkouski, M. *J. Org. Chem.* **1972**, 37, 3561.

⁶² Akabori, S.; Kumagai, T.; Habata, Y.; Sato, S. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1497; Shinkai, S.; Yoshioka, A.; Nakayama, H.; Manabe, O. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1905. For a review, see Shinkai, S.; Manabe, O. *Top. Curr. Chem.* **1984**, 121, 67.

⁶³ Haberfield, P. J. *Am. Chem. Soc.* **1987**, 109, 6177.

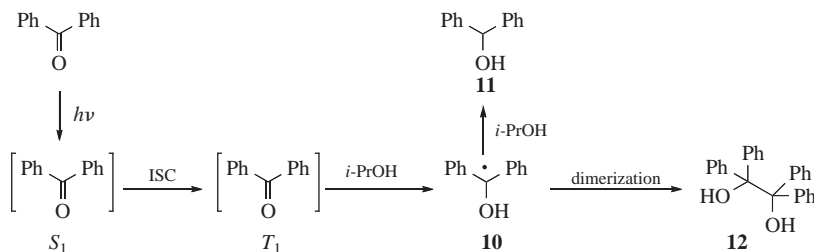
⁶⁴ Haberfield, P. J. *Am. Chem. Soc.* **1987**, 109, 6178.

⁶⁵ See Beer, P.D. *Chem. Soc. Rev.* **1989**, 18, 409. For an example not involving a macrocycle, see Feringa, B.L.; Jager, W.F.; de Lange, B.; Meijer, E.W. *J. Am. Chem. Soc.* **1991**, 113, 5468.

⁶⁶ Sajimon, M.C.; Ramaiah, D.; Muneer, M.; Rath, N.P.; George, M.V. *J. Photochem. Photobiol. A Chem.* **2000**, 136, 209.

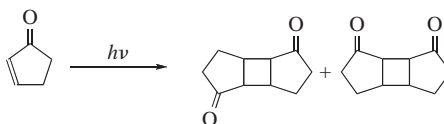
⁶⁷ Sajimon, M.C.; Ramaiah, D.; Thomas, K.G.; George, M.V. *J. Org. Chem.* **2001**, 66, 3182.

Category 5. Hydrogen-Atom Abstraction. When benzophenone is irradiated in isopropyl alcohol, the initially formed S_1 state crosses to the T_1 state, which abstracts hydrogen from the solvent to give the radical **10**. Radical **10** then abstracts another hydrogen to give benzhydrol (**11**) or dimerizes to benzpinacol (**12**):



An example of intramolecular abstraction has already been given (see category 2 in this section).

Category 6. Photodimerization. An example is dimerization of cyclopentenone:⁶⁸



See Reaction 15-63 for a discussion of this and similar reactions.

7.A.viii. The Determination of Photochemical Mechanisms⁶⁹

The methods used for the determination of photochemical mechanisms are largely the same as those used for organic mechanisms in general (Chapter 6): product identification, isotopic tracing, the detection and trapping of intermediates, and kinetics. There are, however, a few new factors: (1) there are generally many products in a photochemical reaction, as many as 10 or 15; (2) in measuring kinetics, there are more variables, since it is possible to study the effect on the rate of the intensity or the wavelength of light; (3) in the detection of intermediates by spectra the technique of *flash photolysis* can be used, which can detect extremely short-lived intermediates.

In addition to these methods, there are two additional techniques.

1. The use of emission (fluorescence and phosphorescence), as well as absorption spectroscopy. From these spectra the presence of as well as the energy and lifetime of singlet and triplet excited states can often be calculated.
2. The study of quantum yields. The *quantum yield* is the fraction of absorbed light that goes to produce a particular result. There are several types. A *primary quantum yield* for a particular process is the fraction of molecules absorbing light that undergo that particular process. Thus, if 10% of all the molecules that are excited to

⁶⁸ Eaton, P.E. *Acc. Chem. Res.* **1968**, *1*, 50. For a review of the photochemistry of α,β -unsaturated ketones, see Schuster, D.I. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, **1989**, pp. 623–756.

⁶⁹ For a review, see Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, **1966**, pp. 580–670.

the S_1 state cross over to the T_1 state, the primary quantum yield for that process is 0.10. However, primary quantum yields are often difficult to measure. A *product quantum yield* (usually designated Φ) for a product P that is formed from a photoreaction of an initially excited molecule A can be expressed as:

$$\Phi = \frac{\text{number of molecules of P formed}}{\text{number of quanta absorbed by A}}$$

Product quantum yields are much easier to measure. The number of quanta absorbed can be determined by an instrument called an *actinometer*, which is actually a standard photochemical system whose quantum yield is known. An example of the information that can be learned from quantum yields is the following. If the quantum yield of a product is finite and invariant with changes in experimental conditions, it is likely that the product is formed in a primary rate-determining process. Another example: In some reactions, the product quantum yields are found to be well over 1 (perhaps as high as 1000). Such a finding indicates a chain reaction (see Sec. 14.A.i for a discussion of chain reactions).

7.B. SONOCHEMISTRY

Sonochemistry (chemical events induced by exposure to ultrasound) occupies an important place in organic chemistry.⁷⁰ The chemical effects of high-intensity ultrasound were extensively studied in aqueous solutions for many years,⁷¹ but are now applied to a variety of organic solvents. The origin of sonochemistry is acoustic cavitation: the creation, growth, and implosive collapse of gas vacuoles in solution by the sound field. Acoustic cavitation is the phenomenon by which intense ultrasonic waves induce the formation, oscillation, and implosion of gas bubbles in liquids.⁷² Liquids irradiated with high-power ultrasound undergo chemical decomposition and emit light.⁷³ These phenomena occur near the end of the collapse of bubbles expanded many times their equilibrium sizes. Chemistry (sonochemistry), light emission (sonoluminescence), and cavitation noise often accompany the process of acoustic cavitation.⁷⁴

Sonochemistry generates gas vacuoles *in situ*. The collapse of gas vacuoles generates transient hot spots with local temperatures of several thousand Kelvin, and pressures of hundreds of atmospheres. A sonochemical hot spot forms where the gas- and liquid-phase

⁷⁰ Mason, T.J., Ed. *Advances in Sonochemistry*, JAI Press, NY, **1990–1994**; Vols. 1–3, Price, G.J., Ed. *Current Trends in Sonochemistry*, Royal Society of Chemistry, Cambridge, UK, **1992**; Suslick, K.S. *Science* **1990**, 247, 1439; Suslick, K.S. *Ultrasound: Its Chemical, Physical, and Biological Effects*, VCH, NY, **1988**; Young, F.R. *Cavitation*, McGraw-Hill, NY, **1989**; Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, Oxford, UK, **1995**; Anbar, M. *Science* **1968**, 161, 1343. For a discussion of ultrasound in the chemistry of heterocycles, see Cella, R.; Stefani, H.A. *Tetrahedron* **2009**, 65, 2619.

⁷¹ Apfel, R.E., in Edmonds, P. *Methods in Experimental Physics*, Academic Press, New York, **1981**; Vol. 19; Makino, K.; Mossoba, M.M.; Riesz, P. *J. Am. Chem. Soc.* **1982**, 104, 3537.

⁷² Stottlemeyer, T.R.; Apfel, R.E. *J. Acoust. Soc. Am.* **1997**, 102, 1413.

⁷³ Suslick, K.S.; Crum, L.A. In *Sonochemistry and Sonoluminescence, Handbook of Acoustics*, Crocker, M.J., Ed., Wiley, NY, **1998**; Chapter 23; Leighton, T.G. *The Acoustic Bubble*, Academic Press, London, **1994**; Chapter 4; Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, **1995**, Chapters 1–4; Hua, I.; Hoffmann, M.R. *Environ. Sci. Technol.* **1997**, 31, 2237.

⁷⁴ Suslick, K.S.; Didenko, Y.T.; Fang, M.M.; Hyeon, T.; Kolbeck, K.J.; McNamara, III, W.B.; Mdeleni, M.M.; Wong, M. *Philos. Trans. R. Soc. London A* **1999**, 357, 335. For problems of sonochemistry and cavitation, see Margulis, M.A. *Ultrasonics Sonochemistry*, **1994**, 1, S87.

reaction zones have effective temperatures of 5200 and 1900 K, respectively.⁷⁵ The high temperatures and pressures that are achieved in the bubbles during the quasiadiabatic collapse⁷⁶ lead to the generation of chemistry and to the emission of light, most probably coming from molecular excited states and molecular recombination. Note that work has been done that shows the commonly held view that bubbles are filled with saturated gas is inconsistent with a realistic estimate of condensation rates.⁷⁷ The alternative view of extensive solvent vapor supersaturation in bubbles uniformly heated to a few thousand kelvin, depending on the conditions, is in accord with sonochemical rates and products.⁷⁸

There is a correlation between sonochemical and sonoluminescence measurements, which is usually not observed. Sonoluminescence is the consequence that both the sonochemical production (under air) of oxidizing species, and the emission of light reflect the variations of the primary sonochemical acts, which are themselves due to variations of the number of "active" bubbles.⁷⁹ Pulsed ultrasound in the high-frequency range (>1 MHz) is extensively used in medical diagnosis, and the effects of pulsed ultrasound in the 20-kHz range using an immersed titanium horn has been reported.⁸⁰

The chemical effects of ultrasound have been studied for >50 years,⁸¹ and applied to colloid chemistry in the 1940s.⁸² Modern interest in the chemical uses of ultrasound involves chemistry in both homogeneous⁸³ and heterogeneous⁸⁴ systems. Organic solvents (e.g., alkanes) support acoustic cavitation and the associated sonochemistry. This leads to carbon-carbon bond cleavage and radical rearrangements, with the peak temperatures reached in such cavities controlled by the vapor pressure of the solvent.⁸⁵

It is often difficult to compare the sonochemical results reported from different laboratories (the reproducibility problem in sonochemistry).⁸⁶ The sonochemical power irradiated into the reaction system can be different for different instruments. Several methods are available to estimate the amount of ultrasonic power entered into a sonochemical reaction,⁸⁶ the most common being calorimetry. This experiment involves measurement of the initial rate of a temperature rise produced when a system is irradiated by power ultrasound. It has

⁷⁵ Suslick, K.S.; Hammerton, D.A.; Cline, Jr., R.E. *J. Am. Chem. Soc.* **1986**, *108*, 5641.

⁷⁶ Didenko, Y.T.; McNamara, III, W.B.; Suslick, K.S. *J. Am. Chem. Soc.* **1999**, *121*, 5817.

⁷⁷ Colussi, A. J.; Hoffmann, M.R. *J. Phys. Chem. A* **1999**, *103*, 11336.

⁷⁸ Colussi, A.J.; Weavers, L.K.; Hoffmann, M.R. *J. Phys. Chem. A* **1998**, *102*, 6927.

⁷⁹ Segebarth, N.; Eulaerts, O.; Reisse, J.; Crum, L.A.; Matula, T.J. *J. Phys. Chem. B* **2002**, *106*, 9181.

⁸⁰ Dekerckheer, C.; Bartik, K.; Lecomte, J.-P.; Reisse, J. *J. Phys. Chem. A* **1998**, *102*, 9177.

⁸¹ Elpiner, I. E. *Ultrasound: Physical, Chemical, and Biological Effects*, Consultants Bureau, NY, **1964**.

⁸² Sollner, K. *Chem. Rev.* **1944**, *34*, 371.

⁸³ Suslick, K.S.; Schubert, P.F.; Goodale, J.W. *J. Am. Chem. Soc.* **1981**, *103*, 7342; Sehgal, C.; Yu, T.J.; Sutherland, R.G.; Verrall, R.E. *J. Phys. Chem.* **1982**, *86*, 2982; Sehgal, C.M.; Wang, S.Y. *J. Am. Chem. Soc.* **1981**, *103*, 6606.

⁸⁴ Han, B.-H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030; Boudjouk, P.; Han, B.-H. *Tetrahedron Lett.* **1981**, *22*, 3813; Han, B.-H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 751; Boudjouk, P.; Han, B.-H.; Anderson, K.R. *J. Am. Chem. Soc.* **1982**, *104*, 4992; Boudjouk, P.; Han, B.-H. *J. Catal.* **1983**, *79*, 489; Racher, S.; Klein, P. *J. Org. Chem.* **1981**, *46*, 3558; Regen, S.L.; Singh, A. *J. Org. Chem.* **1982**, *47*, 1587; Kegelaers, Y.; Eulaerts, O.; Reisse, J.; Segebarth, N. *Eur. J. Org. Chem.* **2001**, 3683.

⁸⁵ Suslick, K.S.; Gawienowski, J.J.; Schubert, P.F.; Wang H.H. *J. Phys. Chem.* **1983**, *87*, 2299.

⁸⁶ Mason, T.J. *Practical Sonochemistry: User's Guide to Applications in Chemistry and Chemical Engineering*, Ellis Horwood, West Sussex, **1991**, pp. 43-46; Broeckart, L.; Caulier, T.; Fabre, O.; Maerschalk, C.; Reisse, J.; Vandercammen, J.; Yang, D.H.; Lepoint, T.; Mullie, F. *Current Trends in Sonochemistry*, Price, G.J., Ed., Royal Society of Chemistry, Cambridge, **1992**, p. 8; Mason, T.J.; Lorimer, J.P.; Bates, D.M.; Zhao, Y. *Ultrasonics Sonochemistry* **1994**, *1*, S91; Mason, T.J.; Lorimer, J.P.; Bates, D.M. *Ultrasonics* **1992**, *30*, 40.

been shown that calorimetric methods combined with the Weissler reaction can be used to standardize the ultrasonic power of individual ultrasonic devices.⁸⁷

Sonochemistry has been used to facilitate or assist many organic reactions,⁸⁸ and there are other applications.⁸⁹ The scope of reactions studied is beyond this work, but some representative examples will be listed. Ultrasound has been used to promote lithiation of organic compounds,⁹⁰ for the generation of carbenes,⁹¹ and reactions of metal carbonyls where sonochemical ligand dissociation has been observed, which often produces multiple CO substitution.⁹² The influence of ultrasound on phase-transfer catalyzed thioether synthesis has been studied.⁹³

Sonochemistry has been applied to acceleration of the *Reformatsky reaction*,⁹⁴ *Diels–Alder reactions*,⁹⁵ the arylation of active methylene compounds⁹⁶ nucleophilic aromatic substitution of haloarenes,⁹⁷ and to hydrostannation and tin hydride reduction.⁹⁸ Other sonochemical applications involve the reaction of benzyl chloride and nitrobenzene,⁹⁹ an S_{RN}1 reaction in liquid ammonia at room temperature,¹⁰⁰ and *Knoevenagel condensation* of aromatic aldehydes.¹⁰¹ Iodination of aliphatic hydrocarbons can be accelerated,¹⁰² and oxyallyl cations have been prepared from α,α' -diiodoketones using sonochemistry.¹⁰³ Sonochemistry has been applied to the preparation of carbohydrate compounds.¹⁰⁴ When sonochemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

7.C. MICROWAVE CHEMISTRY

In 1986, independent work by Gedye et al.,¹⁰⁵ as well as Majetich and co-workers¹⁰⁶ reported the use of microwave irradiation for organic reactions. Gedye described four different types of reactions, including the hydrolysis of benzamide to benzoic acid under acidic conditions, and all reactions showed significant rate enhancements when

⁸⁷ Kimura, T.; Sakamoto, T.; Leveque, J.-M.; Sohmiya, H.; Fujita, M.; Ikeda, S.; Ando, T. *Ultrasonics Sonochemistry* **1996**, 3, S157.

⁸⁸ *Synthetic Organic Sonochemistry* Luche, J.-L. (Universite de Savoie, France), Plenum Press, NY. **1998**; Luche, J.-L. *Ultrasonics Sonochemistry*, **1996**, 3, S215.

⁸⁹ Adewuyi, Y.G. *Ind. Eng. Chem. Res.* **2001**, 40, 4681.

⁹⁰ Boudjouk, P.; Sooriyakumaran, R.; Han, B.H. *J. Org. Chem.* **1986**, 51, 2818, and Ref. 1 therein.

⁹¹ Regen, S.L.; Singh, A. *J. Org. Chem.* **1982**, 47, 1587.

⁹² Suslick, K.S.; Goodale, J.W.; Schubert, P.F.; Wang, H.H. *J. Am. Chem. Soc.* **1983**, 105, 5781.

⁹³ Wang, M.-L.; Rajendran, V. *J. Mol. Catalysis A: Chemical* **2005**, 244, 237.

⁹⁴ Han, B.H.; Boudjouk, P. *J. Org. Chem.* **1982**, 47, 5030.

⁹⁵ Nebois, P.; Bouaziz, Z.; Fillion, H.; Moenini, L.; Piquer, Ma.J.A.; Luche, J.-L.; Riera, A.; Moyano, A.; Pericàs, M.A. *Ultrasonics Sonochemistry* **1996**, 3, 7.

⁹⁶ Mečiarová, M.; Kiripolsky, M.; Toma, Š. *Ultrasonics Sonochemistry* **2005**, 12, 401.

⁹⁷ Mečiarová, M.; Toma, S.; Magdolen, P. *Ultrasonics Sonochemistry* **2003**, 10, 265.

⁹⁸ Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* **1989**, 111, 6849.

⁹⁹ Vinatoru, M.; Stavrescu, R.; Milcoveanu, A.B.; Toma, M.; Mason, T.J. *Ultrasonics Sonochemistry* **2002**, 9, 245.

¹⁰⁰ Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* **1994**, 35, 677.

¹⁰¹ McNulty, J.; Steere, J.A.; Wolf, S. *Tetrahedron Lett.* **1998**, 39, 8013.

¹⁰² Kimura, T.; Fujita, M.; Sohmiya, H.; Ando, T. *Ultrasonics Sonochemistry* **2002**, 9, 205.

¹⁰³ Montaña, A.M.; Grima, P.M. *Tetrahedron Lett.* **2001**, 42, 7809.

¹⁰⁴ Kardos, N.; Luche, J.-L. *Carbohydrate Res.* **2001**, 332, 115.

¹⁰⁵ Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* **1987**, 66, 17.

¹⁰⁶ Giguere, R.J.; Bray, T.; Duncan, S.M.; Majetich, G. *Tetrahedron Lett.* **1986**, 27, 4945.

compared to the same reactions done at reflux conditions.¹⁰⁷ Majetich, Giguere and co-workers¹⁰⁶ reported rate enhancements for microwave-promoted *Diels–Alder*, *Claisen*, and ene reactions. Many publications¹⁰⁸ have appeared that describe chemical synthesis promoted by microwave irradiation, including many review articles¹⁰⁹ and books.¹¹⁰

Microwaves are electromagnetic waves (see Sec. 7.A.i) and there are electric and magnetic field components. Charged particles start to migrate or rotate as the electric field is applied,¹¹¹ which leads to further polarization of polar particles. Because the concerted forces applied by the electric and magnetic components of microwaves are rapidly changing in direction ($2.4 \times 10^9 \text{ s}^{-1}$), warming occurs.¹¹¹ In general, the most common frequencies used for microwave dielectric heating¹¹² are 918 MHz and 2.45 GHz¹¹³ (wavelengths of 33.3 and 12.2 cm, respectively), which are in the region between the IR and radiowave wavelengths in the electromagnetic spectrum. For chemical reactions done with microwave irradiation, rapid heating is usually observed,¹¹⁴ and if a solvent is used superheating of that solvent was always observed.¹¹² Agitation is usually important.¹¹⁵ In the early days of microwave chemistry, reactions were often done in open vessels, but also in sealed Teflon or glass vessels using unmodified domestic household ovens.¹¹⁶ Dielectric heating is direct so if the reaction matrix has a sufficiently large dielectric loss tangent, and contains molecules possessing a dipole moment, a solvent is not required. The use of dry-reaction microwave chemistry is increasingly popular.¹¹⁷

Microwave dielectric heating was initially categorized by thermal effects and nonthermal effects.¹¹⁸ “Thermal effects are those which are caused by the different temperature regime which can be created due to microwave dielectric heating. Nonthermal effects are effects,¹¹⁹ which are caused by effects specifically inherent to the microwaves and are not caused by

¹⁰⁷ Taken from Horeis, G.; Pichler, S.; Stadler, A.; Gössler, W.; Kappe, C.O. *Microwave-Assisted Organic Synthesis - Back to the Roots*, Fifth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5), **2001**. (available at <http://www.mdpi.org/ecsoc-5.htm>).

¹⁰⁸ Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, 43, 6250.

¹⁰⁹ Majetich, G.; Karen, W. in Kingston, H.M.; Haswell, S.J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications*, American Chemical Society, Washington, DC, **1997**, p. 772; Bose, A.K.; Manhas, M.S.; Banik, B.K.; Robb, E.W. *Res. Chem. Intermed.* **1994**, 20, 1; Majetich, G.; Hicks, R. *Res. Chem. Intermed.* **1994**, 20, 61; Strauss, C.R.; Trainor, R.W. *Aust. J. Chem.* **1995**, 48, 1665; Caddick, S. *Tetrahedron* **1995**, 51, 10403; Mingos, D.M.P. *Res. Chem. Intermed.* **1994**, 20, 85; Berlan, J. *Rad. Phys. Chem.* **1995**, 45, 581; Fini, A.; Breccia, A. *Pure Appl. Chem.* **1999**, 71, 573.

¹¹⁰ Kingston, H.M.; Haswell, S.J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications*, American Chemical Society, **1997**; Loupy, A. *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, **2002**; Hayes, B.L. *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, **2002**; Lidström, P.; Tierney, J.P. *Microwave-Assisted Organic Synthesis*, Blackwell Scientific, **2005**; Kappe, C.O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, **2005**.

¹¹¹ Galema, S.A. *Chem. Soc. Rev.* **1997**, 26, 233.

¹¹² Gabriel, C.; Gabriel, S.; Grant, E.H.; Halstead, B.S.J.; Mingos, D.M.P. *Chem. Soc. Rev.* **1998**, 27, 213.

¹¹³ This frequency is usually applied in domestic microwave ovens.

¹¹⁴ See Hoogenboom, R.; Wilms, T.F.A.; Erdmenger, T.; Schubert, U.S. *Austr. J. Chem.* **2009**, 62, 236.

¹¹⁵ Moseley, J.D.; Lenden, P.; Thomson, A.D.; Gilday, J.P. *Tetrahedron Lett.* **2007**, 48, 6084.

¹¹⁶ Caddick, S. *Tetrahedron* **1995**, 51, 10403.

¹¹⁷ Varma, R. S. *Green Chem.* **1999**, 43; Kidawi, M. *Pure Appl. Chem.* **2001**, 73, 147; Varma, R. S. *Pure Appl. Chem.* **2001**, 73, 193.

¹¹⁸ Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* **1997**, 4, 373. Also see Schmink, J.R.; Leadbeater, N.E. *Org. Biomol. Chem.*, **2009**, 7, 3842.

¹¹⁹ See Kuhnert, N. *Angew. Chem. Int. Ed.* **2002**, 41, 1863.

different temperature regimes.”¹¹¹ Some claimed special effects¹²⁰ in microwave chemistry, such as lowering of Gibbs energy of activation, but later study under careful temperature control indicated no special rate effects.¹²¹ When conventional microwave ovens were used, temperature control was difficult, particularly when reactions are carried out in closed reaction vessels. The main contributing factor to any rate acceleration caused by microwave dielectric heating seems to be due to a thermal effect. The thermal effect may be due to a faster initial heating rate or to the occurrence of local regions with higher temperatures.¹¹¹

Conventional microwave ovens are used less often for microwave chemistry today. Microwave reactors for chemical synthesis are commercially available and widely used in academia and in industry. These instruments have built-in magnetic stirring, direct temperature control of the reaction mixture, shielded thermocouples or IR sensors, and the ability to control temperature and pressure by regulating microwave output power.

The applications of microwave chemistry to organic chemistry are literally too numerous to mention. A few representative examples will be given to illustrate the scope and utility. The combined use of microwaves and ultrasound is important in process chemistry and organic synthesis.¹²² Microwave chemistry is widely used in synthesis,¹²³ including organocatalyzed asymmetric reactions.¹²⁴ Examples include the *Heck reaction* (Reaction 13-10),¹²⁵ the *Suzuki reaction* (Reaction 13-12),¹²⁶ the *Sonogashira reaction* (Reaction 13-13),¹²⁷ *Ullman-type couplings* (Reaction 13-3),¹²⁸ cycloaddition reactions (Reactions 15-58–15-66),¹²⁹ dihydroxylation (Reaction 15-48),¹³⁰ and the *Mitsunobu reaction* (Reaction 10-23).¹³¹ There are a multitude of other reactions types from earlier literature that can be found in the cited review articles. When microwave chemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

¹²⁰ Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* **1992**, *57*, 7099 and references therein.

¹²¹ Raner, K.D.; Strauss, C.R.; Vyskoc, F.; Mokbel, L. *J. Org. Chem.* **1993**, *58*, 950, and references cited therein.

¹²² Cravotto, G.; Cintas, P. *Chemistry: European J.* **2007**, *13*, 1902.

¹²³ See Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717; Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128; Roberts, B.A.; Strauss, C.R. *Acc. Chem. Res.* **2005**, *38*, 653; Kuznetsov, D.V.; Raev, V.A.; Kuranov, G.L.; Arapov, O.V.; Kostikov, R.R. *Russ. J. Org. Chem.* **2005**, *41*, 1719. For a discussion of microwave-assisted organic synthesis in near critical water, see Kremsner, J.M.; Kappe, C.O. *Eur. J. Org. Chem.* **2005**, 3672.

¹²⁴ Mossé, S.; Alexakis, A. *Org. Lett.* **2006**, *8*, 3577.

¹²⁵ Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717; Olofsson, K.; Larhed, M. in Lidström, P.; Tierney, J.P. *Microwave-Assisted Organic Synthesis*, Blackwell, Oxford, **2004**, Chap. 2., Andappan, M.M.S.; Nilsson, P.; Larhed, M. *Mol. Diversity* **2003**, *7*, 97.

¹²⁶ Nuteberg, D.; Schaal, W.; Hamelink, E.; Vrang, L.; Larhed, M. *J. Comb. Chem.* **2003**, *5*, 456; Miller, S.P.; Morgan, J.B.; Nepveux, F.J.; Morken, J.P. *Org. Lett.* **2004**, *6*, 131; Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* **2003**, *7*, 125; Gong, Y.; He, W. *Heterocycles* **2004**, *62*, 851; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888; Bai, L.; Wang, J.-X.; Zhang, Y. *Green Chem.* **2003**, *5*, 615; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660.

¹²⁷ Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* **2003**, *7*, 125; Gong, Y.; He, W. *Heterocycles* **2004**, *62*, 851; Leadbeater, N.E.; Marco, M.; Tominack, B.J. *Org. Lett.* **2003**, *5*, 3919; Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2003**, 4713.

¹²⁸ Wu, Y.-J.; He, H.; L'Heureux, A. *Tetrahedron Lett.* **2003**, *44*, 4217; Lange, J.H.M.; Hofmeyer, L.J.F.; Hout, F.A.S.; Osnabrug, S.J.M.; Verveer, P.C.; Kruse, C.G.; Feenstra, R.W. *Tetrahedron Lett.* **2002**, *43*, 1101.

¹²⁹ See Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C.O. *J. Org. Chem.* **2002**, *67*, 7904; Pinto, D.C.G.A.; Silva, A.M.S.; Almeida, L.M.P.M.; Carrillo, J.R.; D'az-Ortiz, A.; de la Hoz, A.; Cavaleiro, J.A.S. *Synlett* **2003**, 1415.

¹³⁰ Dupau, P.; Eppe, R.; Thomas, A.A.; Fokin, V.V.; Sharpless, K.B. *Adv. Synth. Catal.* **2002**, *344*, 421.

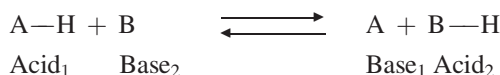
¹³¹ Raheem, I.T.; Goodman, S.N.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2004**, *126*, 706.

Acids and Bases

Two acid–base theories are used in organic chemistry today: the Brønsted theory and the Lewis theory.¹ These theories are quite compatible and are used for different purposes.² However, the Lewis-based idea of electron-donating species (bases) and electron-accepting species (acids) is often the more useful for organic chemistry. Remember also that most organic reactions are not done in an aqueous medium, and focus on electron transfer rather than proton transfer is far more useful.

8.A. BRØNSTED THEORY

According to this theory, an acid is defined as a *proton donor*³ and a base as a *proton acceptor*. However, a base must have a pair of electrons available to share with the proton; this is usually present as an unshared pair, but sometimes is in a π orbital. By this definition, an acid–base reaction is the transfer of a proton from an acid to a base. However, protons do not exist free in solution, but must be attached to an electron pair. In fact, the acid does not “give up” a proton, but rather the base donates electrons to the proton, “pulling it away” to form the conjugate acid. After removal of the proton, the species remaining (the *conjugate base*) still retains the electron pair to which the proton was formerly attached. The conjugate base, in theory at least, can reacquire a proton and is therefore a base. All acids will generate a conjugate base upon reaction with a suitable base, and all bases will generate a *conjugate acid* by reaction with a suitable acid. All acid–base reactions fit the equation



¹ For monographs on acids and bases, see Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, **1985**; Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, **1973**; Finston, H.L.; Rychman, A.C. *A New View of Current Acid–Base Theories*, Wiley, NY, **1982**.

² For discussion of the historical development of acid–base theory, see Bell, R.P. *Q. Rev. Chem. Soc.* **1947**, *1*, 113; Bell, R.P. *The Proton in Chemistry*, 1st ed., Cornell University Press, Ithaca, NY, **1959**, pp. 7–17.

³ According to IUPAC terminology (Bunnett, J.F.; Jones, R.A.Y. *Pure Appl. Chem.* **1988**, *60*, 1115), an acid is a *hydron* donor. The IUPAC recommends that the term *proton* be restricted to the nucleus of the hydrogen isotope of mass 1, while the nucleus of the naturally occurring element, which contains ~0.015% deuterium, be called the *hydron* (the nucleus of mass 2 has always been known as the *deuteron*). This accords with the naturally occurring negative ion, which has long been called the *hydride* ion. In this book, however, we will continue to use *proton* for the naturally occurring form, because most of the literature uses this term.

No charges are shown in this equation, but an acid always has a charge one positive unit higher than that of its conjugate base.

8.A.i Brønsted Acids

According to the Brønsted definition, *acid strength* may be defined as the tendency to give up a proton and *base strength* as the tendency to accept a proton. All acid–base reactions are reversible, and both an acid and a conjugate acid are present in the equilibrium mixture. In one sense, acid–base reactions occur because the acid and the conjugate acid are not of equal strength (i.e., the equilibrium can be shifted to one side or the other). If an acid, say HCl, is placed in contact with the conjugate base of a weaker acid, say acetate ion, the conjugate acid in this reaction would be acetic acid. Since HCl is a stronger acid than acetic acid (see Table 8.1), the equilibrium lies well to the right. As the reaction is written, if the equilibrium lies to the right (higher concentration of acetic acid and a lower concentration of HCl), HCl is the stronger acid. Likewise, acetate is taken to be a stronger base than the chloride ion. If this is a correct statement, treatment of acetic acid with chloride ion should give essentially no reaction, since the weaker acid already has the proton. This is found to be correct.



For a comparison of two different acids, the position of the equilibrium in reaction with a common base allows the relative strengths of acids to be determined.⁴ Likewise, the strength of two different bases will be determined by comparing the equilibrium established when they react with a common acid. By definition, the acid and base are always drawn on the left side of the equation, and the conjugate acid and conjugate base are assumed to be on the right side of the equation.

Of course, if the two acids involved are close to each other in strength, a measurable reaction will occur from both sides. This finding really means that the concentration of acid and base at equilibrium will be close to that of the concentration of the conjugate acid and conjugate base. However, the position of equilibrium will still be over to the side of the weaker acid (unless the acidities are equal within experimental limits). If the concentration of acid and base is higher, the reaction of conjugate acid and conjugate base is more facile, and the compound labeled as the acid is considered to be a weaker acid. If the concentration of the conjugate acid and conjugate base is higher, the reaction of the acid and base is more facile, and the compound labeled as the acid is a stronger acid.

Using these protocols as the definition of acid strength, it is possible to construct a table in which acids are listed in order of acid strength⁵ (Table 8.1).⁶ The conjugate base is shown next to each acid in Table 8.1. Using the axiom that a strong acid generates a weak conjugate base and a weak acid will generate a strong conjugate base, it is clear that if the acids in such a table are listed in *decreasing* order of acid strength, the bases must be listed in *increasing* order of base strength. The $\text{p}K_a$ values⁷ in Table 8.1 are most accurate in the middle of the table.^{8–67}

⁴ Although equilibrium is reached in most acid–base reactions extremely rapidly (see Sec. 8.B), some are slow (especially those in which the proton is lost from a carbon) and in these cases time must be allowed for the system to come to equilibrium.

⁵ For a review of stronger Brønsted acids, see Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

⁶ Table 8.1 is a thermodynamic acidity scale and applies only to positions of equilibria. For the distinction between thermodynamic and kinetic acidity (see Sec. 8.B).

⁷ For a first principles calculation of $\text{p}K$ values in nonaqueous solution, see Ding, F.; Smith, J.M.; Wang, H. *J. Org. Chem.* **2009**, *74*, 2679.

TABLE 8.1 The pK_a Values for Many Types of Acids^a

Acid	Base	Approximate pK_a (relative to water) ^b	References
HF—SbF ₅	SbF ₆ [−]		8
FSO ₃ H—SbF ₅ —SO ₃			66
FSO ₃ H—SbF ₅			66,8
FSO ₃ H	FSO ₃ [−]		66
RNO ₂ H ⁺	RNO ₂	−12	9
ArNO ₂ H ⁺	ArNO ₂	−11	9
HClO ₄	ClO ₄ [−]	−10	10
HI	I [−]	−10	10
RCNH ⁺	RCN	−10	11
$\text{R}-\overset{\text{H}}{\underset{\text{+OH}}{\underset{\parallel}{\text{C}}}}-\text{H}$	$\text{R}-\overset{\text{H}}{\underset{\text{O}}{\underset{\parallel}{\text{C}}}}-\text{H}$	−10	12
H ₂ SO ₄	HSO ₄ [−]		
HBr	Br [−]	−9	10
$\text{Ar}-\overset{\text{OR}^c}{\underset{\text{+OH}}{\underset{\parallel}{\text{C}}}}-\text{OR}^c$	$\text{Ar}-\overset{\text{OR}}{\underset{\text{O}}{\underset{\parallel}{\text{C}}}}-\text{OR}$	−7.4	9
HCl	Cl [−]	−7	10
RSH ₂ ⁺	RSH	−7	9
$\text{Ar}-\overset{\text{OH}^c}{\underset{\text{+OH}}{\underset{\parallel}{\text{C}}}}-\text{OH}^c$	$\text{Ar}-\overset{\text{OH}}{\underset{\text{O}}{\underset{\parallel}{\text{C}}}}-\text{OH}$	−7	14
$\text{Ar}-\overset{\text{H}}{\underset{\text{+OH}}{\underset{\parallel}{\text{C}}}}-\text{H}$	$\text{Ar}-\overset{\text{H}}{\underset{\text{O}}{\underset{\parallel}{\text{C}}}}-\text{H}$	−7	15
$\text{R}-\overset{\text{R}}{\underset{\text{+OH}}{\underset{\parallel}{\text{C}}}}-\text{R}$	$\text{R}-\overset{\text{R}}{\underset{\text{O}}{\underset{\parallel}{\text{C}}}}-\text{R}$	−7	67,11,16

⁸ Gold, V.; Laali, K.; Morris, K.P.; Zdunek, L.Z. *J. Chem. Soc. Chem. Commun.* **1981**, 769; Sommer, J.; Canivet, P.; Schwartz, S.; Rimmelin, P. *Nouv. J. Chim.* **1981**, 5, 45.

⁹ Arnett, E.M. *Prog. Phys. Org. Chem.* **1963**, 1, 223, pp. 324–325.

¹⁰ Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, **1973**.

¹¹ Deno, N.C.; Gaugler, R.W.; Wisotsky, M.J. *J. Org. Chem.* **1966**, 31, 1967.

¹² Levy, G.C.; Cargioli, J.D.; Racela, W. *J. Am. Chem. Soc.* **1970**, 92, 6238. See, however, Brouwer, D.M.; van Doorn, J.A. *Recl. Trav. Chim. Pays-Bas* **1971**, 90, 1010.

¹³ Carboxylic acids, esters, and amides are shown in this table to be protonated on the carbonyl oxygen. See Smith, C.R.; Yates, K. *Can. J. Chem.* **1972**, 50, 771; Benedetti, E.; Di Blasio, B.; Baine, P. *J. Chem. Soc. Perkin Trans. 2* **1980**, 500; Homer, R.B.; Johnson, C.D. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 188–197. It has been shown that some amides protonate at nitrogen: see Perrin, C.L. *Acc. Chem. Res.* **1989**, 22, 268. For a review of alternative proton sites, see Liler, M. *Adv. Phys. Org. Chem.* **1975**, 11, 267.

¹⁴ Stewart, R.; Granger, M.R. *Can. J. Chem.* **1961**, 39, 2508.

¹⁵ Yates, K.; Stewart, R. *Can. J. Chem.* **1959**, 37, 664; Stewart, R.; Yates, K. *J. Am. Chem. Soc.* **1958**, 80, 6355.

¹⁶ Lee, D.G. *Can. J. Chem.* **1970**, 48, 1919.

TABLE 8.1 (Continued)

Acid	Base	Approximate p <i>K</i> _a (relative to water) ^b	References
ArSO ₃ H	ArSO ₃ [−]	−6.5	17
$\text{R}-\overset{\text{+}}{\underset{\text{OH}}{\underset{\parallel}{\text{C}}}}-\text{OR}^c$	$\text{R}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{OR}$	−6.5	9
ArOH ₂ ⁺	ArOH	−6.4	18
$\text{R}-\overset{\text{+}}{\underset{\text{OH}}{\underset{\parallel}{\text{C}}}}-\text{OH}^c$	$\text{R}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{OH}$	−6	9
$\text{Ar}-\overset{\text{+}}{\underset{\text{OH}}{\underset{\parallel}{\text{C}}}}-\text{R}$	$\text{Ar}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{R}$	−6	15,19
$\text{Ar}-\overset{\text{+}}{\underset{\text{H}}{\underset{ }{\text{O}}}}-\text{R}$	$\text{Ar}-\text{O}-\text{R}$	−6	18,20
CH(CN) ₃	[−] C(CN) ₃	−5	21
Ar ₃ NH ⁺	Ar ₃ N	−5	22
$\text{H}-\overset{\text{+}}{\underset{\text{OH}}{\underset{\parallel}{\text{C}}}}-\text{H}$	$\text{H}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{H}$	−4	23
$\text{R}-\overset{\text{+}}{\underset{\text{H}}{\underset{ }{\text{O}}}}-\text{R}$	$\text{R}-\text{O}-\text{R}$	−3.5	11,20,24
R ₃ COH ₂ ⁺	R ₃ COH	−2	24
R ₂ CHOH ₂ ⁺	R ₂ CHOH	−2	24,25
RCH ₂ OH ₂ ⁺	RCH ₂ OH	−2	11,24,25
H ₃ O ⁺	H ₂ O	−1.74	26
$\text{Ar}-\overset{\text{+}}{\underset{\text{OH}}{\underset{\parallel}{\text{C}}}}-\text{NH}_2^c$	$\text{Ar}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NH}_2$	−1.5	27
HNO ₃	NO ₃ [−]	−1.4	10

(continued)

¹⁷ Cerfontain, H.; Koeberg-Telder, A.; Kruk, C. *Tetrahedron Lett.* **1975**, 3639.¹⁸ Arnett, E.M.; Wu, C.Y. *J. Am. Chem. Soc.* **1960**, 82, 5660; Koeberg-Telder, A.; Lambrechts, H.J.A.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1983**, 102, 293.¹⁹ Fischer, A.; Grigor, B.A.; Packer, J.; Vaughan, J. *J. Am. Chem. Soc.* **1961**, 83, 4208.²⁰ Arnett, E.M.; Wu, C.Y. *J. Am. Chem. Soc.* **1960**, 82, 4999.²¹ Boyd, R.H. *J. Phys. Chem.* **1963**, 67, 737.²² Arnett, E.M.; Quirk, R.P.; Burke, J.J. *J. Am. Chem. Soc.* **1970**, 92, 1260.²³ McTigue, P.T.; Sime, J.M. *Aust. J. Chem.* **1963**, 16, 592.²⁴ Deno, N.C.; Turner, J.O. *J. Org. Chem.* **1966**, 31, 1969.²⁵ Chandler, W.D.; Lee, D.G. *Can. J. Chem.* **1990**, 68, 1757.²⁶ For a discussion, see Campbell, M.L.; Waite, B.A. *J. Chem. Educ.* **1990**, 67, 386.²⁷ Grant, H.M.; McTigue, P.; Ward, D.G. *Aust. J. Chem.* **1983**, 36, 2211.

TABLE 8.1 (Continued)

Acid	Base	Approximate pK_a (relative to water) ^b	References
$\text{R}-\text{C}(\text{OH})^+\text{NH}_2^c$	$\text{R}-\text{C}(=\text{O})\text{NH}_2$	-0.5	27
Ar_2NH_2^+	Ar_2NH	1	22
HSO_4^-	SO_4^{2-}	1.99	28
HF	F^-	3.17	28
HONO	NO_2^-	3.29	28
ArNH_3^+	ArNH_2	3-5	29
ArNR_2H^+	ArNR_2	3-5	29
RCOOH	RCOO^-	4-5	29
HCOCH_2CHO	$\text{HO}\bar{\text{C}}\text{HCHO}$	5	30
H_2CO_3^d	HCO_3^-	6.35	28
H_2S	HS^-	7.00	28
ArSH	ArS^-	6-8	32
$\text{CH}_3\text{COCH}_2\text{COCH}_3^e$	$\text{CH}_3\text{CO}\bar{\text{C}}\text{HCOCH}_3$	9	30
HCN	CN^-	9.2	34
NH_4^+	NH_3	9.24	28
ArOH	ArO^-	8-11	35
RCH_2NO_2	RC^-HNO_2	10	36
R_3NH^+	R_3N	10-11	29
RNH_3^+	RNH_2	10-11	29
HCO_3^-	CO_3^{2-}	10.33	28
RSH	RS^-	10-11	32
R_2NH_2^+	R_2NH	11	29
$\text{N}\equiv\text{CCH}_2\text{C}\equiv\text{N}$	$\text{N}\equiv\text{C}\bar{\text{C}}\text{HC}\equiv\text{N}$	11	30,37
$\text{CH}_3\text{COCH}_2\text{COOR}$	$\text{CH}_3\text{CO}\bar{\text{C}}\text{HCOOR}$	11	30
$\text{CH}_3\text{SO}_2\text{CH}_2\text{SO}_2\text{CH}_3$	$\text{CH}_3\text{SO}_2\bar{\text{C}}\text{HSO}_2\text{CH}_3$	12.5	38
$\text{EtOOCCH}_2\text{COOEt}$	$\text{EtOOC}\bar{\text{C}}\text{HCOOEt}$	13	30
CH_3OH	CH_3O^-	15.2	39,40
H_2O	OH^-	15.74	41

²⁸ Bruckenstein, S.; Kolthoff, I.M. in Kolthoff, I.M.; Elving, P.J. *Treatise on Analytical Chemistry*, Vol. 1, pt. 1, Wiley, NY, **1959**, pp. 432-433.

²⁹ Brown, H.C.; McDaniel, D.H.; Häflinger, O. in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, **1955**, pp. 567-662.

³⁰ Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* **1953**, 75, 2439.

³¹ This value includes the CO_2 usually present. The value for H_2CO_3 alone is 3.9 in Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, **1973**.

³² Crampton, M.R. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, **1974**, pp. 396-410.

³³ See Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* **1993**, 115, 11705.

³⁴ Perrin, D.D. *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed., Pergamon, Elmsford, NY, **1982**.

³⁵ Rochester, C.H. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, p. 374.

³⁶ Cram, D.J. *Chem. Eng. News* **1963**, 41 (No. 33, Aug. 19), 94.

³⁷ Bowden, K.; Stewart, R. *Tetrahedron* **1965**, 21, 261.



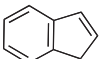
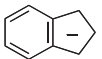
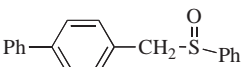
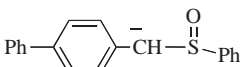
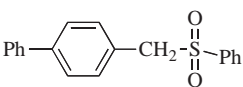
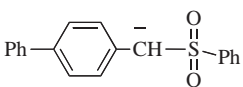
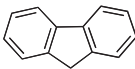
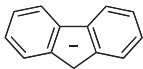
³⁸ Hine, J.; Philips, J.C.; Maxwell, J.I. *J. Org. Chem.* **1970**, 35, 3943. See also, Ang, K.P.; Lee, T.W.S. *Aust. J. Chem.* **1977**, 30, 521.

³⁹ Reeve, W.; Erikson, C.M.; Aluotto, P.F. *Can. J. Chem.* **1979**, 57, 2747.

⁴⁰ See also, Olmstead, W.N.; Margolin, Z.; Bordwell, F.G. *J. Org. Chem.* **1980**, 45, 3295.

⁴¹ Harned, H.S.; Robinson, R.A. *Trans. Faraday Soc.* **1940**, 36, 973.

TABLE 8.1 (Continued)

Acid	Base	Approximate pK_a (relative to water) ^b	References
		16	42
RCH ₂ OH	RCH ₂ O ⁻	16	39
RCH ₂ CHO	RCHCHO ⁻	16	43
R ₂ CHOH	R ₂ CHO ⁻	16.5	39
R ₃ COH	R ₃ CO ⁻	17	39
RCONH ₂	RCONH ⁻	17	44
RCOCH ₂ R	RCOCHR ⁻	19–20 ^f	46
		20	47,48
		20.08 ^a	49
		18.91 ^a	49
		23	47,48
ROOCCH ₂ R	ROOCCHR ⁻	24.5	30
RCH ₂ C≡N	RC ⁻ HC≡N	25	30,50
HC≡CH	HC≡CC ⁻	25	51
Ph ₂ NH	Ph ₂ N ⁻	24.95 ^g	45
EtOCOCH ₃	EtOCOCH ₂ ⁻	25.6	52
PhNH ₂	PhNH ⁻	30.6 ^g	45
Ar ₃ CH	Ar ₃ C ⁻	31.5	47,53
Ar ₂ CH ₂	Ar ₂ CH ⁻	33.5	47,48

(continued)

⁴² Streitwieser, Jr., A.; Nebenzahl, L. *J. Am. Chem. Soc.* **1976**, 98, 2188.⁴³ Guthrie, J.P.; Cossar, J. *Can. J. Chem.* **1986**, 64, 2470.⁴⁴ Homer, R.B.; Johnson, C.D. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 238–240.⁴⁵ The pK_a of acetone in DMSO is reported to be 26.5. See Bordwell, F.G.; Zhang, X.-M. *Accts. Chem. Res.* **1997**, 26, 510.⁴⁶ Guthrie, J.P.; Cossar, J.; Klym, A. *J. Am. Chem. Soc.* **1984**, 106, 1351; Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, 106, 460.⁴⁷ Streitwieser, Jr., A.; Ciuffarin, E.; Hammons, J.H. *J. Am. Chem. Soc.* **1967**, 89, 63.⁴⁸ Streitwieser, Jr., A.; Hollyhead, W.B.; Pudjaatmaka, H.; Owens, P.H.; Kruger, T.L.; Rubenstein, P.A.; MacQuarrie, R.A.; Brokaw, M.L.; Chu, W.K.C.; Niemeyer, H.M. *J. Am. Chem. Soc.* **1971**, 93, 5088.⁴⁹ Streitwieser, A.; Wang, G.P.; Bors, D.A. *Tetrahedron* **1997**, 53, 10103.⁵⁰ For a review of the acidity of cyano compounds, see Hibbert, F. in Patai, S.; Rappoport, Z. *The Chemistry of Triple-bonded Functional Groups*, pt. 1; Wiley, NY, **1983**, pp. 699–736.⁵¹ Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, **1965**, p. 19. See also, Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* **1966**, 88, 460.⁵² Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* **1996**, 118, 3129.⁵³ Streitwieser, Jr., A.; Hollyhead, W.B.; Sonnichsen, G.; Pudjaatmaka, H.; Chang, C.J.; Kruger, T.L. *J. Am. Chem. Soc.* **1971**, 93, 5096.

TABLE 8.1 (Continued)

Acid	Base	Approximate pK_a (relative to water) ^b	References
H ₂	H ⁻	35	54
NH ₃	NH ₂ ⁻	38	55
PhCH ₃	PhCH ₂ ⁻	40	56
CH ₂ =CHCH ₃	$\left[\text{H}_2\text{C}=\overset{\text{H}}{\text{C}}=\text{CH}_2 \right]^{-}$	43	57
PhH	Ph ⁻	43	58
CH ₂ =CH ₂	CH ₂ =CH ⁻	44	59
cyclo-C ₃ H ₆	cyclo-C ₃ H ₅ ⁻	46	60
CH ₄ ^h	CH ₃ ⁻	48	62
C ₂ H ₆	C ₂ H ₅ ⁻	50	63
(CH ₃) ₂ CH ₂ ^h	(CH ₃) ₂ CH ⁻	51	63
(CH ₃) ₃ CH ^h	(CH ₃) ₃ C ⁻		64

^aThe pK_a in THF.^bThe values in boldface are exact values; the others are approximate, especially >18 and < -2.⁶⁵^cSee Ref. 13.^dSee Ref. 31.^eSee Ref. 33.^fSee Ref. 45.^gThe pK_a in DMSO.^hSee Ref. 61.⁵⁴ Buncel, E.; Menon, B. *J. Am. Chem. Soc.* **1977**, 99, 4457.⁵⁵ Buncel, E.; Menon, B. *J. Organomet. Chem.* **1977**, 141, 1.⁵⁶ Albrecht, H.; Schneider, G. *Tetrahedron* **1986**, 42, 4729.⁵⁷ Boerth, D.W.; Streitwieser, Jr., A. *J. Am. Chem. Soc.* **1981**, 103, 6443.⁵⁸ Streitwieser, Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* **1972**, 94, 7936.⁵⁹ Streitwieser, Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* **1978**, 100, 755.⁶⁰ This value is calculated from results given in Streitwieser, Jr., A.; Caldwell, R.A.; Young, W.R. *J. Am. Chem. Soc.* **1969**, 91, 529. For a review of acidity and basicity of cyclopropanes, see Battiste, M.A.; Coxon, J.M. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, **1987**, pp. 255–305.⁶¹ See Daasbjerg, K. *Acta Chem. Scand. B* **1995**, 49, 878 for pK_a values of various hydrocarbons in DMF.⁶² This value is calculated from results given in Streitwieser, Jr., A.; Taylor, D.R. *J. Chem. Soc. D* **1970**, 1248.⁶³ These values are based on those given in Cram, D.J. *Chem. Eng. News* **1963**, 41 (No. 33, Aug. 19), 94, but are corrected to the newer scale of Streitwieser, A.; Streitwieser, Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* **1972**, 94, 7936; Streitwieser, Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* **1978**, 100, 755.⁶⁴ Breslow, R. and co-workers report a value of 71 (Breslow, R.; Grant, J.L. *J. Am. Chem. Soc.* **1977**, 99, 7745), but this was obtained by a different method, and is not comparable to the other values in Table 8.1. A more comparable value is 53. See also, Juan, B.; Schwarz, J.; Breslow, R. *J. Am. Chem. Soc.* **1980**, 102, 5741.⁶⁵ This table gives average values for functional groups. See Brown, H.C.; McDaniel, D.H.; Häflinger, O. in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, **1955**; Serjeant, E.P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution*, Pergamon, Elmsford NY, **1979**; Kortüm, G.; Vogel, W.; Andrussow, K. *Dissociation Constants of Organic Acids in Aqueous Solution*, Butterworth, London, **1961**. The index in the 1979 volume covers both volumes. Kortüm, G.; Vogel, W.; Andrussow, K. *Pure Appl. Chem.* **1960**, 1, 190; Arnett, E.M. *Prog. Phys. Org. Chem.* **1963**, 1, 223; Perrin, D.D. *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth, London, **1965**, and Supplement, 1972; Collumbeau, A. *Bull. Soc. Chim. Fr.* **1968**, 5087; Bordwell, F.G. *Acc. Chem. Res.* **1988**, 21, 456; Perrin, D.D. *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed., Pergamon, Elmsford NY, **1982**; *Pure Appl. Chem.* **1969**, 20, 133.⁶⁶ Gillespie, R.J. *Acc. Chem. Res.* **1968**, 1, 202.⁶⁷ For discussions of pK_a determinations for the conjugate acids of ketones, see Bagno, A.; Lucchini, V.; Scorrano, G. *Bull. Soc. Chim. Fr.* **1987**, 563; Toullec, J. *Tetrahedron Lett.* **1988**, 29, 5541.

The pK_a values are much harder to measure⁶⁸ for very strong and very weak acids, and these values must be regarded as approximate. If one did not have the pK_a values available, it can be determined experimentally that HClO_4 is a stronger acid than H_2SO_4 . A mixture of HClO_4 and H_2SO_4 in 4-methyl-2-pentanone can be titrated to an HClO_4 end point without interference by H_2SO_4 .⁶⁹ Similarly, HClO_4 can be shown to be stronger than HNO_3 or HCl . However, this is not quantitative, and the value of -10 in the table is not much more than an educated guess. The values for RNO_2H^+ , ArNO_2H^+ , HI , RCNH^+ and RSH_2^+ must also be regarded as highly speculative.⁷⁰ A wide variety of pK_a values have been reported for the conjugate acids of even such simple bases as acetone⁶⁷ (-0.24 to -7.2), diethyl ether (-0.30 to -6.2), ethanol (-0.33 to -4.8), methanol (-0.34 to -4.9), and 2-propanol (-0.35 to -5.2), depending on the method used to measure them.⁷¹ Very accurate values can be obtained only for acids weaker than hydronium ion and stronger than water.

A crystallographic scale of acidity has been developed, including the acidity of $\text{C}-\text{H}$ compounds. Measuring the mean $\text{C}-\text{H} \cdots \text{O}$ distances in crystal structures correlated well with conventional $pK_{a(\text{DMSO})}$ values,⁷² where DMSO is dimethyl sulfoxide. An *ab initio* study was able to correlate ring strain in strained hydrocarbons with hydrogen-bond acidity.⁷³ The kinetic acidity of aliphatic hydrocarbons has been determined.⁷⁴

The bottom portion of Table 8.1 consists of very weak acids (pK_a above that of water ≈ 15.8).⁷⁵ In most of these acids, the proton is lost from a carbon atom, and such acids are known as *carbon acids*. The pK_a values for such weak acids are often difficult to measure and are known only approximately. The methods used to determine the relative positions of these acids are discussed in Chapter 5.⁷⁶ The acidity of carbon acids is proportional to the stability of the carbanions that are their conjugate bases (see Sec. 5.B.i).

The extremely strong acids at the top of the table are known as *superacids* (see Sec. 5.A. ii).⁷⁷ The actual species present in the $\text{FSO}_3\text{H}-\text{SbF}_5$ mixture are probably $\text{H}[\text{SbF}_5(\text{SO}_3\text{F})]$

⁶⁸ For a review of methods of determining pK_a values, see Cookson, R.F. *Chem. Rev.* **1974**, *74*, 5.

⁶⁹ Kolthoff, I.M.; Bruckenstein, S. in Kolthoff, I.M.; Elving, P.J. *Treatise on Analytical Chemistry*, Vol. 1, pt. 1, Wiley, NY, **1959**, pp. 475–542, p. 479.

⁷⁰ For reviews of organic compounds protonated at O, N, or S, see Olah, G.A.; White, A.M.; O'Brien, D.H. *Chem. Rev.* **1970**, *70*, 561; Olah, G.A.; White, A.M.; O'Brien, D.H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, **1973**, pp. 1697–1781.

⁷¹ Rochester, C.H. *Acidity Functions*, Academic Press, NY, **1970**. For discussion of the basicity of such compounds, see Liler, M. *Reaction Mechanisms in Sulfuric Acid*, Academic Press, NY, **1971**, pp. 118–139.

⁷² Pedireddi, V.R.; Desiraju, G.R. *J. Chem. Soc. Chem. Commun.* **1992**, 988.

⁷³ Alkorta, I.; Campillo, N.; Rozas, I.; Elguero, J. *J. Org. Chem.* **1998**, *63*, 7759.

⁷⁴ Streitwieser, A.; Keevil, T.A.; Taylor, D.R.; Dart, E.C. *J. Am. Chem. Soc.* **2005**, *127*, 9290.

⁷⁵ See Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Pergamon, NY, **1978**; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, **1965**, pp. 1–45; Streitwieser, Jr., A.; Hammons, J.H. *Prog. Phys. Org. Chem.* **1965**, *3*, 41; Wiberg, K.B. *J. Org. Chem.* **2002**, *67*, 1613.

⁷⁶ See Jones, J.R. *Q. Rev. Chem. Soc.* **1971**, *25*, 365; Fischer, H.; Rewicki, D. *Prog. Org. Chem.* **1968**, *7*, 116; Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Chapter 1, Pergamon, NY, **1978** (an earlier version of this chapter appeared in *Russ. Chem. Rev.* **1974**, *43*, 17); Gau, G.; Assadourian, L.; Veracini, S. *Prog. Phys. Org. Chem.* **1987**, *16*, 237; in Buncl, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, **1980**, the reviews by Pellerite, M.J.; Brauman, J.I. pp. 55–96 (gas-phase acidities); and Streitwieser, Jr., A.; Juaristi, E.; Nebenzahl, L. pp. 323–381.

⁷⁷ See Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids*, Wiley, NY, **1985**; Gillespie, R.J.; Peel, T.E. *Adv. Phys. Org. Chem.* **1971**, *9*, 1; Arata, K. *Adv. Catal.* **1990**, *37*, 165. For a review of methods of measuring superacidity, see Jost, R.; Sommer, J. *Rev. Chem. Intermed.* **1988**, *9*, 171.

and $\text{H}[\text{SbF}_2(\text{SO}_3\text{F})_4]$.⁶⁶ The addition of SO_3 causes formation of the still stronger $\text{H}[\text{SbF}_4(\text{SO}_3\text{F})_2]$, $\text{H}[\text{SbF}_3(\text{SO}_3\text{F})_3]$, and $\text{H}[(\text{SbF}_5)_2(\text{SO}_3\text{F})]$.⁶⁶ There is a study of electrophilic intermediates that are generated in superacids⁷⁸ (also see Chapter 10).

By the use of tables (e.g., Table 8.1), it is possible to determine whether a given acid will react with a given base to give reasonable concentrations of the conjugate acid and base. For tables in which acids are listed in order of decreasing strength, the rule is that *any acid will react with any base in the table that is below it but not with any above it*.⁷⁹ The greater the separation in the table, the better the reaction. It must be emphasized that the order of acid strength in Table 8.1 separation applies when a given acid and base react without a solvent or, when possible, in water. In other solvents, the order may be greatly different (see Sec. 8.G). In the gas phase, where solvation effects are completely or almost completely absent, acidity orders may also differ greatly.⁸⁰ For example, in the gas phase, toluene is a stronger acid than water and *tert*-butoxide ion is a weaker base than methoxide ion⁸¹ (see also Sec. 8.G). It is also possible for the acidity order to change with temperature. For example, $>50^\circ\text{C}$ the order of base strength is $\text{BuOH} > \text{H}_2\text{O} > \text{Bu}_2\text{O}$; from 1 to 50°C the order is $\text{BuOH} > \text{Bu}_2\text{O} > \text{H}_2\text{O}$; while $<1^\circ\text{C}$ the order becomes $\text{Bu}_2\text{O} > \text{BuOH} > \text{H}_2\text{O}$.⁸²

8.A.ii. Brønsted Bases

Basicity may be measured by a parameter known as proton affinity of an anion. The dissociation of a hydrogen ion for a molecule in the gas phase is called the *proton affinity* of the conjugate base.⁸³ A hydrogen-bond basicity scale has been developed that can be used to determine the relative basicity of molecules. Table 8.2 gives the $\text{p}K_{\text{HB}}$ values for several common heteroatom-containing molecules.⁸⁴ This is obtained from the protonated form (conjugated acid) of the base in question. The larger the number, the more basic is that compound. The basicity of aliphatic amines has been calculated,⁸⁵ the ion-pair basicity of amines in THF ⁸⁶ and in water⁸⁷ has been determined, and the basicity of pyridine was examined.⁸⁸ There are secondary deuterium isotope effects for measuring the basicity of secondary amines, and deuteration was found to increase the basicity.⁸⁹ Weaker bases have

⁷⁸ Prakash, G.K.S. *J. Org. Chem.* **2006**, *71*, 3661.

⁷⁹ These reactions are equilibria. What the rule actually says is that the position of equilibrium will be such that the weaker acid predominates. However, this needs to be taken into account only when the acid and base are close to each other in the table (within ~ 2 pK units).

⁸⁰ See Gal, J.; Maria, P. *Prog. Phys. Org. Chem.* **1990**, *17*, 159.

⁸¹ Bohme, D.K.; Lee-Ruff, E.; Young, L.B. *J. Am. Chem. Soc.* **1972**, *94*, 4608, 5153.

⁸² Gerrard, W.; Macklen, E.D. *Chem. Rev.* **1959**, *59*, 1105. For other examples, see Calder, G.V.; Barton, T.J. *J. Chem. Educ.* **1971**, *48*, 338; Hambly, A.N. *Rev. Pure Appl. Chem.* **1965**, *15*, 87, p. 88.

⁸³ Tal'Rose, V.L.; Frankevitch, E.L. *J. Am. Chem. Soc.* **1958**, *80*, 2344; DeKock, R.L. *J. Am. Chem. Soc.* **1975**, *97*, 5592; McDaniel, D.H.; Coffman, N.B.; Strong, J.M. *J. Am. Chem. Soc.* **1970**, *92*, 6697. For a computational study of the proton affinities of ketones, vicinal diketones and α -keto esters, see Taskinen, A.; Nieminen, V.; Toukonniitty, E.; Murzin, D.Yu.; Hotokka, M. *Tetrahedron* **2005**, *61*, 8109.

⁸⁴ For measurement of amine basicity via ion pair stability in ionic liquids (Sec. 9.D.iii), see D'Anna, F.; Renato Noto, R. *Tetrahedron* **2007**, *63*, 11681.

⁸⁵ Caskey, D.C.; Damrauer, R.; McGoff, D. *J. Org. Chem.* **2002**, *67*, 5098.

⁸⁶ Streitwieser, A.; Kim, H.-J. *J. Am. Chem. Soc.* **2000**, *122*, 11783; Garrido, G.; Koort, E.; Ràfols, C.; Bosch, E.; Rodima, T.; Leito, I.; Rosés, M. *J. Org. Chem.* **2006**, *71*, 9062.

⁸⁷ Canle, L.M.; Demirtas, I.; Freire, A.; Maskill, H.; Mishima, M. *Eur. J. Org. Chem.* **2004**, 5031.

⁸⁸ Chmurzynski, L. *J. Heterocyclic Chem.* **2000**, *37*, 71.

⁸⁹ Perrin, C.L.; Ohta, B.K.; Kuperman, J.; Liberman, J.; Erdélyi, M. *J. Am. Chem. Soc.* **2005**, *127*, 9641.

TABLE 8.2 The pK_{HB} Values for Many Types of Bases

Base	Approximate pK_{HB}	Reference
<i>N</i> -Methyl-2-piperidone	2.60	90
Et ₂ NCONEt ₂	2.43	90
<i>N</i> -Methyl-2-pyrrolidinone	2.38	90
PhCONMe ₂	2.23	90
HCONMe ₂	2.10	90
PhCONHMe	2.03	90
18-crown-6	1.98	91
HCONHMe	1.96	90
Aniline	4.60	92
<i>N</i> -methylaniline	4.85	92
PhNHNH ₂	5.27	92
Ph(Me)NNH ₂	4.99	92
15-crown-5	1.82	91
12-crown-4	1.73	91
PhOCONMe ₂	1.70	90
Et ₂ N—CN	1.63	93
Me ₂ N—CN	1.56	93
δ-Valerolactone	1.43	94
Oxetane	1.36	91
γ-Butyrolactone	1.32	94
THF	1.28	91
Cyclopentanone	1.27	95
<i>t</i> -BuOMe	1.19	91
Acetone	1.18	95
MeCOOEt	1.07	95
1,4-Dioxane	1.03	91
Et ₂ O	1.01	91
1,3-Dioxane	0.93	91
1-Methyloxirane	0.97	91
PhCOOMe	0.89	94
MeOCOOMe	0.82	94
PhCHO	0.78	95
Bu ₂ O	0.75	91
HCOOEt	0.66	94
MeCHO	0.65	95
Me ₂ NO ₂	0.41	96
MeNO ₂	0.27	96
PhNO ₂	0.30	96
Furan	−0.40	91

⁹⁰ Le Questel, J.-Y.; Laurence, C.; Lachkar, A.; Helbert, M.; Berthelot, M. *J. Chem. Soc. Perkin Trans. 2* **1992**, 2091.

⁹¹ Berthelot, M.; Besseau, F.; Laurence, C. *Eur. J. Org. Chem.* **1998**, 925.

⁹² Korzhenevskaya, N.G.; Rybachenko, V.I.; Kovalenko, V.V.; Lyashchuk, S.N.; Red'ko, A.N. *Russ. J. Org. Chem.* **2007**, 43, 1475.

⁹³ Berthelot, M.; Helbert, M.; Laurence, C.; LeQuestel, J.-Y.; Anvia, F.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* **1993**, 625.

⁹⁴ Besseau, F.; Laurence, C.; Berthelot, M. *J. Chem. Soc. Perkin Trans. 2* **1994**, 485.

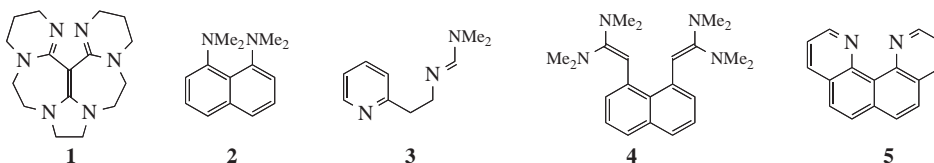
⁹⁵ Besseau, F.; Luçon, M.; Laurence, C.; Berthelot, M. *J. Chem. Soc. Perkin Trans. 2* **1998**, 101.

⁹⁶ Laurence, C.; Berthelot, M.; Luçon, M.; Morris, D.G. *J. Chem. Soc. Perkin Trans. 2* **1994**, 491.

also been examined, and the basicity of carbonyl compounds in carbon tetrachloride has been determined.⁹⁷ Alkenes are weak bases⁹⁸ that react with strong acids (e.g., HCl or HBr, Reaction **15-02**). Note that extremely twisted amides (Sec. 4.Q.ii) exhibit high basicity.⁹⁹

A class of organic compounds termed *superbases* has been developed.¹⁰⁰ Vinamidine type or *Schwesinger proton sponges* (see Sec. 8.F), **1**,¹⁰¹ are dubbed superbases and are probably the most powerful organic neutral bases known. The pK_a (pK_{BH}^+) in MeCN was measure as 31.94. It has been shown that the pK_a values of strong neutral organic (super) bases in acetonitrile are well described by the density functional theory.¹⁰² The fundamental type of proton sponge is 1,8-bis(dimethylamino)naphthalene (**2**, see Sec. 8.F), with a pK_{BH}^+ of 18.18.¹⁰³ Other superbase-type compounds include amidinazines [e.g., N^1, N^1 -dimethyl- N^2 -β-(2-pyridylethyl)-formamidine (**3**)], pK_{BH}^+ in DMSO = 25.1,¹⁰⁴ 1,8-bis(tetramethylguanidino)naphthalene, (**4**),¹⁰⁵ and quinolino[7,8-*h*]quinolines (e.g., **5**) with a pK_{BH}^+ = 12.8.¹⁰⁶

It is important to note that organometallic compounds, such as *Grignard reagents* (RMgX) and organolithium reagents (RLi),¹⁰⁷ are powerful bases. The conjugate bases of both of these bases are alkanes, (R—H), which are very weak acids indeed (see Table 8.1).



⁹⁷ Carrasco, N.; González-Nilo, F.; Rezende, M.C. *Tetrahedron* **2002**, 58, 5141.

⁹⁸ A new scale of π -basicity is proposed. See Stoyanov, E.S.; Stoyanova, I.V.; Reed, C.A. *Chemistry: European J.* **2008**, 14, 7880.

⁹⁹ Ly, T.; Krout, M.; Pham, D.K.; Tani, K.; Stoltz, B.M.; Julian, R.R. *J. Am. Chem. Soc.* **2007**, 129, 1864.

¹⁰⁰ For calculated basicities of super bases see Glasovac, Z.; Eckert-Maksić, M.; Maksić, Z.B. *New J. Chem.*, **2009**, 33, 588.

¹⁰¹ Schwesinger, R.; Mißfeldt, M.; Peters, K.; von Schnering, H.G. *Angew. Chem. Int. Ed.* **1987**, 26, 1165; Schwesinger, R.; Schlemper, H.; Hasenfratz, Ch.; Willaredt, J.; Dimbacher, T.; Breuer, Th.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H.W.; Bordwell, F.G.; Satish, A.V.; Ji, G.Z.; Peters, E.-M.; Peters, K.; von Schnering, H.G. *Liebigs Ann.* **1996**, 1055.

¹⁰² Kovačević, B.; Maksić, Z.B. *Org. Lett.* **2001**, 3, 1523.

¹⁰³ Alder, R.W.; Bowman, P.S.; Steele, W.R.S.; Winterman, D.R. *Chem. Commun.* **1968**, 723; Alder, R.W. *Chem. Rev.* **1989**, 89, 1215.

¹⁰⁴ Raczynska, E.D.; Darowska, M.; Dabkowska, I.; Decouzon, M.; Gal, J.-F.; Maria, P.-C.; Poliart, C.D. *J. Org. Chem.* **2004**, 69, 4023.

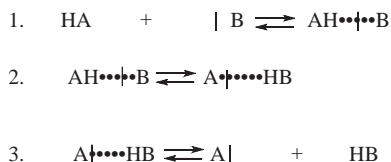
¹⁰⁵ Raab, V.; Kipke, J.; Gschwind, R.M.; Sundermeyer, J. *Chem. Eur. J.* **2002**, 8, 1682.

¹⁰⁶ Krieger, C.; Newsom, I.; Zirnstein, M.A.; Staab, H.A. *Angew. Chem. Int. Ed.* **1989**, 28, 84.

¹⁰⁷ Gorecka-Kobylnska, J.; Schlosser, M. *J. Org. Chem.* **2009**, 74, 222.

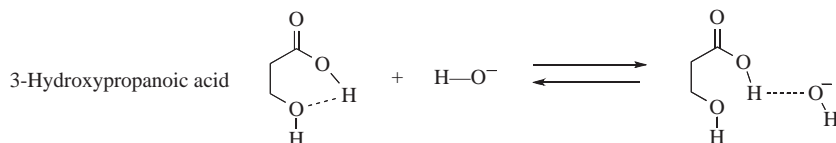
8.B. THE MECHANISM OF PROTON-TRANSFER REACTIONS

Proton transfers between a base and an oxygen or nitrogen acid are usually extremely fast.¹⁰⁸ Such reactions are generally diffusion controlled in the thermodynamically favored direction.¹⁰⁹ In fact, a *normal acid* is defined¹¹⁰ as one whose proton-transfer reactions are completely diffusion controlled, except when the conjugate acid of the base to which the proton is transferred has a *pK* value very close (differs by less than ~ 2 *pK* units) to that of the acid. The normal acid–base reaction mechanism consists of three steps:



The actual proton transfer takes place in the second step the first step is formation of a hydrogen-bonded complex. The product of the second step is another hydrogen-bonded complex, which dissociates in the third step.

However, not all such proton transfers are diffusion controlled. For example, if an internal hydrogen bond exists in a molecule, reaction with an external acid or base is often much slower.¹¹¹ In a case such as 3-hydroxypropanoic acid, the OH^- ion can form a hydrogen bond with the acidic hydrogen only if the internal hydrogen bond breaks. Therefore only some of the collisions between OH^- ions and 3-hydroxypropanoic acid molecules result in proton transfer. In many collisions, the OH^- ions will come away “empty-handed”, resulting in a lower reaction rate. Note that this affects only the rate, not the equilibrium. Other systems are capable of hydrogen bonding (e.g., 1,2-diols). In the case of cyclohexane-1,2-diols, hydrogen bonding, ion–dipole interactions, polarizability, and stereochemistry all play a role in determining the acidity.¹¹² The presence of halogen atoms (e.g., chlorine) can lead to hydrogen-bonding effects.¹¹³ Another factor that can create lower rates is a molecular structure in which the acidic proton is protected within a molecular cavity (e.g., the in–in and out–in isomers shown in Sec. 4.L). See also the proton sponges mentioned in Section 8.F. Proton transfers between an acidic and a basic group within the same molecule can also be slow, if the two groups are too far apart for hydrogen bonding. In such cases, participation of solvent molecules may be necessary.



¹⁰⁸ For reviews of such proton transfers, see Hibbert, F. *Adv. Phys. Org. Chem.* **1986**, 22, 113; Crooks, J.E. in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8; Elsevier, NY, **1977**, pp. 197–250. See Bernasconi, C.F.; Fairchild, D.E.; Montañez, R.L.; Aleshi, P.; Zheng, H.; Lorange, E. *J. Org. Chem.* **2005**, 70, 7721.

¹⁰⁹ See Eigen, M. *Angew. Chem. Int. Ed.* **1964**, 3, 1.

¹¹⁰ See, for example, Hojatti, M.; Kresge, A.J.; Wang, W. *J. Am. Chem. Soc.* **1987**, 109, 4023.

¹¹¹ See Ritchie, C.D.; Lu, S. *J. Am. Chem. Soc.* **1989**, 111, 8542.

¹¹² Chen, X.; Walthall, D.A.; Brauman, J.I. *J. Am. Chem. Soc.* **2004**, 126, 12614.

¹¹³ Abraham, M. H.; Enomoto, K.; Clarke, E. D.; Sexton, G. *J. Org. Chem.* **2002**, 67, 4782.

Proton transfers to or from a carbon atom¹¹⁴ in most cases are much slower than those strictly between oxygen or nitrogen atoms. At least three factors can be responsible for this,¹¹⁵ not all of them applying in every case.

1. Hydrogen bonding is very weak or altogether absent for carbon (Chap 3).
2. Loss of a proton from many carbon acids leads to carbanions that are stabilized by resonance. Calculations show that carbon acidity is influenced by coordination based on electrophile coordination geometry.¹¹⁶ Structural reorganization (movement of atoms to different positions within the molecule) may accompany this process. Chloroform, HCN, and 1-alkynes do not form resonance-stabilized carbanions, and these¹¹⁷ behave kinetically as normal acids.¹¹⁸ It has been reported that carborane acids [e.g., H(CHB₁₁H₅Cl₆)] are the strongest isolable (Lewis-free) Brønsted acids known.¹¹⁹
3. There may be considerable reorganization of solvent molecules around the ion as compared to the neutral molecule.¹²⁰

In connection with factors 2 and 3, it has been proposed¹¹⁵ that any factor that stabilizes the product (e.g., by resonance or solvation) lowers the rate constant if it develops late on the reaction coordinate, but increases the rate constant if it develops early. This is called the *Principle of Imperfect Synchronization*.

Mechanisms of proton transfer have been studied for many compounds, including the reactions of acids with lactams,¹²¹ amides with various bases,¹²² and amines with alkoxide bases.¹²³

8.C. MEASUREMENTS OF SOLVENT ACIDITY¹²⁴

When a solute is added to an acidic solvent it may become protonated by the solvent. This effect can lead to an enhancement of acidity, as in the effect of using formic acid rather than methanol.¹²⁵ An acidity scale has been reported for ionic liquids¹²⁶ (see Sec. 9.D.iii for a discussion of ionic liquids), and the Lewis acidity of ionic liquids has been established

¹¹⁴ See Hibbert, F. in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8, Elsevier, NY, **1977**, pp. 97–196; Kreevoy, M.M. *Isot. Org. Chem.* **1976**, 2, 1; Leffek, K.T. *Isot. Org. Chem.* **1976**, 2, 89.

¹¹⁵ See Bernasconi, C.F. *Tetrahedron* **1985**, 41, 3219.

¹¹⁶ Houk, R.J.T.; Anslyn, E.V.; Stanton, J.F. *Org. Lett.* **2006**, 8, 3461.

¹¹⁷ Kresge, A.J.; Powell, M.F. *J. Org. Chem.* **1986**, 51, 822; Formosinho, S.J.; Gal, V.M.S. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1655.

¹¹⁸ Not all 1-alkynes behave as normal acids; see Aroella, T.; Arrowsmith, C.H.; Hojatti, M.; Kresge, A.J.; Powell, M.F.; Tang, Y.S.; Wang, W. *J. Am. Chem. Soc.* **1987**, 109, 7198.

¹¹⁹ Juhasz, M.; Hoffmann, S.; Stoyanov, E.; Kim, K.-C.; Reed, C.A. *Angew. Chem. Int. Ed.* **2004**, 43, 5352.

¹²⁰ See Kurz, J.L. *J. Am. Chem. Soc.* **1989**, 111, 8631.

¹²¹ Wang, W.; Cheng, P.; Huang, C.; Jong, Y. *Bull. Chem. Soc. Jpn.* **1992**, 65, 562.

¹²² Wang, W.-h.; Cheng, C.-c. *Bull. Chem. Soc. Jpn.* **1994**, 67, 1054.

¹²³ Lambert, C.; Hampel, F.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* **1992**, 31, 1209.

¹²⁴ For fuller treatments, see Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, **1970**, pp. 263–313; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, **1984**, pp. 83–93; Arnett, E.M.; Scorrano, G. *Adv. Phys. Org. Chem.* **1976**, 13, 83.

¹²⁵ Holt, J.; Karty, J.M. *J. Am. Chem. Soc.* **2003**, 125, 2797.

¹²⁶ Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* **2003**, 125, 5264.

using IR.¹²⁷ If the solvent is water and the concentration of solute is not very great, then the pH of the solution is a good measure of the proton-donating ability of the solvent. Unfortunately, this is no longer true in concentrated solutions because activity coefficients are no longer unity. A measurement of solvent acidity is needed that works in concentrated solutions and applies to mixed solvents as well. The *Hammett acidity function*¹²⁸ is a measurement that is used for acidic solvents of high dielectric constant.¹²⁹ For any solvent, including mixtures of solvents (but the proportions of the mixture must be specified), a value H_0 is defined as

$$H_0 = \text{p}K_{\text{BH}^+_{\text{w}}} - \log \frac{[\text{BH}^+]}{[\text{B}]}$$

H_0 is measured by using “indicators” that are weak bases (B) and so are partly converted, in these acidic solvents, to the conjugate acids BH^+ . Typical indicators are *o*-nitroanilinium ion, with a $\text{p}K$ in water of -0.29 , and 2,4-dinitroanilinium ion, with a $\text{p}K$ in water of -4.53 . For a given solvent, $[\text{BH}^+]/[\text{B}]$ is measured for one indicator, usually by spectrophotometric means and with the known $\text{p}K$ in water ($\text{p}K_{\text{BH}^+_{\text{w}}}$) for that indicator, H_0 can be calculated for that solvent system. In practice, several indicators are used, so that an average H_0 is taken. Once H_0 is known for a given solvent system, $\text{p}K_a$ values in it can be calculated for any other acid–base pair.

The symbol H_0 is defined as

$$h_0 = \frac{a_{\text{H}^+} f_{\text{I}}}{f_{\text{HI}^+}}$$

where a_{H^+} is the activity of the proton and f_{I} and f_{HI^+} are the activity coefficients of the indicator and conjugate acid of the indicator,¹³⁰ respectively. The parameter H_0 is related to H_0 by

$$H_0 = -\log h_0$$

so that H_0 is analogous to pH and H_0 to $[\text{H}^+]$, and indeed in dilute aq solution $H_0 = \text{pH}$.

The parameter H_0 reflects the ability of the solvent system to donate protons, but it can be applied only to acidic solutions of high dielectric constant, mostly mixtures of water with acids (nitric, sulfuric, perchloric, etc.). It is apparent that the H_0 treatment is valid only when $f_{\text{I}}/f_{\text{HI}^+}$ is independent of the nature of the base (the indicator). Since this is so only when the bases are structurally similar, the treatment is limited. Even when similar bases are compared, many deviations are found.¹³¹ Other acidity scales¹³² have been set up,

¹²⁷ Yang, Y.-l.; Kou, Y. *Chem. Commun.* **2004**, 226.

¹²⁸ Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* **1932**, 54, 2721.

¹²⁹ See Rochester, C.H. *Acidity Functions*, Academic Press, NY, **1970**; Cox, R.A.; Yates, K. *Can. J. Chem.* **1983**, 61, 2225; Boyd R.H. in Coetzee, J.F.; Ritchie, C.D. *Solute–Solvent Interactions*, Marcel Dekker, NY, **1969**, pp. 97–218.

¹³⁰ See Yates, K.; McClelland, R.A. *Prog. Phys. Org. Chem.* **1974**, 11, 323.

¹³¹ See Kreevoy, M.M.; Baughman, E.H. *J. Am. Chem. Soc.* **1973**, 95, 8178; García, B.; Leal, J.M.; Herrero, L.A.; Palacios, J.C. *J. Chem. Soc. Perkin Trans. 2* **1988**, 1759; Arnett, E.M.; Quirk, R.P.; Burke, J.J. *J. Am. Chem. Soc.* **1970**, 92, 1260.

¹³² For lengthy tables of many acidity scales, with references, see Cox, R.A.; Yates, K. *Can. J. Chem.* **1983**, 61, 2225. For an equation that is said to combine the vast majority of acidity functions, see Zalewski, R.I.; Sarkice, A.Y.; Geltz, Z. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1059.

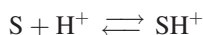
including a scale for C—H acids,¹³³ among them H_- for bases with a charge of -1 , H_R for aryl carbinols,¹³⁴ H_C for bases that protonate on carbon,¹³⁵ and H_A for unsubstituted amides.¹³⁶ It is now clear that there is no single acidity scale that can be applied to a series of solvent mixtures, irrespective of the bases employed.¹³⁷

Although most acidity functions have been applied only to acidic solutions, some work has also been done with strongly basic solutions.¹³⁸ The H_- function, which is used for highly acidic solutions when the base has a charge of -1 , can also be used for strongly basic solvents, in which case it measures the ability of these solvents to abstract a proton from a neutral acid (BH).¹³⁹ When a solvent becomes protonated, its conjugate acid is known as a *lyonium ion*.

Another approach to the acidity function problem was proposed by Bunnett et al.,¹⁴⁰ who derived the equation

$$\log \frac{[\text{SH}^+]}{[\text{S}]} + H_0 = \phi(H_0 + \log [\text{H}^+]) + \text{p}K_{\text{SH}^+}$$

where S is a base that is protonated by an acidic solvent. Thus the slope of a plot of $\log ([\text{SH}^+]/[\text{S}]) + H_0$ against $H_0 + \log [\text{H}^+]$ is the parameter ϕ , while the intercept is the $\text{p}K_a$ of the lyonium ion (SH^+ , referred to infinite dilution in water). The value of ϕ expresses the response of the equilibrium



to changing acid concentration. A negative ϕ indicates that the log of the ionization ratio $[\text{SH}^+]/[\text{S}]$ increases, as the acid concentration increases, more rapidly than $-H_0$. A positive ϕ value indicates the reverse. The *Bunnett–Olsen equation* given above is a linear free–energy relationship (see Sec. 9.C) that pertains to acid–base equilibria. A corresponding equation that applies to kinetic data is

$$\log k_\psi + H_0 = \Phi(H_0 + \log [\text{H}^+]) + \log k_2^0$$

where k_ψ is the pseudo-first-order rate constant for a reaction of a weakly basic substrate taking place in an acidic solution and k_2^0 is the second-order rate constant at infinite dilution in water. In this case, ϕ characterizes the response of the reaction rate to changing acid concentration of the solvent. The *Bunnett–Olsen treatment* has also been applied to basic media, where, in a group of nine reactions in concentrated NaOMe solutions, no correlation

¹³³ See Vianello, R.; Maksić, Z.B. *Eur. J. Org. Chem.* **2004**, 5003.

¹³⁴ Deno, N.C.; Berkheimer, H.E.; Evans, W.L.; Peterson, H.J. *J. Am. Chem. Soc.* **1959**, *81*, 2344.

¹³⁵ Reagan, M.T. *J. Am. Chem. Soc.* **1969**, *91*, 5506.

¹³⁶ Edward, J.T.; Wong, S.C. *Can. J. Chem.* **1977**, *55*, 2492; Liler, M.; Marković, D. *J. Chem. Soc. Perkin Trans. 2* **1982**, 551.

¹³⁷ Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, **1970**, p. 278; Rochester, C.H. *Acidity Functions*, Academic Press, NY, **1970**, p. 21.

¹³⁸ For another approach to solvent basicity scales, see Catalán, J.; Gómez, J.; Couto, A.; Laynez, J. *J. Am. Chem. Soc.* **1990**, *112*, 1678.

¹³⁹ See Rochester, C.H. *Q. Rev. Chem. Soc.* **1966**, *20*, 511; Rochester, C.H. *Acidity Functions*, Academic Press, NY, **1970**, pp. 234–264; Bowden, K. *Chem. Rev.* **1966**, *66*, 119.

¹⁴⁰ Bunnett, J.F.; McDonald, R.L.; Olsen, F.P. *J. Am. Chem. Soc.* **1974**, *96*, 2855.

was found between reaction rates and either H_- or stoichiometric base concentration, but where the rates were successfully correlated by a linear free energy equation similar to those given above.¹⁴¹

A treatment partially based on the *Bunnett–Olsen treatment* is that of Bagno et al.,¹⁴² which formulates medium effects (changes in acidity of solvent) on acid–base equilibria. An appropriate equilibrium is chosen as reference, and the acidity dependence of other reactions compared with it, by use of the linear free energy equation

$$\log \frac{K'}{K_0} = m^* \log \frac{K}{K_0}$$

where the K values are the equilibrium constants for the following: K for the reaction under study in any particular medium; K' for the reference reaction in the same medium; K_0 for the reaction under study in a reference solvent; K'_0 for the reference reaction in the same reference solvent; and m^* is the slope of the relationship [corresponding to $(1 - \phi)$ of the *Bunnett–Olsen treatment*]. This equation has been shown to apply to many acid–base reactions.

Another type of classification system was devised by Bunnett¹⁴³ for reactions occurring in moderately concentrated acid solutions. $\log k_\psi + H_0$ is plotted against $\log a_{\text{H}_2\text{O}}$, where k_ψ is the pseudo-first-order rate constant for the protonated species and $a_{\text{H}_2\text{O}}$ is the activity of water. Most such plots are linear or nearly so. According to Bunnett, the slope of this plot w tells something about the mechanism. Where w is between -2.5 and 0 , water is not involved in the rate-determining step; where w is between 1.2 and 3.3 , water is a nucleophile in the rate-determining step; where w is between 3.3 and 7 , water is a proton-transfer agent. These rules hold for acids in which the proton is attached to oxygen or nitrogen.

A new acidity scale has been developed based on calorimetric measurement of *N*-methylimidazole and *N*-methylpyrrole in bulk solvents.¹⁴⁴ A revised version of this method was shown to give better results in some cases.¹⁴⁵ Another scale of solvent acidities was developed based on the hydrogen-bond donor acidities in aq DMSO.¹⁴⁶ Note that bond energies, acidities, and electron affinities are related in a thermodynamic cycle, and Fattahi and Kass¹⁴⁷ show that by measuring two of these quantities the third can be found.

8.D. ACID AND BASE CATALYSIS¹⁴⁸

Many reactions are catalyzed by acids or bases. Some are catalyzed by both acids and bases. In such cases, the catalyst is involved in a fundamental way in the mechanism. The

¹⁴¹ More O'Ferrall, R.A. *J. Chem. Soc. Perkin Trans. 2* **1972**, 976.

¹⁴² Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* **1987**, 7, 313. See also, Cox, R.A. *Acc. Chem. Res.* **1987**, 20, 27.

¹⁴³ Bunnett, J.F. *J. Am. Chem. Soc.* **1961**, 83, 4956, 4968, 4973, 4978.

¹⁴⁴ Catalán, J.; Couto, A.; Gomez, J.; Saiz, J.L.; Laynez, J. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1181.

¹⁴⁵ Abraham, M.H.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* **1993**, 305.

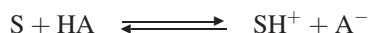
¹⁴⁶ Liu, P.C.; Hoz, S.; Buncel, E. *Gazz. Chim. Ital.* **1996**, 126, 31. See also, Abraham, M.H.; Zhao, Y.J. *J. Org. Chem.* **2004**, 69, 4677.

¹⁴⁷ Fattahi, A.; Kass, S.R. *J. Org. Chem.* **2004**, 69, 9176.

¹⁴⁸ See Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, **1985**, pp. 251–305; Willi, A.V. in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8, Elsevier, NY, **1977**, pp. 1–95; Jones, R.A. Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, **1984**, pp. 72–82; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, **1971**, pp. 19–144.

first step of such a reaction is nearly always a proton transfer between the catalyst and the substrate.

Reactions can be catalyzed by acid or base in two different ways, called *general* and *specific catalysis*. If the rate of an acid-catalyzed reaction run in a solvent (S) is proportional to its conjugate acid [SH⁺], the reaction is said to be subject to *specific acid catalysis*, the acid being the lyonium ion (SH⁺). The acid that is put into the solvent may be stronger or weaker than SH⁺, but the rate is proportional only to the [SH⁺] that is actually present in the solution derived from the equilibrium



The identity of HA is important only to the extent that it determines the position of equilibrium, and hence the [SH⁺]. Most measurements have been made in water, where SH⁺ is H₃O⁺.

In *general acid catalysis*, the rate is increased not only by an increase in [SH⁺], but also by an increase in the concentration of other acids (e.g., in water by phenols or carboxylic acids). These other acids increase the rate even when [SH⁺] is held constant. In this type of catalysis the strongest acids catalyze best, so that, in the example given, an increase in the phenol concentration catalyzes the reaction much less than a similar increase in [H₃O⁺]. This relationship between acid strength of the catalyst and its catalytic ability can be expressed by the *Brønsted catalysis equation*¹⁴⁹

$$\log k = \alpha \log K_{\alpha} + C$$

where k is the rate constant for a reaction catalyzed by an acid of ionization constant K_{α} . According to this equation, when $\log k$ is plotted against $\log K_{\alpha}$ for catalysis of a given reaction by a series of acids, a straight line should be obtained with slope and intercept C . Straight lines are obtained in many cases, but not always. The relationship usually fails when acids of different types are compared. For example, it is much more likely to hold for a group of substituted phenols than for a collection of acids that contains both phenols¹⁵⁰ and carboxylic acids. The Brønsted equation is another linear free energy relationship (see Sec. 9.C).

Analogously, there are *general* and *specific* (S[−] from an acidic solvent SH) *base-catalyzed reactions*. The Brønsted law for bases is

$$\log k = \beta \log K_b + C$$

The Brønsted equations relate a rate constant k to an equilibrium constant K_e . In Chapter 6, the *Marcus equation* was seen to relate a rate term (in that case ΔG^{\ddagger}) to an equilibrium term (ΔG°). When the Marcus treatment is applied to proton transfers¹⁵¹ between a carbon and an oxygen (or a nitrogen), the simplified¹⁵² equation (Sec. 6.I)

$$\Delta G^{\ddagger} = \Delta G_{\text{int}}^{\ddagger} + \frac{1}{2} \Delta G^{\circ} + \frac{(\Delta G^{\circ})^2}{16 \Delta G_{\text{int}}^{\ddagger}}$$

¹⁴⁹ See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, **1982**, pp. 167–179; Bell, R.P. in Chapman, N. B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum Press, **1978**, pp. 55–84; Kresge, A.J. *Chem. Soc. Rev.* **1973**, 2, 475.

¹⁵⁰ See Silva, P.J. *J. Org. Chem.* **2009**, 74, 914.

¹⁵¹ See Marcus, R.A. *J. Phys. Chem.* **1968**, 72, 891; Kresge, A.J. *Chem. Soc. Rev.* **1973**, 2, 475.

¹⁵² Omitting the work terms.

where

$$\Delta G_{\text{int}}^{\ddagger} = \frac{1}{2} (\Delta G_{\text{O},\text{O}}^{\ddagger} + \Delta G_{\text{C},\text{C}}^{\ddagger})$$

can be further simplified: Because proton transfers between oxygen and oxygen (or nitrogen and nitrogen) are much faster than those between carbon and carbon, $\Delta G_{(\text{O},\text{O})}^{\ddagger}$ is much smaller than $\Delta G_{(\text{C},\text{C})}^{\ddagger}$ and one can write¹⁵³

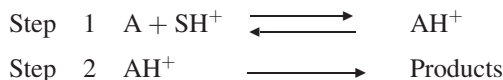
$$\Delta G^{\ddagger} = \frac{1}{2} \Delta G_{\text{C},\text{C}}^{\ddagger} + \frac{1}{2} \Delta G^{\circ} + \frac{(\Delta G^{\circ})^2}{8 \Delta G_{\text{C},\text{C}}^{\ddagger}}$$

Thus, if the carbon part of the reaction is kept constant and only the A of HA is changed (where A is an oxygen or nitrogen moiety), then ΔG^{\ddagger} is dependent only on ΔG° . Differentiation of this equation yields the Brønsted α :

$$\frac{d\Delta G^{\ddagger}}{d\Delta G^{\circ}} = \alpha = \frac{1}{2} \left(1 + \frac{\Delta G^{\circ}}{2 \Delta G_{\text{C},\text{C}}^{\ddagger}} \right)$$

The *Brønsted law* is therefore a special case of the *Marcus equation*.

A knowledge of whether a reaction is subject to general or specific acid catalysis supplies information about the mechanism. For any acid-catalyzed reaction we can write



If the reaction is catalyzed only by the specific acid SH^+ , it means that step 1 is rapid and step 2 is rate controlling. This means that an equilibrium has been rapidly established between A and the strongest acid present in the solution, namely, SH^+ (since this is the strongest acid that can be present in S). On the other hand, if step 2 is faster, there is no time to establish equilibrium and the rate-determining step must be step 1. This step is affected by all the acids that may be present, and the rate reflects the sum of the effects of each acid (general acid catalysis). General acid catalysis is also observed if the slow step is the reaction of a hydrogen-bond complex ($\text{A} \cdots \text{HB}$), since each complex reacts with a base at a different rate. A comparable discussion can be used for general and specific base catalysis.¹⁵⁴ Further information can be obtained from the values α and β in the Brønsted catalysis equations, since these are approximate measures of the extent of proton transfer in the transition state. In most cases, values of α and β are between 1 and 0. A value of α or β near 0 is generally taken to mean that the transition state resembles the reactants; that is, the proton has been transferred very little when the transition state has been reached. A value of α or β near 1 is taken to mean the opposite; that is, in the transition state the proton has been almost completely transferred. However, cases are known in which these generalizations are not followed,¹⁵⁵ and their theoretical basis has been challenged.¹⁵⁶ In general, the proton in the transition state lies closer to the weaker base.

¹⁵³ Albery, W.J. *Annu. Rev. Phys. Chem.* **1980**, 31, 227, p. 244.

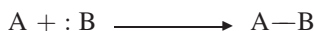
¹⁵⁴ See Jencks, W.P. *Acc. Chem. Res.* **1976**, 9, 425; Stewart, R.; Srinivasan, R. *Acc. Chem. Res.* **1978**, 11, 271; Guthrie, J.P. *J. Am. Chem. Soc.* **1980**, 102, 5286.

¹⁵⁵ See Agmon, N. *J. Am. Chem. Soc.* **1980**, 102, 2164; Murray, C.J.; Jencks, W.P. *J. Am. Chem. Soc.* **1988**, 110, 7561.

¹⁵⁶ Pross, A.; Shaik, S.S. *New J. Chem.* **1989**, 13, 427; Lewis, E.S. *J. Phys. Org. Chem.* **1990**, 3, 1.

8.E. LEWIS ACIDS AND BASES

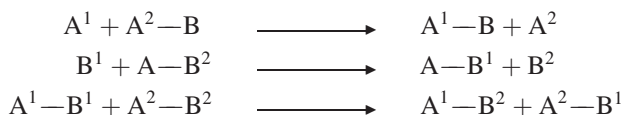
At about the same time that Brønsted proposed his acid–base theory, Lewis put forth a broader theory. A base in the Lewis theory is the same as in the Brønsted one, namely, a compound with an available pair of electrons, either unshared or in a π orbital. However, a *Lewis base* donates electrons to an atom other than H or C.¹⁵⁷ A *Lewis acid* is any species with a vacant orbital.¹⁵⁸ In a Lewis acid–base reaction, the unshared pair of the base forms a covalent bond with the vacant orbital of the acid, as represented by the general equation



in which charges are not shown, since they may differ. A specific example is



In the Brønsted picture, the acid is a proton donor, but in the Lewis picture the proton itself is the acid since it has a vacant orbital. A Brønsted acid becomes, in the Lewis picture, the compound that gives up the actual acid. The advantage of the Lewis theory is that it correlates the behavior of many more processes. For example, AlCl_3 and BF_3 are Lewis acids because they have only six electrons in the outer shell and have room for eight. Lewis acids SnCl_4 and SO_3 have eight, but their central elements, not being in the first row of the periodic table, have room for 10 or 12. Other Lewis acids are simple cations, like Ag^+ . The simple reaction $A + \bar{B} \longrightarrow A-B$ is not very common in organic chemistry, but the scope of the Lewis picture is much larger because reactions of the types shown here, which are very common in organic chemistry, are also Lewis acid–base reactions. In fact, all reactions in which a covalent bond is formed through one species contributing a filled and the other a vacant orbital may be regarded as Lewis acid–base reactions. An *ab initio* analysis of the factors that determine Lewis versus Lowry–Brønsted acidity–basicity is available.¹⁵⁹



When a Lewis acid combines with a base to give a negative ion in which the central atom has a higher than normal valence, the resulting salt is called an *ate complex*.¹⁶⁰ Examples are



¹⁵⁷ Lewis bases are useful catalysts in organic synthesis. See Denmark, S.E.; Beutner, G.L. *Angew. Chem. Int. Ed.* **2008**, 47, 1560.

¹⁵⁸ For a monograph on Lewis acid–base theory, see Jensen, W.B. *The Lewis Acid–Base Concept*, Wiley, NY, **1980**. For a discussion of the definitions of Lewis acid and base, see Jensen, W.B. *Chem. Rev.* **1978**, 78, 1.

¹⁵⁹ Rauk, A.; Hunt, I.R.; Keay, B.A. *J. Org. Chem.* **1994**, 59, 6808.

¹⁶⁰ For a review of ate complexes, see Wittig, G. *Q. Rev. Chem. Soc.* **1966**, 20, 191.

Ate complexes are analogous to the onium salts formed when a Lewis base expands its valence, for example,



Far fewer quantitative measurements have been made of Lewis acid strength compared to that of Brønsted acids.¹⁶¹ A simple table of Lewis acidities based on some quantitative measurement (e.g., that given for Brønsted acids in Table 8.1) is not feasible because Lewis acidity depends on the nature of the base and any solvent that can function as a base. For example, lithium perchlorate functions as a weak Lewis acid in ether.¹⁶² Qualitatively, the following approximate sequence of acidity of Lewis acids of the type MX_n has been suggested, where X is a halogen atom or an inorganic radical: $\text{BX}_3 > \text{AlX}_3 > \text{FeX}_3 > \text{GaX}_3 > \text{SbX}_5 > \text{SnX}_4 > \text{AsX}_5 > \text{ZnX}_2 > \text{HgX}_2$.

8.E.i Hard–Soft Acids–Bases

The facility with which an acid–base reaction takes place depends, of course, on the strengths of the acid and the base. But it also depends on quite another quality, called the *hardness*¹⁶³ or *softness* of the acid or base.¹⁶⁴ Hard and soft acids and bases have these characteristics:

Soft Bases. The donor atoms are of low electronegativity and high polarizability, and are easy to oxidize. They hold their valence electrons loosely.

Hard Bases. The donor atoms are of high electronegativity and low polarizability, and are hard to oxidize. They hold their valence electrons tightly.

Soft Acids. The acceptor atoms are large, have low positive charge, and contain unshared pairs of electrons (*p* or *d*) in their valence shells. They have high polarizability and low electronegativity.

Hard Acids. The acceptor atoms are small, have high positive charge, and do not contain unshared pairs in their valence shells. They have low polarizability and high electronegativity.

A qualitative listing of the hardness of some acids and bases is given in Table 8.3.¹⁶⁵ The treatment has also been made quantitative,¹⁶⁶ with the following operational

¹⁶¹ See Satchell, D.P.N.; Satchell, R.S. *Q. Rev. Chem. Soc.* **1971**, 25, 171; *Chem. Rev.* **1969**, 69, 251. See also, Sandström, M.; Persson, I.; Persson, P. *Acta Chem. Scand.* **1990**, 44, 653; Laszlo, P.; Teston-Henry, M. *Tetrahedron Lett.* **1991**, 32, 3837.

¹⁶² Springer, G.; Elam, C.; Edwards, A.; Bowe, C.; Boyles, D.; Bartmess, J.; Chandler, M.; West, K.; Williams, J.; Green, J.; Pagni, R.M.; Kabalka, G.W. *J. Org. Chem.* **1999**, 64, 2202.

¹⁶³ See Ayers, P.W.; Parr, R.G. *J. Am. Chem. Soc.* **2000**, 122, 2010.

¹⁶⁴ Pearson, R.G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, 89, 1827. For a monograph on the concept, see Ho, T. *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, NY, **1977**; Pearson, R.G. *J. Chem. Educ.* **1987**, 64, 561; Ho, T. *Tetrahedron* **1985**, 41, 1; Pearson, R.G. in Chapman, N.B.; Shorter, J. *Advances in Linear Free-Energy Relationships*, Plenum Press, NY, **1972**, pp. 281–319. For a collection of papers, see Pearson, R.G. *Hard and Soft Acids and Bases*, Dowden, Hutchinson, and Ross, Stroudsburg, PA, **1973**.

¹⁶⁵ Taken from Pearson, R.G. *J. Chem. Ed.* **1968**, 45, 581, 643.

¹⁶⁶ Pearson, R.G. *Inorg. Chem.* **1988**, 27, 734; *J. Org. Chem.* **1989**, 54, 1423. See also, Orsky, A.R.; Whitehead M. *A. Can. J. Chem.* **1987**, 65, 1970.

TABLE 8.3 Hard and Soft Acids and Bases^a

Hard Bases	Soft Bases	Borderline Cases
H ₂ O, OH ⁻ , F ⁻ AcO ⁻ , SO ₄ ²⁻ , Cl ⁻ CO ₃ ²⁻ , NO ₃ ⁻ , ROH RO ⁻ , R ₂ O, NH ₃ RNH ₂	R ₂ S, RSH, RS ⁻ , I ⁻ , R ₃ P, (RO) ₃ P, CN ⁻ , RCN, CO, C ₂ H ₄ , C ₆ H ₆ H ⁻ , R ⁻	ArNH ₂ , C ₅ H ₅ N N ₃ ⁻ , Br NO ₂ ⁻
Hard Acids	Soft Acids	Borderline Cases
H ⁺ , Li ⁺ , Na ⁺ K ⁺ , Mg ²⁺ , Ca ²⁺ Al ³⁺ , Cr ²⁺ , Fe ³⁺ BF ₃ , B(OR) ₃ , AlMe ₃ AlCl ₃ , AlH ₃ , SO ₃ RCO ⁺ HX (hydrogen-bonding molecules)	Cu ⁺ , Ag ⁺ , Pd ²⁺ Pt ²⁺ , Hg ²⁺ , BH ₃ GaCl ₃ , I ₂ , Br ₂ CH ₂ , Carbenes CO ₂	Fe ²⁺ , Co ²⁺ , Cu ²⁺ Zn ²⁺ , Sn ²⁺ , Sb ³⁺ Bi ³⁺ , BMe ₃ , SO ₂ R ₃ C ⁺ , NO ⁺ , GaH ₃ C ₆ H ₅ ⁺

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^aSee Ref. 165.

definition:

$$\eta = \frac{I - A}{2}$$

In this equation, η , the *absolute hardness*, is half the difference between I , the ionization potential, and A , the electron affinity.¹⁶⁷ The softness (σ), is the reciprocal of η . Values of η for some molecules and ions are given in Table 8.4.¹⁶⁸ Note that the proton, which is involved in all Brønsted acid–base reactions, is the hardest acid listed, with $\eta = \infty$ (it has no ionization potential). The above equation cannot be applied to anions, because electron affinities cannot be measured for them. Instead, the assumption is made that η for an anion X⁻ is the same as that for the radical X[•].¹⁶⁹ Other methods are also needed to apply the treatment to polyatomic cations.¹⁶⁹

Once acids and bases have been classified as hard or soft, a simple rule can be given: *hard acids prefer to bond to hard bases, and soft acids prefer to bond to soft bases [the HSAB (hard–soft acid–base) principle]*.¹⁷⁰ The rule has nothing to do with acid or base *strength* but merely says that the product A—B will have extra stability if both A and B are hard or if both are soft. Another rule is that a soft Lewis acid and a soft Lewis base tend to form a covalent bond, while a hard acid and a hard base tend to form ionic bonds.

One application of the first rule given above is found in complexes between alkenes or aromatic compounds and metal ions (see above). Alkenes and aromatic rings are soft bases and should prefer to complex with soft acids. Thus, Ag⁺, Pt²⁺, and Hg²⁺ complexes are common, but complexes of Na⁺, Mg²⁺, or Al³⁺ are rare. Chromium complexes are also common, but in such complexes the chromium is in a low or zero oxidation state (which

¹⁶⁷ See Sauers, R.R. *Tetrahedron* **1999**, 55, 10013.

¹⁶⁸ Parr, R.G.; Pearson, R.G. *J. Am. Chem. Soc.* **1983**, 105, 7512. Note that there is not always a strict correlation between the values in Table 8.4 and the categories of Table 8.3.

¹⁶⁹ Pearson, R.G. *J. Am. Chem. Soc.* **1988**, 110, 7684.

¹⁷⁰ For proofs of this principle, see Chattaraj, P.K.; Lee, H.; Parr, R.G. *J. Am. Chem. Soc.* **1991**, 113, 1855.

TABLE 8.4 Some Absolute Hardness Values in Electron Volts^a

Cations		Molecules		Anions ^b	
Ion	η	Compound	η	Ion	η
H ⁺	∞	HF	11.0	F ⁻	7.0
Al ³⁺	45.8	CH ₄	10.3	H ⁻	6.4
Li ⁺	35.1	BF ₃	9.7	OH ⁻	5.7
Mg ²⁺	32.6	H ₂ O	9.5	NH ₂ ⁻	5.3
Na ⁺	21.1	NH ₃	8.2	CN ⁻	5.1
Ca ²⁺	19.5	HCN	8.0	CH ₃ ⁻	4.9
K ⁺	13.6	(CH ₃) ₂ O	8.0	Cl ⁻	4.7
Zn ²⁺	10.9	CO	7.9	CH ₃ CH ₂ ⁻	4.4
Cr ³⁺	9.1	C ₂ H ₂	7.0	Br ⁻	4.2
Cu ²⁺	8.3	(CH ₃) ₃ N	6.3	C ₆ H ₅ ⁻	4.1
Pt ²⁺	8.0	H ₂ S	6.2	SH ⁻	4.1
Sn ²⁺	7.9	C ₂ H ₄	6.2	(CH ₃) ₂ CH ⁻	4.0
Hg ²⁺	7.7	(CH ₃) ₂ S	6.0	I ⁻	3.7
Fe ²⁺	7.2	(CH ₃) ₃ P	5.9	(CH ₃) ₃ C ⁻	3.6
Pd ²⁺	6.8	CH ₃ COCH ₃	5.6		
Cu ⁺	6.3	C ₆ H ₆	5.3		
		HI	5.3		
		C ₅ H ₅ N	5.0		
		C ₆ H ₅ OH	4.8		
		CH ₂ ^c	4.7		
		C ₆ H ₅ SH	4.6		
		Cl ₂	4.6		
		C ₆ H ₅ NH ₂	4.4		
		Br ₂	4.0		
		I ₂	3.4		

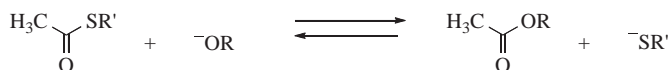
Reprinted with permission from Parr, R.G.; Pearson, R.G.; *J. Chem. Ed.* **1983**, 105, 7512. Copyright © 1983 American Chemical Society.

^aSee Ref. 168.

^bThe same as for the corresponding radical.

^cFor singlet state.

softens it) or attached to other soft ligands. Another application is the reaction:



The HSAB principle predicts that the equilibrium should lie to the right, because the hard acid CH_3CO^+ should have a greater affinity for the hard base (RO^-) than for the soft base (RS^-). Indeed, thiol esters are easily cleaved by RO^- or hydrolyzed by dilute base (^-OH is also a hard base).¹⁷¹ Another application of the rule is discussed in Section 10.G.ii.¹⁷² The

¹⁷¹ Wolman, Y. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, **1974**, p. 677; Maskill, H. *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford **1985**, p. 159.

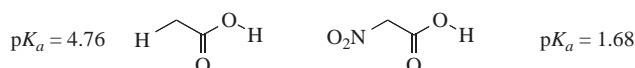
¹⁷² See also, Bochkov, A.F. *J. Org. Chem. USSR* **1986**, 22, 1830, 1837.

HSAB principles have been applied to analyze the reactivity of ketone and ester enolate anions,¹⁷³ and in analyzing catalyst selectivity in synthesis.¹⁷⁴

8.F. THE EFFECTS OF STRUCTURE ON THE STRENGTHS OF ACIDS AND BASES¹⁷⁵

The structure of a molecule can affect its acidity or basicity in a number of ways. Unfortunately, in most molecules two or more of these effects (as well as solvent effects) are operating, and it is usually very difficult or impossible to say how much each effect contributes to the acid or base strength.¹⁷⁶ Small differences in acidity or basicity between similar molecules are particularly difficult to interpret. It is well to be cautious when attributing them to any particular effect.

1. *Field Effects.* These effects were discussed in Section 1.I. In general, changes in substituents can have an effect on acidity. As an example of the influence of field effects on acidity, compare the acidity of acetic acid and 2-nitroacetic acid:



The only difference in the structure of these molecules is the substitution of NO₂ for H. Since NO₂ is a strongly electron-withdrawing group, it withdraws electron density from the negatively charged COO[−] group in the anion of 2-nitroacetic acid (compared with the anion of acetic acid). As the pK_a values indicate, 2-nitroacetic acid is ~1000 times stronger than acetic acid.¹⁷⁷ Any effect that results in electron withdrawal from a negatively charged center (−I effect) is a stabilizing effect because it spreads the charge. Thus, −I groups increase the acidity of uncharged acids (e.g., acetic) because they spread the negative charge of the anion. However, −I groups also increase the acidity of any acid, no matter what the charge. For example, if the acid has a charge of +1 (and its conjugate base is therefore uncharged), a −I group destabilizes the positive center (by increasing and concentrating the positive charge) of the acid, a destabilization that will be relieved when the proton is lost. In general, *groups that withdraw electrons by the field effect increase acidity and decrease basicity, while electron-donating groups act in the opposite direction.* Another example is the molecule (C₆F₅)₃CH, which has three strongly electron-withdrawing C₆F₅ groups and a pK_a of 16,¹⁷⁸ compared with

¹⁷³ Méndez, F.; Gázquez, J.L. *J. Am. Chem. Soc.* **1994**, *116*, 9298.

¹⁷⁴ Woodward, S. *Tetrahedron* **2002**, *58*, 1017.

¹⁷⁵ See Hine, J. *Structural Effects on Equilibria in Organic Chemistry*, Wiley, NY, **1975**; Taft, R.W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247; Petrov, E.S. *Russ. Chem. Rev.* **1983**, *52*, 1144 (NH acids); Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell Univ. Press, Ithaca, NY, **1973**, pp. 86–110. For a monograph on methods of estimating pK values by analogy, extrapolation, and so on, see Perrin, D.D.; Dempsey, B.; Serjeant, E.P. *pK_a Prediction for Organic Acids and Bases*, Chapman and Hall, NY, **1981**.

¹⁷⁶ The varying degrees by which the different factors that affect gas-phase acidities of 25 acids has been calculated: Taft, R.W.; Koppel, I.A.; Topsom, R.D.; Anvia, F. *J. Am. Chem. Soc.* **1990**, *112*, 2047.

¹⁷⁷ For a review of the enhancement of acidity by NO₂, see Lewis, E.S. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, **1982**, pp. 715–729.

¹⁷⁸ Filler, R.; Wang, C. *Chem. Commun.* **1968**, 287.

TABLE 8.5 The pK Values for Some Acids^a

Acid	pK	Acid	pK
HCOOH	3.77	ClCH ₂ COOH	2.86
CH ₃ COOH	4.76	Cl ₂ CHCOOH	1.29
CH ₃ CH ₂ COOH	4.88	Cl ₃ COOH	0.65
CH ₃ (CH ₂) _n COOH (n = 2–7)	4.82–4.95	O ₂ NCH ₂ COOH	1.68
(CH ₃) ₂ CHCOOH	4.86	(CH ₃) ₃ N ⁺ CH ₂ COOH	1.83
(CH ₃) ₃ CCOOH	5.05	HOOCCH ₂ COOH	2.83
		PhCH ₂ COOH	4.31
FCH ₂ COOH	2.66		
ClCH ₂ COOH	2.86	[−] OOCCH ₂ COOH	5.69
BrCH ₂ COOH	2.86		
ICH ₂ COOH	3.12	[−] O ₃ SCH ₂ COOH	4.05
		HOCH ₂ COOH	3.83
ClCH ₂ CH ₂ CH ₂ COOH	4.52	H ₂ C=CHCH ₂ COOH	4.35
CH ₃ CHClCH ₂ COOH	4.06		
CH ₃ CH ₂ CHClCOOH	2.84		

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^aSee Ref. 47.

Ph₃CH, with a pK_a of 31.5 (Table 8.1), an acidity enhancement of $\sim 10^{15}$. Table 8.5 shows pK_a values for some acids. An approximate idea of field effects can be obtained from this table. In the case of the chlorobutyric acids, the effect decreases with distance. It must be remembered, however, that field effects are not the sole cause of the acidity differences noted and that in fact solvation effects may be more important in many cases (see Sec. 8.G).¹⁷⁹ The influence of various substituents on the acidity of acetic acid has been calculated,¹⁸⁰ Substituent effects for weak acids (e.g., phenols and benzyl alcohols) have been discussed.¹⁸¹



Field effects are important in benzoic acid derivatives, and the pK_a of the acid will vary with the nature and placement of the “X” group in **6**.¹⁸² The pK_a of 3-OMe (**6**) is 5.55, but 4-OMe (**6**) is 6.02 in 50% aq methanol,¹⁸³ compared with a pK_a of 5.67 when X = H. When X = 4-NO₂, the pK_a is 4.76 and 4-Br is 5.36.¹⁷² The pK_a of 2,6-diphenylbenzoic acid is 6.39.¹⁸⁴

¹⁷⁹ See Edward, J.T. *J. Chem. Educ.* **1982**, 59, 354; Schwartz, L.M. *J. Chem. Educ.* **1981**, 58, 778.

¹⁸⁰ Headley, A.D.; McMurry, M.E.; Starnes, S.D. *J. Org. Chem.* **1994**, 59, 1863.

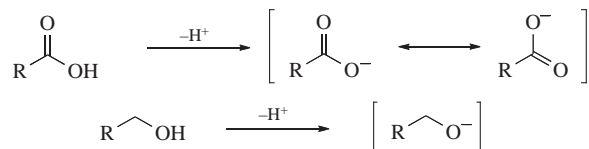
¹⁸¹ Wiberg, K.B. *J. Org. Chem.* **2003**, 68, 875.

¹⁸² For calculated gas-phase acidities of substituted benzoic acids see Wiberg, K.B. *J. Org. Chem.* **2002**, 67, 4787. Also see Gupta, K.; Giri, S.; Chattaraj, P.K. *New J. Chem.* **2008**, 32, 1945.

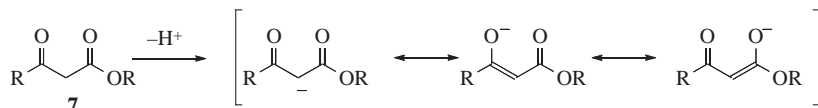
¹⁸³ DeMaria, P.; Fontana, A.; Spinelli, D.; Dell’Erba, C.; Novi, M.; Petrillo, G.; Sancassan, F. *J. Chem. Soc. Perkin Trans. 2* **1993**, 649.

¹⁸⁴ Chen, C.-T.; Siegel, J.S. *J. Am. Chem. Soc.* **1994**, 116, 5959. See also, Sotomatsu, T.; Shigemura, M.; Murata, Y.; Fujita, T. *Bull. Chem. Soc. Jpn.* **1992**, 65, 3157.

2. *Resonance Effects.* Resonance that stabilizes a base, but not its conjugate acid, results in the acid having a higher acidity than otherwise expected and vice versa. An example is found in the higher acidity of carboxylic acids¹⁸⁵ compared with primary alcohols.



The RCOO^- ion is stabilized by resonance not available to the RCH_2O^- ion (or to RCOOH).¹⁸⁶ Note that the RCOO^- is stabilized not only by the fact that there are 2 equiv canonical forms, but also by the fact that the negative charge is spread over both oxygen atoms, and is therefore less concentrated than in RCH_2O^- . The same effect is found in other compounds containing a $\text{C}=\text{O}$ or $\text{C}\equiv\text{N}$ group. Thus amides (RCONH_2) are more acidic than amines (RCH_2NH_2); esters ($\text{RCH}_2\text{COOR}'$) more than ethers ($\text{RCH}_2\text{CH}_2\text{OR}'$); and ketones ($\text{RCH}_2\text{COR}'$) more than alkanes ($\text{RCH}_2\text{CH}_2\text{R}'$) (Table 8.1). The effect is enhanced when two carbonyl groups are attached to the same carbon (because of additional resonance and spreading of charge); for example, β -keto esters (see **7**) are more acidic than simple ketones or carboxylic esters (Table 8.1). Compounds such as (**7**) are generically referred to as *active methylene compounds* ($\text{X}-\text{CH}_2-\text{X}$), where X is an electron-withdrawing group (a carbonyl, cyano, sulfonyl, etc.).¹⁸⁷ The influence of substituents in the α -position of substituted ethyl acetate derivatives has been studied.¹⁸⁸ Extreme examples of this effect are found in the molecules tricyanomethane $[(\text{NC})_3\text{CH}]$, with a $\text{p}K_a$ of -5 (Table 8.1), and 2-(dicyanomethylene)-1,1,3,3-tetracyanopropene $(\text{NC})_2\text{C}=\text{C}[\text{CH}(\text{CN})_2]_2$, whose first $\text{p}K_a$ is below -8.5 and whose second $\text{p}K_a$ is -2.5 .



Resonance effects are also important in aromatic amines. *m*-Nitroaniline is a weaker base than aniline, a fact that can be accounted for by the $-I$ effect of the nitro group. But *p*-nitroaniline is weaker still, though the $-I$ effect should be less because of the greater distance. This result is obtained by taking the canonical form **A** into account. Because **A** contributes to the resonance hybrid,¹⁸⁹ the electron density of

¹⁸⁵ See Exner, O.; Čárský, P. *J. Am. Chem. Soc.* **2001**, *123*, 9564. See also, Liptak, M.D.; Shields, G.C. *J. Am. Chem. Soc.* **2001**, *123*, 7314.

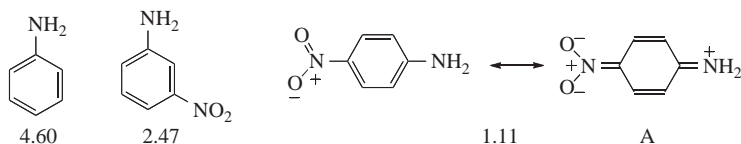
¹⁸⁶ It has been contended that resonance delocalization plays only a minor role in the increased strength of carboxylic acids compared to alcohols, and the "... higher acidity of acids arises principally because the electrostatic potential of the acidic hydrogens is more positive in the neutral acid molecule...": Siggel, M.R.; Streitwieser, Jr., A.; Thomas, T.D. *J. Am. Chem. Soc.* **1988**, *110*, 8022; Thomas, T.D.; Carroll, T.X.; Siggel, M.R. *J. Org. Chem.* **1988**, *53*, 1812. For contrary views, see Exner, O. *J. Org. Chem.* **1988**, *53*, 1810; Perrin, D.D. *J. Am. Chem. Soc.* **1991**, *113*, 2865. See also, Godfrey, M. *Tetrahedron Lett.* **1990**, *31*, 5181.

¹⁸⁷ Copper complexes of active methylene compounds show large $\text{p}K_a$ shifts. See Zhong, Z.; Postnikova, B.J.; Hanes, R.E.; Lynch, V.M.; Anslyn, E.V. *Chemistry: European J.* **2005**, *11*, 2385.

¹⁸⁸ Goumont, R.; Magnier, E.; Kizilian, E.; Terrier, F. *J. Org. Chem.* **2003**, *68*, 6566.

¹⁸⁹ See, however, Krygowski, T.M.; Maurin, J. *J. Chem. Soc. Perkin Trans. 2* **1989**, 695.

the unshared pair is lower in *p*-nitroaniline than in *m*-nitroaniline, where a canonical form (e.g., **A**) is impossible. Note that the pK_a values reported are those of the conjugate acid, the ammonium ion.¹⁹⁰ The basicity is lower in the para compound for two reasons, both caused by the same effect: (1) the unshared pair is less available for attack by a proton, and (2) when the conjugate acid is formed, the resonance stabilization afforded by **A** is no longer available because the previously unshared pair is now being shared by the proton. The acidity of phenols is affected by substituents in a similar manner.¹⁹¹



In general, resonance effects lead to the same result as field effects. That is, here too, electron-withdrawing groups increase acidity and decrease basicity, and electron-donating groups act in the opposite manner. As a result of both resonance and field effects, charge dispersal leads to greater stability.

3. *Periodic Table Correlations.* When comparing Brønsted acids and bases that differ in the position of an element in the periodic table:

- Acidity increases and basicity decreases in going from left to right across a row of the periodic table. Thus acidity increases in the order $\text{CH}_4 < \text{NH}_3 < \text{H}_2\text{O} < \text{HF}$, and basicity decreases in the order $^-\text{CH}_3 > ^-\text{NH}_2 > ^-\text{OH} > \text{F}^-$. This behavior can be explained by the increase in electronegativity upon going from left to right across the table. It is this effect that is responsible for the great differences in acidity between carboxylic acids, amides, and ketones: $\text{RCOOH} \gg \text{RCONH}_2 \gg \text{RCOCH}_3$.
- Acidity increases and basicity decreases in going down a column of the periodic table, despite the decrease in electronegativity. Thus acidity increases in the order $\text{HF} < \text{HCl} < \text{HBr} < \text{HI}$ and $\text{H}_2\text{O} < \text{H}_2\text{S}$, and basicity decreases in the order $\text{NH}_3 > \text{PH}_3 > \text{AsH}_3$. This behavior is related to the size of the species involved. Thus, for example, F^- , which is much smaller than I^- , attracts a proton much more readily because its negative charge occupies a smaller volume, and is therefore more concentrated (note that F^- is also much harder than I^- and is thus more attracted to the hard proton; see Sec. 8.E). This rule does not always hold for positively charged acids. Thus, although the order of acidity for the group 16 hydrides is $\text{H}_2\text{O} < \text{H}_2\text{S} < \text{H}_2\text{Se}$, the acidity order for the positively charged ions is $\text{H}_3\text{O}^+ > \text{H}_3\text{S}^+ > \text{H}_3\text{Se}^+$.¹⁹²

Lewis acidity is also affected by periodic table considerations. In comparing acid strengths of Lewis acids of the form MX_n ¹⁶¹:

- Acids that require only one electron pair to complete an outer shell are stronger than those that require two. Thus GaCl_3 is stronger than ZnCl_2 . This results from the relatively smaller energy gain in adding an electron pair that does not

¹⁹⁰ Smith, J.W. in Patai, S. *The Chemistry of the Amino Group*; Wiley, NY, **1968**, pp. 161–204.

¹⁹¹ Liptak, M.D.; Gross, K.C.; Seybold, P.G.; Feldus, S.; Shields, G.C. *J. Am. Chem. Soc.* **2002**, *124*, 6421.

¹⁹² Taft, R.W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247, see Sec. 5.B.i.

complete an outer shell and from the buildup of negative charge if two pairs come in.

- d. Other things being equal, the acidity of MX_n decreases in going down the periodic table because as the size of the molecule increases, the attraction between the positive nucleus and the incoming electron pair is weaker. Thus BCl_3 is a stronger acid than AlCl_3 .¹⁹³
4. *Statistical Effects.* In a symmetrical diprotic acid, the first dissociation constant is twice as large as expected since there are 2 equiv ionizable hydrogens, while the second constant is only one-half as large as expected because the conjugate base can accept a proton at 2 equiv sites. So K_1/K_2 should be 4, and approximately this value is found for dicarboxylic acids where the two groups are sufficiently far apart in the molecule that they do not influence each other. A similar argument holds for molecules with 2 equiv basic groups.¹⁹⁴
5. *Hydrogen Bonding.* Internal hydrogen bonding can greatly influence acid or base strength. For example, the $\text{p}K$ for *o*-hydroxybenzoic acid is 2.98, while the value for the para isomer is 4.58. Internal hydrogen bonding between the ^-OH and COO^- groups of the conjugate base of the ortho isomer stabilizes it and results in an increased acidity.
6. *Steric Effects.* The proton itself is so small that direct steric hindrance is seldom encountered in proton transfers. Steric effects are much more common in Lewis acid–base reactions in which larger acids are used. Spectacular changes in the order of base strength have been demonstrated when the size of the acid was changed. Table 8.6 shows the order of base strength of simple amines when compared against acids of various size.¹⁹⁵ It can be seen that the usual order of basicity of amines (when the proton is the reference acid) can be completely inverted by using a large enough acid. The strain caused by formation of a covalent bond when the two atoms involved each have three large groups is called *face strain* or *F strain*.

Steric effects can indirectly affect acidity or basicity by affecting the resonance (Sec. 2.F). For example, *o*-*tert*-butylbenzoic acid is ~ 10 times as strong as the para isomer, because the carboxyl group is forced out of the plane by the *tert*-butyl group. Indeed, virtually all ortho benzoic acids are stronger than the corresponding para isomers, regardless of whether the group on the ring is electron donating or electron withdrawing.

Steric effects can also be caused by other types of strain. 1,8-Bis(diethylamino)-2,7-dimethoxynaphthalene (**8**) is an extremely strong base for a tertiary amine ($\text{p}K_a$ of the conjugate acid = 16.3; cf. *N,N*-dimethylaniline, $\text{p}K_a = 5.1$), but proton transfers to and from the nitrogen are exceptionally slow; slow enough to be

¹⁹³ Note that Lewis acidity *decreases*, whereas Brønsted acidity *increases*, going down the table. There is no contradiction here when we remember that in the Lewis picture the actual acid in all Brønsted acids is the same, namely, the proton. In comparing, say, HI and HF, we are not comparing different Lewis acids but only how easily F^- and I^- give up the proton.

¹⁹⁴ The effect discussed here is an example of a symmetry factor. For an extended discussion, see Ebersson, L. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, **1969**, pp. 211–293.

¹⁹⁵ Brown, H.C. *J. Am. Chem. Soc.* **1945**, 67, 378, 1452, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**, pp. 53–64. See also, Brown, H.C.; Krishnamurthy, S.; Hubbard, J.L. *J. Am. Chem. Soc.* **1978**, 100, 3343.

TABLE 8.6 Bases Listed in Increasing Order of Base Strength when Compared with Certain Reference Acids

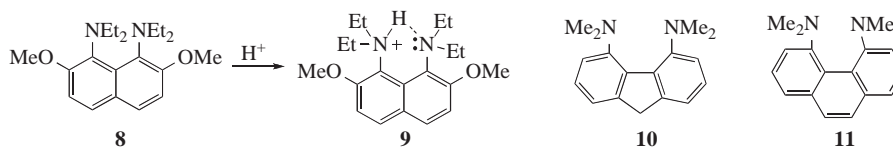
Increasing Order of Base Strength ^a	Reference Acid			
	H ⁺ or BMe ₃	BMe ₃	B(CMe ₃) ₃	
↓	NH ₃	Et ₃ N	Me ₃ N	Et ₃ N
	Me ₃ N	NH ₃	Me ₂ NH	Et ₂ NH
	MeNH ₂	Et ₂ NH	NH ₃	EtNH ₂
	Me ₂ NH	EtNH ₂	MeNH ₂	NH ₃

^aThe order of basicity (when the reference acids were boranes) was determined by the measurement of dissociation pressures.

Adapted material from *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**, pp. 53–64, Herbert C. Brown. Copyright © 1972 by Cornell University. Used by permission of the publisher, Cornell University Press.

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followed by a UV spectrophotometer.¹⁹⁶ Compound **8** is severely strained because the two nitrogen lone pairs are forced to be near each other.¹⁹⁷ Protonation relieves the strain: one lone pair is now connected to a hydrogen, which forms a hydrogen



bond to the other lone pair (shown in **9**). The same effects are found in 4,5-bis(dimethylamino)fluorene (**10**)¹⁹⁸ and 4,5-bis(dimethylamino)phenanthrene (**11**).¹⁹⁹ Compounds (e.g., **8**, **10**, and **11**), are known as *proton sponges*.²⁰⁰ The basicity of a proton sponge has been calculated as the sum of the proton affinity¹⁵² of an appropriate reference monoamine, the strain released on protonation, and the energy of the intramolecular hydrogen bond formed on protonation.²⁰¹ Another type of proton sponge is quino[7,8-*h*]quinoline (**12**).²⁰² Protonation of this compound also gives a stable mono protonated ion similar to **9**, but the steric hindrance found in **8**, **10**, and **11** is absent. Therefore, **12** is a much stronger base than quinoline (**13**) (p*K_a* values of the conjugate acids are 12.8 for **12** and 4.9 for **13**), but proton transfers are not abnormally slow. A cyclam-like macrocyclic tetramine (**15**) was prepared by a coupling reaction of bispidine, and was shown to be a new class of

¹⁹⁶ Hibbert, F.; Simpson, G.R. *J. Chem. Soc. Perkin Trans. 2* **1987**, 243, 613.

¹⁹⁷ For a review of the effect of strain on amine basicities, see Alder, R.W. *Chem. Rev.* **1989**, 89, 1215.

¹⁹⁸ Staab, H.A.; Saupe, T.; Krieger, C. *Angew. Chem. Int. Ed.* **1983**, 22, 731.

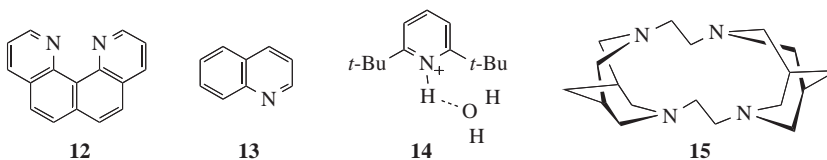
¹⁹⁹ Saupe, T.; Krieger, C.; Staab, H.A. *Angew. Chem. Int. Ed.* **1986**, 25, 451.

²⁰⁰ For a review, see Staab, H.A.; Saupe, T. *Angew. Chem. Int. Ed.* **1988**, 27, 865.

²⁰¹ Howard, S.T. *J. Am. Chem. Soc.* **2000**, 122, 8238.

²⁰² Krieger, C.; Newsom, I.; Zirnstein, M.A.; Staab, H.A. *Angew. Chem. Int. Ed.* **1989**, 28, 84. See also, Staab, H. A.; Zirnstein, M.A.; Krieger, C. *Angew. Chem. Int. Ed.* **1989**, 28, 86.

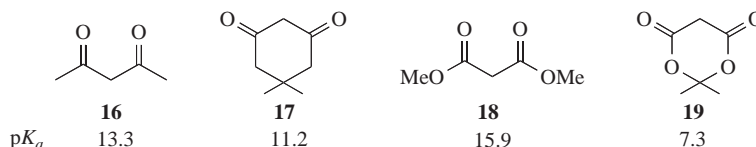
proton sponge.²⁰³



Chiral Lewis acids are known. Indeed, an air stable and storable chiral Lewis acid catalyst has been prepared, a chiral zirconium catalyst combined with molecular sieves powder.²⁰⁴ Association of a bulky silicon group with the bis (trifluoromethanesulfonyl)imide (known as triflimide) anion leads to enhancement of the electrophilic character of R_3SiNTf_2 . The presence of a chiral substituent derived from (–)-myrtenal on the silicon atom led to a chiral silicon Lewis acid.²⁰⁵

Another type of steric effect is the result of an entropy effect. The compound 2,6-di-*tert*-butylpyridine is a weaker base than either pyridine or 2,6-dimethylpyridine.²⁰⁶ The reason is that the conjugate acid **14** is less stable than the conjugate acids of nonsterically hindered pyridines. In all cases, the conjugate acids are hydrogen bonded to a water molecule, but in the case of **14** the bulky *tert*-butyl groups restrict rotations in the water molecule, lowering the entropy.²⁰⁷

The conformation of a molecule can also affect its acidity. The following pK_a values were determined for compounds **16–19**.²⁰⁸



Since ketones are stronger acids than carboxylic esters (Table 8.1), it is not surprising that **16** is a stronger acid than **18**.²⁰⁹ A comparison of **16** with cyclic diketone **17** shows an increase in acidity of only 2.1 pK units, while a comparison of **18** with cyclic diester **19** shows an increase of 8.6 units. Indeed, **19** (called *Meldrum's acid*) is an unusually strong acid for a 1,3-diester. In order to account for this very large effect of a ring, MO calculations were carried out for two conformations of methyl acetate and of its enolate ion.²¹⁰ Loss of a proton is easier by ~ 5 kcal mol^{–1} (21 kJ mol^{–1}) for the syn than for the anti conformer of the ester.

²⁰³ Miyahara, Y.; Goto, K.; Inazu, T. *Tetrahedron Lett.* **2001**, 42, 3097.

²⁰⁴ Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, 4, 3395.

²⁰⁵ Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, 41, 9651.

²⁰⁶ Brown, H.C.; Kanner, B. *J. Am. Chem. Soc.* **1953**, 75, 3865; **1966**, 88, 986.

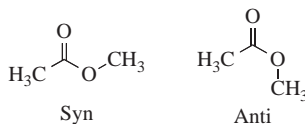
²⁰⁷ Meot-Ner, M.; Smith, S.C. *J. Am. Chem. Soc.* **1991**, 113, 862, and references cited therein. See also, Benoit, R.L.; Fréchette, M.; Lefebvre, D. *Can. J. Chem.* **1988**, 66, 1159.

²⁰⁸ Arnett, E.M.; Harrelson, Jr., J.A. *J. Am. Chem. Soc.* **1987**, 109, 809.

²⁰⁹ For a discussion of why esters and amides are weaker acids than ketones, see Fersner, A.; Karty, J.M.; Mo, Y. *J. Org. Chem.* **2009**, 74, 7245.

²¹⁰ Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* **1988**, 110, 1870; Wiberg, K.B.; Laidig, K.E. *J. Am. Chem. Soc.* **1988**, 110, 1872.

In an acyclic molecule like **18**, the preferred conformations are anti, but in *Meldrum's acid* (**19**) the conformation on both sides is constrained to be syn.



Facial differences in proton reactivity can lead to enantioselective deprotonation. Enantioselective deprotonation is also achieved by using a chiral base and/or a chiral complexing agent. Enantioselective deprotonation in cyclic ketones,²¹¹ and with heterodimer bases has been studied.²¹² When a Lewis acid coordinates to a base, the resulting complex can have conformational properties that influence reactivity. Coordination of SnCl_4 with aldehydes and esters, for example, leads to a complex where the conformation is determined by interactions of the $\text{C}=\text{O} \cdots \text{SnCl}_4$ unit with substituents attached to the carbonyl.²¹³

7. *Hybridization*. An s orbital has a lower energy than a p orbital. Therefore, the more s character a hybrid orbital contains, the lower the energy of that orbital. It follows that a carbanion at an sp carbon is more stable than a corresponding carbanion at an sp^2 carbon. Thus $\text{HC}\equiv\text{C}^-$, which has more s character in its unshared pair than $\text{CH}_2=\text{CH}^-$ or CH_3CH_2^- (sp vs sp^2 vs sp^3 , respectively), is a much weaker base. This explains the relatively high acidity of acetylenes and HCN. Another example is that alcohol and ether oxygen atoms, where the unshared pair is sp^3 , are more strongly basic than carbonyl oxygen atoms, where the unshared pair is sp^2 (Table 8.1).

An understanding of the reactivity of bases arises from the study of their structures in solution and in the crystalline state. Due to the importance of dialkylamide bases, there is a significant body of work, led by independent work by Williard and by Collum, that has attempted to understand the structures of these reactive molecules. It is clear that the dialkylamide bases are aggregates. Note that the simplest member of the amide base family, lithium amide (LiNH_2), was shown to be monomeric and unsolvated, as determined using a combination of gas-phase synthesis and millimeter/submillimeter-wave spectroscopy.²¹⁴ Both monomeric LiNH_2 and LiNMe_2 are planar.²¹⁵ Lithium diisopropylamide (LiNiPr_2 , LDA) was isolated from a THF solution and X-ray crystallography revealed a dimeric structure (**20**; $\text{R} = i\text{Pr}$, $\text{S} = \text{THF}$) in the solid state.²¹⁶ Lithium diisopropylamide was also shown to be a dimer in solutions of THF²¹⁷ and/or HMPA (see **20**, $\text{R} = i\text{Pr}$ and $\text{S} = \text{THF}$, HMPA).²¹⁸ In the presence of HMPA, many derivatives of **20** tend to be mixed aggregates.²¹⁹ Extremely hindered LiNR_2 ($\text{R} = 2\text{-adamantyl}$) are

²¹¹ Majewski, M.; Wang, F. *Tetrahedron* **2002**, 58, 4567.

²¹² Amedjkouh, M. *Tetrahedron Asym.* **2004**, 15, 577.

²¹³ Gung, B.W.; Yanik, M.M. *J. Org. Chem.* **1996**, 61, 947.

²¹⁴ Grotjahn, D.B.; Sheridan, P.M.; Al Jihad, I.; Ziurys, L.M. *J. Am. Chem. Soc.* **2001**, 123, 5489.

²¹⁵ Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C.; Silvi, B. *J. Org. Chem.* **2001**, 66, 6476.

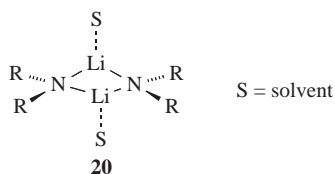
²¹⁶ Williard, P.G.; Salvino, J.M. *J. Org. Chem.* **1993**, 58, 1. For a study of the oligomer structure of LDA at low ligand concentrations, see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* **2001**, 123, 199.

²¹⁷ Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, 33, 3769.

²¹⁸ Aubrecht, K.B.; Collum, D.B. *J. Org. Chem.* **1996**, 61, 8674.

²¹⁹ Romesberg, F.E.; Collum, D.B. *J. Am. Chem. Soc.* **1994**, 116, 9198, 9187. For a study of other mixed aggregates, see Thomas, R.D.; Huang, J. *J. Am. Chem. Soc.* **1999**, 121, 11239.

monomeric under all conditions.²²⁰ In hydrocarbon solvents, lithium tetramethylpiperidide [LTMP, $\text{RR}'\text{NLi}$, where $\text{RR}' = -\text{CMe}_2(\text{CH}_2)_3\text{C}(\text{Me}_2)-$] forms cyclic trimers and tetramers, with the tetrameric species predominating.²²¹ In THF, lithium hexamethyldisilazide [LHMDS, $(\text{Me}_3\text{Si})_2\text{NLi}$] forms a five-coordinate tetrasolvate $[(\text{Me}_3\text{Si})_2\text{NLi}(\text{thf})_4]$,²²² but in ether there is an equilibrium mixture of monomer and dimer.²²³ A review is available that discusses the solution structures of amide bases LiNR_2 .²²⁴ Chiral lithium amide bases are known and they show similar behavior in solution.²²⁵ Chelation effects are common in enantioenriched amide bases, which also form aggregates.²²⁶ The aggregation state of lithium phenylacetonitrile has been studied.²²⁷ Dianion aggregates can be generated, and in the case of the lithiation reaction of *N*-silyl allylamine, X-ray structure determination showed the presence of three uniquely different aggregates.²²⁸ A mixed aggregate is formed when the lithium enolate of a ketone is mixed with a lithium amide.²²⁹



Similar information is available for other bases. Lithium phenoxide (LiOPh) is a tetramer in THF.²³⁰ Lithium 3,5-dimethylphenoxide is a tetramer in ether, but addition of HMPA leads to dissociation to a monomer.²³¹

Enolate anions are nucleophiles in reactions with alkyl halides (Reaction **10-68**), with aldehydes and ketones (Reactions **16-34** and **16-36**) and with acid derivatives (Reaction **16-85**). Enolate anions are also bases, reacting with water, alcohols and other protic solvents, and even the carbonyl precursor to the enolate anion. Enolate anions exist as aggregates, and the effect of solvent on aggregation and reactivity of lithium enolate anions has been studied.²³² Alkyl substitution has a significant influence on the energetics of enolate anions.²³³

²²⁰ Sakuma, K.; Gilchrist, J.H.; Romesberg, F.E.; Cajthami, C.E.; Collum, D.B. *Tetrahedron Lett.* **1993**, 34, 5213.

²²¹ Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* **1994**, 116, 7949.

²²² Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* **1995**, 117, 9863. See also, Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* **1996**, 118, 2217, 3529. See Romesberg, F.E.; Bernstein, M.P.; Gilchrist, J.H.; Harrison, A.T.; Fuller, D. J.; Collum, D.B. *J. Am. Chem. Soc.* **1993**, 115, 3475 for the structure in HMPA.

²²³ Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* **1994**, 116, 6009.

²²⁴ Collum, D.B. *Acc. Chem. Res.* **1993**, 26, 227. For NMR studies of LiNEt_2 and ring laddering see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* **1999**, 121, 10198.

²²⁵ Hilmersson, G.; Davidsson, Ö. *J. Org. Chem.* **1995**, 60, 7660. See O'Brien, P. J. *Chem. Soc. Perkin Trans. 1* **1998**, 1439; Sott, R.; Grandander, J.; Dinér, P.; Hilmersson, G. *Tetrahedron Asymm.* **2004**, 15, 267.

²²⁶ Arvidsson, P.I.; Hilmersson, G.; Ahlberg, P. *J. Am. Chem. Soc.* **1999**, 121, 183.

²²⁷ Carlier, P.R.; Madura, J.D. *J. Org. Chem.* **2002**, 67, 3832.

²²⁸ Williard, P.G.; Jacobson, M. A. *Org. Lett.* **2000**, 2, 2753. For the structure and bonding of dilithiodiamines see Pratt, L.M.; Mu, R. *J. Org. Chem.* **2004**, 69, 7519.

²²⁹ Sun, C.; Williard, P.G. *J. Am. Chem. Soc.* **2000**, 122, 7829. See also, Pratt, L.M.; Streitwieser, A. *J. Org. Chem.* **2003**, 68, 2830.

²³⁰ Jackman, L.M.; Çizmeciyen, D.; Williard, P.G.; Nichols, M.A. *J. Am. Chem. Soc.* **1993**, 115, 6262.

²³¹ Jackman, L.M.; Chen, X. *J. Am. Chem. Soc.* **1992**, 114, 403.

²³² Streitwieser, A.; Juaristi, E.; Kim, Y.-J.; Pugh, J.K. *Org. Lett.* **2000**, 2, 3839.

²³³ Alconcel, L.S.; Deyerl, H.-J.; Continetti, R.E. *J. Am. Chem. Soc.* **2001**, 123, 12675.

8.G. THE EFFECTS OF THE MEDIUM ON ACID AND BASE STRENGTH

Structural features are not the only factors that affect acidity or basicity. The same compound can have its acidity or basicity changed when the reaction conditions are changed. The effect of temperature (Sec. 8.A) has already been mentioned. More important is the effect of the solvent, which can exert considerable influence on acid and base strengths by differential solvation.²³⁴ If a base is more solvated than its conjugate acid, its stability is increased relative to the conjugate acid. For example, Table 8.6 shows that in reactions with a proton, where steric effects are absent, methylamine is a stronger base than ammonia and dimethylamine is stronger still.²³⁵ These results are easily explainable if one assumes that methyl groups are electron donating. However, trimethylamine, which should be even stronger, is a weaker base than dimethylamine or methylamine. This apparently anomalous behavior can be explained by differential hydration.²³⁶ Thus, NH_4^+ is much better hydrated (by hydrogen bonding to the water solvent) than NH_3 because of its positive charge.²³⁷ It has been estimated that this effect contributes ~ 11 pK units to the base strength of ammonia.²³⁸ When methyl groups replace hydrogen, this difference in hydration decreases²³⁹ until, for trimethylamine, it contributes only ~ 6 pK units to the base strength.¹⁹⁵ Thus two effects act in opposite directions, the field effect increasing the basicity as the number of methyl groups increases and the hydration effect decreasing it. Taken together, the strongest base is dimethylamine and the weakest is ammonia in solution. If alkyl groups are electron donating, one would expect that in the gas phase,²⁴⁰ where the solvation effect does not exist, the basicity order of amines toward the proton should be $\text{R}_3\text{N} > \text{R}_2\text{NH} > \text{RNH}_2 > \text{NH}_3$, and this has indeed been confirmed, for $\text{R} = \text{Me}$, as well as $\text{R} = \text{Et}$ and Pr .²⁴¹ Aniline too, in the gas phase, is a stronger base than NH_3 ,²⁴² so

²³⁴ See Epshtein, L.M.; Iogansen, A.V. *Russ. Chem. Rev.* **1990**, 59, 134; Dyumaev, K.M.; Korolev, B.A. *Russ. Chem. Rev.* **1980**, 49, 1021; Taft, R.W.; Bordwell, F.G. *Acc. Chem. Res.* **1988**, 21, 463; Heemstra, J.M.; Moore, J. S. *Tetrahedron* **2004**, 60, 7287.

²³⁵ See Smith, J.W. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, **1968**, pp. 161–204.

²³⁶ Aue, D.H.; Webb, H.M.; Bowers, M.T. *J. Am. Chem. Soc.* **1972**, 94, 4726; **1976**, 98, 311, 318; Mucci, A.; Domain, R.; Benoit, R.L. *Can. J. Chem.* **1980**, 58, 953. See also, Drago, R.S.; Cundari, T.R.; Ferris, D.C. *J. Org. Chem.* **1989**, 54, 1042.

²³⁷ For discussions of the solvation of ammonia and amines, see Jones, III, F.M.; Arnett, E.M. *Prog. Phys. Org. Chem.* **1974**, 11, 263; Grunwald, E.; Ralph, E.K. *Acc. Chem. Res.* **1971**, 4, 107.

²³⁸ Condon, F.E. *J. Am. Chem. Soc.* **1965**, 87, 4481, 4485.

²³⁹ For two reasons: (1) the alkyl groups are poorly solvated by the water molecules, and (2) the strength of the hydrogen bonds of the BH^+ ions decreases as the basicity of B increases: Lau, Y.K.; Kebarle, P. *Can. J. Chem.* **1981**, 59, 151.

²⁴⁰ See Liebman, J.F. *Mol. Struct. Energ.* **1987**, 4, 49; Dixon, D.A.; Lias, S.G. *Mol. Struct. Energ.* **1987**, 2, 269; Bohme, D.K. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, **1982**, pp. 731–762; Arnett, E.M. *Acc. Chem. Res.* **1973**, 6, 404. See Lias, S.G.; Liebman, J.F.; Levin, R.D. *J. Phys. Chem. Ref. Data*, **1984**, 13, 695. See also, the tables of gas-phase acidities and basicities in the following articles, and their cited references: Meot-Ner, M.; Kafafi, S.A. *J. Am. Chem. Soc.* **1988**, 110, 6297; Headley, A.D. *J. Am. Chem. Soc.* **1987**, 109, 2347; Fujio, M.; McIver, Jr., R.T.; Taft, R.W. *J. Am. Chem. Soc.* **1981**, 103, 4017; Lau, Y.K.; Nishizawa, K.; Tse, A.; Brown, R.S.; Kebarle, P. *J. Am. Chem. Soc.* **1981**, 103, 6291.

²⁴¹ Briggs, J.P.; Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* **1972**, 94, 5128; Aue, D.H.; Webb H.M.; Bowers, M. T. *J. Am. Chem. Soc.* **1972**, 94, 4726; **1976**, 98, 311, 318.

²⁴² Ikuta, S.; Kebarle, P. *Can. J. Chem.* **1983**, 61, 97.

its much lower basicity in aqueous solution (pK_a of PhNH_3^+ 4.60 compared with 9.24 for aq NH_4^+) is caused by similar solvation effects and not by resonance and field electron-withdrawing effects of a phenyl group. Similarly, pyridine²⁴³ and pyrrole²⁴⁴ are both much less basic than NH_3 in aqueous solution (pyrrole²⁴⁵ is neutral in aqueous solution), but *more* basic in the gas phase. Care must be taken in attributing relative acidities or basicities to any particular effect. Solvent has a significant influence on the *Hammett reaction constant* (Sec. 11.D), which influences the acidity of substituted benzoic acids.²⁴⁶

In the case of Lewis acids, protic solvents (e.g., water or alcohol) can strongly influence their reactivity, cause it to react via an alternative path to the one desired, or even cause decomposition. Rare earth metal triflates have been used to develop water tolerant Lewis acids that can be used in many organic reactions.²⁴⁷

For simple alcohols, the order of gas-phase *acidity* is completely reversed from that in aqueous solution. In solution, the acidity is in the order $\text{H}_2\text{O} > \text{MeCH}_2\text{OH} > \text{Me}_2\text{CHOH} > \text{Me}_3\text{COH}$, but in the gas phase the order is precisely the opposite.²⁴⁸ Once again solvation effects can be invoked to explain the differences. Comparing the two extremes, H_2O and Me_3COH , we see that the OH^- ion is very well solvated by water while the bulky Me_3CO^- is much more poorly solvated because the water molecules cannot get as close to the oxygen. Thus in solution H_2O gives up its proton more readily. When solvent effects are absent, however, the intrinsic acidity is revealed and Me_3COH is a stronger acid than H_2O . This result demonstrates that simple alkyl groups cannot be simply regarded as electron donating. If methyl is an electron-donating group, then Me_3COH should be an intrinsically weaker acid than H_2O , yet it is stronger. A similar pattern is found with carboxylic acids, where simple aliphatic acids (e.g., propanoic) are stronger than acetic acid in the gas phase,²⁴⁹ although weaker in aqueous solution (Table 8.5). The evidence in these and other cases²⁵⁰ is that alkyl groups can be electron donating when connected to unsaturated systems, but may have either no effect or may actually be electron withdrawing in other systems. It appears that the intrinsic gas-phase acidity order of alcohols as well as the basicity order of amines is due to the effect of alkyl groups, because of their polarizability, which can spread both positive and negative charges.²⁵¹ It has been calculated that even in the case of alcohols the field effects of the alkyl groups are still operating normally, but are swamped by the greater polarizability effects.²⁵² Polarizability effects on anionic centers

²⁴³ Taft, R.W.; Taagepera, M.; Summerhays, K.D.; Mitsky, J. *J. Am. Chem. Soc.* **1973**, *95*, 3811.

²⁴⁴ Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* **1973**, *95*, 3504.

²⁴⁵ See Catalan, J.; Abboud, J.L.M.; Elguero, J. *Adv. Heterocycl. Chem.* **1987**, *41*, 187.

²⁴⁶ Bartnicka, H.; Bojanowska, I.; Kalinowski, M.K. *Aust. J. Chem.* **1993**, *46*, 31.

²⁴⁷ Kobayashi, S. *Synlett*, **1994**, 689.

²⁴⁸ Arnett, E.M.; Small, L.E.; McIver, Jr., R.T.; Miller, J.S. *J. Am. Chem. Soc.* **1974**, *96*, 5638; Blair, L.K.; Isolani, P.C.; Riveros, J.M. *J. Am. Chem. Soc.* **1973**, *95*, 1057; McIver, Jr., R.T.; Scott, J.A.; Riveros, J.M. *J. Am. Chem. Soc.* **1973**, *95*, 2706. Also see Bartmess, J.E.; McIver, Jr., R.T. *J. Am. Chem. Soc.* **1977**, *99*, 4163.

²⁴⁹ See Caldwell, G.; Renneboog, R.; Kebarle, P. *Can. J. Chem.* **1989**, *67*, 611.

²⁵⁰ Brauman, J.I.; Blair, L.K. *J. Am. Chem. Soc.* **1971**, *93*, 4315; Laurie, V.W.; Muentner, J.S. *J. Am. Chem. Soc.* **1966**, *88*, 2883.

²⁵¹ Brauman, J.I.; Riveros, J.M.; Blair, L.K. *J. Am. Chem. Soc.* **1971**, *93*, 3914; Huheey, J.E. *J. Org. Chem.* **1971**, *36*, 204; Radom, L. *Aust. J. Chem.* **1975**, *28*, 1; Aitken, E.J.; Bahl, M.K.; Bomben, K.D.; Gimzewski, J.K.; Nolan, G.S.; Thomas, T.D. *J. Am. Chem. Soc.* **1980**, *102*, 4873.

²⁵² Taft, R.W.; Taagepera, M.; Abboud, J.M.; Wolf, J.F.; DeFrees, D.J.; Hehre, W.J.; Bartmess, J.E.; McIver, Jr., R. *J. Am. Chem. Soc.* **1978**, *100*, 7765. For a scale of polarizability parameters, see Hehre, W.J.; Pau, C.; Headley, A.D.; Taft, R.W.; Topsom, R.D. *J. Am. Chem. Soc.* **1986**, *108*, 1711.

TABLE 8.7 Thermodynamic Values for the Ionizations of Acetic and Chloroacetic Acids in H₂O at 25°C^a

Acid	p <i>K</i> _a	ΔG		ΔH		$T\Delta S$	
		kcal mol ⁻¹	kJ mol ⁻¹	kcal mol ⁻¹	kJ mol ⁻¹	kcal mol ⁻¹	kJ mol ⁻¹
CH ₃ COOH	4.76	+6.5	+27	-0.1	-0.4	-6.6	-28
ClCH ₂ COOH	2.86	+3.9	+16	-1.1	-4.6	-5.0	-21
Cl ₃ CCOOH	0.65	+0.9	+3.8	+1.5	+6.3	+0.6	+2.5

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^aSee Ref. 256.

are a major factor in gas-phase acid–base reactions.²⁵³ It has been shown (by running reactions on ions that are solvated in the gas phase) that solvation by even one molecule of solvent can substantially affect the order of basicities.²⁵⁴

The effect on the orientation of solvent molecules when an acid or base is converted to its conjugate is an important aspect of solvent effects. For example, consider an acid (RCOOH) converted to RCOO⁻ in aqueous solution. The solvent molecules, by hydrogen bonding, arrange themselves around the COO⁻ group in a much more orderly fashion than they had been arranged around the COOH group (because they are more strongly attracted to the negative charge). This leads to a considerable loss of freedom and a decrease in entropy. Thermodynamic measurements show that for simple aliphatic and halogenated aliphatic acids in aqueous solution at room temperature, the entropy ($T\Delta S$) usually contributes much more to the total free energy change ΔG than does the enthalpy ΔH .²⁵⁵ Two examples are shown in Table 8.7.²⁵⁶ Resonance and field effects of functional groups therefore affect the acidity of RCOOH in two distinct ways. They affect the enthalpy (electron-withdrawing groups increase acidity by stabilizing RCOO⁻ by charge dispersal), but they also affect the entropy (by lowering the charge on the COO⁻ group and by changing the electron-density distribution in the COOH group, electron-withdrawing groups alter the solvent orientation patterns around both the acid and the ion, and consequently change ΔS).

A change from a protic to an aprotic solvent can also affect the acidity or basicity, since there is a difference in solvation of anions by a protic solvent (which can form hydrogen bonds) and an aprotic one.²⁵⁷ The effect can be extreme: In DMF, picric acid is stronger than HBr,²⁵⁸ though in water HBr is far stronger. This particular result can be attributed to size. That is, the large ion (O₂N)₃C₆H₂O⁻ is better solvated by DMF than the smaller

²⁵³ Bartmess, J.E.; Scott, J.A.; McIver, Jr., R.T. *J. Am. Chem. Soc.* **1979**, 101, 6056.

²⁵⁴ Bohme, D.K.; Rakshit, A.B.; Mackay, G.I. *J. Am. Chem. Soc.* **1982**, 104, 1100.

²⁵⁵ Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* **1971**, 25, 521; Gerrard, W.; Macklen, E.D. *Chem. Rev.* **1959**, 59, 1105. See also, Wilson, B.; Georgiadis, R.; Bartmess, J.E. *J. Am. Chem. Soc.* **1991**, 113, 1762.

²⁵⁶ Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* **1971**, 25, 521; p. 529.

²⁵⁷ For a review, see Parker, A.J. *Q. Rev. Chem. Soc.* **1962**, 16, 163.

²⁵⁸ Sears, P.G.; Wolford, R.K.; Dawson, L.R. *J. Electrochem. Soc.* **1956**, 103, 633.

ion Br^- .²⁵⁹ The ionic strength of the solvent also influences acidity or basicity, since it has an influence on activity coefficients.

In summary, solvation can have powerful effects on acidity and basicity. In the gas phase, the effects discussed in Section 8.F, especially resonance and field effects, operate unhindered by solvent molecules. Electron-withdrawing groups generally increase acidity (and decrease basicity); electron-donating groups act in the opposite way. In solution, especially aqueous solution, these effects still largely persist (which is why $\text{p}K$ values in Table 8.5 do largely correlate with resonance and field effects), but in general are much weakened, and occasionally reversed.¹⁷⁹

²⁵⁹ Miller, J.; Parker, A.J. *J. Am. Chem. Soc.* **1961**, 83, 117.

Effects of Structure and Medium on Reactivity

When the equation for a reaction of, say, carboxylic acids, is written, it is customary to use the formula RCOOH , where R is a generic alkyl group, which implies that all carboxylic acids undergo the reaction. Since most compounds with a given functional group usually give more or less the same reactions, the custom is useful, and the practice is used in this text. It allows a large number of individual reactions to be classified together and serves as an aid both for memory and understanding. Nevertheless, it must be borne in mind that a given functional group does not always react the same way, regardless of what molecule it is a part of. In other words, a reaction at the functional group is influenced by the rest of the molecule. This influence may be great enough to stop the reaction completely or to make it take an entirely different course. Even when two compounds with the same functional group undergo the same reaction, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. The greatest variations may be expected when additional functional groups are present.

The effects of structure on reactivity can be divided into three major types: field, resonance (or mesomeric), and steric.¹ In most cases, two or all three of these are operating, and it is usually not easy to tell how much of the rate enhancement (or decrease) is caused by each of the three effects.

9.A. RESONANCE AND FIELD EFFECTS

It is often particularly difficult to separate resonance and field effects; they are frequently grouped together under the heading of *electrical effects*.² Field effects were discussed in Section 1.I. Table 1.3 contains a list of some $+I$ and $-I$ groups. As for resonance effects, in Section 2.F it was shown how the electron density distribution in aniline is not the same as it would be if there were no resonance interaction between the ring and the NH_2 group. Most groups that contain an unshared pair on an atom connected to an unsaturated system display a similar effect; that is, the electron density on the group is less than expected, and the density on the unsaturated system is greater. Such groups are said to be electron donating by the

¹ See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, **1982**. For a general theoretical approach to organic reactivity, see Pross, A. *Adv. Phys. Org. Chem.* **1985**, 21, 99.

² See Topsom, R.D. *Prog. Phys. Org. Chem.* **1987**, 16, 125, *Mol. Struct. Energ.* **1987**, 4, 235.

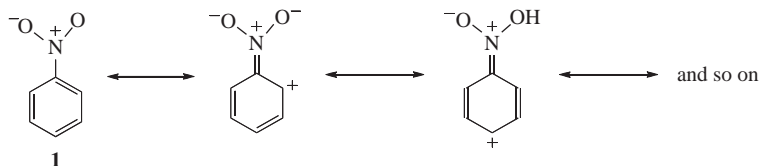
TABLE 9.1 Some Groups with $+M$ and $-M$ Effects, Not Listed in Order of Strength of Effect^a

$+M$		$-M$	
O^-	SR	NO_2	CHO
S^-	SH	CN	COR
NR_2	Br	COOH	SO_2R
NHR	I	COOR	SO_2OR
NH_2	Cl	CONH ₂	NO
NHCOR	F	CONHR	Ar
OR	R	CONR ₂	
OH	Ar		
OCOR			

^aArgon (Ar) appears in both lists because it is capable of both kinds of effect.

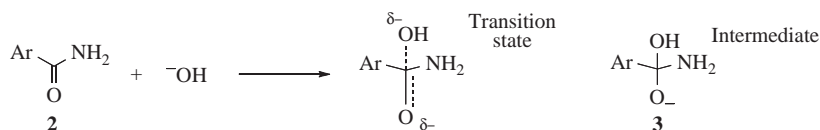
resonance effect ($+M$ groups). Alkyl groups, which do not have an unshared pair, are also $+M$ groups, presumably because of hyperconjugation (see Sec. 2.M).

On the other hand, groups that have a multiple-bonded electronegative atom directly connected to an unsaturated system are $-M$ groups. In such cases, canonical forms can be drawn in which electrons are delocalized from the unsaturated system into the group, as in nitrobenzene (**1**). Table 9.1 contains a list of some $+M$ and $-M$ groups.



The resonance effect of a group, whether $+M$ or $-M$, operates only when the group is directly connected to an unsaturated system, so that, for example, in explaining the effect of the CH_3O group on the reactivity of the $COOH$ in $CH_3OCH_2CH_2COOH$, only the field effect of the CH_3O need be considered. This is one way of separating the two effects. In *p*-methoxybenzoic acid both effects must be considered. The field effect operates through space, solvent molecules, or the σ bonds of a system, while the resonance effect operates through π electrons.

It must be emphasized once again that neither by the resonance nor by the field effect are any electrons actually being donated or withdrawn, though these terms are convenient (and we will use them). As a result of both effects, the electron-density distribution is not the same as it would be without the effect (see Sec. 1.I, 2.F). Complicating the study of these effects on the reactivity of compounds is the fact that a given group may have an effect in the transition state that is considerably more or less than it has in the molecule that does not react.



In the alkaline hydrolysis of aromatic amides (Reaction 16-60), the rate-determining step is the attack of hydroxide ion at the carbonyl carbon. The conversion of **2** to **3**

TABLE 9.2 Relative Rates of Reaction of RBr with Ethanol^a

R	Relative Rate
CH ₃	17.6
CH ₃ CH ₂	1
CH ₃ CH ₂ CH ₂	0.28
(CH ₃) ₂ CHCH ₂	0.030
(CH ₃) ₃ CCH ₂	4.2×10^{-6}

Reproduced from Hughes, E.D. *Q. Rev. Chem. Soc.* **1948**, 2, 107 with permission from the Royal Society of Chemistry.

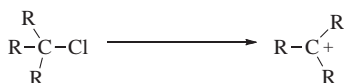
^aSee Ref. 3.

illustrates the nature of electrical effects (resonance and field) on reactivity. In the transition state, which has a structure somewhere between that of the starting amide (2) and the intermediate (3), the electron density on the carbonyl carbon is increased. Therefore, electron-withdrawing groups ($-I$ or $-M$) on the aromatic ring will lower the free energy of the transition state (by spreading the negative charge). These groups have much less effect on the free energy of 2. Since G is lowered for the transition state, but not substantially for 2, ΔG^\ddagger is lowered and the reaction rate is increased (Chapter 6). Conversely, electron-donating groups ($+I$ or $+M$) should decrease the rate of this reaction. Of course, many groups are $-I$ and $+M$, and for these it is not always possible to predict which effect will predominate.

9.B. STERIC EFFECTS

It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electrical effects alone. In these cases, it can often be shown that steric effects have a significant influence on the rate. For example, Table 9.2 lists relative rates for the S_N2 ethanolysis of certain alkyl halides (see Sec. 10.A.i).³ All these compounds are primary bromides; the branching is on the second carbon, so that field-effect differences should be small. As Table 9.2 shows, the rate decreases with increasing branching and reaches a very low value for neopentyl bromide. This reaction is known to involve an attack by the nucleophile from a position opposite to that of the bromine (see Sec. 10.A.i). The great decrease in rate can be attributed to *steric hindrance* in the transition state of the reaction, which makes attack of the nucleophile more difficult. Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the resonance or field effects of the groups in the 2 or the 6 positions. Similarly, once 2,6-disubstituted benzoic acids are esterified, the esters are difficult to hydrolyze.

Not all steric effects decrease reaction rates. In the hydrolysis of RCl by an S_N1 mechanism (see Sec. 10.A.ii), the first step, which is rate determining, involves ionization of the alkyl chloride to a carbocation:



³ Hughes, E.D. *Q. Rev. Chem. Soc.* **1948**, 2, 107.

TABLE 9.3 Rates of Hydrolysis of Tertiary Alkyl Chlorides at 25 °C in 80% Aqueous Ethanol^a

Halide	Rate	Halide	Rate
Me ₃ Cl	0.033	Et ₃ CCl	0.099
Me ₂ EtCCl	0.055	Me ₃ (<i>i</i> Pr)CCl	0.029
MeEt ₂ CCl	0.086	Me(<i>i</i> Pr) ₂ CCl	0.45

Reproduced with permission Brown, H.C.; Fletcher, R.S. *J. Am. Chem. Soc.* **1949**, *71*, 1845. Copyright © 1949 American Chemical Society.

^aSee Ref. 6.

The central carbon in the alkyl chloride is sp^3 hybridized, with angles of $\sim 109.5^\circ$, but when it is converted to the carbocation, the hybridization becomes sp^2 and the preferred angle is 120° . If the halide is tertiary and the three alkyl groups are large enough, they will be pushed together by the enforced tetrahedral angle, resulting in strain (see Sec. 4.Q.iv). This type of strain is called *B strain*⁴ (for back strain), and can be relieved by ionization to the carbocation.⁵

The rate of ionization (and hence the solvolysis rate) of a molecule in which there is B strain is expected to be larger than in cases where B strain is not present. Table 9.3 shows that this is so.⁶ Substitution of ethyl groups for the methyl groups of *tert*-butyl chloride does not cause B strain; the increase in rate is relatively small, and the rate smoothly rises with the increasing number of ethyl groups. The increase is caused by normal field and resonance (hyperconjugation) effects. Substitution by one isopropyl group is not greatly different. But with the second isopropyl group the crowding is now great enough to cause B strain, and the rate is increased 10-fold. Substitution of a third isopropyl group increases the rate still more. Another example where B strain increases the rate of solvolysis is found with the highly crowded molecules tri-*tert*-butylcarbinol, di-*tert*-butylneopentylcarbinol, *tert*-butyldineopentylcarbinol, and trineopentylcarbinol, where rates of solvolysis of the *p*-nitrobenzoate esters are faster than that of *tert*-butyl nitrobenzoate by factors of 13,000, 19,000, 68,000, and 560, respectively.⁷

Another type of strain, which can affect rates of cyclic compounds, is called *I strain* (internal strain).⁸ This type of strain results from changes in ring strain in going from a tetrahedral to a trigonal carbon or vice versa. For example, as mentioned above, S_N1 solvolysis of an alkyl halide involves a change in the bond angle of the central carbon from $\sim 109.5^\circ$ to $\sim 120^\circ$. This change is highly favored in 1-chloro-1-methylcyclopentane because it relieves eclipsing strain (Sec. 4.Q.iv); thus this compound undergoes solvolysis in 80% ethanol at 25 °C, 43.7 times faster than the reference compound *tert*-butyl chloride.⁹ In the corresponding cyclohexyl compound, this factor is absent because the substrate does not have eclipsing strain (Sec. 4.Q.iv), and this compound undergoes the reaction at about one-third the rate of *tert*-butyl chloride. The reasons for this small decrease in rate are not clear. Corresponding behavior is found in the other direction, in changes from a trigonal to a tetrahedral carbon. Thus cyclohexanone undergoes addition reactions faster than cyclopentanone. Similar considerations apply to larger rings. Rings of

⁴ Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**, pp. 114–121.

⁵ See Stirling, C.J.M. *Tetrahedron* **1985**, *41*, 1613; *Pure Appl. Chem.* **1984**, *56*, 1781.

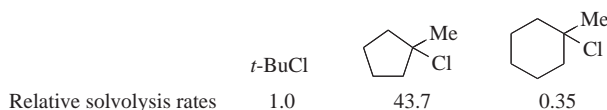
⁶ Brown, H.C.; Fletcher, R.S. *J. Am. Chem. Soc.* **1949**, *71*, 1845.

⁷ Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* **1968**, *90*, 4421.

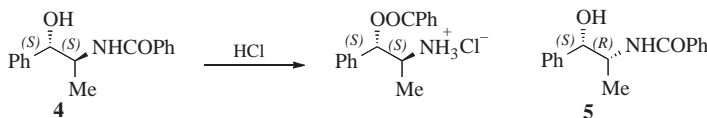
⁸ See Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**, pp. 105–107, 126–128.

⁹ Brown, H.C.; Borkowski, M. *J. Am. Chem. Soc.* **1952**, *74*, 1894. See also, Brown, H.C.; Ravindranathan, M.; Peters, E.N.; Rao, C.G.; Rho, M.M. *J. Am. Chem. Soc.* **1977**, *99*, 5373.

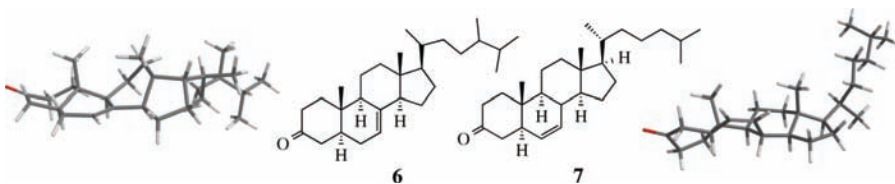
7–11 members exhibit eclipsing and transannular strain; and in these systems reactions in which a tetrahedral carbon becomes trigonal generally proceed faster than in open-chain systems.¹⁰ *I*-Strain has been shown to be a factor in other reactions as well.¹¹



Conformational effects on reactivity can be considered under the heading of steric effects,¹² but in these cases the effect of a group X and that of another group X' upon reactivity at a site Y are not considered. But the effect of the conformation of the molecule must be considered. Many reactions fail entirely unless the molecules are able to assume the proper conformation. An example is the rearrangement of *N*-benzoylnorephedrine. The two diastereomers of this compound (**4** and **5**) behave very differently when treated with alcoholic HCl. In one of the isomers, nitrogen-to-oxygen migration takes place, while the other does not react at all.¹³ In order for the migration to take place, the nitrogen must be near the oxygen (*gauche* to it). When **4** assumes this conformation, the methyl and phenyl groups are anti to each other, which is a favorable position, but when **5** has the nitrogen *gauche* to the oxygen, the methyl must be *gauche* to the phenyl, which is so unfavorable that the reaction does not occur. Other examples are electrophilic additions to C=C double bonds (see Sec. 15.A.i) and E2 elimination reactions (see Sec. 17.A.i.). Also, many examples are known where axial and equatorial groups behave differently.¹⁴



In steroids and other rigid systems, a functional group in one part of the molecule can strongly affect the rate of a reaction taking place at a remote part of the same molecule by altering the conformation of the whole skeleton. An example of this effect, called *conformational transmission*, is found in ergost-7-en-3-one (**6**) and cholest-6-en-3-one (**7**), where **7** condenses with benzaldehyde 15 times faster than **6**.¹⁵ The reaction site in both cases is the carbonyl group, and the rate increases because moving the double bond from the 7 to the 6 position causes a change in conformation at the carbonyl group (the difference in the side chain at C-17 does not affect the rate). Molecular models of **6** and **7** are provided for illustration.



¹⁰ See Schneider, H.; Thomas, F. *J. Am. Chem. Soc.* **1980**, *102*, 1424.

¹¹ Sands, R.D. *J. Org. Chem.* **1994**, *59*, 468.

¹² See Green, B.S.; Arad-Yellin, R.; Cohen, M.D. *Top. Stereochem.* **1986**, *16*, 131; Öki, M. *Acc. Chem. Res.* **1984**, *17*, 154; Seeman, J.I. *Chem. Rev.* **1983**, *83*, 83. See also, Öki, M.; Tsukahara, J.; Moriyama, K.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 223, and other papers in this series.

¹³ Fodor, G.; Bruckner, V.; Kiss, J.; Óhegyi, G. *J. Org. Chem.* **1949**, *14*, 337.

¹⁴ See Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, **1962**, pp. 219–234.

¹⁵ Barton, D.H.R.; McCapra, F.; May, P.J.; Thudium, F. *J. Chem. Soc.* **1960**, 1297.

9.C. QUANTITATIVE TREATMENTS OF THE EFFECT OF STRUCTURE ON REACTIVITY¹⁶

Suppose a reaction is performed on a substrate molecule that can be represented as XGY, where Y is the site of the reaction, X a variable substituent, and G is a skeleton group to which X and Y are attached. In such a molecule, changing X from H to CH₃ results in a rate increase by a factor, of say, 10. What part of the increase is due to each of the effects previously mentioned? The obvious way to approach such a problem is to try to find compounds in which one or two of the factors are absent or at least negligible. This is difficult because factors that seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.¹⁷ For the cases of *m*- and *p*-XC₆H₄Y, Hammett set up the equation

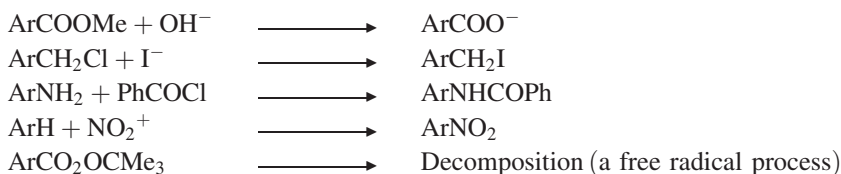
$$\log \frac{k}{k_0} = \sigma \rho$$

where k_0 is the rate constant or equilibrium constant for X = H, k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions, and σ is a constant characteristic of the group X. The equation is called the *Hammett equation*.

The value of ρ was set at 1.00 for ionization of XC₆H₄COOH in water at 25°C. The values of σ_m and σ_p were then calculated for each group (for a group X, σ is different for the meta and para positions). Once a set of σ values was obtained, ρ values could be obtained for other reactions from the rates of just two X-substituted compounds, if the σ values of the X groups were known (in practice, at least four well-spaced values are used to calculate ρ because of experimental error and because the treatment is not exact). With the ρ value calculated and the known σ values for other groups, rates can be predicted for reactions that have not yet been run.

The σ values are numbers that sum up the total electrical effects (resonance plus field) of a group X when attached to a benzene ring. The treatment usually fails for the ortho position. The Hammett treatment has been applied to many reactions and to many functional groups. It correlates an enormous amount of data quite well. Jaffé's review article¹⁷ listed ρ values for 204 reactions,¹⁸ many of which have different ρ values for different conditions. Among them are reactions as disparate as the following reactions.

Rate constants for the following:

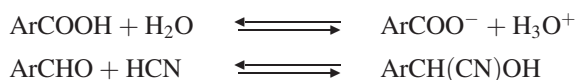


¹⁶ See Exner, O. *Correlation Analysis of Chemical Data*, Plenum, NY, **1988**; Johnson, C.D. *The Hammett Equation*, Cambridge University Press, Cambridge, **1973**; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, **1982**; Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, **1978**. Also see Connors, K.A. *Chemical Kinetics*, VCH, NY, **1990**, pp. 311–383; Lewis, E.S. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions* (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 4th ed., Wiley, NY, **1986**, pp. 871–901; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, **1984**, pp. 38–68; Hine, J. *Structural Effects in Organic Chemistry*, Wiley, NY, **1975**, pp. 55–102. For a historical perspective, see Grunwald, E. *CHEMTECH* **1984**, 698.

¹⁷ For a review, see Jaffé, H.H. *Chem. Rev.* **1953**, 53, 191.

¹⁸ Additional ρ values are given in Wells, P.R. *Chem. Rev.* **1963**, 63, 171 and van Bekkum, H.; Verkade, P.E.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* **1959**, 78, 821.

Equilibrium constants for



The *Hammett equation* also has been shown to apply to many physical measurements, including IR frequencies and NMR chemical shifts.¹⁹ The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free radical reagents, the important thing being that the mechanism be the same *within* a given reaction series.

However, there are many reactions that do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group can enter into direct resonance interaction with the reaction site in the transition state (i.e., the substrate is XY rather than XGY). For these cases, two new sets of σ values have been devised: σ^+ values (proposed by H.C. Brown) for cases in which an electron-donating group interacts with a developing positive charge in the transition state (this includes the important case of electrophilic aromatic substitutions; see Chapter 11), and σ^- values, where electron-withdrawing groups interact with a developing negative charge. Table 9.4 gives σ , σ^+ , and σ^- values for some common X groups.²⁰ As shown in the table, σ is not very different from σ^+ for most electron-withdrawing groups. The values of σ_m^- are not shown in the table, since they are essentially the same as the σ_m values.

A positive value of σ indicates an electron-withdrawing group and a negative value an electron-donating group.²¹ The constant ρ measures the susceptibility of the reaction to electrical effects.²² Reactions with a positive ρ are helped by electron-withdrawing groups and vice versa. The following ρ values for the ionization of some carboxylic acids illustrate this.²³

TABLE 9.4 The σ , σ^+ , and σ^- Values for Some Common Groups^a

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
O ⁻	-0.81 ^b	-0.47 ^b	-4.27 ^c	-1.15 ^c	
NMe ₂	-0.63	10.10	-1.7		
NH ₂	-0.57	-0.09	-1.3	-0.16	
OH	-0.38 ^d	0.13 ^d	-0.92 ^c		
OMe	-0.28 ^d	0.10	-0.78	0.05	
CMe ₃	-0.15	-0.09	-0.26	-0.06	
Me	-0.14	-0.06	-0.31	-0.10 ^f	
H	0	0	0	0	0
Ph	0.05 ^g	0.05	-0.18	0 ^g	
COO ⁻	0.11 ^b	0.02 ^b	-0.41 ^c	-0.10 ^c	

(continued)

¹⁹ For a review of *Hammett* treatment of NMR chemical shifts, see Ewing, D.F. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, **1978**, pp. 357–396.

²⁰ Unless otherwise noted, σ values are from Exner, O. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, **1978**, pp. 439–540, and σ^+ values from Okamoto, Y.; Inukai, T.; Brown, H.C. *J. Am. Chem. Soc.* **1958**, *80*, 4969; Brown, H.C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979. σ^- values, except as noted, are from Jaffé, H.H. *Chem. Rev.* **1953**, *53*, 191. Also see Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* **1991**, *91*, 165; Egorochkin, A.N.; Razuvaev, G.A. *Russ. Chem. Rev.* **1987**, *56*, 846. For values for heteroaromatic groups, see Mamaev, V.P.; Shkurko, O.P.; Baram, S.G. *Adv. Heterocycl. Chem.* **1987**, *42*, 1.

²¹ See Dubois, J.E.; Ruasse, M.; Argile, A. *J. Am. Chem. Soc.* **1984**, *106*, 4840; Ruasse, M.; Argile, A.; Dubois, J.E. *J. Am. Chem. Soc.* **1984**, *106*, 4846; Lee, I.; Shim, C.S.; Chung, S.Y.; Kim, H.Y.; Lee, H.W. *J. Chem. Soc. Perkin Trans. 2* **1988**, 1919.

²² Hine, J. *J. Am. Chem. Soc.* **1960**, *82*, 4877.

²³ Binev, I.G.; Kuzmanova, R.B.; Kaneti, J.; Juchnovski, I.N. *J. Chem. Soc. Perkin Trans. 2* **1982**, 1533.

TABLE 9.4 (Continued)

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
F	0.15	0.34	-0.07	0.35	
Cl	0.24	0.37	0.11	0.40	
Br	0.26	0.37	0.15	0.41	
I	0.28 ^g	0.34	0.14	0.36	
N=NPh ^h	0.34	0.28	0.17		
COOH ⁱ	0.44	0.35	0.42	0.32	0.73
COOR	0.44	0.35	0.48	0.37	0.68
COMe	0.47	0.36			0.87
CF ₃	0.53	0.46		0.57 ^f	
NH ₃ ⁺	0.60 ^c	0.86 ^d			
CN ^j	0.70	0.62	0.66	0.56	1.00
SO ₂ Me	0.73	0.64			
NO ₂	0.81	0.71	0.79	0.73 ^f	1.27
NMe ₃ ⁺	0.82 ^k	0.88 ^k	0.41	0.36	
N ₂ ⁺	1.93 ^l	1.65 ^l	1.88 ^l		3 ^m

^aSee Ref. 20.^bSee Ref. 24.^cSee Ref. 25.^dSee Ref. 26.^eSee Ref. 27.^fSee Ref. 28.^gSee Ref. 29.^hSee Ref. 30.ⁱSee Ref. 31.^jSee Ref. 32.^kSee Ref. 33.^lSee Ref. 34.^mSee Ref. 35.

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²⁴ Hine, J. *J. Am. Chem. Soc.* **1960**, *82*, 4877; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge Univ. Press, Cambridge, **1984**, p. 42.

²⁵ See Hine, J. *J. Am. Chem. Soc.* **1960**, *82*, 4877.

²⁶ Matsui, T.; Ko, H.C.; Hepler, L.G. *Can. J. Chem.* **1974**, *52*, 2906.

²⁷ de la Mare, P.B.D.; Newman, P.A. *Tetrahedron Lett.* **1982**, *23*, 1305 give this value as -1.6.

²⁸ Amin, H.B.; Taylor, R. *Tetrahedron Lett.* **1978**, 267.

²⁹ Sjöström, M.; Wold, S. *Chem. Scr.* **1976**, *9*, 200.

³⁰ Byrne, C.J.; Happer, D.A.R.; Hartshorn, M.P.; Powell, H.K.J. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1649.

³¹ For a review of directing and activating effects of C=O, C=C, C=N, and C=S groups, see Charton, M. in Patai, S. *The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, **1989**, pp. 239–298.

³² For a review of directing and activating effects of C≡N and C≡C groups, see Charton, M. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, **1983**, pp. 269–323.

³³ McDaniel, D.H.; Brown, H.C. *J. Org. Chem.* **1958**, *23*, 420.

³⁴ Ustynyuk, Yu.A.; Subbotin, O.A.; Buchneva, L.M.; Gruzdnova, V.N.; Kazitsyna, L.A. *Doklad. Chem.* **1976**, *227*, 175.

³⁵ Lewis, E.S.; Johnson, M.D. *J. Am. Chem. Soc.* **1959**, *81*, 2070.

$\text{XC}_6\text{H}_4\text{—COOH}$	1.00	$\text{XC}_6\text{H}_4\text{—CH=CH—COOH}$	0.47
$\text{XC}_6\text{H}_4\text{—CH}_2\text{—COOH}$	0.49	$\text{XC}_6\text{H}_4\text{—CH}_2\text{CH}_2\text{—COOH}$	0.21

This example shows that the insertion of a CH_2 or a CH=CH group diminishes electrical effects to about the same extent, while a CH_2CH_2 group diminishes them much more. A $\rho > 1$ would mean that the reaction is more sensitive to electrical effects than is the ionization of $\text{XC}_6\text{H}_4\text{COOH}$ ($\rho = 1.00$).

Similar calculations have been made for compounds with two groups X and X' on one ring, where the σ values are sometimes additive and sometimes not,³⁶ for other ring systems, (e.g., naphthalene)³⁷ and heterocyclic rings,³⁸ and for ethylenic and acetylenic systems.³⁹

The *Hammett equation* is a *linear free energy relationship* (LFER). This relationship can be demonstrated as follows for the case of equilibrium constants (for rate constants a similar demonstration can be made with ΔG^\ddagger instead of ΔG). For each reaction, where X is any group,

$$\Delta G = -RT \ln K$$

For the unsubstituted case,

$$\Delta G_0 = -RT \ln K_0$$

The Hammett equation can be rewritten

$$\log K - \log K_0 = \sigma \rho$$

so that

$$\frac{-\Delta G}{2.3 RT} = \frac{\Delta G_0}{2.3 RT} = \sigma \rho$$

and

$$-\Delta G = \sigma \rho 2.3 RT - \Delta G_0$$

For a given reaction under a given set of conditions, σ , R , T , and ΔG_0 are all constant, so that σ is linear with ΔG .

The Hammett equation is not the only LFER.⁴⁰ Some, like the Hammett equation, correlate structural changes in reactants, but the *Grunwald–Winstein relationship*

³⁶ Stone, R.M.; Pearson, D.E. *J. Org. Chem.* **1961**, *26*, 257.

³⁷ Berliner, E.; Winikov, E.H. *J. Am. Chem. Soc.* **1959**, *81*, 1630; See also, Well, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys. Org. Chem.* **1968**, *6*, 147.

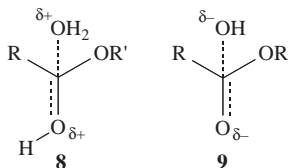
³⁸ See Charton, M. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, **1978**, pp. 175–268; Tomasik, P.; Johnson, C.D. *Adv. Heterocycl. Chem.* **1976**, *20*, 1.

³⁹ See Ford, G.P.; Katritzky, A.R.; Topsom, R.D. in *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, **1978**, pp. 269–311; Charton, M. *Prog. Phys. Org. Chem.* **1973**, *10*, 81.

⁴⁰ See Exner, O. *Prog. Phys. Org. Chem.* **1990**, *18*, 129.

(see Sec. 10.G.iv) correlates changes in solvent and the *Brønsted relation* (see Sec. 8.D) relates acidity to catalysis. The *Taft equation* is a structure–reactivity equation that correlates only field effects.⁴¹

Taft, following Ingold,⁴² assumed that for the hydrolysis of carboxylic esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester-hydrolysis mechanisms, Reaction **16-59**). Rate differences would therefore be caused only by the field effects of R and R'



in RCOOR'. This system is presumably good to use for this purpose because the transition state for acid-catalyzed hydrolysis (**8**) has a greater positive charge (and is hence destabilized by $-I$ and stabilized by $+I$ substituents) than the starting ester, while the transition state for base-catalyzed hydrolysis (**9**) has a greater negative charge than the starting ester. Field effects of substituents X could therefore be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a series XCH₂COOR',⁴³ where R' is held constant.³⁸ From these rate constants, a value σ_I could be determined by the equation⁴⁴

$$\sigma_I + 0.181 \left[\log \left(\frac{k}{k_0} \right)_B - \log \left(\frac{k}{k_0} \right)_A \right]$$

In this equation, $(k/k_0)_B$ is the rate constant for basic hydrolysis of XCH₂COOR' divided by the rate constant for basic hydrolysis of CH₃COOR', $(k/k_0)_A$ is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. The substituent constant σ_I is for a group X, substituted at a saturated carbon, which reflects only field effects.⁴⁵ Once a set of σ_I values was obtained, it was found that the equation

$$\sigma_I + 0.181 \left[\log \left(\frac{k}{k_0} \right)_B - \log \left(\frac{k}{k_0} \right)_A \right]$$

⁴¹ For reviews of the separation of resonance and field effects, see Charton, M. *Prog. Phys. Org. Chem.* **1981**, 13, 119; Shorter, J. *Q. Rev. Chem. Soc.* **1970**, 24, 433; *Chem. Ber.* **1969**, 5, 269. For a review of field and inductive effects, see Reynolds, W.F. *Prog. Phys. Org. Chem.* **1983**, 14, 165. For a review of field effects on reactivity, see Grob, C.A. *Angew. Chem. Int. Ed.* **1976**, 15, 569.

⁴² Ingold, C.K. *J. Chem. Soc.* **1930**, 1032.

⁴³ Also see Draffehn, J.; Ponsold, K. *J. Prakt. Chem.* **1978**, 320, 249.

⁴⁴ The symbol σ_F is also used in the literature; sometimes in place of σ_I , and sometimes to indicate only the field (not the inductive) portion of the total effect (Sec. 1.G).

⁴⁵ There is another set of values (called σ^* values) that are also used to correlate field effects. These are related to σ_I values by $\sigma_{I(X)} = 0.45\sigma$. Only σ_I , and not σ^* values are discussed.

TABLE 9.5 The σ_I and σ_R^0 Values for Some Groups^a

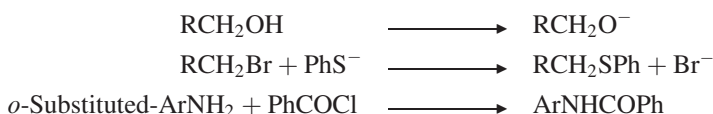
Group (R)	σ_I	σ_R^0	Group (R)	σ_I	σ_R^0
CMe ₃	-0.07	-0.17	OMe	0.27	-0.42
Me	-0.05	-0.13	OH	0.27	-0.44
H	0	0	I	0.39	-0.12
PhCH ₂	0.04		CF ₃	0.42	0.08
NMe ₃ ^b	0.06	-0.55	Br	0.44	-0.16
Ph	0.10	-0.10	Cl	0.46	-0.18
CH ₃ COCH ₂	0.10		F	0.50	-0.31
NH ₂	0.12	-0.50	CN	0.56	0.08
CH ₃ CO	0.20	0.16	SO ₂ Me	0.60	0.12
COOEt	0.20	0.16	NO ₂	0.65	0.15
NHAc	0.26	-0.22	NMe ₃ ⁴⁹	0.86	

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^aSee Ref. 47.

^bSee Ref. 48.

holds for a number of reactions, among them:⁴⁶



As with the Hammett equation, σ_I is constant for a given reaction under a given set of conditions. For very large groups, the relationship may fail because of the presence of steric effects, which are not constant. The equation also fails when X enters into resonance with the reaction center to different extents in the initial and transition states. A list of some σ_I values is given in Table 9.5.⁴⁷ The σ_I values are about what is expected for pure field-effect values (see Sec. 1.I) and are additive, as field effects (but not resonance or

⁴⁶ Wells, P.R. *Chem. Rev.* **1963**, *63*, 171, p. 196.

⁴⁷ These values are from Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* **1979**, *44*, 4766, but the values for NHAc, OH, and I are from Wells, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys. Org. Chem.* **1968**, *6*, 147, the values for Ph and NMe₃⁺ are from Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R. *J. Am. Chem. Soc.* **1959**, *81*, 5352; Taft, R.W.; Deno, N.C.; Skell, P.S. *Annu. Rev. Phys. Chem.* **1958**, *8*, 287, and the value for CMe₃ is from Seth-Paul, W.A.; de Meyer-van Duyse, A.; Tollenaere, J.P. *J. Mol. Struct.* **1973**, *19*, 811. The values for the CH₂Ph and CH₂COCH₃ groups were calculated from σ^* values by the formula given in ref. 45. Also see Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119; Taylor, P.J.; Wait, A.R. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1765.

⁴⁸ For σ_R^0 values for some other NR₂ groups, see Korzhenevskaya, N.G.; Titov, E.V.; Chotii, K.Yu.; Chekhuta, V.G. *J. Org. Chem. USSR* **1987**, *28*, 1109.

⁴⁹ It has been shown that charged groups (called polar substituents) cannot be included with uncharged groups (dipolar substituents) in one general scale of electrical substituent effects: Marriott, S.; Reynolds, J.D.; Topsom, R. D. *J. Org. Chem.* **1985**, *50*, 741.

steric effects) would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (cf. the values of R in Table 9.5 for $R = \text{Ph}$ and CH_3CO). An inspection of Table 9.5 shows that σ_I values for most groups are fairly close to the σ_m values (Table 9.4) for the same groups. This result is not surprising, since σ_m values would be expected to arise almost entirely from field effects, with little contribution from resonance.

Since σ_p values represent the sum of resonance and field effects, these values can be divided into resonance and field contributions if σ_I is taken to represent the field-effect portion.⁵⁰ The resonance contribution σ_R ⁵¹ is defined as:

$$\sigma_R = \sigma_p - \sigma_I$$

As it stands, however, this equation is not very useful because the σ_R value for a given group, which should be constant if the equation is to have any meaning, is actually not constant, but depends on the nature of the reaction.⁵² In this respect, the σ_I values are much better. Although they vary with solvent in some cases, σ_I values are essentially invariant throughout a wide variety of reaction series. However, it is possible to overcome⁵³ the problem of varying σ_R values by using a special set of σ_R values, called σ_R^0 ,⁵⁴ that measure the ability to delocalize π electrons into or out of an unperturbed or "neutral" benzene ring. Several σ_R^0 scales have been reported; the most satisfactory values are obtained from ^{13}C chemical shifts of substituted benzenes.⁵⁵ Table 9.5 lists some values of σ_R^0 , most of which were obtained in this way.⁵⁶

An equation, for example,

$$\log \frac{k}{k_0} = \rho_I \sigma_I + \rho_R \sigma_R^0$$

which treats resonance and field effects separately, is known as a *dual substituent parameter equation*.⁵⁷

The only groups in Table 9.5 with negative values of σ_I are the alkyl groups methyl and *tert*-butyl. There has been some controversy on this point.⁵⁸ One opinion is that σ_I values decrease in the series methyl, ethyl, isopropyl, *tert*-butyl (respectively, -0.046 , -0.057 , -0.065 , -0.074).⁵⁹ Other evidence, however, has led to the belief that all alkyl groups have

⁵⁰ Taft, R.W. *J. Phys. Chem.* **1960**, *64*, 1805; Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* **1958**, *80*, 2436; Taft, R.W.; Deno, N.C.; Skell, P.S. *Annu. Rev. Phys. Chem.* **1958**, *9*, 287, see pp. 290–293.

⁵¹ Ehrenson, S.; Brownlee, R.T.C.; Taft, R.W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1. See also, Taft, R.W.; Topsom, R.D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1; Charton, M. *Prog. Phys. Org. Chem.* **1987**, *16*, 287.

⁵² Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* **1959**, *81*, 5343; Reynolds, W.F.; Dais, P.; MacIntyre, D.W.; Topsom, R.D.; Marriott, S.; von Nagy-Felsobuki, E.; Taft, R.W. *J. Am. Chem. Soc.* **1983**, *105*, 378.

⁵³ Also see Happer, D.A.R.; Wright, G.J. *J. Chem. Soc. Perkin Trans. 2* **1979**, 694.

⁵⁴ Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R.E. *J. Am. Chem. Soc.* **1959**, *81*, 5352.

⁵⁵ Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* **1979**, *44*, 4766. See also, Marriott, S.; Topsom, R.D. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1045.

⁵⁶ For a set of σ_R values for use in XY^+ systems, see Charton, M. *Mol. Struct. Energ.* **1987**, *4*, 271.

⁵⁷ See de Ligny, C.L.; van Houwelingen, H.C. *J. Chem. Soc. Perkin Trans. 2* **1987**, 559.

⁵⁸ See Shorter, J. in Chapman, N.B.; Shorter, J. *Advances in Linear Free Energy Relationships*, Plenum, NY, **1972**, pp. 98–103.

⁵⁹ See Screttas, C.G. *J. Org. Chem.* **1979**, *44*, 3332; Hanson, P. *J. Chem. Soc. Perkin Trans. 2* **1984**, 101.

TABLE 9.6 The F and R Values for Some Groups^a

Group	F	R	Group	F	R
COO ⁻	-0.27	0.40	OMe	0.54	-1.68
Me ₃ C	-0.11	-0.29	CF ₃	0.64	0.76
Et	-0.02	-0.44	I	0.65	-0.12
Me	-0.01	-0.41	Br	0.72	-0.18
H	0	0	Cl	0.72	-0.24
Ph	0.25	-0.37	F	0.74	-0.60
NH ₂	0.38	-2.52	NHCOMe	0.77	-1.43
COOH	0.44	0.66	CN	0.90	0.71
OH	0.46	-1.89	NMe ₃ ⁺	1.54	
COOEt	0.47	0.67	N ₂ ⁺	2.36	2.81
COMe	0.50	0.90			

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^aSee Ref. 63.

approximately the same field effect and that the σ_I values are invalid as a measure of the intrinsic field effects of alkyl groups.⁶⁰

Another attempt to divide σ values into resonance and field contributions⁶¹ is that of Swain and Lupton, who show that the large number of sets of σ values (σ_m , σ_p , σ_{p-} , σ_{p+} , σ_I , σ_R^0 , etc., as well as others we have not mentioned) are not entirely independent and that linear combinations of two sets of new values F (which expresses the field-effect contribution) and R (the resonance contribution) satisfactorily express 43 sets of values.⁶² Each set is expressed as:

$$\sigma = f_F + r_R$$

where f and r are weighting factors. Some F and R values for common groups are given in Table 9.6.⁶³ From the calculated values of f and r , Swain and Lupton⁶³ calculated that the importance of resonance, % R , is 20% for σ_m , 38% for σ_p , and 62% for σ_p^+ .⁶⁴ This is another dual substituent parameter approach.

Taft and co-workers⁶⁵ were also able to isolate steric effects.⁶⁵ For the acid-catalyzed hydrolysis of esters in aqueous acetone, long (k/k_0) was shown to be insensitive to polar effects.⁶⁶ In cases where resonance interaction was absent, this value was proportional only

⁶⁰ See DeTar, D.F. *J. Org. Chem.* **1980**, 45, 5166; *J. Am. Chem. Soc.* **1980**, 102, 7988.

⁶¹ See Shorter, J. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, **1978**, pp. 119–173, pp. 126–144; Afanas'ev, I.B. *J. Chem. Soc. Perkin Trans. 2* **1984**, 1589; Ponec, R. *Coll. Czech. Chem. Commun.* **1983**, 48, 1564.

⁶² Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* **1983**, 105, 492 and references cited therein.

⁶³ From Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* **1983**, 105, 492. Also see Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* **1991**, 91, 165.

⁶⁴ The Swain-Lupton treatment has been criticized by Reynolds, W.F.; Topsom, R.D. *J. Org. Chem.* **1984**, 49, 1989; Hoefnagel, A.J.; Oosterbeek, W.; Wepster, B.M. *J. Org. Chem.* **1984**, 49, 1993; Charton, M. *J. Org. Chem.* **1984**, 49, 1997. For a reply, see Swain, C.G. *J. Org. Chem.* **1984**, 49, 2005. See Charton, M. *Prog. Phys. Org. Chem.* **1981**, 13, 119; Nakazumi, H.; Kitao, T.; Zollinger, H. *J. Org. Chem.* **1987**, 52, 2825.

⁶⁵ See Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* **1988**, 43, 173; Gallo, R. *Prog. Phys. Org. Chem.* **1983**, 14, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, 12, 91.

⁶⁶ Also see De Tar, D.F.; Delahunty, C. *J. Am. Chem. Soc.* **1983**, 105, 2734.

TABLE 9.7 The E_s , v , and V^a Values for Some Groups^a

Group	E_s	v	$V^a \times 10^2$	Group	E_s	v	$V^a \times 10^2$
H	0	0		Cyclohexyl	-2.03	0.87	6.25
F	-0.46	0.27	1.22	<i>i</i> -Bu	-2.17	0.98	5.26
CN	-0.51			<i>sec</i> -Bu	-2.37	1.02	6.21
OH	-0.55			CF ₃	-2.4	0.91	3.54
OMe	-0.55		3.39	<i>t</i> -Bu	-2.78	1.24	7.16
NH ₂	-0.61			NMe ₃ ⁺	-2.84		
Cl	-0.97	0.55	2.54	Neopentyl	-2.98	1.34	5.75
Me	-1.24	0.52	2.84	CCl ₃	-3.3	1.38	6.43
Et	-1.31	0.56	4.31	CBr ₃	-3.67	1.56	7.29
I	-1.4	0.78	4.08	(Me ₃ CCH ₂) ₂ CH	-4.42	2.03	
Pr	-1.6	0.68	4.78	Et ₃ C	-5.04	2.38	
<i>i</i> Pr	-1.71	0.76	5.74	Ph ₃ C	-5.92	2.92	

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^aSee Ref. 68.

to steric effects (and any others⁶⁷ that are not field or resonance). The equation is

$$\log \frac{k}{k_0} = E_s$$

Some E_s values are given in Table 9.7,⁶⁸ where hydrogen is taken as standard, with a value of 0.⁶⁹ This treatment is more restricted than those previously discussed, since it requires more assumptions, but the E_s values are approximately in order of the size of the groups. Charton⁷⁰ show that E_s values for substituents of types CH₂X, CHX₂, and CX₃ are linear functions of the *van der Waals radii* for these groups.

Two other steric parameters are independent of any kinetic data. Charton's v values are derived from *van der Waals radii*,⁷¹ and Meyer's V^a values from the volume of the portion of the substituent that is within 0.3 nm of the reaction center.⁷² The V^a values are obtained by molecular mechanics calculations based on the structure of the molecule. Table 9.7 gives v and V^a values for some groups.⁷³ As can be seen in the table, there is a fair, but not perfect, correlation among the E_s , v , and V^a values. Other sets of steric values (e.g., E_S^1 ,⁷⁴ E_S^* ,⁷⁵ Ω_s ,⁷⁶ and δ_f ,⁷⁷ have also been proposed.⁷³

⁶⁷ See McClelland, R.A.; Steenken, S. *J. Am. Chem. Soc.* **1988**, 110, 5860.

⁶⁸ Taken from Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* **1988**, 43, 173; Gallo, R. *Prog. Phys. Org. Chem.* **1983**, 14, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, 12, 91. Charton, M. *J. Org. Chem.* **1976**, 41, 2217; and Meyer, A.Y. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1567.

⁶⁹ In Taft's original work, Me was given the value 0. The E_s values in Table 9.7 can be converted to the original values by adding 1.24.

⁷⁰ Charton, M. *J. Am. Chem. Soc.* **1969**, 91, 615.

⁷¹ Charton, M. *J. Am. Chem. Soc.* **1975**, 97, 1552; *J. Org. Chem.* **1976**, 41, 2217. See also, Charton, M. *J. Org. Chem.* **1978**, 43, 3995; Idoux, J.P.; Schreck, J.O. *J. Org. Chem.* **1978**, 43, 4002.

⁷² Meyer, A.Y. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1567.

⁷³ See DeTar, D.F. *J. Org. Chem.* **1980**, 45, 5166; *J. Am. Chem. Soc.* **1980**, 102, 7988.

⁷⁴ MacPhee, J.A.; Panaye, A.; Dubois, J.E. *J. Org. Chem.* **1980**, 45, 1164; Dubois, J.E.; MacPhee, J.A.; Panaye, A. *Tetrahedron* **1980**, 36, 919. See also, Datta, D.; Sharma, G.T. *J. Chem. Res. (S)* **1987**, 422.

⁷⁵ Fellous, R.; Luft, R. *J. Am. Chem. Soc.* **1973**, 95, 5593.

⁷⁶ Komatsuzaki, T.; Sakakibara, K.; Hirota, M. *Tetrahedron Lett.* **1989**, 30, 3309; *Chem. Lett.* **1990**, 1913.

⁷⁷ Beckhaus, H. *Angew. Chem. Int. Ed.* **1978**, 17, 593.

Since the *Hammett equation* has been so successful in the treatment of the effects of groups in the meta and para positions, it is not surprising that attempts have been made to apply it to ortho positions also.⁷⁸ The effect on a reaction rate or equilibrium constant of a group in the ortho position is called the *ortho effect*.⁷⁹ Despite the many attempts made to quantify ortho effects, no set of values has so far commanded general agreement. However, the Hammett treatment is successful for ortho compounds when the group Y in *o*-XC₆H₄Y is separated from the ring; for example, ionization constants of *o*-XC₆H₄OCH₂CO₂H can be successfully correlated.⁸⁰

Linear free energy relationships can have mechanistic implications. If $\log k/k_0$ is linear with the appropriate σ , it is likely that the same mechanism operates throughout the series. If not, a smooth curve usually indicates a gradual change in mechanism, while a pair of intersecting straight lines indicates an abrupt change,⁸¹ although nonlinear plots can also be due to other causes (e.g., complications arising from side reactions). If a reaction series follows σ^+ or σ^- better than σ it generally means that there is extensive resonance interaction in the transition state.⁸²

Information can also be obtained from the magnitude and sign of ρ . For example, a strongly negative ρ value indicates a large electron demand at the reaction center, from which it may be concluded that a highly electron-deficient center, perhaps an incipient carbocation, is involved. Conversely, a positive ρ value is associated with a developing negative charge in the transition state.⁸³ The $\sigma\rho$ relationship even applies to free radical reactions, because free radicals can have some polar character (Sec. 14.A.ii), though ρ values here are usually small (less than ~ 1.5) whether positive or negative. Reactions involving cyclic transition states (Sec. 6.B) also exhibit very small ρ values.

9.D. EFFECT OF MEDIUM ON REACTIVITY AND RATE

There is no question that the solvent chosen for a given reaction has a profound influence on the course of that reaction. Protic versus aprotic solvents, as well as polar versus nonpolar solvents, can have effects ranging from solubility to solvent assisted ionization or stabilization of transition states. Reactions can also be done neat in one of the reactants, in the gas phase, on solid support, or in the solid phase. Environmental friendly chemistry (green chemistry) is becoming increasingly important, and chemical reactions in non-polluting (often non-organic) solvents are of particular interest.⁸⁴ This section will describe alternative reaction media as well as other medium-related things that influence chemical reactions.

⁷⁸ See Fujita, T.; Nishioka, T. *Prog. Phys. Org. Chem.* **1976**, *12*, 49; Charton, M. *Prog. Phys. Org. Chem.* **1971**, *8*, 235. See also, Robinson, C.N.; Horton, J.L.; Fosheé, D.O.; Jones, J.W.; Hanissian, S.H.; Slater, C.D. *J. Org. Chem.* **1986**, *51*, 3535.

⁷⁹ This is not the same as the ortho effect discussed in Section 11.B.iv.

⁸⁰ Charton, M. *Can. J. Chem.* **1960**, *38*, 2493.

⁸¹ See Schreck, J.O. *J. Chem. Educ.* **1971**, *48*, 103.

⁸² See, however, Gawley, R.E. *J. Org. Chem.* **1981**, *46*, 4595.

⁸³ Also see Williams, A. *Acc. Chem. Res.* **1984**, *17*, 425.

⁸⁴ Clark, J.H. *Green Chem.* **1999**, *1*, 1; Cave, G.W.V.; Raston, C.L.; Scott, J.L. *Chem. Commun.* **2001**, 2159.

9.D.i High Pressure

Acceleration of some chemical reactions is possible when high-pressure techniques are employed.^{85,86} The effects on a given reaction can be predicted to a certain extent because the thermodynamic properties of solutions are well known. The rate of a reaction can be expressed in terms of the activation volume, (ΔV^\ddagger)

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^\ddagger}{RT}$$

so rate constants vary with pressure.⁸⁶ “The activation volume⁸⁷ is the difference in partial molal volume between the transition state and the initial state. From a synthetic point of view, this could be approximated by the molar volume.”⁸⁶ If the volume of activation is negative, the rate of the reaction will be accelerated by increasing pressure. As the pressure increases, the value of ΔV^\ddagger decreases and the system does not strictly obey the equation shown above at pressures > 10 kbar (1 bar = 0.986924 atm = 1.1019716 kg cm⁻²). If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. There is a correlation between pressure and steric interactions in organic reactions.⁸⁸ Cleavage of a bond, dispersal of charge, or neutralization of the transition state and diffusion control lead to a positive volume of activation. Matsumoto et al. summarized the reactions for which rate enhancement is expected at high pressure.⁸⁶

1. Reactions in which the molecularity number (number of molecules) decreases when starting materials are converted to products: cycloadditions and condensations.
2. Reactions that proceed via cyclic transition states.
3. Reactions that take place through dipolar transition states.
4. Reactions with steric hindrance.

Many high-pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, and this influences the viscosity of the medium (the viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important, leading to another influence of high pressure on reactivity.^{86,89} In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place. The temperature is lowered and the pressure is reduced to isolate the products.

⁸⁵ Jenner, G. *Tetrahedron* **2002**, 58, 5185; Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, New York, **1991**.

⁸⁶ Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1; Matsumoto, K.; Sera, A. *Synthesis*, **1985**, 999. Also see Benito-López, F.; Egberink, R.J.M.; Reinhoudt, D.N.; Verboom, W. *Tetrahedron* **2008**, 64, 10023.

⁸⁷ See le Noble, W.J. *Progr. Phys. Org. Chem.* **1967**, 5, 207; Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, **1981**; Asano, T.; le Noble, W.J. *Chem. Rev.* **1978**, 78, 407.

⁸⁸ Jenner, G. *Tetrahedron* **2005**, 61, 3621.

⁸⁹ Firestone, R.A.; Vitale, M.A. *J. Org. Chem.* **1981**, 46, 2160.

9.D.ii Water and Other Non-Organic Solvents

Although some reactions may be done in water,⁹⁰ chemical reactions of organic substrates usually employ an organic solvent (e.g., a hydrocarbon, ether, dichloromethane, small molecular weight alcohols, and so on), but other more exotic solvents are available. For example, poly(ethylene glycol), or PEG, has been used as a solvent medium for catalytic hydrogenation (Reaction **15-11**).⁹¹ For some reactions in organic solvents, the presence of water may cause unwanted side reactions, and methods have been developed to detect the presence of water in those solvents.⁹²

With the exception of small molecular weight molecules with polar functional groups and polyfunctional molecules or salts, organic chemicals have poor solubility in water. Nonetheless, some reactions show a faster rate of reaction in water or in aqueous media.⁹³ The first indication that water accelerated a reaction was in a patent by Hopff and Rautenstrauch in 1939,⁹⁴ who reported that yields in the *Diels–Alder Reaction* (**15-60**) were enhanced in aqueous detergent solutions. In an early study, Berson et al.⁹⁵ showed a clear relationship between the endo/exo product ratio and solvent polarity, in the Diels–Alder reaction of cyclopentadiene and acrylates. Breslow and Rideout.⁹⁶ showed there was a hydrophobic acceleration for an intermolecular *Diels–Alder reaction* in which cyclopentadiene reacted with methyl vinyl ketone. Clearly, there is an accelerating effect on some chemical reactions when done in water that is useful in organic chemistry.⁹⁷

When nonpolar compounds are suspended in water, their relative insolubility causes them to associate, diminishing the water–hydrocarbon interfacial area (a hydrophobic effect).⁹⁸ This association is greater in water than in methanol and brings the reactive partners into close proximity, increasing the rate of reaction. Any additive that increases the hydrophobic effect will increase the rate.⁹⁶

Organic chemical reactions have been done in supercritical fluids, including supercritical water.⁹⁹ A supercritical fluid can be either liquid or gas, but it is used in a state above the temperature and pressure where gases and liquids can coexist. The properties of a supercritical fluid are different from those of either gases or liquids under standard conditions, with no distinct liquid and gas phases at temperatures and pressures above its critical point. The critical point is the temperature, pressure, and so on, at which there are no phase boundaries. Carbon dioxide can be used as a reaction solvent when pressurized (supercritical carbon dioxide, scCO₂). Carbon dioxide is nontoxic,

⁹⁰ *Organic Reactions in Water: Principles, Strategies and Applications*, Lindström, U.M. (Ed.), Blackwell, Oxford, **2007**; Chanda, A.; Fokin, V.V. *Chem. Rev.* **2009**, *109*, 725.

⁹¹ Chandrasekhar, S.; Prakash, S.J.; Rao, C.L. *J. Org. Chem.* **2006**, *71*, 2196. PEG has also been used for the synthesis of β -amino sulfides. See Kamal, A.; Reddy, D.R.; Rajendar *Tetrahedron Lett.* **2006**, *47*, 2261.

⁹² Sun, H.; Wang, B.; DiMagno, S.G. *Org. Lett.* **2008**, *10*, 4413.

⁹³ See Pirrung, M.C. *Chemistry: European J.* **2006**, *12*, 1312.

⁹⁴ Hopff, H.; Rautenstrauch, C.W. *U.S. Patent* 2,262,002, **1939** [*Chem. Abstr.* *36*: 1046⁹, **1942**].

⁹⁵ Berson, J.A.; Hamlet, Z.; Mueller, W.A. *J. Am. Chem. Soc.* **1962**, *84*, 297.

⁹⁶ Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

⁹⁷ Engberts, J.B.F.N.; Blandamer, M.J. *Chem. Commun.* **2001**, 1701; Lindström, U.M. *Chem. Rev.* **2002**, *102*, 2751; Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.

⁹⁸ For a review of chemical reactions in aqueous media with a focus on C—C bond formation, see Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. For microwave assisted synthesis in water, see Dallinger, D.; Kappe, C.O. *Chem. Rev.* **2007**, *107*, 2563.

⁹⁹ Weingärtner, H.; Franck, E.U. *Angew. Chem. Int. Ed.* **2005**, *44*, 2672; Fraga-Dubreuil, J.; Poliakoff, M. *Pure Appl. Chem.* **2006**, *78*, 1971.

inexpensive, abundant, and easily recycled. These properties have made it attractive as an extraction solvent.¹⁰⁰ The low critical temperature of CO₂ (T_c) 31.1 °C ensures that scCO₂ is a safe solvent for many applications.¹⁰¹ There are solubility issues that suggest scCO₂ is a rather polar solvent.¹⁰² For example, many systems with hydrocarbon chains are not very soluble in CO₂.¹⁰³ Water/carbon dioxide emulsions have also been employed.¹⁰⁴ The use of (scCO₂) has been explored in many reactions,¹⁰⁵ including catalysis.¹⁰⁶ Some applications of this technique include the electrochemical synthesis of conducting polymers¹⁰⁷ and highly cross-linked polymers¹⁰⁸ in scCO₂, the synthesis of octyl palmitate,¹⁰⁹ of carbonated fatty methyl esters,¹¹⁰ and of methyl carbamates.¹¹¹ A carbonylation reaction was done in scCO₂ in the course of a synthesis of trisubstituted cyclopentanes and cyclohexanes as key components of substance P antagonists.¹¹² A continuous flow acid-catalyzed dehydration of alcohols was accomplished in scCO₂.¹¹³ Supercritical fluids are playing an increasingly important role in synthetic organic chemistry.¹¹⁴

Other supercritical fluids can be used for chemical reactions, such as supercritical ammonia in the synthesis of labeled guanidines.¹¹⁵

9.D.iii Ionic Solvents

Environmentally friendly solvents,¹¹⁶ which include ionic liquids, are of great interest.¹¹⁷ An ionic liquid is a salt in which the ions are poorly coordinated, usually leading to their being liquid at <100 °C and sometimes at room temperature.¹¹⁸ In such ionic species, there is usually at least one ion with a delocalized charge, whereas the other component is usually organic. This combination inhibits the formation of a stable crystal lattice. The structure and solvation properties of solutes in ionic liquids have been studied.¹¹⁹ It was discovered

¹⁰⁰ See Raynie, D.E. *Anal. Chem.* **2004**, 76, 4659.

¹⁰¹ Subramaniam, B.; Rajewski, R. A.; Snively, K. *J. Pharm. Sci.* **1997**, 86, 885.

¹⁰² Raveendran, P.; Ikushima, Y.; Wallen, S.L. *Acc. Chem. Res.* **2005**, 38, 478.

¹⁰³ Consani, K.A.; Smith, R.D.J. *Supercrit. Fluids* **1990**, 3, 51.

¹⁰⁴ Jacobson, G.B.; Lee, Jr., C.T.; da Rocha, S.R.P.; Johnston, K.P. *J. Org. Chem.* **1999**, 64, 1207; Jacobson, G.B.; Lee, Jr., C.T.; Johnston, K.P. *J. Org. Chem.* **1999**, 64, 1201.

¹⁰⁵ Gopalan, A.D.; Wai, C.M.; Jacobs, H.K. *Supercritical Carbon Dioxide: Separations and Processes*, American Chemical Society (distributed by Oxford University Press), Washington, DC. **2003**; Beckman, E.J. *Ind. Eng. Chem. Res.* **2003**, 42, 1598; Wang, S.; Kienzle, F. *Ind. Eng. Chem. Res.* **2000**, 39, 4487.

¹⁰⁶ Leitner, W. *Acc. Chem. Res.* **2002**, 35, 746.

¹⁰⁷ Anderson, P.E.; Badlani, R.N.; Mayer, J.; Mabrouk, P.A. *J. Am. Chem. Soc.* **2002**, 124, 10284.

¹⁰⁸ Cooper, A.I.; Hems, W.P.; Holmes, A.B. *Macromolecules* **1999**, 32, 2156.

¹⁰⁹ Madras, G.; Kumar, R.; Modak, J. *Ind. Eng. Chem. Res.* **2004**, 43, 7697, 1568.

¹¹⁰ Doll, K.M.; Erhan, S.Z. *J. Agric. Food Chem.* **2005**, 53, 9608.

¹¹¹ Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* **2005**, 70, 2771.

¹¹² Kuethe, J.T.; Wong, A.; Wu, J.; Davies, I.W.; Dormer, P.G.; Welch, C.J.; Hillier, M.C.; Hughes, D.L.; Reider, P.J. *J. Org. Chem.* **2002**, 67, 5993.

¹¹³ Gray, W.K.; Smail, F.R.; Hitzler, M.G.; Ross, S.K.; Poliakoff, M. *J. Am. Chem. Soc.* **1999**, 121, 10711.

¹¹⁴ See Prajapati, D.; Gohain, M. *Tetrahedron* **2004**, 60, 815.

¹¹⁵ Jacobson, G.B.; Westerberg, G.; Markides, K.E.; Langstrom, B. *J. Am. Chem. Soc.* **1996**, 118, 6868.

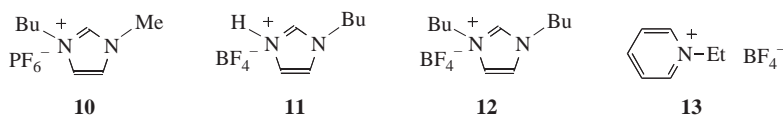
¹¹⁶ *Alternative Solvents for Green Chemistry*, Kerton, F.M.; Clark J.M.; Kraus, G.A. Royal Society of Chemistry, Cambridge, **2009**.

¹¹⁷ But also see Scammells, P.J.; Scott, J.L.; Singer, R.D. *Austr. J. Chem.* **2005**, 58, 155.

¹¹⁸ For a discussion of physical properties, see Ludwig, R.; Kragl, U. *Angew. Chem. Int. Ed.* **2007**, 46, 6582.

¹¹⁹ Hardacre, C.; Holbrey, J.D.; Nieuwenhuyzen, M.; Youngs, T.G.A. *Acc. Chem. Res.* **2007**, 40, 1146; Greaves, T.L.; Drummond, C.J. *Chem. Rev.* **2008**, 108, 206. See also Lungwitz, R.; Strehmel, V.; Spange, S. *New J. Chem.* **2010**, 34, 1135.

that some ionic liquids are suitable as a medium for chemical reactions.¹²⁰ Both methylimidazolium and pyridinium ions form the basis of common ionic liquids that have been used in organic chemistry.¹²¹ One of the most common ionic liquids used as a solvent is 1-butyl-3-methylimidazolium as the hexafluorophosphate, (**10**, Bmim PF₆).¹²² Hydrogenbutylimidazolium tetrafluoroborate (HBuIm, **11**) and 1,3-dibutylimidazolium, tetrafluoroborate (DiBuIm, **12**), for example,¹²³ have been reported to facilitate *Diels–Alder Reactions* (**15–60**).¹²⁴ It is known that a proton on C-2 of imidazolium cations (e.g., **10–12**) is relatively acidic.¹²⁵ Carbene formation is common and the anion generated by treatment with base can undergo substitution reactions.¹²⁵ These facts lead to a caution that undesired side reactions are possible when these ionic liquids are employed as solvents.^{125,126} Pyridinium-based ionic liquids [e.g., ethylpyridinium tetrafluoroborate (**13**)] have also been used.¹²⁷ Several room temperature ionic liquids have been synthesized from amino acids.¹²⁸



Ionic solvents have been used to facilitate heterocyclic reactions,¹²⁹ several catalytic reactions,¹³⁰ the *Heck Reaction* (**13–9**)¹³¹ and other Pd catalyzed C—C bond-forming reactions,¹³² the oxidation of alcohols with hypervalent iodine reagents (**19–3**),¹³³ and the catalytic asymmetric dihydroxylation of alkenes (**15–48**) using a recoverable and reusable Os/ligand complex.¹³⁴ The camphorsulfonate anion has been used as a counterion for imidazolium salts, and shown to increase the number of unsolvated imidazolium cations.¹³⁵ This ionic liquid was then shown to influence the endo/exo ratio in a stereoselective *Diels–Alder Reaction* (**15–60**).¹³⁵ Other catalytic reactions in ionic liquids are known.¹³⁶ Other chiral ionic

¹²⁰ Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, 39, 3772; Earle, M.J.; Seddon, K.R. *Pure. Appl. Chem.* **2000**, 72, 1391; *Ionic Liquids in Synthesis*, Wasserscheid, P.; Welton, T.; Wiley–VCH, NY, **2002**; *Chemistry in Alternative Reaction Media*, Adams, D.J.; Dyson, P.J.; Taverner, S.J.; Wiley, **2003**. For a discussion of the solvating ability, see Chiappe, C.; Malvaldi, M.; Pomelli, C.S. *Pure Appl. Chem.* **2009**, **81**, 767.

¹²¹ Rogers, R.D.; Voth, G.A. *Acc. Chem. Res.* **2007**, 40, 1077;

¹²² Dupont, J.; Consorti, C.S.; Suarez, P.A.Z.; de Souza, R.F. *Org. Synth. Coll. Vol. X*, 184.

¹²³ For discussion of HBuIm and DiBuIm, see Harlow, K.J.; Hill, A.F.; Welton, T. *Synthesis* **1996**, 697; Holbrey, J.D.; Seddon, K.R. *J. Chem. Soc., Dalton Trans.* **1999**, 2133; Larsen, A.S.; Holbrey, J.D.; Tham, F.S.; Reed, C.A. *J. Am. Chem. Soc.* **2000**, 122, 7264.

¹²⁴ Jaegar, D.A.; Tucker, C.E. *Tetrahedron Lett.* **1989**, 30, 1785.

¹²⁵ Handy, S.T.; Okello, M. *J. Org. Chem.* **2005**, 70, 1915.

¹²⁶ For a discussion of the reactivity of ionic liquids, see Chowdhury, S.; Mohan, R.S.; Scott, J.L. *Tetrahedron* **2007**, 63, 2363.

¹²⁷ See Xiao, Y.; Malhotra, S.V. *Tetrahedron Lett.* **2004**, 45, 8339.

¹²⁸ Fukumoto, K.; Yoshizawa, M.; Ohno, H. *J. Am. Chem. Soc.* **2005**, 127, 2398. Also see Chen, X.; Li, X.; Hu, A.; Wang, F. *Tetrahedron Asymmetry* **2008**, 19, 1.

¹²⁹ Martins, M.A.P.; Frizzo, C.P.; Moreira, D.N.; Zanatta, N.; Bonaccorso, H.G. *Chem. Rev.* **2008**, 108, 2015.

¹³⁰ See Toma, Š.; Mečiarová, M.; Šebesta, R. *Eur. J. Org. Chem.* **2009**, 321.

¹³¹ Handy, S.T.; Okello, M.; Dickenson, G. *Org. Lett.* **2003**, 5, 2513.

¹³² Calò, V.; Nacci, A.; Monopoli, A. *Eur. J. Org. Chem.* **2006**, 3791.

¹³³ Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Narsaiah, A.V. *Tetrahedron* **2004**, 60, 2131.

¹³⁴ Branco, L.C.; Afonso, C.A.M. *J. Org. Chem.* **2004**, 69, 4381.

¹³⁵ Nobuoka, K.; Kitaoka, S.; Kunimitsu, K.; Iio, M.; Harran, T.; Wakisaka, A.; Ishikawa, Y. *J. Org. Chem.* **2005**, 70, 10106.

¹³⁶ Părvulescu, V.I.; Hardacre, C. *Chem. Rev.* **2007**, 107, 2615.

liquids are known.¹³⁷ Reactions performed in an ionic liquid are a rapidly growing area of organic chemistry, and has been expanded to include microwave reactions (see Sec. 7.C) in ionic solvents.¹³⁸ The development and use of ionic solvents is a growth area of organic chemistry.¹³⁹ Also note that some ionic liquids are categorized as Lewis base (Sec. 8.E), which will influence the acidity of dissolved compounds.¹⁴⁰ There are also acidic Brønsted ionic liquids.¹⁴¹

9.D.iv. Solventless Reactions

In some cases, it should be possible to accomplish a chemical transformation without the use of a solvent. Dry media reaction under microwave irradiation is an important area of study (see Sec. 7.C).¹⁴² There are several advantages of solventless reactions: (1) the possibility of direct formation of high-purity compounds, (2) the possibility of sequential reactions, (3) fast kinetics, (4) lower energy usage, (5) minimal need for preformed salts and metal–metalloid complexes, (6) simplicity and low equipment cost, and (7) the possibility of avoiding functional group protection–deprotection.¹⁴³ Potential difficulties include the possibility of hot spots and runaway reactions, and difficulties in handling solid or highly viscous materials.¹⁴⁴ An example of this approach is the aldol condensation, where a single aldol product was obtained in high yield.¹⁴⁵ 3-Carboxylcoumarins have been produced via a solventless aldol.¹⁴³

¹³⁷ Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.C. *Tetrahedron Asymmetry* **2005**, *16*, 3921; Pernak, J.; Feder-Kubis, J. *Tetrahedron Asymmetry* **2006**, *17*, 1728; Luo, S.-P.; Xu, D.-Q.; Yue, H.-D.; Wang, L.-P.; Yang, W.-L.; Xu, Z.-Y. *Tetrahedron Asymmetry* **2006**, *17*, 2028.

¹³⁸ See Leadbeater, N.E.; Torenus, H.M. *J. Org. Chem.* **2002**, *67*, 3145.

¹³⁹ For studies to expand the polarity range of ionic solvents see Dzyuba, S.V.; Bartsch, R.A. *Tetrahedron Lett.* **2002**, *43*, 4657. See *Ionic Liquids: From Knowledge to Application*, Plechkova, N.V.; Rogers, R.D.; Seddon, K.R. (Eds.), American Chemical Society, Washington, DC (distributed by Oxford University Press), **2010**.

¹⁴⁰ MacFarlane, D.R.; Pringle, J.M.; Johansson, K.M.; Forsyth, S.A.; Forsyth, M. *Chem. Commun.* **2006**, 1905.

¹⁴¹ Hajipour, A.R.; Rafiee, F. *Org. Prep. Proceed. Int.* **2010**, *42*, 285.

¹⁴² Kidwai, M. *Pure Appl. Chem.* **2001**, *73*, 147.

¹⁴³ Cave, G.W.V.; Raston, C.L.; Scott, J.L. *Chem. Commun.* **2001**, 2159; Toda, F.; Tanaka, K. *Chem. Rev.* **2000**, *100*, 1025.

¹⁴⁴ Raston, C.L. *Chemistry in Australia* **2004**, 10.

¹⁴⁵ Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3207.

INTRODUCTION

Part II of this book will be directly concerned with organic reactions and their mechanisms. The reactions have been classified into 10 chapters, based primarily on reaction type: substitutions, additions to multiple bonds, eliminations, rearrangements, and oxidation–reduction reactions. Substitutions are classified on the basis of mechanism as well as substrate. Chapters 10 and 13 include nucleophilic substitutions at aliphatic and aromatic substrates, respectively. Chapters 12 and 11 deal with electrophilic substitutions at aliphatic and aromatic substrates, respectively. All free radical substitutions are discussed in Chapter 14. Additions to multiple bonds are classified not according to mechanism, but according to the type of multiple bond. Additions to carbon–carbon multiple bonds are dealt with in Chapter 15; additions to other multiple bonds in Chapter 16. One chapter is devoted to each of the three remaining reaction types: Chapter 17, eliminations; Chapter 18, rearrangements; Chapter 19, oxidation–reduction reactions. This last chapter covers only those oxidation–reduction reactions that could not be conveniently treated in any of the other categories (except for oxidative eliminations).

Each chapter in Part II consists of two main sections. The first section of each chapter (except Chapter 19) deals with mechanism and reactivity. For each reaction type the various mechanisms are discussed in turn, with particular attention given to the evidence for each mechanism and to the factors that cause one mechanism rather than another to prevail in a given reaction. Following this, each chapter contains a section on reactivity, including, where pertinent, a consideration of orientation and the factors affecting it.

The second main section of each chapter is a treatment of the reactions belonging to the category indicated by the title of the chapter. It is not possible to discuss in a book of this nature all or nearly all known reactions. However, an attempt has been made to include all the important reactions of standard organic chemistry that can be used to prepare relatively pure compounds in reasonable yields. In order to present a well-rounded picture and to include some reactions that are traditionally discussed in textbooks, a number of reactions that do not fit into the above category have been included. However, certain special areas have been covered only lightly or not at all. Among these are polymerization reactions, and the preparation and reactions of heterocyclic compounds, carbohydrates, steroids, and compounds containing phosphorus, silicon, arsenic, boron, and mercury. The basic principles involved in these areas are of course no different from those in the areas more fully treated.

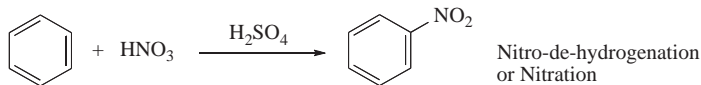
Each reaction is discussed in its own numbered section.¹ These are numbered consecutively within a chapter, each section number is preceded by the chapter number, so that Reaction **16-1** is the first reaction of Chapter 16 and Reaction **13-21** is the 21st reaction of Chapter 13. The order in which the reactions are presented is not arbitrary, but is based on an orderly outline that depends on the type of reaction. Within each section, the scope and utility of the reaction are discussed and references are given to review articles, if any. If there are features of the mechanism that especially pertain to that reaction, these are also discussed within the section rather than in the first part of the chapter where the discussion of mechanism is more general.

II.A. IUPAC NOMENCLATURE FOR TRANSFORMATIONS

There has long been a need for a method of naming reactions. Many reactions have been given the names of their discoverers or those who popularized them (e.g., *Claisen*, *Diels–Alder*, *Stille*, *Wittig*, *Cope*, *Dess–Martin*). In the past, this was necessary because mechanisms were not well understood, and a *named reaction* was a convenient way to identify certain transformations. Nowadays, the reasons for assigning a name are less clear and there may be as many as 800–1000 named reactions. Some believe that this practice has gotten out of hand, while others believe it to be the best way to organize key reactions. Named reactions are useful to a point, but each name must be individually memorized, and there are many reactions that do not have such names. The IUPAC Commission on Physical Organic Chemistry produced a *system* for naming, not reactions, but transformations (a reaction includes all reactants; a transformation shows only the substrate and product, omitting the reagents). The advantages of a systematic method are obvious. Once the system is known, no memorization is required; the name can be generated directly from the equation. The system includes rules for naming eight types of transformation: substitutions, additions, eliminations, attachments and detachments, simple rearrangements, coupling and uncoupling, insertions and extrusions, and ring opening and closing. Only the most basic rules are given for the first three of these types, which, however, will suffice for naming many transformations.²

II.A.i. Substitutions

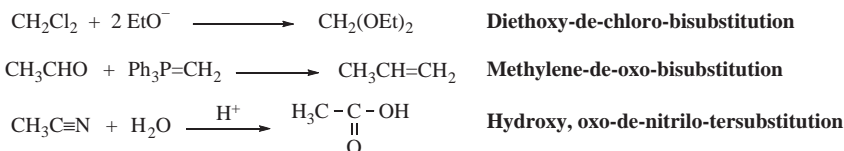
A name consists of the entering group, the syllable “de”, and the leaving group. If the leaving group is hydrogen, it may be omitted (in all examples, the substrate is written on the left).



¹ The classification of reactions into sections is, of course, to some degree arbitrary. Each individual reaction is different, and custom generally decides how we group them together. Individual preferences also play a part. No claim is made that the classification system used in this book is more valid than any other. For another way of classifying reactions, see Fujita, S. *J. Chem. Soc., Perkin Trans. 2* **1988**, 597.

² For a more complete set of rules, see Jones, R.A.Y.; Bunnett, J.F. *Pure Appl. Chem.* **1989**, 61, 725.

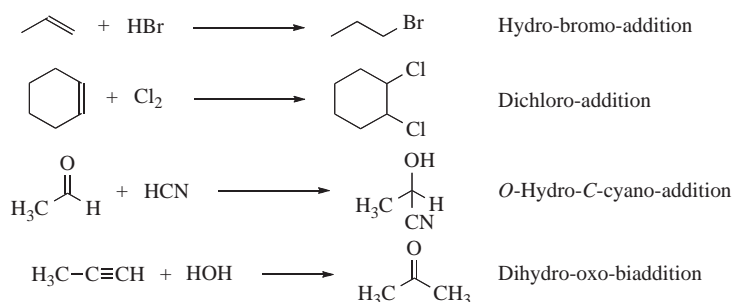
Multivalent substitutions are named by a modification of this system that includes suffixes (e.g., “bisubstitution” and “tersubstitution”).



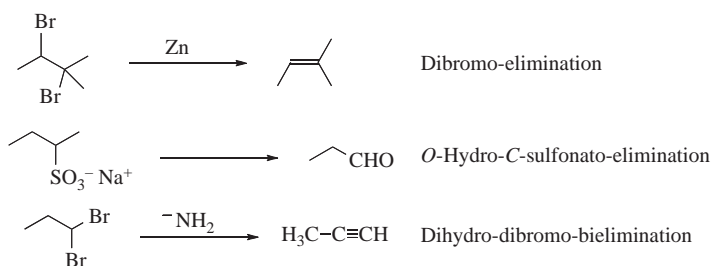
(Note: The nitrilo group is $\equiv\text{N}$.)

II.A.ii. Additions

For simple 1,2-additions, the names of both addends are given followed by the suffix “addition”. The addends are named in order of priority in the *Cahn–Ingold–Prelog system* (Sec. 4.E.i), the lower-ranking addend coming first. Multivalent addition is indicated by “biaddition”, and so on,



Eliminations are named the same way as additions, except that “elimination” is used instead of “addition”.



In the reaction sections of this book, IUPAC names are used for most transformations (these names will be printed in the same typeface used above), including examples of all eight types.³ As will become apparent, some transformations require more rules than we have given here.² However, it is hoped that the simplicity of the system will also be apparent.

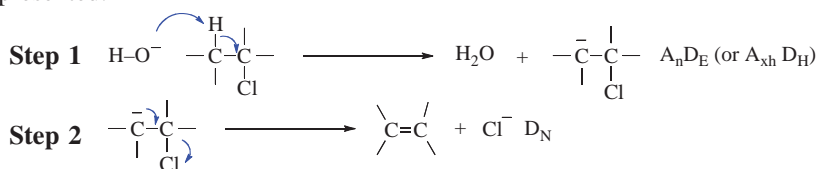
³ For some examples, see: attachments (18-27, 19-29), detachments (19-72), simple rearrangements (18-7, 18-29), coupling (10-56, 19-34), uncoupling (19-9, 19-75), insertions (12-21, 18-9), extrusions (17-35, 17-38), ring opening (10-14, 10-35), ring closing (10-9, 15-60).

Two further notes: (1) Many transformations can be named using either of two reactants as the substrate. For example, the transformation methylene-de-oxo-bisubstitution above, can also be named ethylidene-de-triphenylphosphorandiyl-bisubstitution. In this book, unless otherwise noted, we will show only those names in which the substrate is considered to undergo the reactions indicated by the titles of the chapters. Thus the name we give to Reaction **11-11** ($\text{ArH} + \text{RCI} \rightarrow \text{ArR}$) is alkyl-de-hydrogenation, not aryl-de-chlorination, although the latter name is also perfectly acceptable under the IUPAC system. (2) The IUPAC rules recognize that some transformations are too complex to be easily fitted into the system, so they also include a list of names for some complex transformations, which are IUPAC approved, but nonsystematic (for some examples, see Reactions **12-44**, **18-34**).

II.B. IUPAC SYSTEM FOR SYMBOLIC REPRESENTATION OF MECHANISMS

In addition to providing a system for naming transformations, the IUPAC Commission on Physical Organic Chemistry has also produced one for representing mechanisms.⁴ As will be seen, many mechanisms (but by no means all) are commonly referred to by designations (e.g., $\text{S}_{\text{N}}2$, $\text{A}_{\text{AC}}2$, E1_{cB} , and $\text{S}_{\text{RN}}1$), many of them devised by C.K. Ingold and co-workers. While these designations have been useful (and we will continue to use them in this book), the sheer number of them can be confusing, especially since the symbols do not give a direct clue to what is happening. For example, there is no way to tell directly from the symbols how $\text{S}_{\text{N}}2'$ is related to $\text{S}_{\text{N}}2$ (see Sec. 10.A.i). The IUPAC system is based on a very simple description of bond changes.⁵ The letter A represents formation of a bond (association); D the breaking of a bond (dissociation). These are *primitive changes*. The basic description of a mechanism consists of these letters, with subscripts to indicate where the electrons are going. In any mechanism, the *core atoms* are defined as (1) the two atoms in a multiple bond that undergoes addition, or (2) the two atoms that will be in a multiple bond after elimination, or (3) the single atom at which substitution takes place.

As an example of the system, this is how an E1_{cB} mechanism (Sec. 17.A.iii) would be represented:



Overall designation: $\text{A}_{\text{n}}\text{D}_{\text{E}} + \text{D}_{\text{N}}$ (or $\text{A}_{\text{xh}}\text{D}_{\text{H}} + \text{D}_{\text{N}}$). In this case, the overall reaction is



and the core atoms are the two carbons in boldface.

⁴ Guthrie, R.D. *Pure Appl. Chem.* **1989**, *61*, 23. For a briefer description, see Guthrie, R.D.; Jencks, W.P. *Acc. Chem. Res.* **1989**, *22*, 343.

⁵ There are actually two IUPAC systems. The one used in this book (Ref. 4) is intended for general use. A more detailed system, which describes every conceivable change happening in a system, and which is designed mostly for computer handling and storage, is given by Littler, J.S. *Pure Appl. Chem.* **1989**, *61*, 57. The two systems are compatible; the Littler system uses the same symbols as the Guthrie system, but has additional symbols.

Step 1, First Symbol.

A bond is being formed between O and H. Bond formation is represented by A. For this particular case, the system gives two choices for subscript. In any process, the subscript is N if a core atom is forming a bond to a nucleophile (A_N) or breaking a bond to a nucleofuge (D_N). If a noncore atom is doing the same thing, lowercase n is used instead. Since H and O are noncore atoms, the lowercase n is used, and the formation of the O—H bond is designated by A_n . However, because involvement of H^+ is so common in organic mechanisms, the rules allow an alternative. The subscript H or h may replace N or n. The symbol xh denotes that the H^+ comes from or goes to an unspecified carrier atom X. Thus the term A_{xh} means that a bond is being formed between H (moving without electrons) and an outside atom, in this case O. The same subscript, xh, would be used if the outside atom were any other nucleophilic atom, say, N or S.

Step 1, Second Symbol.

A bond is being broken between C and H. The symbol is D. In any process, the subscript is E if a core atom is forming a bond to an electrophile (A_E) or breaking a bond to an electrofuge (D_E). Since C is a core atom, the symbol here is D_E . Alternatively, the symbol could be D_H . The rules allow A_H or D_H to replace A_E or D_E if the electrophile or electrofuge is H^+ . Because a core atom is involved in this primitive change the H in the subscript is capitalized.

Step 1. Combined Symbols.

In Step 1, two bond changes take place simultaneously. In such cases, they are written together with no space or punctuation: A_nD_E or $A_{xh}D_H$

Step 2.

Only one bond is broken in this step and no bonds are formed. (The movement of a pair of unshared electrons into the C—C bond, forming a double bond, is not designated by any symbol. In this system, bond multiplicity changes are understood without being specified.) Thus the symbol is D. The broken bond is between a core atom (C) and a nucleofuge (Cl), so the designation is D_N .

The overall designation can be either $A_nD_N + D_N$ or $A_{xh}D_H + D_N$. The + symbol shows that there are two separate steps. If desired, rate-limiting steps can be shown by the symbol. In this case, if the first step is the slow step [old designation ($E1_{cB}$)_I], the designation would be $A_nD_E + D_N$ or $A_{xh}D_H + D_N$.

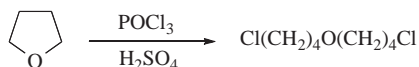
For most mechanisms (other than rearrangements), there will be only two A or D terms with uppercase subscripts, and the nature of the reaction can be immediately recognized by looking at them. If both are A, the reaction is an addition; if both are D (as in $A_nD_E + D_N$) it is an elimination. If one is A and the other D, the reaction is a substitution.

Here, we have given only a brief description of the system. Other IUPAC designations will be shown in Part II, where appropriate. For more details, further examples, and additional symbols, see Ref. 4.

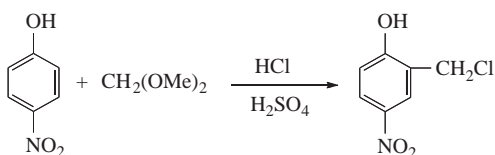
II.C. ORGANIC SYNTHESSES REFERENCES

At the end of many numbered sections there is a list of *Organic Syntheses* references (abbreviated OS). With the exception of a few very common reactions (12-3, 12-23, 12-24,

and 12–38), and to the extent that it is possible, the list includes *all* OS references for each reaction. The volumes of OS that have been covered are Collective Volumes I–XI. There are indices to OS.⁶ Organic Syntheses can now be accessed online.⁷ Certain ground rules were followed in assembling these lists. A reaction in which two parts of a molecule independently undergo simultaneous reaction is listed under both reactions. Similarly, if two reactions happen (or might happen) rapidly in succession without the isolation of an intermediate, the reactions are listed in both places. For example, at OS IV, 266 is



This reaction is treated as Reaction 10–49 followed by Reaction 10–12 and is listed in both places. However, certain reactions are not listed because they are trivial examples. An instance of this is the reaction found at OS III, 468:



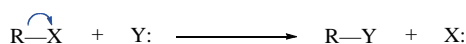
This is a chloromethylation reaction and is consequently listed in Reaction 11–14. However, in the course of the reaction formaldehyde is generated from the acetal. This reaction is not listed in Reaction 10–6 (hydrolysis of acetals), because it is not really a preparation of formaldehyde.

⁶ Smith, M.B. Fieser and Fieser's Reagents for Organic Syntheses, Collective Index For Volumes 1–22, Wiley, New York, **2005**; Smith, J.G.; Fieser, M. Fieser and Fieser's Reagents for Organic Synthesis: Collective Index for, Volumes 1–12, Wiley, New York, **1990**; Liotta, D.C.; Volmer, M. Organic Syntheses Reaction Guide, Wiley: NY, **1991**, which covers the series through Vol. 68. For an older index to Organic Syntheses (through Vol. 45), see Sugawara, S.; Nakai, S. Reaction Index of Organic Syntheses, Wiley: NY, **1967**.

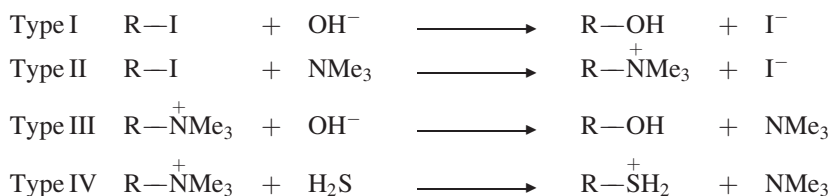
⁷ Available at <http://www.orgsyn.org/>.

Aliphatic Substitution, Nucleophilic and Organometallic

In nucleophilic aliphatic substitution the attacking (electron donating) reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with an electron pair:



As written, this equation says nothing about charges. Nucleophile Y may be neutral or negatively charged; RX may be neutral or positively charged; so there are four charge types, examples of which follows:



In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases. When Y is the solvent, the reaction is called *solvolysis*. Nucleophilic substitution at an aromatic carbon is considered in Chapter 13.

Nucleophilic substitution at an alkyl carbon is said to *alkylate* the nucleophile. For example, the above reaction between RI and NMe₃ is an *alkylation* of trimethylamine. Nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile, and such reactions are found in Chapter 16.

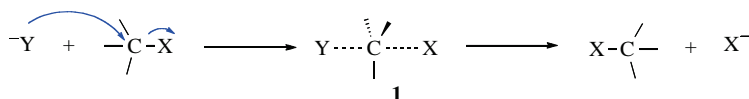
10.A. MECHANISMS

Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions. In all of them, however, the *attacking* reagent carries the electron pair with it. Mechanisms that

occur at a saturated carbon atom are considered first.¹ By far the most common are the S_N1 and S_N2 mechanisms.

10.A.i. The S_N2 Mechanism

The designation S_N2 stands for *substitution nucleophilic bimolecular*. The IUPAC designation (Sec. 9.F) is A_ND_N. In this mechanism, there is *backside attack*,² which means that the nucleophile approaches the substrate from a position 180° away from the leaving group. This approach will minimize steric and electronic repulsion of the substrate and the incoming nucleophile. The reaction is a one-step process with no intermediate (see below, and Sec. 10.A.iv). The C—Y bond is formed as the C—X bond is broken to generate *pentacoordinate transition state 1*.



The energy necessary to break the C—X bond is supplied by the collision of the nucleophile (Y) with the carbon bearing the leaving group (X). The top of the curve of free energy of activation is taken to be the transition state, and the position of the atoms for this reaction are shown in transition state **1**. The transition state is not a real structure, of course, but the energetic midpoint of the reaction. There are various computational methods to ascertain characteristics of a given transition state, and the experimental examination of kinetic isotope effects has been used to infer information about the transition state.³ The group X must leave as the group Y comes in, because at no time can the carbon have more than eight electrons in its outer shell. When the transition state is reached, the central carbon atom has gone from its initial *sp*³ hybridization to essentially *sp*² with an approximately perpendicular *p* orbital. One lobe of this *p* orbital overlaps with the nucleophile and the other with the leaving group. This is the reason a frontside S_N2 mechanism has never been observed. In a hypothetical frontside transition state, both the nucleophile and the leaving group would have to overlap with the same lobe of the *p* orbital. The backside mechanism involves the maximum amount of overlap throughout the course of the reaction. At the energy point of the transition state, the three nonreacting substituents and the central carbon are approximately coplanar. They will be exactly coplanar if both the entering and leaving group are the same.

There is a large amount of evidence for the S_N2 mechanism. First, there is the kinetic evidence.⁴ Since both the nucleophile and the substrate are involved in the rate-determining step (the only step, in this case), the reaction should be first order

¹ See Hartshorn, S.R. *Aliphatic Nucleophilic Substitution*, Cambridge University Press, Cambridge, **1973**; Katritzky, A.R.; Brycki, B.E. *Chem. Soc. Rev.* **1990**, 19, 83; Richard, J.P. *Adv. Carbocation Chem.* **1989**, 1, 121; Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, **1962**.

² See Sun, L.; Hase, W. L.; Song, K. *J. Am. Chem. Soc.* **2001**, 123, 5753. Nucleophilicity and leaving group ability for frontside and backside attack have been studied. See Bento, A.P.; Bickelhaupt, F.M. *J. Org. Chem.* **2008**, 73, 7290.

³ Hasanayn, F.; Streitwieser, A.; Al-Rifai, R. *J. Am. Chem. Soc.* **2005**, 127, 2249. See also Cruickshank, F.R.; Hyde, A.J.; Pugh, D. *J. Chem. Ed.* **1977**, 54, 288.

⁴ For a theoretical investigation of a kinetic isotope effect, see Matsson, O.; Dybala-Defratyka, A.; Rostkowski, M.; Paneth, P.; Westaway, K.C. *J. Org. Chem.* **2005**, 70, 4022.

in each component, second order overall, and satisfy the rate expression shown in Eq. (10-1).

$$\text{Rate} = k[\text{RX}][\text{Y}] \quad (10-1)$$

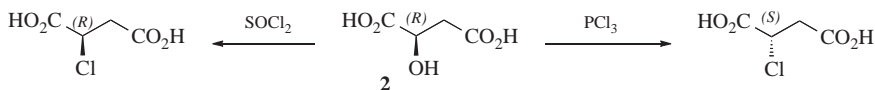
This rate law has been found to apply. Note that the 2 in S_N2 stands for bimolecular. It must be remembered that this is not always the same as second order (see Sec. 6.J.vi). If a large excess of nucleophile is present (e.g., if it is the solvent⁵) the mechanism may still be bimolecular, although the experimentally determined kinetics will be first order, Eq. (10-2).

$$\text{Rate} = k[\text{RX}] \quad (10-2)$$

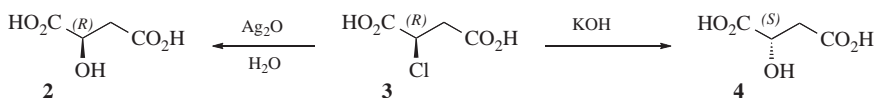
As previously mentioned (Sec. 6.J.vi), such kinetics are called *pseudo-first order*.

The kinetic evidence is a necessary but not a sufficient condition; other mechanisms will be encountered that are also consistent with these data. Much more convincing evidence is obtained from the fact that the mechanism predicts inversion of configuration when substitution occurs at a chiral carbon and this has been observed many times. This inversion of configuration (see Sec. 4.E.ii) that proceeds through transition state **1** is called the *Walden inversion* and was observed long before the S_N2 mechanism was formulated by Hughes and Ingold.⁶

At this point, it is useful to see just how it was originally proved that a given substitution reaction proceeds with inversion of configuration, even before the mechanism was known. Walden presented a number of examples⁷ in which inversion *must* have taken place. For example, (+)-malic acid (**2**) could be converted to (+)-chlorosuccinic acid by thionyl chloride and to (–)-chlorosuccinic acid by phosphorus pentachloride.



One was an inversion and the other a retention of configuration, but the question was which was which? The signs of rotation are of no help in answering this question since rotation need not be related to configuration (Sec. 4.F). Another example discovered by Walden is formation of **3** from **4**.⁸



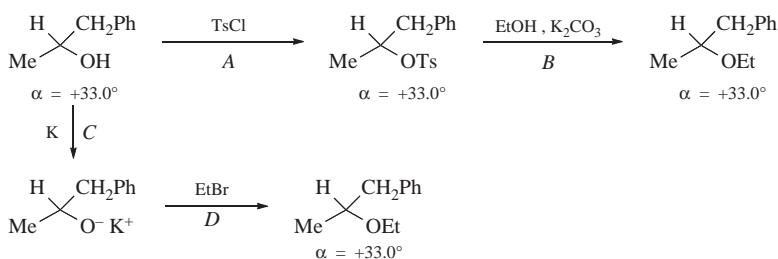
⁵ For a discussion of this type of solvent effect, see Arnaut, L.G.; Formosinho, S.J. *Chemistry: European J.* **2007**, *13*, 8018.

⁶ Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *J. Chem. Soc.* **1937**, 1252. The idea that the addition of one group and removal of the other are simultaneous was first suggested by Lewis, G.N. in *Valence and the Structure of Atoms and Molecules*, Chemical Catalog Company, NY, **1923**, p. 113. The idea that a one-step substitution leads to inversion was proposed by Olsen, A.R. *J. Chem. Phys.* **1933**, *1*, 418.

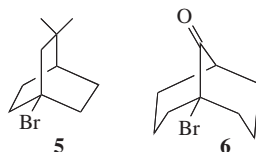
⁷ Walden, P. *Ber.* **1893**, *26*, 210; **1896**, *29*, 133; **1899**, *32*, 1855.

⁸ For a discussion of these cycles, see Kryger, L.; Rasmussen, S.E. *Acta Chem. Scand.* **1972**, *26*, 2349.

A series of experiments designed to settle the matter of exactly where inversion takes place was performed by Phillips,⁹ Kenyon,¹⁰ and co-workers. In 1923, Phillips and co-workers⁹ carried out the following cycle based on (+)-1-phenyl-2-propanol. In this cycle, (+)-1-phenyl-2-propanol is converted to its ethyl ether by two routes, path *AB* giving the (–) ether, and path *CD* giving the (+) ether. Therefore, at least one of the four steps must be an inversion. It is extremely unlikely that there is inversion in step *A*, *C*, or *D*, since in all these steps the C—O bond is unbroken, and in none of them could the oxygen of the bond have come from the reagent. There is a high probability that *A*, *C*, and *D* proceeded with retention, leaving *B* as the inversion. A number of other such cycles were carried out, always with nonconflicting results.¹⁰ These experiments not only definitely showed that certain specific reactions proceed with inversion, but also established the configurations of many compounds.



Walden inversion has been found at a primary carbon atom by the use of a chiral substrate containing a deuterium and a hydrogen atom at the carbon bearing the leaving group.¹¹ Inversion of configuration has also been found for $\text{S}_{\text{N}}2$ reactions proceeding in the gas phase.¹² High-pressure mass spectrometry has been used to probe the energy surface for gas-phase $\text{S}_{\text{N}}2$ reactions, which have two transition states (a “loose” and a “tight” transition state).¹³



Another kind of evidence for the $\text{S}_{\text{N}}2$ mechanism comes from compounds with potential leaving groups at bridgehead carbons. If the $\text{S}_{\text{N}}2$ mechanism is correct, these compounds should not be able to react by this mechanism, since the nucleophile cannot approach from the rear. Among the many known examples of unsuccessful reaction attempts at bridgeheads under $\text{S}_{\text{N}}2$ conditions¹⁴ are treatment of the [2.2.2] system (**5**) with ethoxide

⁹ Phillips, H. *J. Chem. Soc.* **1923**, 123, 44. See Garwood, D.C.; Cram, D.J. *J. Am. Chem. Soc.* **1970**, 92, 4575; Cram, D.J.; Cram, J.M. *Fortschr. Chem. Forsch.* **1972**, 31, 1.

¹⁰ See Kenyon, J.; Phillips, H.; Shutt, G.R. *J. Chem. Soc.* **1935**, 1663 and references cited therein.

¹¹ Streitwieser, Jr., A. *J. Am. Chem. Soc.* **1953**, 75, 5014.

¹² Speranza, M.; Angelini, G. *J. Am. Chem. Soc.* **1980**, 102, 3115 and references cited therein; Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* **2003**, 9, 2209. See Riveros, J.M.; José, S.M.; Takashima, K. *Adv. Phys. Org. Chem.* **1985**, 21, 197.

¹³ Li, C.; Ross, P.; Szulejko, J.E.; McMahon, T.B. *J. Am. Chem. Soc.* **1996**, 118, 9360.

¹⁴ See Müller, P.; Mareda, J. in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, **1990**, pp. 189–217; Fort, Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* **1966**, 1, 283.

ion¹⁵ and treatment of the [3.3.1] system (6) with sodium iodide in acetone.¹⁶ In these cases, open-chain analogues underwent the reactions readily. As a final example of evidence for the S_N2 mechanism, the reaction between optically active 2-octyl iodide and radioactive iodide ion may be mentioned:



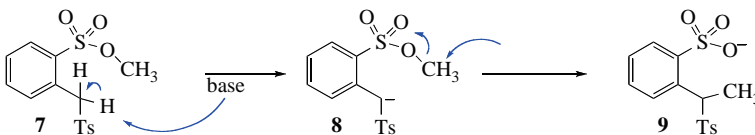
Racemization is expected in this reaction, since if the pure *R* isomer is the starting material each exchange will produce an (*S*) isomer. With increasing concentration of (*S*) isomer, it will begin to compete for I[−] with the *R* isomer, until at the end a racemic mixture is left. The point investigated was a comparison of the rate of inversion with the rate of uptake of radioactive ^{*}I[−]. It was found¹⁷ that the rates were identical within experimental error:

$$\text{Rate of inversion} \quad 2.88 \pm 0.03 \times 10^{-5}$$

$$\text{Rate of exchange} \quad 3.00 \pm 0.25 \times 10^{-5}$$

The rate of racemization was the parameter actually measured, which is twice the rate of inversion, since each inversion creates, in effect, two racemic molecules. The significance of this result is that it shows that every act of exchange is an act of inversion.

Eschenmoser and co-workers¹⁸ provided strong evidence that the transition state in an S_N2 reaction must be linear. Base treatment of methyl α-tosyl-*o*-toluenesulfonate (7) gives the *o*-(1-tosylethyl)benzenesulfonate ion (9). The role of the base is to remove the benzylic proton α- to the tosyl group to give the ion 8. It might be supposed that the negatively charged carbon of 8 attacks the methyl group in an internal S_N2 process, but this is not the case. Crossover experiments¹⁸ (See 11-27) have shown that the negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule; that is, the reaction is intermolecular (see 8) and not intramolecular, despite the more favorable entropy of the latter pathway (Sec. 6.D). It is likely that intramolecular attack does not take place because complete linearity cannot be attained. This behavior is in sharp contrast to that in cases in which the leaving group is not constrained (Sec. 10.C), where intramolecular S_N2 mechanisms operate freely.



There is evidence, both experimental and theoretical, that there are intermediates in at least some S_N2 reactions in the gas phase, in charge-type I reactions, where a negative ion nucleophile attacks a neutral substrate.¹⁹ Two energy minima, one before and one after the

¹⁵ Doering, W. von E.; Levitz, M.; Sayigh, A.; Sprecher, M.; Whelan, Jr., W.P. *J. Am. Chem. Soc.* **1953**, 75, 1008. Actually, a slow substitution was observed in this case, but not by an S_N2 mechanism.

¹⁶ Cope, A.C.; Synerholm, M.E. *J. Am. Chem. Soc.* **1950**, 72, 5228.

¹⁷ Hughes, E.D.; Juliusburger, F.; Masterman, S.; Topley, B.; Weiss, J. *J. Chem. Soc.* **1935**, 1525.

¹⁸ Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, 53, 2059. See also, King, J.F.; McGarrity, M.J. *J. Chem. Soc., Chem. Commun.* **1979**, 1140.

¹⁹ See Angel, L.A.; Ervin, K.M. *J. Am. Chem. Soc.* **2003**, 125, 1014.

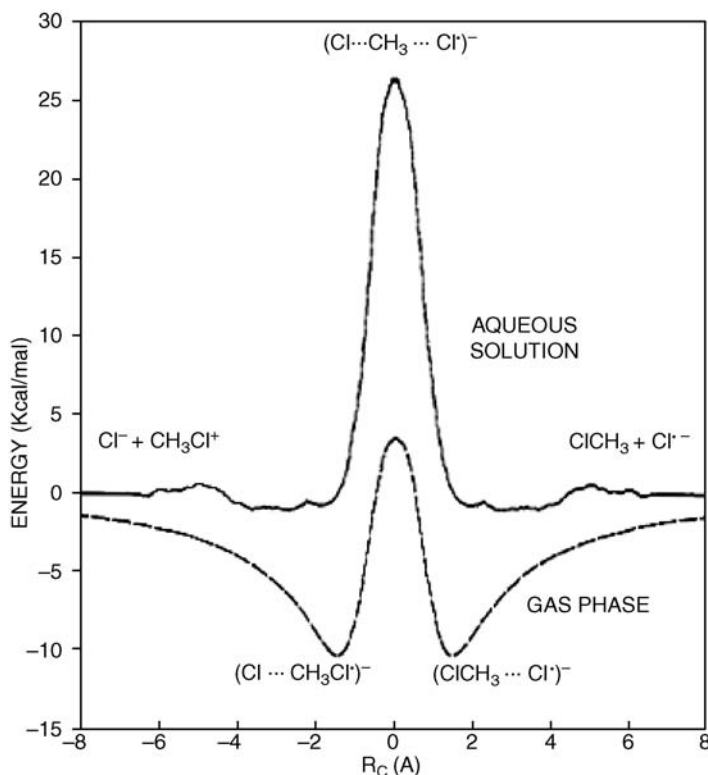


FIG. 10.1. Free energy profile for the gas phase (solid line) and aqueous solution (dashed line) S_N2 reaction between CH_3Cl and Cl^- , from molecular orbital calculations.²⁰ [Reprinted with permission from Chandrasekhar, J.; Smith, S.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1985**, *107*, 154. Copyright © 1985 American Chemical Society.

transition state, appear in the reaction coordinate (Fig. 10.1).²⁰ The energy surface for the S_N2 *Menshutkin* reaction (**10-31**) has been examined. It was shown that charge separation was promoted by the solvent.²¹ An *ab initio* study of the S_N2 reaction at primary and secondary carbon centers has looked at the energy barrier (at the transition state) to the reaction.²² These minima correspond to unsymmetrical ion-dipole complexes.²³ Theoretical calculations also show such minima in certain solvents (e.g., *N,N*-dimethylformamide DMF), but not in water.²⁴ In general, polar aprotic solvents (those that do not have an acidic hydrogen $X-H$, where $X=O, S, N$, etc.), favor polarized transition state 1.²⁵ The rate of the reaction is generally slower in protic solvents (e.g., alcohol or water).

²⁰ Taken from Chandrasekhar, J.; Smith, S.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1985**, *107*, 154.

²¹ Gao, J.; Xia, X. *J. Am. Chem. Soc.* **1993**, *115*, 9667.

²² Lee, I.; Kim, C.K.; Chung, D.S.; Lee, B.-S. *J. Org. Chem.* **1994**, *59*, 4490.

²³ Evanseck, J.D.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1987**, *109*, 2349; Kozaki, T.; Morihashi, K.; Kikuchi, O. *J. Am. Chem. Soc.* **1989**, *111*, 1547; Jorgensen, W.L. *Acc. Chem. Res.* **1989**, *22*, 184.

²⁴ Chandrasekhar, J.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1985**, *107*, 2974.

²⁵ For a discussion of environmentally benign substitution reactions, see Vogel, P.; Figueira, S.; Muthukrishnan, S.; Mack, J. *Tetrahedron Lett.* **2009**, *50*, 55.

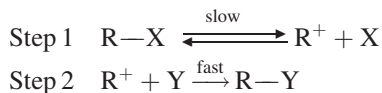
The S_N2 reactions can occur at atoms other than carbon, X (e.g., nitrogen or sulfur²⁶), and analogous to the phenomenon observed for S_N2 reactions at carbon.²⁷ the valence of the element X, controls the intrinsic barrier for the reaction in accord with the properties seen in the periodic table.²⁸

For a list of some of the more important reactions that operate by the S_N2 mechanism, see Table 10.7.

Note that in some reactions, (e.g., bromine transfer between carbanions via nucleophilic attack on bromine), anomalous kinetic behavior is observed. The largest rate constants are associated with bromine transfer between cyano-activated carbanions and the smallest relate to the removal of bromine from the nitromethane and nitroethane moieties.²⁹ The Brønsted plot (log *k* vs Δ*pK_a*) for this reaction shows that unlike any normal Brønsted plot, which by definition displays a positive slope, the plot for MeNO₂ and EtNO₂ is negative. In deprotonation reactions of carbon compounds, the reactivity of nitroethane and nitromethane were shown to be anomalous.³⁰ In the series nitromethane, ethane, and isopropane, compounds with higher acidity undergo slower deprotonation (i.e., the Brønsted plot displays a negative slope), contrary to expectations.³¹

10.A.ii. The S_N1 Mechanism

The most ideal version of the S_N1 mechanism (*substitutional nucleophilic unimolecular*) consists of two steps³² (once again, possible charges on the substrate and nucleophile are not shown):



The first step is a slow ionization of the substrate and is the rate-determining step. The second is a rapid reaction between the intermediate carbocation and the nucleophile. There are, of course, transition states for both step 1 (R···X) and step 2 (R⁺···Y).³³ The reactive nature of the carbocation can be expressed by its electrophilic character, or *electrophilicity*. A theoretical discussion concerning the origin of the electrophilicity concept was proposed by Parr et al.³⁴ In general, a good electrophile was characterized by having a high value of electronegativity (or a high value of electronic chemical potential), and a low value of chemical hardness (Sec. 8.E.i). The effect of substitution has been studied³⁵ in the context of superelectrophilicity (where carbocations are generated in superacidic media). Solvent effects have also been studied.³⁶ Electrophilicity scales

²⁶ See Reactions **10-60–10-68** and Bachrach, S.M.; Gailbreath, B.D. *J. Org. Chem.* **2001**, *66*, 2005.

²⁷ Hoz, S.; Basch, H.; Wolk, J.L.; Hoz, T.; Rozental, E. *J. Am. Chem. Soc.* **1999**, *121*, 7724.

²⁸ Yi, R.; Basch, H.; Hoz, S. *J. Org. Chem.* **2002**, *67*, 5891.

²⁹ Grinblat, J.; Ben-Zion, M.; Hoz, S. *J. Am. Chem. Soc.*, **2001**, *123*, 10738.

³⁰ Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* **1953**, *75*, 2439.

³¹ Yamataka, H.; Mustanir; Mishima, M. *J. Am. Chem. Soc.* **1999**, *121*, 10223.

³² See Mayr, H.; Minegishi, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 4493. For a discussion of dynamic processes associated with the S_N1 mechanism, see Peters, K.S. *Chem. Rev.* **2007**, *107*, 859.

³³ For a related computational study, see Ruff, F.; Farkas, Ö.; Kucsman, Á. *Eur. J. Org. Chem.* **2006**, 5570.

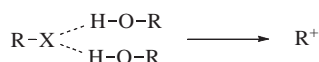
³⁴ Parr, R. G.; Szentpály, L.V.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922. Also see Denekamp, C.; Sandler, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 2093.

³⁵ See Pérez, P. *J. Org. Chem.* **2004**, *69*, 5048.

³⁶ Pérez, P.; Toro-Labbé, A.; Contreras, R. *J. Am. Chem. Soc.* **2001**, *123*, 5527.

have been proposed using other carbocations,³⁷ and there is an electrophilicity index.³⁸ Carbocation intermediates have been studied for the reaction $\text{Ar}_2\text{CH}-\text{O}_2\text{CR} \rightarrow \text{Ar}_2\text{CH}^+$, and the relative ionization rates with the same anionic leaving group does not correlate with the corresponding relative reactivities of the carbocation toward a common nucleophile.³⁹

Returning to the $\text{S}_{\text{N}}1$ mechanism, ionization of a leaving group to form the carbocation is always assisted by the solvent,⁴⁰ since the energy necessary to break the bond is largely recovered by solvation of R^+ and of X. For example, the ionization of $t\text{-BuCl}$ to $t\text{-Bu}^+$ and Cl^- in the gas phase without a solvent requires $150 \text{ kcal mol}^{-1}$ (630 kJ mol^{-1}). In the absence of a solvent, such a process simply would not take place, except at very high temperatures. In water, this ionization requires only 20 kcal mol^{-1} (84 kJ mol^{-1}). The difference is solvation energy. This means that the water is effectively “pulling” the leaving group away from the substrate. In cases where the role of the solvent is solely to assist in departure of the leaving group from the frontside the mechanism is called *limiting* $\text{S}_{\text{N}}1$. In other words, there is a complete absence of backside ($\text{S}_{\text{N}}2$) participation by solvent molecules. There is kinetic and other evidence⁴¹ that two molecules of a protic solvent form weak hydrogen bonds with X in order to pull the leaving group X away from RX.



In the IUPAC system, the $\text{S}_{\text{N}}1$ mechanism is $\text{D}_{\text{N}} + \text{A}_{\text{N}}$ or $\text{D}_{\text{N}}^{\ddagger} + \text{A}_{\text{N}}$ (where \ddagger denotes the rate-determining step). The IUPAC designations for the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms thus clearly show the essential differences between them: $\text{A}_{\text{N}}\text{D}_{\text{N}}$ indicates that bond breaking is concurrent with bond formation; $\text{D}_{\text{N}} + \text{A}_{\text{N}}$ shows that the former happens first.

In looking for evidence for the $\text{S}_{\text{N}}1$ mechanism, the first thought is that it should be a first-order reaction following the rate law:

$$\text{Rate} = k[\text{RX}] \quad (10-3)$$

Since the slow step involves only the substrate, the rate should be dependent only on the concentration of that. Although the solvent is necessary to assist in the process of ionization, it does not enter the rate expression, because it is present in large excess. However, the simple rate law given in Eq. (10-3) is not sufficient to account for all the data. Many cases are known where pure first-order kinetics are followed, but in many other cases more complicated kinetics are found. This fact can be explained by taking into account the

³⁷ Pérez, P.; Toro-Labbé, A.; Aizman, A.; Contreras, R. *J. Org. Chem.* **2002**, *67*, 4747.

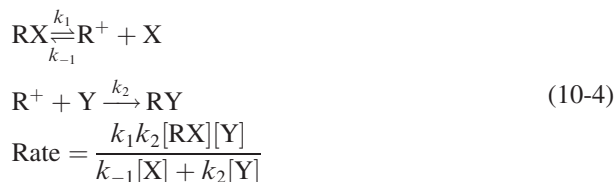
³⁸ Chattaraj, P.K.; Sarkar, U.; Roy, D.R. *Chem. Rev.* **2006**, *106*, 2065.

³⁹ Schaller, H.F.; Tishkov, A.A.; Feng, X.; Mayr, H. *J. Am. Chem. Soc.* **2008**, *130*, 3012.

⁴⁰ See Okamoto, K. *Adv. Carbocation Chem.* **1989**, *1*, 171; Blandamer, M.J.; Scott, J.M.W.; Robertson, R.E. *Prog. Phys. Org. Chem.* **1985**, *15*, 149. Also see Dvorko, G.F.; Ponomareva, E.A.; Kulik, N.I. *Russ. Chem. Rev.* **1984**, *53*, 547.

⁴¹ Blandamer, M.J.; Burgess, J.; Duce, P.P.; Symons, M.C.R.; Robertson, R.E.; Scott, J.M.W. *J. Chem. Res. (S)* **1982**, 130.

reversibility of the first step. The X formed in this step competes with Y for the cation and the rate law must be modified as shown (see Chap 6).



At the beginning of the reaction, when the concentration of X is very small, $k_{-1}[\text{X}]$ is negligible compared with $k_2[\text{Y}]$ and the rate law is reduced to Eq. (10-3). Indeed, $\text{S}_{\text{N}}1$ reactions generally do display simple first-order kinetics in their initial stages. Most kinetic studies of $\text{S}_{\text{N}}1$ reactions fall into this category. In the later stages of $\text{S}_{\text{N}}1$ solvolyses, $[\text{X}]$ becomes large and Eq. (10-4) predicts that the rate should decrease. This is found to be the case for diarylmethyl halides,⁴² although not for *tert*-butyl halides, which follow Eq. (10-3) for the entire reaction.⁴³ An explanation for this difference is that *tert*-butyl cations are less selective than the relatively stable diarylmethyl type (Sec. 5.A.ii). Although halide ion is a much more powerful nucleophile than water, there is much more water available since it is the solvent.⁴⁴ The selective diphenylmethyl cation survives many collisions with solvent molecules before combining with a reactive halide. However, some of the collisions with solvent lead to product, so despite the fact that the halide ion is more reactive, the slower reaction with solvents leads to product because of the overwhelming number of solvent molecules.

If the X formed during the reaction can decrease the rate, at least in some cases, it should be possible to *add* X from the outside and further decrease the rate in that way. This retardation of rate by addition of X is called *common-ion effect* or the *mass-law effect*. Once again, addition of halide ions decreases the rate for diphenylmethyl, but not for *tert*-butyl halides.

One factor that complicates the kinetic picture is the *salt effect*. An increase in ionic strength of the solution usually increases the rate of an $\text{S}_{\text{N}}1$ reaction (Sec. 10.G.iv). But when the reaction is of charge type II, where both Y and RX are neutral, so that X is negatively charged (and most solvolyses are of this charge type), the ionic strength increases as the reaction proceeds and this increases the rate. This effect must be taken into account in studying the kinetics. Incidentally, the fact that the addition of outside ions *increases* the rate of most $\text{S}_{\text{N}}1$ reactions makes especially impressive the *decrease* in rate caused by the common ion.

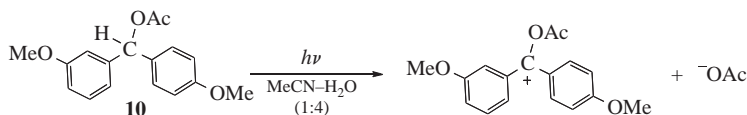
Note that the pseudo-first-order rate law for an $\text{S}_{\text{N}}2$ reaction in the presence of a large excess of Y [Eq. (10-1)] is the same as that for an ordinary $\text{S}_{\text{N}}1$ reaction [Eq. (10-3)]. It is thus not possible to tell these cases apart by simple kinetic measurements. However, they can often be distinguished by the common-ion effect mentioned above. Addition of a common ion will not markedly affect the rate of an $\text{S}_{\text{N}}2$ reaction beyond the effect caused by other ions. Unfortunately, as seen above, not all $\text{S}_{\text{N}}1$ reactions show the common-ion effect, and this test fails for *tert*-butyl and similar cases.

⁴² Benfey, O.T.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* **1952**, 2488.

⁴³ Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* **1940**, 960.

⁴⁴ In the experiments mentioned, the solvent was actually "70" or "80%" aq acetone. The "80%" aq acetone consists of 4 vol of dry acetone and 1 vol of water.

Kinetic studies also provide other evidence for the S_N1 mechanism. One technique used ^{19}F NMR to follow the solvolysis of trifluoroacetyl esters.⁴⁵ If this mechanism operates essentially as shown above, the rate should be the same for a given substrate under a given set of conditions, *regardless of the identity of the nucleophile or its concentration*. In one experiment, benzhydryl chloride (Ph_2CHCl) was treated in SO_2 with the nucleophiles fluoride ion, pyridine, and triethylamine at several concentrations of each nucleophile.⁴⁶ In each case, the initial rate of the reaction was approximately the same when corrections were made for the salt effect. The same type of behavior has been shown in a number of other cases, even when the reagents are as different in their nucleophilicities (see Sec. 10.G.ii) as H_2O and HO^- .



It is normally not possible to detect the carbocation intermediate of an S_N1 reaction directly, because its lifetime is very short. However, in the case of 3,4-dimethoxydiphenylmethyl acetate (**10**), and certain other substrates in polar solvents, it was possible to initiate the reaction photolytically, and under these conditions the UV spectra of the intermediate carbocations could be obtained,⁴⁷ providing additional evidence for the S_N1 mechanism. Further, addition of water to a colorless solution of $\text{Ar}_2\text{CH}-\text{OAc}$ (Ar = morpholinophenyl) in acetone, leads to direct observation of the intermediate carbocation.⁴⁸

Further evidence for the S_N1 mechanism is that reactions run under S_N1 conditions fail or proceed very slowly at the bridgehead positions¹³ of [2.2.1] (norbornyl) systems⁴⁹ (e.g., 1-chloroapocamphane, **8**). If S_N1 reactions require carbocations and if carbocations must be planar or nearly planar, then it is no surprise that bridgehead 1-norbornyl carbon atoms, which cannot assume planarity, do not become the seat of carbocations. As an example, **11**, boiled 21 h with 30% KOH in 80% ethanol or 48 h with aq ethanolic silver nitrate, gave no reaction in either case,⁵⁰ although analogous open-chain systems reacted readily. According to this theory, S_N1 reactions should be possible with larger rings, since near-planar carbocations might be expected there. This turns out to be the case. For example, [2.2.2] bicyclic systems undergo S_N1 reactions much faster than smaller bicyclic systems, although the reaction is still slower than with open-chain systems.⁵¹ Proceeding to a still larger system, the bridgehead [3.2.2] cation (**12**) is actually stable enough to be kept in solution in $\text{SbF}_5\text{-SO}_3\text{ClF}$ at temperatures below -50°C ⁵² (see also, Sec. 10.G, category 6). Other small bridgehead systems that undergo S_N1 reactions are the [3.1.1] (e.g., **13**)⁵³ and

⁴⁵ Creary, X.; Wang, Y.-X. *J. Org. Chem.* **1992**, 57, 4761. Also see, Farcasiu, D.; Marino, G.; Harris, J.M.; Hovanes, B.A.; Hsu, C.S. *J. Org. Chem.* **1994**, 59, 154.

⁴⁶ Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* **1940**, 1011.

⁴⁷ McClelland, R.A.; Kanagasabapathy, V.M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, 110, 6913.

⁴⁸ Schaller, H.F.; Mayr, H. *Angew. Chem. Int. Ed.* **2008**, 47, 3958.

⁴⁹ Fort, Jr., R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, **1973**, pp. 1783–1835.

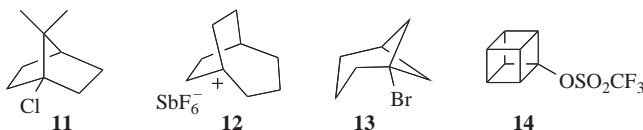
⁵⁰ Bartlett, P.D.; Knox, L.H. *J. Am. Chem. Soc.* **1939**, 61, 3184.

⁵¹ For synthetic examples, see Kraus, G.A.; Hon, Y. *J. Org. Chem.* **1985**, 50, 4605.

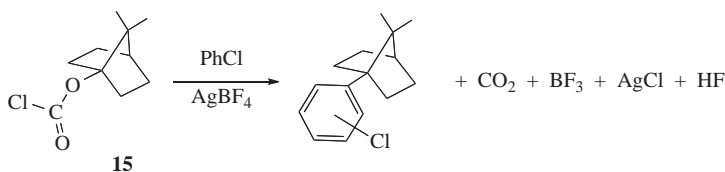
⁵² Olah, G.A.; Liang, G.; Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* **1972**, 74, 4927.

⁵³ Della, E.W.; Pigou, P.E.; Tsanaktsidis, J. *J. Chem. Soc., Chem. Commun.* **1987**, 833.

the cubyl (e.g., **14**)⁵⁴ systems. *Ab initio* calculations show that the cubyl cation, although it cannot be planar, requires less energy to form than the 1-norbornyl cation.⁵⁵ There are reactions where the cationic carbon is not coplanar with conjugating substituents (e.g., phenyl), and formation of the carbocation is more difficult but the reaction proceeds.⁵⁶



Certain nucleophilic substitution reactions that normally involve carbocations can take place at norbornyl bridgeheads⁵⁷ (though it is not certain that carbocations are actually involved in all cases) if the leaving group used is of the type that cannot function as a nucleophile (and thus come back) once it has gone, and in the displacement of ClCO_2 in **15**. In this example,⁵⁸ chlorobenzene is the nucleophile (see Reaction **11-10**).



Additional evidence for the $\text{S}_{\text{N}}1$ mechanism, in particular, for the intermediacy of carbocations, is that solvolysis rates of alkyl chlorides in ethanol parallel carbocation stabilities, as determined by heats of ionization measured in superacid solutions (Sec. 5.A.ii).⁵⁹ It is important to note that some solvolysis reactions proceed by an $\text{S}_{\text{N}}2$ mechanism.⁶⁰

10.A.iii. Ion Pairs in the $\text{S}_{\text{N}}1$ Mechanism⁶¹

Like the kinetic evidence, the stereochemical evidence for the $\text{S}_{\text{N}}1$ mechanism is less clear-cut than it is for the $\text{S}_{\text{N}}2$ mechanism.⁶² If there is a free carbocation, it is planar (Sec. 5.A.ii), and the nucleophile should attack with equal facility from either side of the plane, resulting in complete racemization. Although many first-order substitutions do give complete racemization, many others do not. Typically there is 5–20% inversion, although in a few cases, a small amount of retention of configuration has been found. These and other results have led to the conclusion that in many $\text{S}_{\text{N}}1$ reactions at least some of the products are not formed from free carbocations, but rather from *ion pairs*. According to this

⁵⁴ Eaton, P.E.; Yang, C.; Xiong, Y. *J. Am. Chem. Soc.* **1990**, *112*, 3225; Moriarty, R.M.; Tuladhar, S.M.; Penmasta, R.; Awasthi, A.K. *J. Am. Chem. Soc.* **1990**, *112*, 3228.

⁵⁵ Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* **1990**, *112*, 3227.

⁵⁶ Lee, I.; Kim, N.D.; Kim, C.K. *Tetrahedron Lett.* **1992**, *33*, 7881.

⁵⁷ White, E.H.; McGirk, R.H.; Aufdermarsh, Jr., C.A.; Tiwari, H.P.; Todd, M.J. *J. Am. Chem. Soc.* **1973**, *95*, 8107; Beak, P.; Harris, B.R. *J. Am. Chem. Soc.* **1974**, *96*, 6363.

⁵⁸ For a review of reactions with the OCOCl leaving group, see Beak, P. *Acc. Chem. Res.* **1976**, *9*, 230.

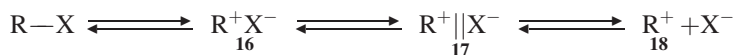
⁵⁹ See Arnett, E.M.; Molter, K.E. *Acc. Chem. Res.* **1985**, *18*, 339.

⁶⁰ Lee, I.; Lee, Y.S.; Lee, B.-S.; Lee, H.W. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1441.

⁶¹ See Beletskaya, I.P. *Russ. Chem. Rev.* **1975**, *44*, 1067; Harris, J.M. *Prog. Phys. Org. Chem.* **1974**, *11*, 89; Raber, D.J.; Harris, J.M.; Schleyer, P.v.R. in Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, Vol. 2, Wiley, NY, **1974**, pp. 247–374.

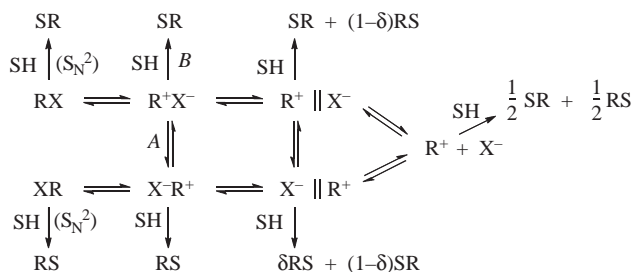
⁶² For an alternative view, See Uggerud, E. *J. Org. Chem.* **2001**, *66*, 7084.

concept,⁶³ S_N1 reactions proceed in this manner:



where **16** (an *intimate, contact, or tight ion pair*), **17** (a *loose, or solvent-separated ion pair*),⁶⁴ or **18** (the dissociated ions, which means that each is surrounded by molecules of solvent).⁶⁵ The reaction in which the intimate ion pair recombines to give the original substrate is referred to as *internal return*. The reaction products can result from attack by the nucleophile at any stage. In the intimate ion pair (**16**), R⁺ does not behave like the free cation of **18**. There is probably significant bonding between R⁺ and X⁻ and asymmetry may well be maintained.⁶⁶ Here, X⁻ “solvates” the cation on the side from which it departed, while solvent molecules near **16** can only solvate it from the opposite side. Nucleophilic attack by a solvent molecule on **16** thus leads to inversion. Note that there is evidence for concerted pathways in some ion pairing reactions.⁶⁷

Ignoring the possibilities of elimination or rearrangement (see Chapters 17 and 18), a complete picture of the possibilities for solvolysis reactions⁶⁸ in a solvent SH is represented by the following scheme,⁶⁹ although in any particular case it is unlikely that all these reactions occur:



In this scheme, (RS) and (SR) represent enantiomers, and so on, and δ represents some fraction. The following are the possibilities: (1) Direct attack by SH on RX gives SR (complete inversion) in a straight S_N2 process. (2) If the intimate ion pair R⁺X⁻ is formed, the solvent can attack at this stage. This can lead to total inversion if reaction A does not take place or to a combination of inversion and racemization if there is competition between A and B. (3) If the solvent-separated ion pair is formed, SH can attack here. The stereochemistry is not maintained as tightly and more racemization (perhaps total) is expected. (4) Finally, if free R⁺ is formed, it is planar, and attack by SH gives complete racemization.

The ion-pair concept thus predicts that S_N1 reactions can display either complete racemization or partial inversion. The fact that this behavior is generally found is evidence

⁶³ Proposed by Winstein, S.; Clippinger, E.; Fainberg, A.H.; Heck, R.; Robinson, G.C. *J. Am. Chem. Soc.* **1956**, 78, 328.

⁶⁴ Marcus, Y.; Hefter, G. *Chem. Rev.* **2006**, 106, 4585.

⁶⁵ See Kessler, H.; Feigel, M. *Acc. Chem. Res.* **1982**, 15, 2.

⁶⁶ Fry, J.L.; Lancelot, C.J.; Lam, L.K.M.; Harris, J.M.; Bingham, R.C.; Raber, D.J.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1970**, 92, 2538.

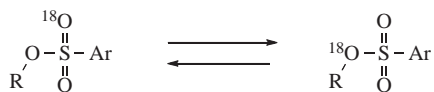
⁶⁷ Savéant, J.-M. *J. Am. Chem. Soc.* **2008**, 130, 4732.

⁶⁸ See Richard, J.P.; Toteva, M.M.; Amyes, T.L. *Org. Lett.* **2001**, 3, 2225.

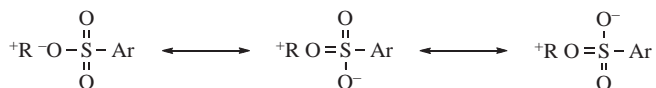
⁶⁹ Shiner Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* **1971**, 93, 2553.

that ion pairs are involved in many S_N1 reactions. There is much other evidence for the intervention of ion pairs,⁷⁰ including ion–molecule pairs.⁷¹

1. The compound 2-octyl brosylate was labeled at the sulfone oxygen with ^{18}O and solvolyzed. The unreacted brosylate recovered at various stages of solvolysis had the ^{18}O considerably, although not completely, scrambled:⁷²



In an intimate ion pair, the three oxygen atoms become equivalent:



Similar results were obtained with several other sulfonate esters.⁷³ The possibility must be considered that the scrambling resulted from ionization of one molecule of ROSO_2Ar to R^+ and ArSO_2O^- followed by attack by the ArSO_2O^- ion on *another* carbocation or perhaps on a molecule of ROSO_2Ar in an S_N2 process. However, this was ruled out by solvolyzing unlabeled substrate in the presence of labeled HOSO_2Ar . These experiments showed that there was some intermolecular exchange (3–20%), but not nearly enough to account for the amount of scrambling found in the original experiments. Similar scrambling was found in solvolysis of labeled carboxylic esters ($\text{R}-^{18}\text{O}-\text{COR}'$), where the leaving group is $\text{R}'\text{COO}^-$.⁷⁴ Also in this case, the external addition of RCOO^- did not result in significant exchange. However, it has been proposed that the scrambling could result from a concerted process, not involving ion-pair intermediates, and there is some evidence for this view.⁷⁵

2. The *special salt effect*. The addition of LiClO_4 or LiBr in the acetolysis of certain tosylates produced an initial steep rate acceleration that then decreased to the normal linear acceleration (caused by the ordinary salt effect).⁷⁶ This result is interpreted as: the ClO_4^- (or Br^-) traps the solvent-separated ion pair to give $\text{R}^+ \parallel \text{ClO}_4^-$ which, being unstable under these conditions, goes to product. Hence, the amount of solvent-separated ion pair that would have returned to the starting material is reduced, and the rate of the overall reaction is increased. The special salt effect has been directly observed by the use of picosecond absorption spectroscopy.⁷⁷

⁷⁰ See McManus, S.P.; Safavy, K.K.; Roberts, F.E. *J. Org. Chem.* **1982**, *47*, 4388; Kinoshita, T.; Komatsu, K.; Ikai, K.; Kashimura, K.; Tanikawa, S.; Hatanaka, A.; Okamoto, K. *J. Chem. Soc. Perkin Trans. 2* **1988**, 1875; Ronco, G.; Petit, J.; Guyon, R.; Villa, P. *Helv. Chim. Acta* **1988**, *71*, 648; Kevill, D.N.; Kyong, J.B.; Weitz, F.L. *J. Org. Chem.* **1990**, *55*, 4304.

⁷¹ Jia, Z.S.; Ottosson, H.; Zeng, X.; Thibblin, A. *J. Org. Chem.* **2002**, *67*, 182.

⁷² Diaz, A.F.; Lazdins, I.; Winstein, S. *J. Am. Chem. Soc.* **1968**, *90*, 1904.

⁷³ Paradisi, C.; Bunnett, J.F. *J. Am. Chem. Soc.* **1985**, *107*, 8223; Fujio, M.; Sanematsu, F.; Tsuno, Y.; Sawada, M.; Takai, Y. *Tetrahedron Lett.* **1988**, *29*, 93.

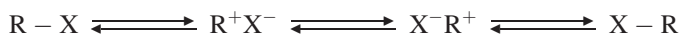
⁷⁴ Goering, H.L.; Hopf, H. *J. Am. Chem. Soc.* **1971**, *93*, 1224 and references cited therein.

⁷⁵ Dietze, P.E.; Wojciechowski, M. *J. Am. Chem. Soc.* **1990**, *112*, 5240.

⁷⁶ Cristol, S.J.; Noreen, A.L.; Nachtigall, G.W. *J. Am. Chem. Soc.* **1972**, *94*, 2187.

⁷⁷ Simon, J.D.; Peters, K.S. *J. Am. Chem. Soc.* **1982**, *104*, 6142.

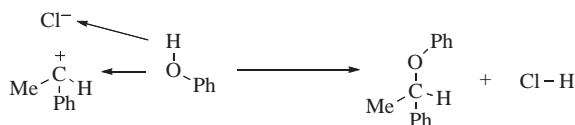
3. The possibilities of racemization or inversion of the *product* (*RS*) of a solvolysis reaction were discussed previously. However, the formation of an ion pair followed by internal return can also affect the stereochemistry of the *substrate* molecule *RX*. Cases have been found where internal return racemizes an original optically active *RX*, an example being solvolysis in aq acetone of α -*p*-anisylethyl *p*-nitrobenzoate,⁷⁸ while in other cases partial or complete retention is found (e.g., solvolysis in aq acetone of *p*-chlorobenzhydryl *p*-nitrobenzoate).⁷⁹ Racemization of *RX* is presumably caused by the equilibrium pathway:



Evidence for ion pairs includes some cases where internal return involves racemization, it has been shown that such racemization is *faster* than solvolysis. For example, optically active *p*-chlorobenzhydryl chloride racemizes ~ 30 times faster than it solvolyzes in acetic acid.⁸⁰

Molecular orbital calculations⁸¹ on *tert*-BuCl show that the C—Cl distance in the intimate ion pair is 2.9 Å and the onset of the solvent-separated ion pair takes place at ~ 5.5 Å (cf. the C—Cl bond length of 1.8 Å).

In a few cases, S_N1 reactions have been found to proceed with partial retention (20–50%) of configuration. Ion pairs have been invoked to explain some of these.⁸² For example, it has been proposed that the phenolysis of optically active α -phenylethyl chloride, in which the ether of net retained configuration is obtained, involves a four-center mechanism:



This conclusion is strengthened by the fact that partial retention was obtained in this system only with chloride or other neutral leaving groups; with leaving groups bearing a positive charge, which are much less likely to form hydrogen bonds with the solvent, no retention was found.⁸³ Partial retention can also arise when the ion pair is shielded at the backside by an additive (e.g., acetonitrile, acetone, or aniline).⁸⁴

The difference between the S_N1 and S_N2 mechanisms is in the timing of the steps. In the S_N1 mechanism, first *X* leaves, then *Y* attacks. In the S_N2 case, the two

⁷⁸ Goering, H.L.; Briody, R.G.; Sandrock, G. *J. Am. Chem. Soc.* **1970**, 92, 7401.

⁷⁹ Goering, H.L.; Briody, R.G.; Levy, J.F. *J. Am. Chem. Soc.* **1963**, 85, 3059.

⁸⁰ Winstein, S.; Gall, J.S.; Hojo, M.; Smith, S. *J. Am. Chem. Soc.* **1960**, 82, 1010. See also, Shiner, Jr., V.J.; Hartshorn, S.R.; Vogel, P.C. *J. Org. Chem.* **1973**, 38, 3604.

⁸¹ Jorgensen, W.L.; Buckner, J.K.; Huston, S.E.; Rossky, P.J. *J. Am. Chem. Soc.* **1987**, 109, 1891.

⁸² Okamoto, K. *Pure Appl. Chem.* **1984**, 56, 1797. Also see Lee, I.; Kim, H.Y.; Kang, H.K.; Lee, H.W. *J. Org. Chem.* **1988**, 53, 2678; Lee, I.; Kim, H.Y.; Lee, H.W.; Kim, I.C. *J. Phys. Org. Chem.* **1989**, 2, 35.

⁸³ Okamoto, K.; Kinoshita, T.; Shingu, H. *Bull. Chem. Soc. Jpn.* **1970**, 43, 1545.

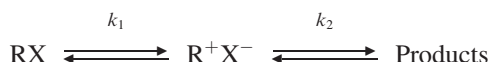
⁸⁴ Kinoshita, T.; Ueno, T.; Ikai, K.; Fujiwara, M.; Okamoto, K. *Bull. Chem. Soc. Jpn.* **1988**, 61, 3273; Kinoshita, T.; Komatsu, K.; Ikai, K.; Kashimura, K.; Tanikawa, S.; Hatanaka, A.; Okamoto, K. *J. Chem. Soc. Perkin Trans. 2* **1988**, 1875.

things happen simultaneously. One could imagine a third possibility: first the attack of Y and then the removal of X. This is not possible at a saturated carbon, since it would mean that there are more than eight electrons in the outer shell of carbon. However, this type of mechanism is possible and indeed occurs at other types of substrate (Sec. 10.F and Chap 13).

10.A.iv. Mixed S_N1 and S_N2 Mechanisms

Some reactions of a given substrate under a given set of conditions display all the characteristics of S_N2 mechanisms; other reactions seem to proceed by S_N1 mechanisms, but cases are found that cannot be characterized so easily. There seems to be something in between, a mechanistic “borderline” region.⁸⁵ At least two broad theories have been devised to explain these phenomena. One theory holds that intermediate behavior is caused by a mechanism that is neither “pure” S_N1 nor “pure” S_N2, but some “in-between” type. According to the second theory, there is no intermediate mechanism at all, and borderline behavior is caused by simultaneous operation, in the same flask, of both the S_N1 and S_N2 mechanisms; that is, some molecules react by the S_N1, while others react by the S_N2 mechanism.

One formulation of the intermediate-mechanism theory is that of Sneen et al.⁸⁶ The formulation is in fact very broad and applies not only to borderline behavior, but to all nucleophilic substitutions at a saturated carbon.⁸⁷ According to Sneen, et al.⁸⁸ all S_N1 and S_N2 reactions can be accommodated by one basic mechanism (the *ion-pair mechanism*). The substrate first ionizes to an intermediate ion pair that is then converted to products:



The difference between the S_N1 and S_N2 mechanisms is that in the former case the *formation* of the ion pair (k_1) is rate determining, while in the S_N2 mechanism its *destruction* (k_2) is rate determining. Borderline behavior is found where the rates of formation and destruction of the ion pair are of the same order of magnitude.⁸⁸ However, a number of investigators have asserted that these results could also be explained in other ways.⁸⁹

There is evidence for the Sneen formulation where the leaving group has a positive charge. In this case, there is a cation–molecule pair ($\text{RX}^+ \rightarrow \text{R}^+ \text{X}^-$).⁹⁰ instead of the ion pair that would be present if the leaving group were uncharged. Katritzky et al.⁹¹ found that

⁸⁵ For an essay on borderline mechanisms in general, see Jencks, W.P. *Chem. Soc. Rev.* **1982**, 10, 345.

⁸⁶ Sneen, R.A.; Felt, G.R.; Dickason, W.C. *J. Am. Chem. Soc.* **1973**, 95, 638 and references cited therein; Sneen, R.A. *Acc. Chem. Res.* **1973**, 6, 46.

⁸⁷ See Kevill, D.N.; Degenhardt, C.R. *J. Am. Chem. Soc.* **1979**, 101, 1465.

⁸⁸ See Sneen, R.A.; Felt, G.R.; Dickason, W.C. *J. Am. Chem. Soc.* **1973**, 95, 638 and references cited therein; Sneen, R.A. *Acc. Chem. Res.* **1973**, 6, 46; Blandamer, M.J.; Robertson, R.E.; Scott, J.M.W.; Vrielink, A. *J. Am. Chem. Soc.* **1980**, 102, 2585; Stein, A.R. *Can. J. Chem.* **1987**, 65, 363.

⁸⁹ See Raber, D.J.; Harris, J.C.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1971**, 93, 4821; McLennan, D.J. *Acc. Chem. Res.* **1976**, 9, 281; Stein, A.R. *J. Org. Chem.* **1976**, 41, 519; Katritzky, A.R.; Musumarra, G.; Sakizadeh, K. *J. Org. Chem.* **1981**, 46, 3831. For a reply, see Sneen, R.A.; Robbins, H.M. *J. Am. Chem. Soc.* **1972**, 94, 7868. See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, **1982**, pp. 442–450.

⁹⁰ See Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1629.

⁹¹ Katritzky, A.R.; Sakizadeh, K.; Gabrielsen, B.; le Noble, W.J. *J. Am. Chem. Soc.* **1984**, 106, 1879.

when such a reaction was run at varying high pressures, there was a minimum in the plot of rate constant versus pressure. A minimum of this sort usually indicates a change in mechanism, and the interpretation in this case was that the normal S_N2 mechanism operates at higher pressures and the cation–molecule mechanism at lower pressures.

An alternative view that also favors an intermediate mechanism is that of Schleyer and co-workers,⁹² who believe that the key to the problem is varying degrees of nucleophilic solvent assistance to ion-pair formation. They have proposed an S_N2 (intermediate) mechanism.⁹³

Among the experiments that have been cited for the viewpoint that borderline behavior results from simultaneous S_N1 and S_N2 mechanisms is the behavior of 4-methoxybenzyl chloride in 70% aq acetone.⁹⁴ In this solvent, hydrolysis⁹⁵ (i.e., conversion to 4-methoxybenzyl alcohol) occurs by an S_N1 mechanism. When azide ions are added, the alcohol is still a product, but now 4-methoxybenzyl azide is another product. Addition of azide ions increases the rate of ionization (by the salt effect), but *decreases* the rate of hydrolysis. If more carbocations are produced, but fewer go to the alcohol, then some azide must be formed by reaction with carbocations: an S_N1 process. However, the rate of ionization is always *less* than the total rate of reaction, so some azide must also form by an S_N2 mechanism.⁹⁴ Thus, the conclusion is that S_N1 and S_N2 mechanisms operate simultaneously.⁹⁶

Some nucleophilic substitution reactions that seem to involve a “borderline” mechanism actually do not. Thus, one of the principal indications that a “borderline” mechanism is taking place has been the finding of partial racemization and partial inversion. However, this type of stereochemical behavior is quite consistent with a strictly S_N2 process.⁹⁷ The reaction of optically active 2-octyl brosylate in 75% aq dioxane, gave inverted 2-octanol in 77% optical purity.⁹⁷ When sodium azide was added, 2-octyl azide was obtained along with the 2-octanol, *but the latter was now 100% inverted*. It is apparent that, in the original case, 2-octanol was produced by two different processes: An S_N2 reaction leading to inverted product, and another process in which some intermediate leads to racemization or retention. When azide ions were added, they scavenged this intermediate, so that the entire second process now went to produce azide, while the S_N2 reaction, unaffected by addition of azide, still went on to give inverted 2-octanol. What is the nature of the intermediate in the second process? At first thought, it is a carbocation, so that this would be another example of simultaneous S_N1 and S_N2 reactions. However, solvolysis of 2-octyl brosylate in pure methanol or of 2-octyl methanesulfonate in pure water, in the absence of azide ions, gave methyl 2-octyl ether or 2-octanol, respectively, *with 100% inversion of configuration*, indicating that the mechanism in these solvents was pure S_N2 . Since methanol and water are more polar than 75% aq dioxane and since an increase in polarity of solvent increases the rate of S_N1 reactions at the expense of S_N2 (Sec. 10.G.iii), it is

⁹² Bentley, T.W.; Bowen, C.T.; Morten, D.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1981**, 103, 5466.

⁹³ Also see Laureillard, J.; Casadevall, A.; Casadevall, E. *Tetrahedron* **1984**, 40, 4921; *Helv. Chim. Acta* **1984**, 67, 352. For evidence against the S_N2 (intermediate) mechanism, see Richard, J.P.; Amyes, T.L.; Vontor, T. *J. Am. Chem. Soc.* **1991**, 113, 5871.

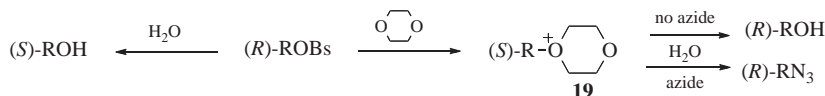
⁹⁴ Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* **1990**, 112, 9507. Also see Richard, J.P.; Rothenberg, M.E.; Jencks, W.P. *J. Am. Chem. Soc.* **1984**, 106, 1361; Richard, J.P.; Jencks, W.P. *J. Am. Chem. Soc.* **1984**, 106, 1373, 1383; Katritzky, A.R.; Brycki, B.E. *J. Phys. Org. Chem.* **1988**, 1, 1; Stein, A.R. *Can. J. Chem.* **1989**, 67, 297.

⁹⁵ The relationship between electrophilicity and rate coefficients is discussed in Aizman, A.; Contreras, R.; Pérez, P. *Tetrahedron* **2005**, 61, 889.

⁹⁶ See, however, Sneen, R.A.; Larsen, J.W. *J. Am. Chem. Soc.* **1969**, 91, 6031.

⁹⁷ Weiner, H.; Sneen, R.A. *J. Am. Chem. Soc.* **1965**, 87, 287.

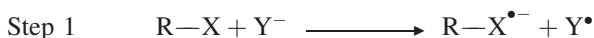
extremely unlikely that any S_N1 process could occur in 75% aq dioxane. The intermediate in the second process is thus not a carbocation. Its nature is suggested by the fact that, in the absence of azide ions, the amount of inverted 2-octanol decreased with an increasing percentage of dioxane in the solvent. Thus the intermediate is an oxonium ion (**19**) formed by an S_N2 attack *by dioxane*. This ion is not a stable product, but reacts with water in another S_N2 process to produce 2-octanol with retained configuration.



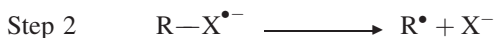
That part of the original reaction that resulted in retention of configuration⁹⁸ is thus seen to stem from two successive S_N2 reactions and not from any “borderline” behavior.⁹⁹

10.B. SET MECHANISMS

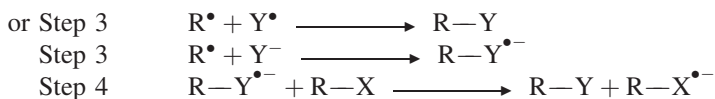
In certain reactions, where nucleophilic substitutions would seem obviously indicated, there is evidence that radicals and/or radical ions are actually involved.¹⁰⁰ The first step in such a process is transfer of an electron from the nucleophile to the substrate to form a radical anion:



Mechanisms that begin this way are called *SET mechanisms*.¹⁰¹ Once formed, the radical ion cleaves:



The radicals formed in this way can go on to product by reacting with the Y^\bullet produced in Step 1 or with the original nucleophilic ion Y^- , in which case an additional step is necessary:



In the latter case, the radical ion $\text{R-X}^{\bullet-}$ is formed by Step 4, as well as by Step 1, so that a chain reaction (Sec. 14.A.i) can take place.

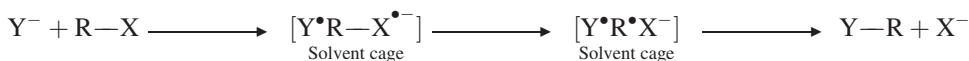
⁹⁸ According to this scheme, the configuration of the isolated RN_3 should be retained. It was, however, largely inverted, owing to a competing S_N2 reaction where N_3^- directly attacks ROBs.

⁹⁹ See Streitwieser, Jr., A.; Walsh, T.D.; Wolfe, Jr., J.R. *J. Am. Chem. Soc.* **1965**, *87*, 3682; Streitwieser, Jr., A.; Walsh, T.D. *J. Am. Chem. Soc.* **1965**, *87*, 3686; Beronius, P.; Nilsson, A.; Holmgren, A. *Acta Chem. Scand.* **1972**, *26*, 3173. See also, Knier, B.L.; Jencks, W.P. *J. Am. Chem. Soc.* **1980**, *102*, 6789.

¹⁰⁰ Bank, S.; Noyd, D.A. *J. Am. Chem. Soc.* **1973**, *95*, 8203; Ashby, E.C.; Goel, A.B.; Park, W.S. *Tetrahedron Lett.* **1981**, *22*, 4209. For discussions of the relationship between S_N2 and SET mechanisms, see Lewis, E.S. *J. Am. Chem. Soc.* **1989**, *111*, 7576; Shaik, S.S. *Acta Chem. Scand.* **1990**, *44*, 205.

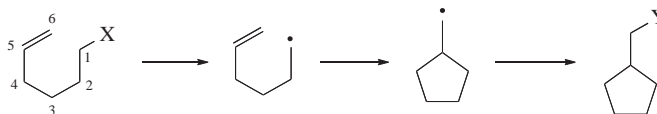
¹⁰¹ See Savéant, J. *Adv. Phys. Org. Chem.* **1990**, *26*, 1; Ashby, E.C. *Acc. Chem. Res.* **1988**, *21*, 414. See also, Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212; Chanon, M. *Acc. Chem. Res.* **1987**, *20*, 214. See Rossi, R.A.; Pierini, A.B.; Peñéñory, A.B. *Chem. Rev.* **2003**, *103*, 71.

One type of evidence for an SET mechanism is the finding of some racemization. A free radical would likely result in a completely racemized product RY, but it has been suggested¹⁰² that inversion can also take place in some SET processes. The suggestion is that in Step 1 the Y[−] still approaches from the back side, even though an ordinary S_N2 mechanism will not follow, and that the radical R[•], once formed, remains in a solvent cage with Y[•] still opposite X[−], so that Steps 1–3 can lead to inversion.

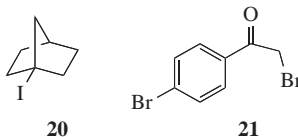


Reactions with SET mechanisms typically show predominant, although not 100%, inversion.

Other evidence cited¹⁰³ for SET mechanisms has been detection of radical or radical-ion intermediates by ESR¹⁰⁴ or CIDNP; the finding that such reactions can take place at 1-norbornyl bridgeheads;¹⁰⁵ and the formation of cyclic side products when the substrate has a double bond in the 5,6-position (such substrates are called *radical probes*).



Free radicals with double bonds in this position are known to cyclize readily (Sec. 15.A.iii).¹⁰⁶



The SET mechanism is chiefly found where X = I or NO₂ (see Reaction 10-67). A closely related mechanism, the S_{RN}1, takes place with aromatic substrates (Chap 13).¹⁰⁷ In that mechanism, the initial attack is by an electron donor, rather than a nucleophile. The S_{RN}1 mechanism has also been invoked for reactions of enolate anions with 2-iodobicyclo[4.1.0]heptane.¹⁰⁸ An example is the reaction of 1-iodobicyclo[2.2.1]heptane (**20**) with NaSnMe₃ or LiPPh₂, and some other nucleophiles, to give the substitution product.¹⁰⁹ Another is the reaction of bromo 4-bromoacetophenone (**21**) with Bu₄NBr in cumene.¹¹⁰ The two mechanisms, S_N2 versus SET, have been compared and contrasted.¹¹¹ There are

¹⁰² Daasbjerg, K.; Lund, T.; Lund, H. *Tetrahedron Lett.* **1989**, 30, 493.

¹⁰³ See also, Fuhlendorff, R.; Lund, T.; Lund, H.; Pedersen, J.A. *Tetrahedron Lett.* **1987**, 28, 5335.

¹⁰⁴ See, for example, Russell, J.A.; Pecoraro, J.M. *J. Am. Chem. Soc.* **1979**, 101, 3331.

¹⁰⁵ Santiago, A.N.; Morris, D.G.; Rossi, R.A. *J. Chem. Soc., Chem. Commun.* **1988**, 220.

¹⁰⁶ See Newcomb, M.; Curran, D.P. *Acc. Chem. Res.* **1988**, 21, 206; Newcomb, M. *Acta Chem. Scand.* **1990**, 44, 299. For replies to this criticism, see Ashby, E.C. *Acc. Chem. Res.* **1988**, 21, 414; Ashby, E.C.; Pham, T.N.; Amrollah-Madjdabadi, A.A. *J. Org. Chem.* **1991**, 56, 1596.

¹⁰⁷ In this book, there is a distinction between the SET and S_{RN}1 mechanisms. However, many workers use the designation SET to refer to the S_{RN}1, the chain version of the SET, or both.

¹⁰⁸ Nazareno, M.A.; Rossi, R.A. *J. Org. Chem.* **1996**, 61, 1645.

¹⁰⁹ Ashby, E.C.; Sun, X.; Duff, J.L. *J. Org. Chem.* **1994**, 59, 1270.

¹¹⁰ Haberfield, P. *J. Am. Chem. Soc.* **1995**, 117, 3314.

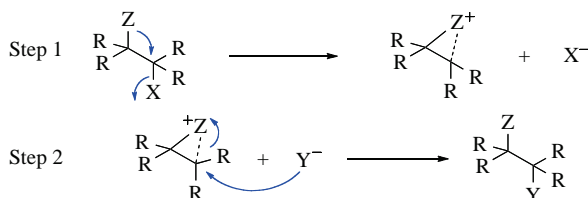
¹¹¹ Shaik, S.S. *Acta Chem. Scand.* **1990**, 44, 205.

also reactions where it is reported that radical, carbanion, and carbene pathways occur simultaneously.¹¹²

The mechanisms so far considered can, in theory at least, operate on any type of saturated (or for that matter unsaturated) substrate. There are other mechanisms that are more limited in scope.

10.C. THE NEIGHBORING-GROUP MECHANISM¹¹³

It is occasionally found with certain substrates that (1) the rate of reaction is greater than expected, and (2) the configuration at a chiral carbon is *retained* and not inverted or racemized. In these cases, there is usually a group with an unshared pair of electrons β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called the *neighboring-group mechanism* and consists essentially of two S_N2 substitutions, each causing an inversion so the net result is retention of configuration.¹¹⁴ In the first step of this reaction, the neighboring group acts as a nucleophile, pushing out the leaving group, but still retaining attachment to the molecule. In the second step, the external nucleophile displaces the neighboring group by a backside attack:



The reaction obviously must go faster than if Y were attacking directly, since if the latter process were faster, it would be happening. The neighboring group Z is said to be lending *anchimeric assistance*. The rate law followed in the neighboring-group mechanism is the first-order law shown in Eq. (10-2) or (10-3); that is, Y does not take part in the rate-determining step.

The reason attack by Z is faster than that by Y is that the group Z is more available. In order for Y to react, it must collide with the substrate, but Z is immediately available by virtue of its position. A reaction between the substrate and Y involves a large decrease in entropy of activation (ΔS^\ddagger), since the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of ΔS^\ddagger (see Sec. 6.D).¹¹⁵

It is not always easy to determine when a reaction rate has been increased by anchimeric assistance. In order to be certain, it is necessary to know what the rate would be without participation by the neighboring group. An obvious way to examine this question is to compare the rates of the reaction with and without the neighboring group, (e.g., $\text{HOCH}_2\text{CH}_2\text{Br}$ vs $\text{CH}_3\text{CH}_2\text{Br}$). However, this will certainly not give an accurate determination of the extent of participation, since the steric and field effects of H and OH are not the same. Furthermore, no matter what the solvent, the shell of solvent molecules that surrounds the polar protic OH group must differ greatly from that which surrounds the

¹¹² Ashby, E.C.; Park, B.; Patil, G.S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, 58, 424.

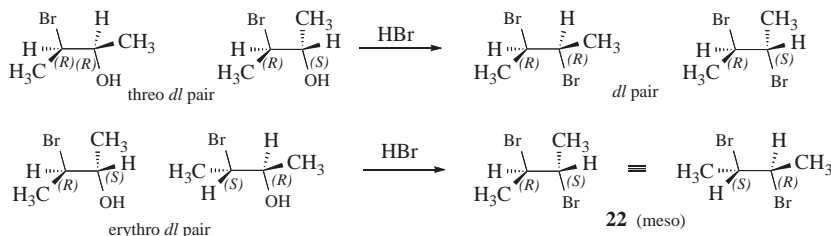
¹¹³ See Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1, Plenum, NY, **1976**.

¹¹⁴ See McCortney, B.A.; Jacobson, B.M.; Vreeke, M.; Lewis, E.S. *J. Am. Chem. Soc.* **1990**, 112, 3554.

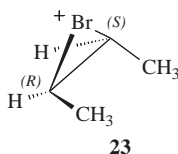
¹¹⁵ See Page, M.I. *Chem. Soc. Rev.* **1973**, 2, 295.

nonpolar H. Because of these considerations, it is desirable to have a large increase in the rate, preferably > 50-fold, before a rate increase is attributed to neighboring-group participation.

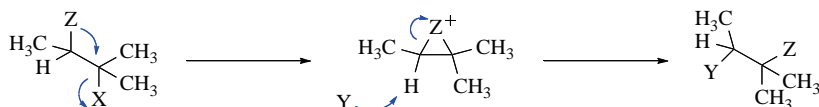
The first important evidence for the existence of this mechanism was the demonstration that retention of configuration can occur if the substrate is suitable. It was shown that the threo *dl* pair of 3-bromo-2-butanol when treated with HBr gave *dl*-2,3-dibromobutane, while the erythro pair gave the meso isomer (**22**).¹¹⁶



This result indicated that retention had taken place. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The meso and *dl* dibromides have different boiling points and indexes of refraction and were identified by these properties. Even more convincing evidence was that either of the two threo isomers alone gave not just one of the enantiomeric dibromides, but the *dl* pair. The reason for this is that the intermediate present after the attack by the neighboring group (**23**) is symmetrical, so the external nucleophile Br[−] can attack both carbon atoms equally well. Intermediate **23** is a *bromonium ion*, the existence of which has been demonstrated in several types of reactions (see Reaction 15-39).



Although **23** is symmetrical, intermediates in most neighboring-group mechanisms are not, and it is therefore possible to get not a simple substitution product, but a rearrangement. This will happen if Y attacks not the carbon atom from which X left, but the one to which Z was originally attached:

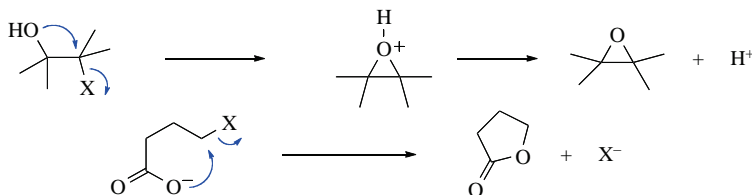


In such cases, substitution and rearrangement products are often produced together. For a discussion of rearrangements, see Chapter 18.

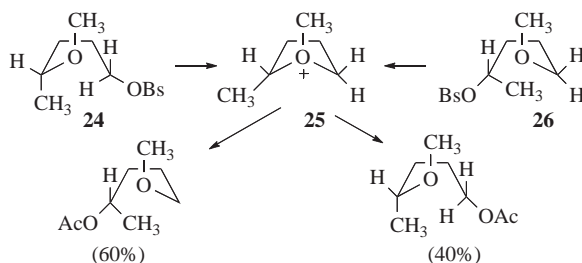
Another possibility is that the intermediate may be stable or may find some other way to stabilize itself. In such cases, Y never attacks at all and the product is cyclic. These are simple internal S_N2 reactions.¹¹⁷ Two examples are formation of epoxides and lactones:

¹¹⁶ Winstein, S.; Lucas, H.J. *J. Am. Chem. Soc.* **1939**, 61, 1576, 2845.

¹¹⁷ For a theoretical treatment of strain energy release and intrinsic barriers for internal S_N2 reactions, see Wolk, J.L.; Rozental, E.; Basch, H.; Hoz, S. *J. Org. Chem.* **2006**, 71, 3876.



The fact that acetolysis of both 4-methoxy-1-pentyl brosylate (**24**) and 5-methoxy-2-pentyl brosylate (**25**) gave the same mixture of products is further evidence for participation by a neighboring group.¹¹⁸ In this case, the intermediate **26** is common to both substrates.



The neighboring-group mechanism operates only when the ring size is right for a particular type of Z. For example, for $\text{MeO}(\text{CH}_2)_n\text{OBs}$, neighboring-group participation was important for $n = 4$ or 5 (corresponding to a five- or six-membered intermediate), but not for $n = 2, 3$, or 6 .¹¹⁹ However, optimum ring size is not the same for all reactions, even with a particular Z. In general, the most rapid reactions occur when the ring size is three, five, or six, depending on the reaction type. The likelihood of four-membered ring neighboring-group participation is increased when there are alkyl groups α or β to the neighboring group.¹²⁰

The following are some of the more important neighboring groups: COO^- (but not COOH), COOR , COAr , OCOR ,¹²¹ OR , OH , O^- ,¹²² NH_2 , NHR , NR_2 , NHCOR , SH , SR , S^- ,¹²³ SO_2Ph ,¹²⁴ I , Br , and Cl . The effectiveness of halogens as neighboring groups decreases in the order $\text{I} > \text{Br} > \text{Cl}$.¹²⁵ The Cl substituents is a very weak neighboring group, and can be shown to act in this way only when the solvent does not interfere. For example, when 5-chloro-2-hexyl tosylate is solvolyzed in acetic acid, there is little participation by the Cl , but when the solvent is changed to trifluoroacetic acid, which is much less nucleophilic, neighboring-group participation by the Cl becomes the major reaction

¹¹⁸ Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 3991, 3998.

¹¹⁹ Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 4012.

¹²⁰ Eliel, E.L.; Clawson, L.; Knox, D.E. *J. Org. Chem.* **1985**, *50*, 2707; Eliel, E.L.; Knox, D.E. *J. Am. Chem. Soc.* **1985**, *107*, 2946.

¹²¹ See Wilen, S.H.; Delguzzo, L.; Saferstein, R. *Tetrahedron* **1987**, *43*, 5089.

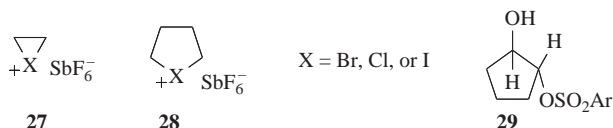
¹²² See Perst, H. *Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, **1971**, pp. 100–127. Also see Franci, M.M.; Hansell, G.; Patel, B.P.; Swindell, C.S. *J. Am. Chem. Soc.* **1990**, *112*, 3535.

¹²³ See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**, pp. 141–145.

¹²⁴ Lambert, J.B.; Beadle, B.M.; Kuang, K. *J. Org. Chem.* **1999**, *64*, 9241.

¹²⁵ Peterson, P.E. *Acc. Chem. Res.* **1971**, *4*, 407, and references cited therein.

pathway.¹²⁶ Thus, Cl acts as a neighboring group *only when there is need for it* (for other examples of the *principle of increasing electron demand*, see Sec. 10.C.i).



A number of intermediates of halogen participation (halonium ions),¹²⁷ (e.g., **27** and **28**), have been prepared as stable salts in $\text{SbF}_5\text{—SO}_2$ or $\text{SbF}_5\text{—SO}_2\text{ClF}$ solutions.¹²⁸ Some have even been crystallized. Attempts to prepare four-membered homologues of **27** and **28** were not successful.¹²⁹ There is no evidence that F can act as a neighboring group.¹²³

The principle that a neighboring group lends assistance in proportion to the need for such assistance also applies to differences in leaving-group ability. Thus, $p\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_2\text{O}$ (the nosylate group) is a better leaving group than $p\text{-MeC}_6\text{H}_4\text{SO}_2\text{O}$ (the tosylate group). Experiments have shown that the OH group in *trans*-2-hydroxycyclopentyl arenesulfonates (**29**) acts as a neighboring group when the leaving group is tosylate, but not when it is nosylate, apparently because the nosylate group leaves so rapidly that it does not require assistance.¹³⁰

10.C.i. Neighboring-Group Participation by π and σ Bonds: Nonclassical Carbocations¹³¹

For all the neighboring groups listed in Section 10.C, the nucleophilic attack is made by an atom with an unshared pair of electrons. In this section, neighboring-group participation by $\text{C}=\text{C}$ π bonds and C—C and C—H σ bonds will be considered. There has been a great deal of controversy over whether such bonds can act as neighboring groups and about the existence and structure of the intermediates involved. These intermediates are called *nonclassical* (or *bridged*) carbocations. In *classical carbocations* (Chap 5), the positive charge is *localized* on one carbon atom or delocalized by resonance involving an unshared pair of electrons or a double or triple bond in the allylic position. In a *nonclassical carbocation*,¹³² the positive charge is *delocalized* by a double or triple bond that is not in the allylic position or by a single bond. Examples are

¹²⁶ Peterson, P.E.; Bopp, R.J.; Chevli, D.M.; Curran, E.L.; Dillard, D.E.; Kamat, R.J. *J. Am. Chem. Soc.* **1967**, 89, 5902. See also, Reich, I.L.; Reich, H.J. *J. Am. Chem. Soc.* **1974**, 96, 2654.

¹²⁷ See Olah, G.A. *Halonium Ions*, Wiley, NY, **1975**; Koster, G.F. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, **1983**, pp. 1265–1351.

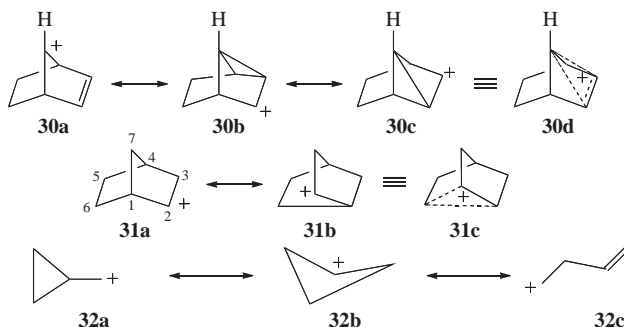
¹²⁸ See Henrichs, P.M.; Peterson, P.E. *J. Org. Chem.* **1976**, 41, 362; Vancik, H.; Percac, K.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* **1991**, 807.

¹²⁹ Olah, G.A.; Bollinger, J.M.; Mo, Y.K.; Brinich, J.M. *J. Am. Chem. Soc.* **1972**, 94, 1164.

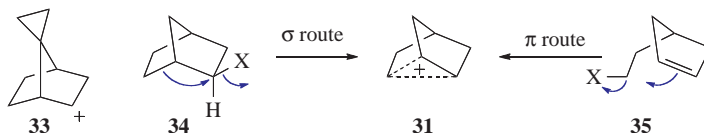
¹³⁰ Haupt, F.C.; Smith, M.R. *Tetrahedron Lett.* **1974**, 4141.

¹³¹ See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, **1972**; Bartlett, P.D. *Nonclassical Ions*, W.A. Benjamin, NY, **1965**. Barkhash, V.A. *Top. Curr. Chem.* **1984**, 116/117, 1; McManus, S.P.; Pittman Jr., C.U. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, **1973**, pp. 302–321.

¹³² Olah, G.A. *J. Org. Chem.* **2005**, 70, 2413.



the 7-norbornenyl cation (**30**), the norbornyl cation (**31**),¹³³ and the cyclopropylmethyl cation (**32**). A cyclopropyl group (as in **33**) is capable of stabilizing the norbornyl cation, inhibiting this rearrangement.¹³⁴ Carbocation **30** is called a *homoaallylic* carbocation, because in **30a** there is one carbon atom between the positively charged carbon and the double bond. Many of these carbocations can be produced in more than one way if the proper substrates are chosen. For example, **31** can be generated by the departure of a leaving group



from **34** or from **35**.¹³⁵ The first of these pathways is called the σ route to a nonclassical carbocation, because participation of a σ bond is involved. The second is called the π route.¹³⁶ The argument against the existence of nonclassical carbocations is essentially that the structures **30a–30c** (or **31a**, **31b**, etc.) are not canonical forms, but real structures and that there is rapid equilibration among them. This debate remained an active area of interest for some reactions for many years.¹³⁷ In one study, the solvolysis and rearrangement of 2-bicyclo[3.2.2]nonanyl tosylate in methanol generated ethers derived from the 2-bicyclo[3.2.2]nonanyl and 2-bicyclo[3.3.1]nonanyl systems that were rationalized in terms of a classical carbocation.¹³⁸ Density functional and *ab initio* calculations indicated that the products of the 2-bicyclo[3.2.2]nonanyl tosylate solvolysis were found to have nonclassical structures.¹³⁹

In discussing nonclassical carbocations, care must be taken to make the distinction between neighboring-group participation and the existence of nonclassical carbocations.¹⁴⁰ If a nonclassical carbocation exists in any reaction, then an ion with electron delocalization, as shown in the above examples, is a discrete reaction intermediate. If a carbon–carbon double or single bond participates in the departure of the leaving group to

¹³³ Sieber, S.; Schleyer, P.v.R.; Vancik, H.; Mesic, M.; Sunko, D.E. *Angew. Chem. Int. Ed.* **1993**, 32, 1604; Schleyer, P.v.R.; Sieber, S. *Angew. Chem. Int. Ed.* **1993**, 32, 1606.

¹³⁴ Herrmann, R.; Kirmse, W. *Liebigs Ann. Chem.* **1995**, 703.

¹³⁵ Bartlett, P.D.; Bank, S.; Crawford, R.J.; Schmid, G.H. *J. Am. Chem. Soc.* **1965**, 88, 1288.

¹³⁶ Winstein, S.; Carter, P. *J. Am. Chem. Soc.* **1961**, 83, 4485.

¹³⁷ For example, see Brunelle, P.; Sorensen, T.S.; Taeschler, C. *J. Org. Chem.* **2001**, 66, 7294.

¹³⁸ Okazaki, T.; Terakawa, E.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* **2000**, 65, 1680.

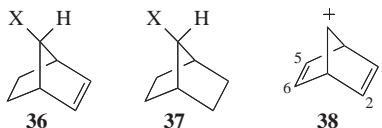
¹³⁹ Smith, W. B. *J. Org. Chem.* **2001**, 66, 376.

¹⁴⁰ This was pointed out by Cram, D.J. *J. Am. Chem. Soc.* **1964**, 86, 3767.

form a carbocation, it may be that a nonclassical carbocation is involved, but there is no necessary relation. In any particular case, either or both of these possibilities are possible.

In the following pages, some of the evidence bearing on the questions of the participation of π and σ bonds is considered, which bears on the existence of nonclassical carbocations,¹⁴¹ although a thorough discussion is beyond the scope of this book.¹⁰⁰

1. **C=C as a Neighboring Group.**¹⁴² The most striking evidence that C=C can act as a neighboring group is that acetolysis of **36**-OTs is 10^{11} times faster than that of **37**-OTs and *proceeds with retention of configuration*.¹⁴³ The rate data alone do not necessarily prove that acetolysis of **36**-OTs involves a nonclassical intermediate (**30d**), but it is certainly strong evidence that the C=C group assists in the departure of the OTs.



Evidence that **30** is indeed a nonclassical ion comes from an NMR study of the relatively stable norbornadienyl cation (**38**). The ^1H NMR spectrum shows that the 2 and 3 protons are not equivalent to the 5 and 6 protons.¹⁴⁴ Thus there is interaction between the charged carbon and one double bond, which is evidence for the existence of **30d**.¹⁴⁵ In the case of **36**, the double bond is geometrically fixed in an especially favorable position for backside attack on the carbon bearing the leaving group (hence the very large rate enhancement), but there is much evidence that other double bonds in the homoallylic position,¹⁴⁶ as well as in positions farther away,¹⁴⁷ can also lend anchimeric assistance, although generally with much lower rate ratios. One example of the latter is the compound β -(*syn*-7-norbornenyl)ethyl brosylate (**39**), which at 25°C undergoes acetolysis $\sim 140,000$ times faster than the saturated analogue **40**.¹⁴⁸ Triple bonds¹⁴⁹ and allenes¹⁵⁰ can also act as neighboring groups.

¹⁴¹ See Brown, H.C. *The Nonclassical Ion Problem*, Plenum, NY, **1977**. This book also includes rebuttals by Schleyer, P.v.R. See also, Brown, H.C. *Pure Appl. Chem.* **1982**, *54*, 1783.

¹⁴² See Story, P.R.; Clark, Jr., B.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, **1972**, pp. 1007–1060; Richey, Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, **1970**, pp. 77–101.

¹⁴³ Winstein, S.; Shatavsky, M. *J. Am. Chem. Soc.* **1956**, *78*, 592.

¹⁴⁴ Story, P.R.; Snyder, L.C.; Douglass, D.C.; Anderson, E.W.; Kornegay, R.L. *J. Am. Chem. Soc.* **1963**, *85*, 3630. See Story, P.R.; Clark, Jr., B.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, **1972**, pp. 1026–1041; Lustgarten, R.K.; Brookhart, M.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2347.

¹⁴⁵ See Gassman, P.G.; Doherty, M.M. *J. Am. Chem. Soc.* **1982**, *104*, 3742 and references cited therein; Laube, T. *J. Am. Chem. Soc.* **1989**, *111*, 9224.

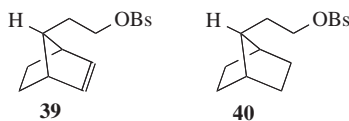
¹⁴⁶ See Schleyer, P.v.R.; Bentley, T.W.; Koch, W.; Kos, A.J.; Schwarz, H. *J. Am. Chem. Soc.* **1987**, *109*, 6953; Fernández-Mateos, A.; Rentzsch, M.; Sánchez, L.R.; González, R.R. *Tetrahedron* **2001**, *57*, 4873.

¹⁴⁷ See Ferber, P.H.; Gream, G.E. *Aust. J. Chem.* **1981**, *34*, 1051; Orlovic, M.; Borcic, S.; Humski, K.; Kronja, O.; Imper, V.; Polla, E.; Shiner, Jr., V.J. *J. Org. Chem.* **1991**, *56*, 1874.

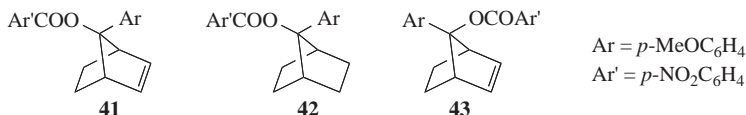
¹⁴⁸ Bly, R.S.; Bly, R.K.; Bedenbaugh, A.O.; Vail, O.R. *J. Am. Chem. Soc.* **1967**, *89*, 880.

¹⁴⁹ See Peterson, P.E.; Vidrine, D.W. *J. Org. Chem.* **1979**, *44*, 891; Rappoport, Z. *React. Intermed. (Plenum)* **1983**, *3*, 440.

¹⁵⁰ Von Lehman, T.; Macomber, R. *J. Am. Chem. Soc.* **1975**, *97*, 1531.



Evidence has been presented to show that participation by a potential neighboring group can be reduced or eliminated if an outside nucleophile is present that is more effective than the neighboring group in attacking the central carbon (see above), or if a sufficiently good leaving group is present (see above). In another example of the principle of increasing electron demand, Gassman et al.¹⁵¹ showed that neighboring-group participation can also be reduced if the stability of the potential carbocation is increased. They found that the presence of a *p*-anisyl group at the 7 position of **36** and **37** exerts a powerful leveling effect on the rate differences. Thus, solvolysis in acetone–water at 85 °C of **38** was only ~ 2.5 times faster than that of the saturated compound **42**. Furthermore, both **41** and its stereoisomer **43** gave the same mixture of solvolysis products, showing that the stereoselectivity in the solvolysis of **36** is not present here. The difference between **41** and **36** is that in the case of **41** the positive charge generated at the 7 position in the transition state is greatly stabilized by the *p*-anisyl group. Apparently, the stabilization by the *p*-anisyl group is so great that further stabilization that would come from participation by the C=C bond is not needed.¹⁵² The use of a phenyl instead of a *p*-anisyl group is not sufficient to stop participation by the double bond completely, although it does reduce it.¹⁵³ These results essentially emphasize the previous conclusion that *a neighboring group lends anchimeric assistance only when there is sufficient demand for it*.¹⁵⁴ The π -bond of a neighboring alkene group can assist solvolysis via π -participation.¹⁵⁵



The ability of C=C to serve as a neighboring group can depend on its electron density. When the strongly electron-withdrawing CF₃ group was attached to a double-bond carbon of **44**, the solvolysis rate was lowered by a factor of ~ 10⁶.¹⁵⁶ A second CF₃ group had an equally strong effect. In this case, two CF₃ groups decrease the electron density of the C=C bond to the point that the solvolysis rate for **44** (R¹ = R² = CF₃) was about the same as (actually ~ 17 times slower than) the rate for the saturated substrate **37** (X = OMos). Thus, the two CF₃ groups completely remove the ability of the C=C bond to act as a neighboring group.

¹⁵¹ Gassman, P.G.; Zeller, J.; Lamb, J.T. *Chem. Commun.* **1968**, 69.

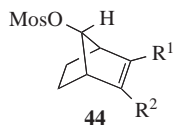
¹⁵² See Olah, G.A.; Berrier, A.L.; Arvanaghi, M.; Prakash, G.K.S. *J. Am. Chem. Soc.* **1981**, 103, 1122.

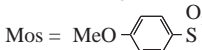
¹⁵³ Gassman, P.G.; Fentiman, Jr., A.F. *J. Am. Chem. Soc.* **1969**, 91, 1545; **1970**, 92, 2549.

¹⁵⁴ See Lambert, J.B.; Mark, H.W.; Holcomb, A.G.; Magyar, E.S. *Acc. Chem. Res.* **1979**, 12, 317.

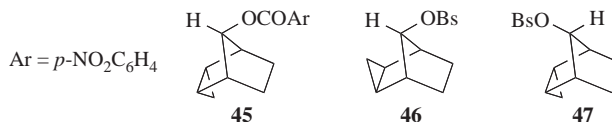
¹⁵⁵ Malnar, I.; Juric, S.; Vrcek, V.; Gjuranovic, Z.; Mihalic, Z.; Kronja, O. *J. Org. Chem.* **2002**, 67, 1490.

¹⁵⁶ Gassman, P.G.; Hall, J.B. *J. Am. Chem. Soc.* **1984**, 106, 4267.

 44	Substituents	Relative Rates
	$R^1 = R^2 = H$	1.4×10^{12}
	$R^1 = H, R^2 = CF_3$	1.5×10^6
	$R^1 = R^2 = CF_3$	1

Mos = 

2. *Cyclopropyl¹⁵⁷ as a Neighboring Group.*¹⁵⁸ In Section 4.Q.i, the properties of a cyclopropane ring were shown to be similar to those of a double bond in some ways. Therefore it is not surprising that a suitably placed



cyclopropyl ring can also be a neighboring group. Thus *endo-anti*-tricyclo[3.2.1.0^{2,4}]octan-8-yl *p*-nitrobenzoate (**45**) solvolyzed $\sim 10^{14}$ times faster than the *p*-nitrobenzoate of **37-OH**.¹⁵⁹ Obviously, a suitably placed cyclopropyl ring can be even more effective¹⁶⁰ as a neighboring group than a double bond.¹⁶¹ The need for suitable placement is emphasized by the fact that **47** solvolyzed only about five times faster than **37-OBs**,¹⁶² while **46** solvolyzed three times *slower* than **37-OBs**.¹⁶³ In the case of **45** and of all other cases known where cyclopropyl lends considerable anchimeric assistance, the developing *p* orbital of the carbocation is orthogonal to the participating bond of the cyclopropane ring.¹⁶⁴ An experiment designed to test whether a developing *p* orbital that would be parallel to the participating bond would be assisted by that bond showed no rate enhancement.¹⁶⁴ This result is in contrast to the behavior of cyclopropane rings directly attached to positively charged carbons, where the *p* orbital is parallel to the plane of the ring (Sec. 5.A.ii, and category 4.b below). Rate enhancements, although considerably smaller, have also been reported for suitably placed cyclobutyl rings.¹⁶⁵

3. *Aromatic Rings as Neighboring Groups.*¹⁶⁶ There is a great deal of evidence that aromatic rings in the β position can function as neighboring groups.¹⁶⁷

¹⁵⁷ In this section, systems are considered in which at least one carbon separates the cyclopropyl ring from the carbon bearing the leaving group. For a discussion of systems in which the cyclopropyl group is directly attached to the leaving-group carbon, see below, category 4.b.

¹⁵⁸ For a review, see Haywood-Farmer, J. *Chem. Rev.* **1974**, 74, 315.

¹⁵⁹ Tanida, H.; Tsuji, T.; Irie, T. *J. Am. Chem. Soc.* **1967**, 89, 1953; Battiste, M.A.; Deyrup, C.L.; Pincock, R.E.; Haywood-Farmer, J. *J. Am. Chem. Soc.* **1967**, 89, 1954.

¹⁶⁰ For a competitive study of cyclopropyl versus double-bond participation, see Lambert, J.B.; Jovanovich, A.P.; Hamersma, J.W.; Koeng, F.R.; Oliver, S.S. *J. Am. Chem. Soc.* **1973**, 95, 1570.

¹⁶¹ Also see Gassman, P.G.; Creary, X. *J. Am. Chem. Soc.* **1973**, 95, 2729; Takakis, I.M.; Rhodes, Y.E. *Tetrahedron Lett.* **1983**, 24, 4959.

¹⁶² Haywood-Farmer, J. *Chem. Rev.* **1974**, 74, 315.

¹⁶³ Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* **1969**, 91, 3020. Also see Rhodes, Y.E.; Takino, T. *J. Am. Chem. Soc.* **1970**, 92, 4469; Hanack, M.; Krause, P. *Liebigs Ann. Chem.* **1972**, 760, 17.

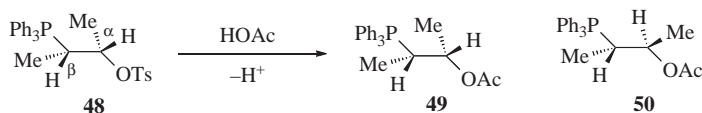
¹⁶⁴ Gassman, P.G.; Seter, J.; Williams, F.J. *J. Am. Chem. Soc.* **1971**, 93, 1673. See Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* **1969**, 91, 3020; Chenier, P.J.; Jenson, T.M.; Wulff, W.D. *J. Org. Chem.* **1982**, 47, 770.

¹⁶⁵ See Schipper, P.; Driessen, P.B.J.; de Haan, J.W.; Buck, H.M. *J. Am. Chem. Soc.* **1974**, 96, 4706; Ohkata, K.; Doecke, C.W.; Klein, G.; Paquette, L.A. *Tetrahedron Lett.* **1980**, 21, 3253.

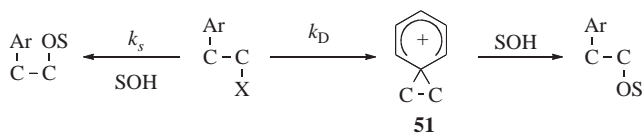
¹⁶⁶ See Lancelot, L.A.; Cram, D.J.; Schleyer, P.v.R. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, **1972**, pp. 1347–1483.

¹⁶⁷ Kevill, D.N.; D'Souza, M.J. *J. Chem. Soc. Perkin Trans. 2* **1997**, 257.

Stereochemical evidence was obtained by solvolysis of L-*threo*-3-phenyl-2-butyl tosylate (**48**) in acetic acid.¹⁶⁸ Of the acetate product, 96% was the *threo* isomer and only ~ 4% was *erythro*. Moreover, both the (+) and (-) *threo* isomers (**49** and **50**) were produced in



approximately equal amounts (a racemic mixture). When solvolysis was conducted in formic acid, even less *erythro* isomer was obtained. This result is similar to that found on reaction of 3-bromo-2-butanol with HBr (Sec. 10.C) and leads to the conclusion that configuration is retained because phenyl acts as a neighboring group. However, evidence from rate studies is not so simple. If β -aryl groups assist the departure of the leaving group, solvolysis rates should be enhanced. In general, they are not. However, solvolysis rate studies in 2-arylethyl systems are complicated by the fact that, for primary and secondary systems, two pathways can exist.¹⁶⁹ In one of these (designated k_{Δ}), the aryl, behaving as a neighboring group, pushes out the leaving



group to give a bridged ion, called a *phenonium ion* (**51**), and is in turn pushed out by the solvent (SOH), so the net result is substitution with retention of configuration (or rearrangement, if **51** is opened from the other side). The other pathway (k_s) is simple S_N2 attack by the solvent at the leaving-group carbon. The net result is substitution with inversion and no possibility of rearrangement. Whether the leaving group is located at a primary or a secondary carbon, there is no cross over between these pathways; they are completely independent.¹⁷⁰ Both the k_{Δ} and k_s pathways are unimportant when the leaving group is at a tertiary carbon. In these cases, the mechanism is S_N1 and open carbocations $\text{ArCH}_2\text{CR}_2^+$ are intermediates. This pathway is designated k_c . Which of the two pathways (k_s or k_{Δ}) predominates in any given case depends on the solvent and on the nature of the aryl group. As expected from the results we have seen for Cl as a neighboring group (see above), the k_{Δ}/k_s ratio is highest for solvents that are poor nucleophiles and so compete very poorly with the aryl group. For several common solvents, the k_{Δ}/k_s ratio increases in the order $\text{EtOH} < \text{CH}_3\text{CO}_2\text{H} < \text{HCO}_2\text{H} < \text{CF}_3\text{CO}_2\text{H}$.¹⁷¹ In accord with this, the following percentages of retention were obtained in solvolysis of 1-phenyl-2-propyl tosylate at 50 °C: solvolysis in EtOH 7%, $\text{CH}_3\text{CO}_2\text{H}$ 35%, and HCO_2H 85%.¹⁷¹ This finding indicates that k_s predominates in EtOH (phenyl participates very little),

¹⁶⁸ Cram, D.J. *J. Am. Chem. Soc.* **1949**, 71, 3863; **1952**, 74, 2129.

¹⁶⁹ Brookhart, M.; Anet, F.A.L.; Cram, D.J.; Winstein, S. *J. Am. Chem. Soc.* **1966**, 88, 5659; Lee, C.C.; Unger, D.; Vassie, S. *Can. J. Chem.* **1972**, 50, 1371.

¹⁷⁰ Brown, H.C.; Kim, C.J. *J. Am. Chem. Soc.* **1971**, 93, 5765.

¹⁷¹ Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* **1969**, 91, 4300. See also, Schadt, F.L.; Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1978**, 100, 228.

TABLE 10.1 Approximate k_{Δ}/k_s Ratios for Acetolysis of p -ZC₆H₄CH₂CH₂OTs at 90 °C^a

Z	k_{Δ}/k_s
MeO	30
Me	11
H	1.3
Cl	0.3

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^aSee Ref. 145.

while k_{Δ} predominates in HCO₂H. Trifluoroacetic acid is a solvent of particularly low nucleophilic power, and in this solvent the reaction proceeds entirely by k_{Δ} .¹⁷² Deuterium labeling showed 100% retention.¹⁷³ This case provides a clear example of neighboring-group rate enhancement by phenyl. The rate of solvolysis of PhCH₂CH₂OTs at 75 °C in CF₃COOH is 3040 times the rate for CH₃CH₂OTs.¹⁷²

With respect to the aromatic ring, the k_{Δ} pathway is electrophilic aromatic substitution (Chapter 11). Groups on the ring that activate that reaction (Sec. 11.B.i) are predicted to increase, and deactivating groups will decrease the rate of this pathway. This prediction has been borne out by several investigations. The p -nitro derivative of **48** solvolyzed in acetic acid 190 times slower than **48**, and there was much less retention of configuration; the acetate produced was only 7% threo and 93% erythro.¹⁷⁴ At 90 °C, acetolysis of p -ZC₆H₄CH₂CH₂OTs gave the rate ratios shown in Table 10.1.¹⁷⁵ Throughout this series k_s is fairly constant, as it should be since it is affected only by the rather remote field effect of Z. It is k_{Δ} that changes substantially as Z is changed from activating to deactivating. The evidence is thus fairly clear that participation by aryl groups depends greatly on the nature of the group. For some groups (e.g., p -nitrophenyl), in some solvents (e.g., acetic acid), there is essentially no neighboring-group participation at all,¹⁷⁶ while for others (e.g., p -methoxyphenyl), neighboring-group participation is substantial. The combined effect of solvent and structure is shown in Table 10.2, where the figures shown were derived by three different methods.¹⁷⁷ The decrease in neighboring-group effectiveness when aromatic rings are substituted by electron-withdrawing groups is reminiscent of the similar case of C=C bonds substituted by CF₃ groups (see above, category 1).

¹⁷² Nordlander, J.E.; Kelly, W.J. *J. Am. Chem. Soc.* **1969**, 91, 996.

¹⁷³ Jablonski, R.J.; Snyder, E.I. *J. Am. Chem. Soc.* **1969**, 91, 4445.

¹⁷⁴ Thompson, J.A.; Cram, D.J. *J. Am. Chem. Soc.* **1969**, 91, 1778. See also Kingsbury, C.A.; Best, D.C. *Bull. Chem. Soc. Jpn.* **1972**, 45, 3440.

¹⁷⁵ Coke, J.L.; McFarlane, F.E.; Mourning, M.C.; Jones, M.G. *J. Am. Chem. Soc.* **1969**, 91, 1154; Jones, M.G.; Coke, J.L. *J. Am. Chem. Soc.* **1969**, 91, 4284. See also, Harris, J.M.; Schadt, F.L.; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* **1969**, 91, 7508.

¹⁷⁶ See Ando, T.; Shimizu, N.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Tetrahedron Lett.* **1973**, 117.

¹⁷⁷ Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1969**, 91, 4291, 4296; Lancelot, C.J.; Harper, J.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1969**, 91, 4294; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* **1969**, 91, 4297.

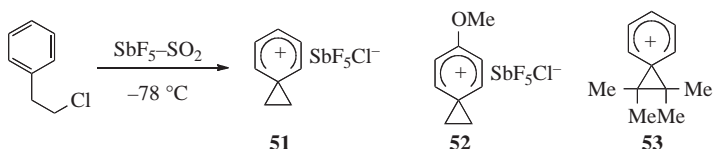
TABLE 10.2 Percent of Product Formed by the k_{Δ} Pathway in Solvolysis of p -ZC₆H₄CH₂CH₂OTs^a

Z	Solvent	Percent by k_{Δ}
H	CH ₃ COOH	35–38
H	HCOOH	72–79
MeO	CH ₃ COOH	91–93
MeO	HCOOH	99

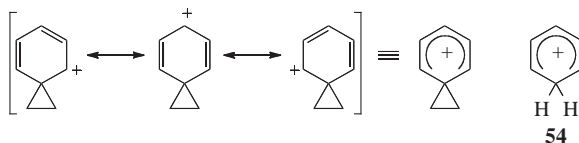
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^aSee Ref. 177.

Several phenonium ions have been prepared as stable ions in solution where they can be studied by NMR, among them **52**,¹⁷⁸ **53**,¹⁷⁹ and the unsubstituted **51**.¹⁸⁰ These were prepared¹⁸¹ by the method shown for **51**: treatment of the corresponding β -arylethyl chloride with SbF₅—SO₂ at low temperatures. These conditions are even more



extreme than the solvolysis in CF₃COOH mentioned earlier. The absence of any nucleophile eliminates not only the k_s pathways but also nucleophilic attack on **51**. Although **51** is not in equilibrium with the open-chain ion PhCH₂CH₂⁺, which is primary and hence unstable, **53** is in equilibrium with the open-chain tertiary ions PhCMe₂C⁺Me₂ and PhC⁺MeCMe₃, although only **53** is present in appreciable concentration. Proton and ¹³C NMR show that **51**–**53** are classical carbocations where the only resonance is in the six-membered ring. The three-membered ring is a normal cyclopropane ring that is influenced only to a relatively small extent by the positive charge on the adjacent ring. Nuclear magnetic resonance spectra show that the six-membered rings have no aromatic character, but are similar in structure to the arenium ions (e.g., **54**), that are intermediates in electrophilic aromatic substitution (Chapter 11). A number of phenonium ions, including **51**, have also been reported to be present in the gas phase, where their existence has been inferred from reaction products and from ¹³C labeling.¹⁸²



¹⁷⁸ Ramsey, B.; Cook Jr., J.A.; Manner, J.A. *J. Org. Chem.* **1972**, 37, 3310.

¹⁷⁹ Olah, G.A.; Comisarow, M.B.; Kim, C.J. *J. Am. Chem. Soc.* **1969**, 91, 1458. See, however, Ramsey, B.; Cook, Jr., J.A.; Manner, J.A. *J. Org. Chem.* **1972**, 37, 3310.

¹⁸⁰ Olah, G.A.; Spear, R.J.; Forsyth, D.A. *J. Am. Chem. Soc.* **1976**, 98, 6284.

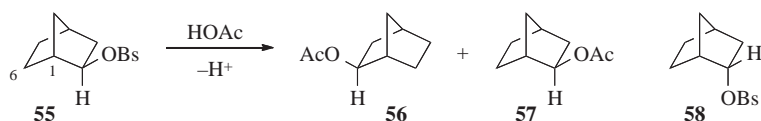
¹⁸¹ See Olah, G.A.; Singh, B.P.; Liang, G. *J. Org. Chem.* **1984**, 49, 2922; Olah, G.A.; Singh, B.P. *J. Am. Chem. Soc.* **1984**, 106, 3265.

¹⁸² Mishima, M.; Tsuno, Y.; Fujio, M. *Chem. Lett.* **1990**, 2277.

It is thus clear that β -aryl groups can function as neighboring groups.¹⁸³ Much less work has been done on aryl groups located in positions farther away from the leaving group, but there is evidence that these too can lend anchimeric assistance.¹⁸⁴

4. *The Carbon–Carbon Single Bond as a Neighboring Group.*¹⁸⁵

- a. *The 2-Norbornyl System.* In the investigations to determine whether a C—C σ bond can act as a neighboring group, by far the greatest attention has been paid to the 2-norbornyl system.¹⁸⁶ Winstein et al.¹⁸⁷ found that solvolysis in acetic acid of optically active *exo*-2-norbornyl brosylate (**55**, OB = brosylate) gave a racemic mixture of the two *exo* acetates; no *endo* isomers were formed:



Furthermore, **55** solvolyzed ~ 350 times faster than its *endo* isomer (**58**). Similar high *exo/endo* rate ratios have been found in many other [2.2.1] systems. These two results [(1) that solvolysis of an optically active *exo* isomer gave only racemic *exo* isomers and (2) the high *exo/endo* rate ratio] were interpreted by Winstein et al.¹⁸⁷ as indicating that the 1,6-bond assists in the departure of the leaving group and that a nonclassical intermediate (**59**) is involved. They reasoned that solvolysis of the *endo* isomer (**58**) is not assisted by the 1,6-bond because it is not in a favorable position for backside attack, and that consequently solvolysis of **58** takes place at a “normal” rate. Therefore the much faster rate for the solvolysis of **55** must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of **59**, since in **59** the 1 and 2 positions are equivalent and would be attacked by the nucleophile with equal facility, but only from the *exo* direction in either case. Incidentally, acetolysis of **58** also leads exclusively to the *exo* acetates (**56** and **57**), so that in this case Winstein et al.¹⁸⁷ postulated that a classical ion (**60**) is first formed and then converted to the more stable **59**. Evidence for this interpretation is that the product from solvolysis of **58** is not racemic, but contains somewhat more **57** than **56** (corresponding to 3–13% inversion, depending on the solvent), suggesting that when **60** is formed, some of it goes to give **57** before it can collapse to **59**.

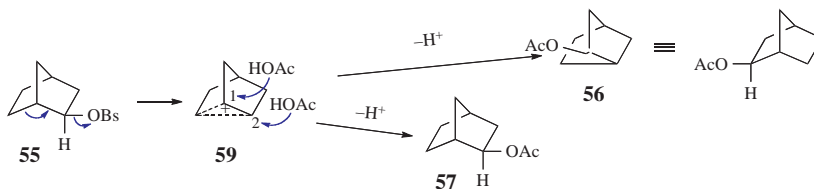
¹⁸³ See Tanida, H. *Acc. Chem. Res.* **1968**, *1*, 239; Shiner, Jr., V.J.; Seib, R.C. *J. Am. Chem. Soc.* **1976**, *98*, 862; Ferber, P.H.; Gream, G.E. *Aust. J. Chem.* **1981**, *34*, 2217; Fujio, M.; Goto, M.; Seki, Y.; Mishima, M.; Tsuno, Y.; Sawada, M.; Takai, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1097. For a discussion of evidence obtained from isotope effects, see Scheppele, S.E. *Chem. Rev.* **1972**, *72*, 511, p. 522.

¹⁸⁴ Jackman, L.M.; Haddon, V.R. *J. Am. Chem. Soc.* **1974**, *96*, 5130; Gates, M.; Frank, D.L.; von Felten, W.C. *J. Am. Chem. Soc.* **1974**, *96*, 5138; Ando, T.; Yamawaki, J.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 219.

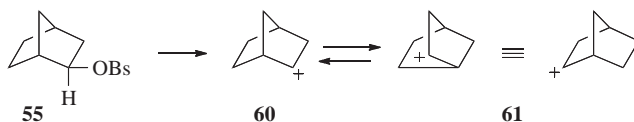
¹⁸⁵ See Olah, G.A. *Angew. Chem. Int. Ed.* **1973**, *12*, 173, pp. 192–198.

¹⁸⁶ See Olah, G.A.; Prakash, G.K.S.; Williams, R.E. *Hypercarbon Chemistry*, Wiley, NY, **1987**, pp. 157–170; Grob, C.A. *Angew. Chem. Int. Ed.* **1982**, *21*, 87; Sargent, G.D. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, **1972**, pp. 1099–1200; Sargent, G.D. *Q. Rev. Chem. Soc.* **1966**, *20*, 301; Gream, G.E. *Rev. Pure Appl. Chem.* **1966**, *16*, 25. Also see Kirmse, W. *Acc. Chem. Res.* **1986**, *19*, 36. See also, Ref. 190.

¹⁸⁷ Winstein, S.; Clippinger, E.; Howe, R.; Vogelfanger, E. *J. Am. Chem. Soc.* **1965**, *87*, 376.



The concepts of σ participation and the nonclassical ion **59** were challenged by H.C. Brown,¹⁴¹ who suggested that the two results can also be explained by postulating that **55** solvolyzes without participation of the 1,6 bond to give the classical ion **60**, which is in rapid equilibrium with **61**. This rapid interconversion has been likened to the action of a windshield wiper.¹⁸⁸ Obviously, in going from **60** to **61** and back again, **59** must be present, but in Brown's view it is a transition state and not an intermediate. Brown's explanation for the stereochemical result was that exclusive exo attack is a property to be expected from any 2-norbornyl system, not only for the cation but even for reactions not involving cations, because of steric hindrance to attack from the endo side. There is a large body of data showing that exo attack on norbornyl systems is fairly general in many reactions. A racemic mixture will be obtained if **60** and **61** are present in equal amounts, since they are equivalent and exo attack on **60** and **61** gives, respectively, **57** and **56**. Brown explained the high exo/endo rate ratios by contending that it is not the endo rate that is normal and the exo rate abnormally high, but the exo rate that is normal and the endo rate abnormally *low*, because of steric hindrance to removal of the leaving group in that direction.¹⁸⁹



A vast amount of work has been done¹⁹⁰ on solvolysis of the 2-norbornyl system in an effort to determine whether the 1,6-bond participates and whether **59** is an intermediate. Most,¹⁹¹ although not all,¹⁹² chemists now accept the intermediacy of **59**.

Besides the work done on solvolysis, of 2-norbornyl compounds, the 2-norbornyl cation has also been extensively studied at low temperatures; there is much evidence that under these conditions the ion is definitely nonclassical. Olah and co-workers prepared the 2-norbornyl cation in stable solutions at temperatures below -150°C in $\text{SbF}_5\text{--SO}_2$ and $\text{FSO}_3\text{H--SbF}_5\text{--SO}_2$, where the structure is static

¹⁸⁸ For another view, see Biemann, R.; Fuso, F.; Grob, C.A. *Helv. Chim. Acta* **1988**, *71*, 312; Flury, P.; Grob, C.A.; Wang, G.Y.; Lennartz, H.; Roth, W.R. *Helv. Chim. Acta* **1988**, *71*, 1017.

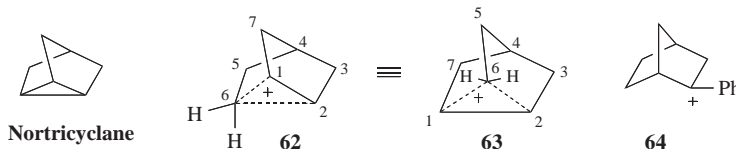
¹⁸⁹ See Menger, F.M.; Perinis, M.; Jerkunica, J.M.; Glass, L.E. *J. Am. Chem. Soc.* **1978**, *100*, 1503.

¹⁹⁰ See Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* **1988**, *53*, 661; Grob, C.A. *Acc. Chem. Res.* **1983**, *16*, 426; Brown, H.C. *Acc. Chem. Res.* **1983**, *16*, 432; Walling, C. *Acc. Chem. Res.* **1983**, *16*, 448. Also see Arnett, E.M.; Hofelich, T.C.; Schriver, G.W. *React. Intermed. (Wiley)* **1985**, *3*, 189, pp. 193–202.

¹⁹¹ See Lajunen, M. *Acc. Chem. Res.* **1985**, *18*, 254; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* **1988**, *53*, 661.

¹⁹² Also see Werstiuk, N.H.; Dhanoa, D.; Timmins, G. *Can. J. Chem.* **1983**, *61*, 2403; Brown, H.C.; Ikegami, S.; Vander Jagt, D.L. *J. Org. Chem.* **1985**, *50*, 1165; Nickon, A.; Swartz, T.D.; Sainsbury, D.M.; Toth, B.R. *J. Org. Chem.* **1986**, *51*, 3736.

and hydride shifts are absent.^{193,194} Studies by ^1H and ^{13}C NMR, as well as by laser Raman spectra and X-ray electron spectroscopy, led to the conclusion¹⁹⁴ that under these conditions the ion is nonclassical.¹⁹⁵ A similar result has been reported for the 2-norbornyl cation in the solid state, where at 77 and even 5 K, ^{13}C NMR spectra gave no evidence of the freezing out of a single classical ion.¹⁹⁶



Olah and co-workers represented the nonclassical structure as a corner-protonated nortricyclane (**62**); the symmetry is better seen when the ion is drawn, as in **63**. Almost all the positive charge resides on C-1 and C-2 and very little on the bridging carbon C-6. Other evidence for the nonclassical nature of the 2-norbornyl cation in stable solutions comes from heat of reaction measurements showing that the 2-norbornyl cation is more stable (by $\sim 6\text{--}10\text{ kcal mol}^{-1}$ or $25\text{--}40\text{ kJ mol}^{-1}$) than would be expected without the bridging.¹⁹⁷ Studies of IR spectra of the 2-norbornyl cation in the gas phase also show the nonclassical structure.¹⁹⁸ *Ab initio* calculations show that the nonclassical structure corresponds to an energy minimum.¹⁹⁹

The spectra of other norbornyl cations have also been investigated at low temperatures. Spectra of the tertiary 2-methyl- and 2-ethylnorbornyl cations show less delocalization,²⁰⁰ and the 2-phenylnorbornyl cation (**64**) is essentially classical,²⁰¹ as are the 2-methoxy-²⁰² and 2-chloronorbornyl cations.²⁰³ Recall (Sec. 5.A.ii) that methoxy and halo groups also stabilize a positive charge. The ^{13}C NMR data show that electron-withdrawing groups on the benzene ring of **64** cause the ion to become less classical, while electron-donating groups enhance the classical nature of the ion.²⁰⁴

b. *The Cyclopropylmethyl System.* Apart from the 2-norbornyl system, the greatest amount of effort in the search for C—C participation has been devoted to the

¹⁹³ The presence of hydride shifts (Reaction 18-01) under solvolysis conditions has complicated the interpretation of the data.

¹⁹⁴ Olah, G.A. *Acc. Chem. Res.* **1976**, 9, 41; Saunders, M. *Acc. Chem. Res.* **1983**, 16, 440. See also, Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* **1988**, 110, 4112.

¹⁹⁵ See Kramer, G.M.; Scouten, C.G. *Adv. Carbocation Chem.* **1989**, 1, 93. See, however, Olah, G.A.; Prakash, G. K.S.; Farnum, D.G.; Clausen, T.P. *J. Org. Chem.* **1983**, 48, 2146.

¹⁹⁶ Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* **1990**, 112, 8991.

¹⁹⁷ See Lossing, F.P.; Holmes, J.L. *J. Am. Chem. Soc.* **1984**, 106, 6917 and references cited therein.

¹⁹⁸ Koch, W.; Liu, B.; DeFrees, D.J.; Sunko, D.E.; Vancik, H. *Angew. Chem. Int. Ed.* **1990**, 29, 183.

¹⁹⁹ See, for example, Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* **1989**, 111, 1527.

²⁰⁰ Olah, G.A.; DeMember, J.R.; Lui, C.Y.; White, A.M. *J. Am. Chem. Soc.* **1969**, 91, 3958. See also, Forsyth, D. A.; Panyachotipun, C. *J. Chem. Soc., Chem. Commun.* **1988**, 1564.

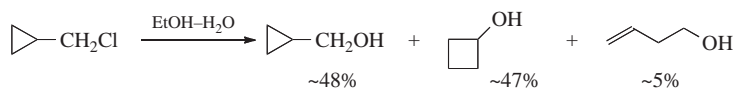
²⁰¹ Olah, G.A. *Acc. Chem. Res.* **1976**, 9, 41. See also, Farnum, D.G.; Wolf, A.D. *J. Am. Chem. Soc.* **1974**, 96, 5166.

²⁰² Nickon, A.; Lin, Y. *J. Am. Chem. Soc.* **1969**, 91, 6861. See also, Montgomery, L.K.; Grendze, M.P.; Huffman, J.C. *J. Am. Chem. Soc.* **1987**, 109, 4749.

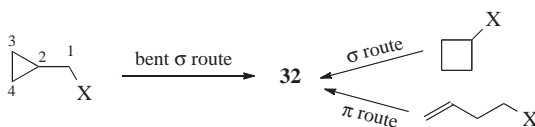
²⁰³ Fry, A.J.; Farnham, W.B. *J. Org. Chem.* **1969**, 34, 2314.

²⁰⁴ Farnum, W.B.; Botto, R.E.; Chambers, W.T.; Lam, B. *J. Am. Chem. Soc.* **1978**, 100, 3847. See also, Olah, G.A.; Berrier, A.L.; Prakash, G.K.S. *J. Org. Chem.* **1982**, 47, 3903.

cyclopropylmethyl system.²⁰⁵ It has long been known that cyclopropylmethyl substrates solvolyze with abnormally high rates and that the products often include not only unrearranged cyclopropylmethyl, but also cyclobutyl and homoallylic compounds. An example is²⁰⁶



Cyclobutyl substrates also solvolyze abnormally rapidly and give similar products. Indeed, computational studies on the cyclobutylmethyl cation suggest it is nonclassical (Sec. 10.C.i). Furthermore, when the reactions are carried out with labeled substrates, considerable, although not complete, scrambling is observed. For these reasons, it has been suggested that a common intermediate (some kind of nonclassical intermediate, e.g., **32**) is present in these cases. This common intermediate could then be obtained by three routes:



In recent years, much work has been devoted to the study of these systems, and it is apparent that matters are not so simple, although there is much that is still not completely understood, some conclusions can be drawn.

- i. In the solvolysis of simple primary cyclopropylmethyl systems, the rate is enhanced because of participation by the σ bonds of the ring.²⁰⁷ The ion that forms initially is an unrearranged cyclopropylmethyl cation²⁰⁸ that is *symmetrically* stabilized; that is, both the 2,3 and 2,4 σ bonds help stabilize the positive charge. As seen previously (Sec. 5.A.ii) that a cyclopropyl group stabilizes an adjacent positive charge even better than a phenyl group. One way of representing the structure of this cation is as shown in **65**. Among the evidence that **65** is a symmetrical ion is that substitution of one or more methyl groups in the 3 and 4 positions increases the rate of solvolysis of cyclopropylcarbonyl 3,5-dinitrobenzoates by approximately a factor of 10 for *each* methyl group.²⁰⁹ If only one of the σ bonds (say, the 2,3 bond) stabilizes the cation, then methyl substitution at the 3 position should increase the rate, and a second methyl group at the 3 position should increase it still more, but a second methyl group at the 4 position should have little effect.²¹⁰

²⁰⁵ See in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, **1972**, the articles by Richey, Jr., H.G. pp. 1201–1294, and by Wiberg, K.B.; Hess, Jr., B.A.; Ashe III, A.J. pp. 1295–1345; Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem. Int. Ed.* **1968**, 7, 577.

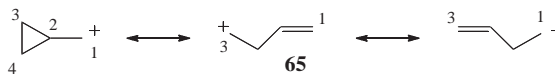
²⁰⁶ Roberts, D.D.; Mazur, R.H. *J. Am. Chem. Soc.* **1951**, 73, 2509.

²⁰⁷ See Roberts, D.D.; Snyder, Jr., R.C. *J. Org. Chem.* **1979**, 44, 2860, and references cited therein.

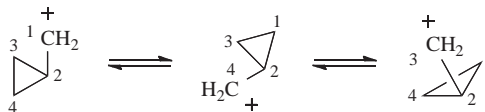
²⁰⁸ Wiberg, K.B.; Ashe, III, A.J. *J. Am. Chem. Soc.* **1968**, 90, 63.

²⁰⁹ Schleyer, P.v.R.; Van Dine, G.W. *J. Am. Chem. Soc.* **1966**, 88, 2321. See also, Kevill, D.N.; Abduljaber, M.H. *J. Org. Chem.* **2000**, 65, 2548.

²¹⁰ See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, **1972**, the article by Wiberg, K.B.; Hess, Jr., B.A.; Ashe, III, A.J. pp. 1300–1303.

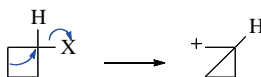


- ii. The most stable geometry of simple cyclopropylmethyl cations is the bisected one shown in Section 5.A.ii. There is much evidence that in systems where this geometry cannot be obtained, solvolysis is greatly slowed.²¹¹
- iii. Once a cyclopropylmethyl cation is formed, it can rearrange to two other cyclopropylmethyl cations:



This rearrangement, which accounts for the scrambling, is completely stereospecific.²¹² The rearrangements probably take place through a non-planar cyclobutyl cation intermediate or transition state. The formation of cyclobutyl and homoallylic products from a cyclopropylmethyl cation is also completely stereospecific. These products may arise by direct attack of the nucleophile on **65** or on the cyclobutyl cation intermediate.²¹³ A planar cyclobutyl cation is ruled out in both cases because it would be symmetrical and the stereospecificity would be lost.

- iv. The rate enhancement in the solvolysis of secondary cyclobutyl substrates is probably caused by participation by a bond leading directly to **65**, which accounts for the fact that solvolysis of cyclobutyl and of cyclopropylmethyl substrates often gives similar product mixtures. There is no evidence that requires cyclobutyl cations to be intermediates in most secondary cyclobutyl systems, although tertiary cyclobutyl cations can be solvolysis intermediates.



- v. The unsubstituted cyclopropylmethyl cation has been generated in superacidic solutions at low temperatures, where ¹³C NMR spectra have led to the conclusion that it consists of a mixture of the bicyclobutonium ion (**32**) and the bisected cyclopropylmethyl cation (**65**), in equilibrium with **32**.²¹⁴ Molecular orbital calculations show that these two species are energy minima, and that both have nearly the same energy.²¹³

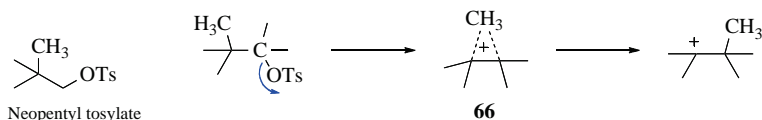
²¹¹ See Rhodes, Y.E.; DiFate, V.G. *J. Am. Chem. Soc.* **1972**, *94*, 7582. See, however, Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* **1975**, *97*, 1927.

²¹² Majerski, Z.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1971**, *93*, 665.

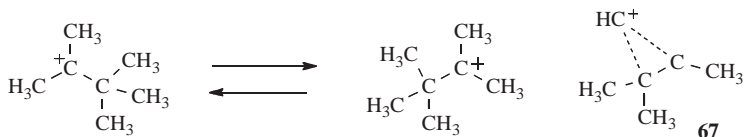
²¹³ Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* **1988**, *110*, 7325; Saunders, M.; Laidig, K.E.; Wiberg, K. B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1988**, *110*, 7652.

²¹⁴ Staral, J.S.; Yavari, I.; Roberts, J.D.; Prakash, G.K.S.; Donovan, D.J.; Olah, G.A. *J. Am. Chem. Soc.* **1978**, *100*, 8016. See also, Prakash, G.K.S.; Arvanaghi, M.; Olah, G.A. *J. Am. Chem. Soc.* **1985**, *107*, 6017; Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* **1990**, *112*, 8992.

c. *Methyl as a Neighboring Group.* Both the 2-norbornyl and cyclopropylmethyl system contain a σ bond that is geometrically constrained to be in a particularly favorable position for participation as a neighboring group. However, there have been a number of investigations to determine whether a C—C bond can lend anchimeric assistance even in a simple open-chain compound, (e.g., neopentyl tosylate). On solvolysis, neopentyl systems undergo almost exclusive rearrangement and **66** must lie on the reaction path, but the two questions



that have been asked are (1) Is the departure of the leaving group concerted with the formation of the $\text{CH}_3\text{—C}$ bond (e.g., does the methyl participate)? (2) Is **66** an intermediate or only a transition state? With respect to the first question, there is evidence, chiefly from isotope effect studies, which indicates that the methyl group in the neopentyl system does indeed participate,²¹⁵ although it may not greatly enhance the rate. As to the second question, evidence that **66** is an intermediate is that small amounts of cyclopropanes (10–15%) can be isolated in these reactions.²¹⁶ Cation **66** is a protonated cyclopropane and would give cyclopropane on loss of a proton.²¹⁷ In an effort to isolate a species that has structure **66**, the 2,3,3-trimethyl-2-butyl cation was prepared in superacid solutions at low temperatures.²¹⁸ However, ^1H and ^{13}C NMR, as well as Raman spectra, showed this to be a pair of rapidly equilibrating open ions. Of course, **67** must lie on the reaction path connecting the two open ions, but it is evidently a transition state and not an intermediate. However, evidence from X-ray photoelectron spectroscopy (XPS) has shown that the 2-butyl cation is substantially methyl bridged.²¹⁹



d. *Silylalkyl as a Neighboring Group.* Rates of solvolysis are enhanced in molecules that contain a silylalkyl or silylaryl group β -to the carbon bearing the leaving group. This is attributed to formation of a cyclic transition state involving the silicon.²²⁰

²¹⁵ See Yamataka, H.; Ando, T.; Nagase, S.; Hanamura, M.; Morokuma, K. *J. Org. Chem.* **1984**, 49, 631. For an opposing view, see Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* **1984**, 20, 11.

²¹⁶ Silver, M.S.; Meek, A.G. *Tetrahedron Lett.* **1971**, 3579; Dupuy, W.E.; Hudson, H.R. *J. Chem. Soc. Perkin Trans. 2* **1972**, 1715.

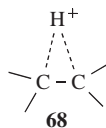
²¹⁷ For further discussions of protonated cyclopropanes, see Sec. 15.B.iv, 18.A.ii.

²¹⁸ Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* **1971**, 93, 459.

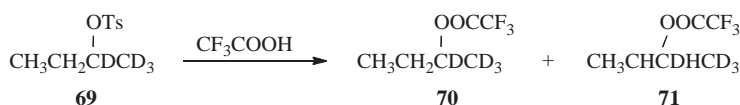
²¹⁹ Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* **1988**, 110, 4112. See also, Carneiro, J.W.; Schleyer, P.v.R.; Koch, W.; Raghavachari, K. *J. Am. Chem. Soc.* **1990**, 112, 4064.

²²⁰ Fujiyama, R.; Munechika, T. *Tetrahedron Lett.* **1993**, 34, 5907.

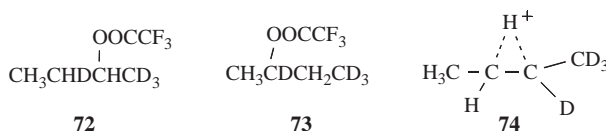
5. *Hydrogen as a Neighboring Group.* The questions relating to hydrogen are similar to those relating to methyl. There is no question that hydride can migrate, but the two questions are (1) Does the hydrogen atom



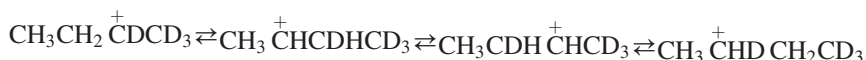
participate in the departure of the leaving group? (2) Is **68** an intermediate or only a transition state? There is some evidence that a β hydrogen can participate.²²¹ Evidence that **68** can be an intermediate in solvolysis



reactions comes from a study of the solvolysis in trifluoroacetic acid of deuterated *sec*-butyl tosylate **69**. In this solvent of very low nucleophilic power, the products were an equimolar mixture of **70** and **71**,²²² but



no **72** or **73** was found. If this reaction did not involve neighboring hydrogen at all (pure $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$), the product would be only **70**. On the other hand, if hydrogen does migrate, but only open cations are involved, then there should be an equilibrium among these four cations:



leading not only to **70** and **71**, but also to **72** and **73**. The results are most easily compatible with the intermediacy of the bridged ion **74**, which can then be attacked by the solvent equally at the 2 and 3 positions. Attempts to prepare **68** as a stable ion in superacid solutions at low temperatures have not been successful.²²¹

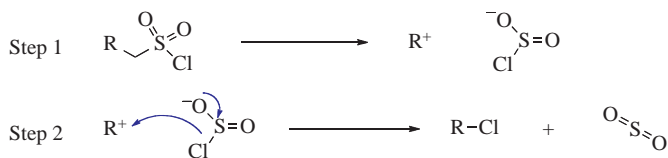
10.D. THE $\text{S}_{\text{N}}\text{i}$ MECHANISM

In a few reactions, nucleophilic substitution proceeds with retention of configuration, even where there is no possibility of a neighboring-group effect. In the $\text{S}_{\text{N}}\text{i}$ mechanism (*substitution nucleophilic internal*), part of the leaving group must be able to attack the substrate, detaching itself from the rest of the leaving group in the process. The IUPAC

²²¹ See Buzek, P.; Schleyer, P.v.R.; Sieber, S.; Koch, W.; Carneiro, J.W. de M.; Vancik, H.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* **1991**, 671; Imhoff, M.A.; Ragain, R.M.; Moore, K.; Shiner, V.J. *J. Org. Chem.* **1991**, 56, 3542.

²²² Dannenberg, J.J.; Barton, J.K.; Bunch, B.; Goldberg, B.J.; Kowalski, T. *J. Org. Chem.* **1983**, 48, 4524; Allen, A.D.; Ambidge, I.C.; Tidwell, T.T. *J. Org. Chem.* **1983**, 48, 4527.

designation is $D_N + A_N D_e$. The first step is the same as the very first step of the S_N1 mechanism: dissociation into an intimate ion pair.²²³ But in the second step part of the leaving group attacks, necessarily from the front since it is unable to get to the rear, which results in retention of configuration.



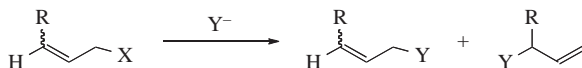
The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides usually proceeds in this way, with the first step in this case being $ROH + SOCl_2 \rightarrow ROSOCl$ (these alkyl chlorosulfites can be isolated).

Evidence for this mechanism is as follows: The addition of pyridine to the mixture of alcohol and thionyl chloride results in the formation of alkyl halide with *inverted* configuration. Inversion results because the pyridine reacts with $ROSOCl$ to give $ROSONC_5H_5$ before anything further can take place. The Cl^- freed in this process now attacks from the rear. The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism, but the decomposition by simple heating of $ROSOCl$ is first order.²²⁴

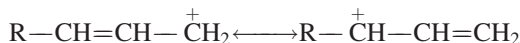
The S_Ni mechanism is relatively rare. Another example is the decomposition of $ROCOCl$ (alkyl chloroformates) into RCI and CO_2 .²²⁵

10.E. NUCLEOPHILIC SUBSTITUTION AT AN ALLYLIC CARBON: ALLYLIC REARRANGEMENTS

Allylic substrates rapidly undergo nucleophilic substitution reactions (see Sec. 10.G.i, category 3), but we discuss them in a separate section because they are commonly accompanied by a certain kind of rearrangement known as an *allylic rearrangement*.²²⁶ When allylic substrates are treated with nucleophiles under S_N1 conditions, two products are usually obtained: the normal one and a rearranged one.



Two products are formed because an allylic type of carbocation is a resonance hybrid



²²³ Lee, C.C.; Clayton, J.W.; Lee, C.C.; Finlayson, A.J. *Tetrahedron* **1962**, *18*, 1395.

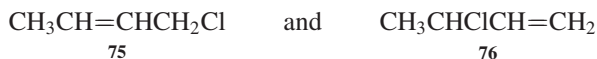
²²⁴ Lewis, E.S.; Boozer, C.E. *J. Am. Chem. Soc.* **1952**, *74*, 308.

²²⁵ Lewis, E.S.; Witte, K. *J. Chem. Soc. B* **1968**, 1198. Also see Kice, J.L.; Hanson, G.C. *J. Org. Chem.* **1973**, *38*, 1410; Cohen, T.; Solash, J. *Tetrahedron Lett.* **1973**, 2513; Verrinder, D.J.; Hourigan, M.J.; Prokipcak, J.M. *Can. J. Chem.* **1978**, *56*, 2582.

²²⁶ See DeWolfe, R.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, pp. 417–437. For comprehensive older reviews, see DeWolfe, R.H.; Young, W.G. *Chem. Rev.* **1956**, *56*, 753; in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, **1964**, the sections by Mackenzie, K. pp. 436–453 and DeWolfe, R.H.; Young, W.G. pp. 681–738.

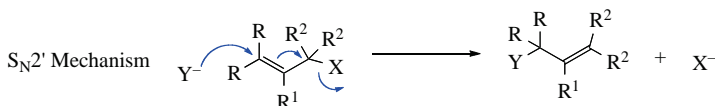
so that C-1 and C-3 each carry a partial positive charge and both are attacked by Y. Of course, an allylic rearrangement is undetectable in the case of symmetrical allylic cations, as in the case where R = H, unless isotopic labeling is used. This mechanism has been called the S_N1' mechanism. The IUPAC designation is $1/D_N + 3/A_N$, the numbers 1 and 3 signifying the *relative* positions where the nucleophile attacks and from which the nucleofuge leaves.

As with other S_N1 reactions, there is clear evidence that S_N1' reactions can involve ion pairs. If the intermediate attacked by the nucleophile is a completely free carbocation, then, say,



should give the same mixture of alcohols when reacting with hydroxide ion, since the carbocation from each should be the same. When treated with 0.8 M aq NaOH at 25 °C, **75** gave 60% $\text{CH}_3\text{CH}=\text{CHCH}_2\text{OH}$ and 40% $\text{CH}_3\text{CHOHCH}=\text{CH}_2$, while **76** gave the products in yields of 38 and 62%, respectively.²²⁷ This phenomenon is called the *product spread*. In this case, and in most others, the product spread is in the direction of the starting compound. With increasing polarity of solvent,²²⁸ the product spread decreases and in some cases is entirely absent. It is evident that in such cases the high polarity of the solvent completely stabilizes free carbocations. There is other evidence for the intervention of ion pairs in many of these reactions. When $\text{H}_2\text{C}=\text{CHCMe}_2\text{Cl}$ was treated with acetic acid, both acetates were obtained, but also some $\text{ClCH}_2\text{CH}=\text{CMe}_3$,²²⁹ and the isomerization was faster than the acetate formation. This could not have arisen from a completely free Cl^- returning to the carbon, since the rate of formation of the rearranged chloride was unaffected by the addition of external Cl^- . All these facts indicate that the first step in these reactions is the formation of an unsymmetrical intimate ion pair that undergoes a considerable amount of internal return and in which the counterion remains close to the carbon from which it departed. Thus, **75** and **76**, for example, give rise to two *different* intimate ion pairs. The field of the anion polarizes the allylic cation, making the nearby carbon atom more electrophilic, so that it has a greater chance of attracting the nucleophile.²³⁰

Nucleophilic substitution at an allylic carbon can also take place by an S_N2 mechanism, in which case no allylic rearrangement usually takes place. However, allylic rearrangements can also take place under S_N2 conditions, by the following mechanism, in which the nucleophile attacks at the γ carbon rather than the usual position:²³¹



²²⁷ DeWolfe, R.H.; Young, W.G. *Chem. Rev.* **1956**, 56, 753 give several dozen such examples.

²²⁸ Katritzky, A.R.; Fara, D.C.; Yang, H.; Tamm, K.; Tamm, T.; Karelson, M. *Chem. Rev.* **2004**, 104, 175.

²²⁹ Young, W.G.; Winstein, S.; Goering, H.L. *J. Am. Chem. Soc.* **1951**, 73, 1958.

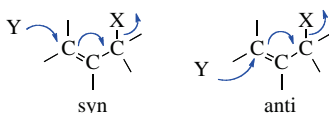
²³⁰ See Kantner, S.S.; Humski, K.; Goering, H.L. *J. Am. Chem. Soc.* **1982**, 104, 1693; Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* **1986**, 313.

²³¹ See Magid, R.M. *Tetrahedron* **1980**, 36, 1901, see pp. 1901–1910.

The IUPAC designation is 3/1/A_ND_N. This mechanism is a second-order allylic rearrangement; it usually comes about where S_N2 conditions hold but where a substitution sterically retards the normal S_N2 mechanism.²³² There are few well-established cases of the S_N2' mechanism on substrates of the type C=C—CH₂X, but compounds of the form C=C—CR₂X give the S_N2' rearrangement almost exclusively²³³ when they give bimolecular reactions at all. Increasing the size of the nucleophile can also increase the extent of the S_N2' reaction at the expense of the S_N2.²³³ In certain cases, the leaving group can also have an effect on whether the rearrangement occurs. Thus PhCH=CHCH₂X, treated with LiAlH₄, gave 100% S_N2 reaction (no rearrangement) when X = Br or Cl, but 100% S_N2' when X = PPh₃⁺ Br[−].²³⁴ The solvent also plays a role in some cases, with more polar solvents giving more S_N2' product.²³⁵

The S_N2' mechanism, as shown above, involves the simultaneous movement of three pairs of electrons. However, Bordwell et al.²³⁶ contended that there is no evidence requiring that this bond making and bond breaking be in fact concerted, and that a true S_N2' mechanism is a myth. There is evidence both for²³⁷ and against²³⁸ this proposal. There is also a review of the S_N' reaction.²³⁹

The stereochemistry of S_N2' reactions has been investigated. It has been found that both syn²⁴⁰ (the nucleophile enters on the side from which the leaving group departs) and anti²⁴¹ reactions can take place, depending on the nature of X and Y,²⁴² although the syn pathway predominates in most cases.



When a molecule has a nucleofuge capable of giving the S_Ni reaction in an allylic position, it is possible for the nucleophile to attack at the γ position instead of the α position. This reaction is called the S_Ni' mechanism and has been demonstrated on 2-buten-1-ol and 3-buten-2-ol, both of which gave 100% allylic rearrangement



²³² Streitwieser, A.; Jayasree, E.G.; Leung, S.S.-H.; Choy, G.S.-C. *J. Org. Chem.* **2005**, 70, 8486.

²³³ Bordwell, F.G.; Clemens, A.H.; Cheng, J. *J. Am. Chem. Soc.* **1987**, 109, 1773. Also see, Young, J.-j.; Jung, L.-j.; Cheng, K.-m. *Tetrahedron Lett.* **2000**, 41, 3411.

²³⁴ Hirab, T.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1984**, 49, 4084.

²³⁵ Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *Tetrahedron Lett.* **2004**, 45, 3225.

²³⁶ Bordwell, F.G.; Mecca, T.G. *J. Am. Chem. Soc.* **1972**, 94, 5829. See also Dewar, M.J.S. *J. Am. Chem. Soc.* **1984**, 106, 209.

²³⁷ See Uebel, J.J.; Milaszewski, R.F.; Arlt, R.E. *J. Org. Chem.* **1977**, 42, 585.

²³⁸ See Fry, A. *Pure Appl. Chem.* **1964**, 8, 409; Georgoulis, C.; Ville, G. *Bull. Soc. Chim. Fr.* **1985**, 485; Meislich, H.; Jasne, S.J. *J. Org. Chem.* **1982**, 47, 2517.

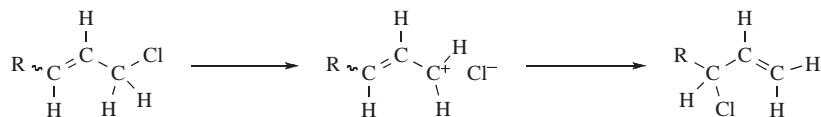
²³⁹ Paquette, L.A.; Stirling, C.J.M. *Tetrahedron* **1992**, 48, 7383.

²⁴⁰ See Magid, R.M.; Fruchey, O.S. *J. Am. Chem. Soc.* **1979**, 101, 2107; Bäckvall, J.E.; Vågberg, J.O.; Genêt, J.P. *J. Chem. Soc., Chem. Commun.* **1987**, 159.

²⁴¹ See Stork, G.; Schoofs, A.R. *J. Am. Chem. Soc.* **1979**, 101, 5081.

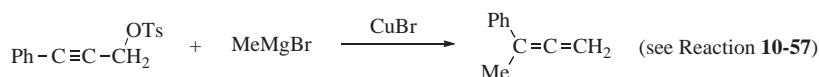
²⁴² Bach, R.D.; Wolber, G.J. *J. Am. Chem. Soc.* **1985**, 107, 1352; Stohrer, W. *Angew. Chem. Int. Ed.* **1983**, 22, 613.

when treated with thionyl chloride in ether.²⁴³ Ordinary allylic rearrangements (S_N1') or S_N2' mechanisms could not be expected to give 100% rearrangement in *both* cases. In the case shown, the nucleophile is only part of the leaving group, not the whole. But it is also possible to have reactions in which a simple leaving group, (e.g., Cl) comes off to form an ion pair²⁴⁴ and then returns not to the position where it originated but to the allylic position:

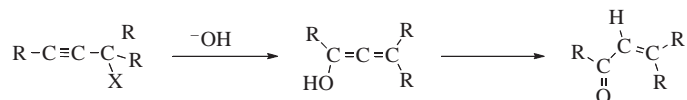


Most S_N1' reactions are of this type.

Allylic rearrangements have also been demonstrated in propargyl systems, for example,²⁴⁵



The product in this case is an allene,²⁴⁶ but such shifts can also give triple-bond compounds or, if Y = OH, an enol will be obtained that tautomerizes to an α,β -unsaturated aldehyde or ketone.



When X = OH, this conversion of acetylenic alcohols to unsaturated aldehydes or ketones is called the *Meyer-Schuster rearrangement*.²⁴⁷ The propargyl rearrangement can also go the other way; that is, 1-haloalkenes, treated with organocopper compounds, give alkynes.²⁴⁸

The S_N2' reaction has been shown to predominate in reactions of mixed cuprates (Reaction 10-58) with allylic mesylates,²⁴⁹ and in ring-opening reactions of aziridines.²⁵⁰ A related reaction is the opening of cyclopropylcarbinyl halides with organocuprates where the cyclopropane ring reacts similarly to the C=C unit of an alkene to give a homoallylic substituted product.²⁵¹ This latter reaction is interesting since the reaction of **77** with piperidine leads to the S_N2' product (**78**) in ~ 87% yield, but there is ~ 8% of the direct substitution product, (**79**). Since the carbon bearing the bromine is very hindered,

²⁴³ Young, W.G. *J. Chem. Educ.* **1962**, 39, 456. See Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1984**, 25, 3055.

²⁴⁴ For a theoretical study, see Streitwieser, A.; Jayasree, E.G.; Hasanayn, F.; Leung, S.S.-H. *J. Org. Chem.* **2008**, 73, 9426.

²⁴⁵ Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1975**, 94, 112.

²⁴⁶ See Schuster, H.F.; Coppola, G.M. *Allenenes in Organic Synthesis*, Wiley, NY, **1984**, pp. 12–19, 26–30; Taylor, D.R. *Chem. Rev.* **1967**, 67, 317, pp. 324–328. See Larock, R.C.; Reddy, Ch.K. *Org. Lett.* **2000**, 2, 3325.

²⁴⁷ See Swaminathan, S.; Narayanan, K.V. *Chem. Rev.* **1971**, 71, 429; Andres, J.; Cardenas, R.; Silla, E.; Tapi, O. *J. Am. Chem. Soc.* **1988**, 110, 666.

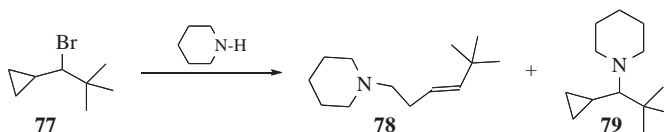
²⁴⁸ Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1984**, 25, 3059, 3063.

²⁴⁹ Ibuka, T.; Taga, T.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N.; Chounan, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* **1993**, 58, 1207.

²⁵⁰ Wipf, P.; Fritch, P.C. *J. Org. Chem.* **1994**, 59, 4875.

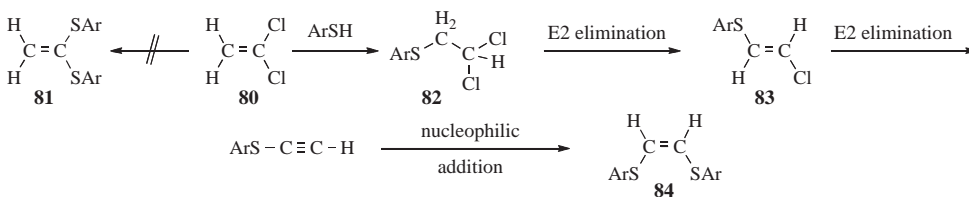
²⁵¹ Smith, M.B.; Hrubiec, R.T. *Tetrahedron* **1984**, 40, 1457; Hrubiec, R.T.; Smith, M.B. *J. Org. Chem.* **1984**, 49, 385.

formation of **72** is somewhat unusual under these conditions. As Bordwell has suggested (see above), this may not be a true S_N2 process.



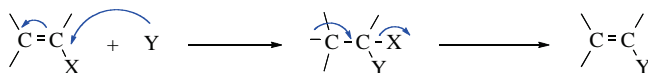
10.F. NUCLEOPHILIC SUBSTITUTION AT AN ALIPHATIC TRIGONAL CARBON: THE TETRAHEDRAL MECHANISM

All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. These reactions are discussed in Chapter 16. Nucleophilic substitution at vinylic carbons is considered in Section 10.6 and at aromatic carbons in Chapter 13.



Nucleophilic substitution at a vinylic carbon²⁵² is difficult (see Sec. 10.G.i), but many examples are known. The most common mechanisms are the tetrahedral mechanism and the closely related *addition–elimination mechanism*. Both of these mechanisms are impossible at a saturated substrate. The addition–elimination mechanism has been demonstrated for the reaction between 1,1-dichloroethene (**80**) and ArS^- catalyzed by ^-OEt .²⁵³ The product was not the 1,1-dithiophenoxy compound (**81**), but the “rearranged” compound **84**. Isolation of **82** and **83** showed that an addition–elimination mechanism had taken place. In the first step, ArSH adds to the double bond (nucleophilic addition, Sec. 15.A.ii) to give the saturated **82**. The second step is an E2 elimination reaction (Sec. 17.A.i) to give the alkene **83**. A second elimination and addition give **84**.

The tetrahedral mechanism, often also called addition–elimination (*AdN-E*), takes place with much less facility than with carbonyl groups, since the negative charge of the intermediate must be borne by a carbon, which is less electronegative than oxygen, sulfur, or nitrogen:

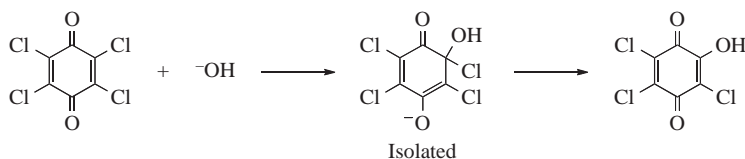


Such an intermediate can also stabilize itself by combining with a positive species. When it does, the reaction is nucleophilic addition to a $\text{C}=\text{C}$ double bond (see Chap 15). It

²⁵² See Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1986**, 104, 309; Shainyan, B.A. *Russ. Chem. Rev.* **1986**, 55, 511; Modena, G. *Acc. Chem. Res.* **1971**, 4, 73.

²⁵³ Truce, W.E.; Boudakian, M.M. *J. Am. Chem. Soc.* **1956**, 78, 2748.

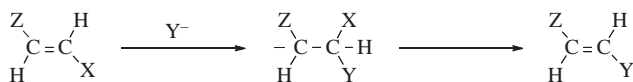
is not surprising that with vinylic substrates addition and substitution often compete. For chloroquinones, where the charge is spread by resonance, tetrahedral intermediates have been isolated:²⁵⁴



In the case of $\text{Ph}(\text{MeO})\text{C}=\text{C}(\text{NO}_2)\text{Ph} + \text{RS}^-$, the intermediate lived long enough to be detected by UV spectroscopy.²⁵⁵

Since both the tetrahedral and addition–elimination mechanisms begin the same way, it is usually difficult to tell them apart, and often no attempt is made to do so. The strongest kind of evidence for the addition–elimination sequence is the occurrence of a “rearrangement”, but of course the mechanism could still take place even if no rearrangement is found. Evidence²⁵⁶ that a tetrahedral or an addition–elimination mechanism takes place in certain cases (as opposed, e.g., to an $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism) is that the reaction rate increases when the leaving group is changed from Br to Cl to F (this is called the *element effect*).²⁵⁷ This finding clearly demonstrates that the carbon–halogen bond does not break in the rate-determining step (as it would in both the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms), because fluorine is by far the poorest leaving group among the halogens in both the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ reactions (Sec. 10.G.iii). The rate is faster with fluorides in the cases cited, because the superior electron-withdrawing character of the fluorine makes the carbon of the C–F bond more positive, and hence more susceptible to nucleophilic attack.

Ordinary vinylic substrates react very poorly if at all by these mechanisms, but substitution is greatly enhanced in substrates of the type $\text{ZCH}=\text{CHX}$, where Z is an electron-withdrawing group (HCO , RCO ,²⁵⁸ EtOOC , ArSO_2 , NC , F , etc.), since these β groups stabilize the carbanion:



Many such examples are known. In most cases, where the stereochemistry has been investigated, retention of configuration is observed,²⁵⁹ but stereoconvergence [the same product mixture from an (*E*) or (*Z*) substrate] has also been observed,²⁶⁰ especially where the carbanionic carbon bears two electron-withdrawing groups. Although rare, nucleophilic substitution with inversion has also been reported as in the intramolecular substitution of the C–Br bond of 2-bromobut-2-enylamines by the pendant nitrogen atom, giving

²⁵⁴ Hancock, J.W.; Morrell, C.E.; Rhom, D. *Tetrahedron Lett.* **1962**, 987.

²⁵⁵ Bernasconi, C.F.; Fassberg, J.; Killion, Jr., R.B.; Rappoport, Z. *J. Org. Chem.* **1990**, 55, 4568.

²⁵⁶ See Rappoport, Z.; Peled, P. *J. Am. Chem. Soc.* **1979**, 101, 2682, and references cited therein.

²⁵⁷ Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. *J. Am. Chem. Soc.* **1987**, 109, 6687.

²⁵⁸ See Rybinskaya, M.I.; Nesmeyanov, A.N.; Kochetkov, N.K. *Russ. Chem. Rev.* **1969**, 38, 433.

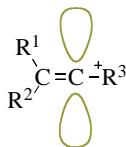
²⁵⁹ Rappoport, Z. *Adv. Phys. Org. Chem.* **1969**, 7, see pp. 31–62; Shainyan, B.A. *Russ. Chem. Rev.* **1986**, 55, 516.

See also, Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* **1987**, 109, 6698.

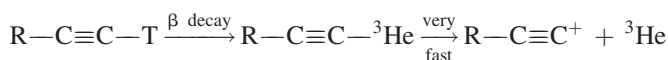
²⁶⁰ See Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* **1986**, 108, 4112; Park, K.P.; Ha, H. *Bull. Chem. Soc. Jpn.* **1990**, 63, 3006.

2-ethylene aziridines by way of stereochemical inversion.²⁶¹ It is not immediately apparent why the tetrahedral mechanism should lead to retention, but this behavior has been ascribed, on the basis of MO calculations, to hyperconjugation involving the carbanionic electron pair and the substituents on the adjacent carbon.²⁶²

Vinylc substrates are in general very reluctant to undergo S_N1 reactions, but they can be made to do so in two ways:²⁶³ (1) By the use of a group that stabilizes the vinylic cation. For example, α -aryl vinylic halides $\text{ArBrC}=\text{CR}'_2$ have often been shown to give S_N1 reactions.²⁶⁴ The S_N1 reactions have also been demonstrated with other stabilizing groups: cyclopropyl,²⁶⁵ vinylic,²⁶⁶ alkynyl,²⁶⁷ and an adjacent double-bond ($\text{R}_2\text{C}=\text{C}=\text{CR}'\text{X}$).²⁶⁸ (2) Even without a stabilization, by the use of a very good leaving group [e.g., OSO_2CF_3 (triflate)].²⁶⁹ The stereochemical outcome of S_N1 reactions at a vinylic substrate is often randomization,²⁷⁰ that is, either a cis or a trans substrate gives a 1:1 mixture of cis and trans products, indicating that vinylic cations are linear. Another indication that vinylic cations prefer to be linear is the fact that reactivity in cycloalkenyl systems decreases with decreasing ring size.²⁷¹ However, a linear vinylic cation need not give random products.²⁷² The empty p orbital lies in the plane of the double bond, so entry of the nucleophile can be and often is influenced by the relative size of R^1 and R^2 .²⁷³ It must be emphasized that even where vinylic substrates do give S_N1 reactions, the rates are generally lower than those of the corresponding saturated compounds.



Alkynyl cations are so unstable that they cannot be generated even with very good leaving groups. However, one way in which they have been generated was by formation of a tritiated substrate.



²⁶¹ Shiers, J.J.; Shipman, M.; Hayes, J.-F.; Slawin, A.M.Z. *J. Am. Chem. Soc.* **2004**, *126*, 6868.

²⁶² Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* **1979**, *101*, 5095.

²⁶³ See Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chapter 5, Academic Press, NY, **1979**; Stang, P.J. *Acc. Chem. Res.* **1978**, *11*, 107; Rappoport, Z. *Acc. Chem. Res.* **1976**, *9*, 265.

²⁶⁴ See Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chap. 6, Academic Press, NY, **1979**.

²⁶⁵ Hanack, M.; Bässler, T.; Eymann, W.; Heyd, W.E.; Kopp, R. *J. Am. Chem. Soc.* **1974**, *96*, 6686.

²⁶⁶ Grob, C.A.; Spaar, R. *Helv. Chim. Acta* **1970**, *53*, 2119.

²⁶⁷ Hassdenteufel, J.R.; Hanack, M. *Tetrahedron Lett.* **1980**, 503. See also, Kobayashi, S.; Nishi, T.; Koyama, I.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1980**, 103.

²⁶⁸ Schiavelli, M.D.; Gilbert, R.P.; Boynton, W.A.; Boswell, C.J. *J. Am. Chem. Soc.* **1972**, *94*, 5061.

²⁶⁹ See Hanack, M.; Märkl, R.; Martinez, A.G. *Chem. Ber.* **1982**, *115*, 772.

²⁷⁰ Kelsey, D.R.; Bergman, R.G. *J. Am. Chem. Soc.* **1971**, *93*, 1941.

²⁷¹ Pfeifer, W.D.; Bahn, C.A.; Schleyer, P.v.R.; Bocher, S.; Harding, C.E.; Hummel, K.; Hanack, M.; Stang, P.J. *J. Am. Chem. Soc.* **1971**, *93*, 1513.

²⁷² See Clarke, T.C.; Bergman, R.G. *J. Am. Chem. Soc.* **1974**, *96*, 7934; Summerville, R.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1972**, *94*, 3629; **1974**, *96*, 1110.

²⁷³ Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc., Chem. Commun.* **1972**, 857.

Vinyl halides can react by a $S_{RN}1$ mechanism (Sec. 13.A.iv) in some cases. An example is the $FeCl_2$ catalyzed reaction of 1-bromo-2-phenylethene and the enolate anion of pinacolone ($t\text{-BuCOCH}_2^-$), which gave a low yield of substitution products along with alkynes.²⁸¹

10.G. REACTIVITY

A large amount of work has been done on this subject. Although a great deal is known, much is still poorly understood, and many results are anomalous and hard to explain. In this section, only approximate generalizations are attempted. The work discussed here, and the conclusions reached, pertain to reactions taking place in solution. Some investigations have also been carried out in the gas phase.²⁸²

10.G.i. The Effect of Substrate Structure

The effect on the reactivity of a change in substrate structure depends on the mechanism.

1. *Branching at the α and β Carbons.* For the S_N2 mechanism, branching at either the α or the β carbon decreases the rate. Tertiary systems seldom²⁸³ react by the S_N2 mechanism and neopentyl systems react so slowly as to make such reactions, in general, synthetically useless.²⁸⁴ Experiments show that methyl halide reacts 30 times faster than ethyl, whereas isopropyl halides react 40 times slower than ethyl.²⁸⁵ The presence of π bonds accelerates the rate, as illustrated by the fact that allyl halides react 40 times faster than ethyl halides, and benzyl halides react 120 times faster.²⁸⁵ The reason for the low rates for secondary and especially tertiary is almost certainly steric. This statement includes the primary neopentyl halides, which react 20,000 times slower than ethyl halides.²⁸⁶ The transition state **1** is more crowded when larger groups are close to the central carbon.²⁸⁷

The tetrahedral mechanism for substitution at a carbonyl carbon (Chapter 16) is also slowed or blocked completely by α or β branching for similar reasons. Solvolysis in such systems is linked to relief of B-strain, but solvent participation can overshadow this as steric hindrance increases.²⁸⁸ Severe steric strain can cause distortion from coplanarity in the carbocation intermediate,²⁸⁹ although there seems to be no loss of

²⁸¹ Galli, C.; Gentili, P.; Rappoport, Z. *J. Org. Chem.* **1994**, 59, 6786.

²⁸² See DePuy, C.H.; Gronert, S.; Mullin, A.; Bierbaum, V.M. *J. Am. Chem. Soc.* **1990**, 112, 8650.

²⁸³ For a reported example, see Edwards, O.E.; Grieco, C. *Can. J. Chem.* **1974**, 52, 3561.

²⁸⁴ See Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* **1974**, 96, 3171.

²⁸⁵ See Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, **1962**, p. 13.

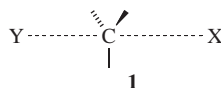
²⁸⁶ For evidence, see Caldwell, G.; Magnera, T.F.; Kebabian, P. *J. Am. Chem. Soc.* **1984**, 106, 959.

²⁸⁷ For a discussion of the interplay between steric and electronic effects, see Fernández, I.; Frenking, G.; Uggerud, E. *Chemistry: Eur. J.* **2009**, 15, 2166.

²⁸⁸ Liu, K.-T.; Hou, S.-J.; Tsao, K.-L. *J. Org. Chem.* **1998**, 63, 1360.

²⁸⁹ Fujio, M.; Nomura, H.; Nakata, K.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Matsushita, T.; Nishimoto, K.; Tsuno, Y. *Tetrahedron Lett.* **1994**, 35, 5005.

resonance stability.²⁹⁰ Adding electron-donating substituents to such molecules improves coplanarity in the cation.²⁹¹ For example, esters of the formula R_3CCOOR' cannot generally be hydrolyzed by the tetrahedral mechanism (see Reaction 16-59), and R_3CCO_2H acids cannot be easily esterified.²⁹² Synthetic advantage can be taken of this fact, for example, with a molecule containing two ester groups only the less hindered one is hydrolyzed.



For the S_N1 mechanism, branching as the α carbon increases the rate, as shown by rate data for alkyl bromides.²⁹³ The secondary bromide isopropyl bromide reacts 11.6 times faster than bromoethane in water at 50 °C, and *tert*-butyl bromide (a tertiary halide) reacts 1.2×10^6 times faster.²⁹³ This result is explained by the stability order of alkyl cations (tertiary > secondary > primary). Of course, the rates are not actually dependent on the stability of the ions, but on the difference in free energy between the starting compounds and the transition states. The *Hammond postulate* (Sec. 6.G) is used to make the assumption that the transition states resemble the cations and that anything (e.g., branching) that lowers the free energy of the ions also lowers it for the transition states. For simple alkyl groups, the S_N1 mechanism is important under all conditions only for tertiary substrates.²⁹⁴ As previously indicated (Sec. 10.A.iv), secondary substrates generally react by the S_N2 mechanism,²⁹⁵ except that the S_N1 mechanism may become important at high solvent polarities. Isopropyl bromide reacts less than twice as fast as ethyl bromide in the relatively nonpolar 60% ethanol (cf. this with the 10^4 ratio for *tert*-butyl bromide, where the mechanism is certainly S_N1), but in the more polar water the rate ratio is 11.6.²⁹³ The 2-adamantyl system is an exception; it is a secondary system that reacts by the S_N1 mechanism because backside attack is hindered for steric reasons.²⁹⁶ Because there is no S_N2 component, this system provides an opportunity for comparing the pure S_N1 reactivity of secondary and tertiary substrates. It has been found that substitution of a methyl group for a hydrogen of 2-adamantyl substrates (thus changing a secondary to a tertiary system) increases solvolysis rates by a factor of $\sim 10^8$.²⁹⁷ Simple primary substrates react by the S_N2 mechanism (or with participation by neighboring alkyl or hydrogen), but not by the

²⁹⁰ Fujio, M.; Nakata, K.; Kuwamura, T.; Nakamura, H.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Tsuno, Y. *Tetrahedron Lett.* **1992**, 34, 8309.

²⁹¹ Liu, K.T.; Tsao, M.-L.; Chao, I. *Tetrahedron Lett.* **1996**, 37, 4173.

²⁹² See DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* **1987**, 52, 2074.

²⁹³ See Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, **1962**, p. 43.

²⁹⁴ See Zamashchikov, V.V.; Bezbozhnaya, T.V.; Chanysheva, I.R. *J. Org. Chem. USSR* **1986**, 22, 1029.

²⁹⁵ See Dietze, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* **1986**, 108, 4549; Dietze, P.E.; Hariri, R.; Khattak, J. *J. Org. Chem.* **1989**, 54, 3317.

²⁹⁶ Fry, J.L.; Harris, J.M.; Bingham, R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1970**, 92, 2540; Schleyer, P.v.R.; Fry, J.L.; Lam, L.K.M.; Lancelot, C.J. *J. Am. Chem. Soc.* **1970**, 92, 2542. Also see Dutler, R.; Rauk, A.; Sorensen, T.S.; Whitworth, S.M. *J. Am. Chem. Soc.* **1989**, 111, 9024.

²⁹⁷ Fry, J.L.; Engler, E.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1972**, 94, 4628. See also, Gassman, P.G.; Pascone, J.M. *J. Am. Chem. Soc.* **1973**, 95, 7801.

S_N1 mechanism, even when solvolyzed in solvents of very low nucleophilicity²⁹⁸ (e.g., trifluoroacetic acid or trifluoroethanol²⁹⁹), and even when very good leaving groups (e.g., OSO_2F) are present³⁰⁰ (see, however, Sec. 10.G.iii).

For some tertiary substrates, the rate of S_N1 reactions is greatly increased by the relief of B strain in the formation of the carbocation (see Sec. 9.B). Except where B strain is involved, β branching has little effect on the S_N1 mechanism, except that carbocations with β branching undergo rearrangements readily. Of course, isobutyl and neopentyl are primary substrates, and for this reason react very slowly by the S_N1 mechanism, but not more slowly than the corresponding ethyl or propyl compounds.

To sum up, primary and secondary substrates generally react by the S_N2 mechanism and tertiary by the S_N1 mechanism. However, tertiary substrates seldom undergo nucleophilic substitution at all. Elimination is always a possible side reaction of nucleophilic substitutions (wherever a β hydrogen is present), and with tertiary substrates it usually predominates. With a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value. However, tertiary substrates that can react by the SET mechanism (e.g., $p\text{-NO}_2\text{C}_6\text{H}_4\text{CMe}_2\text{Cl}$) give very good yields of substitution products when treated with a variety of nucleophiles.³⁰¹

2. *Unsaturation at the α Carbon.* Vinylic, acetylenic,³⁰² and aryl substrates are very unreactive toward nucleophilic substitutions. For these systems, both the S_N1 and S_N2 mechanisms are greatly slowed or stopped altogether. One reason that has been suggested for this is that sp^2 (and even more, sp) carbon atoms have a higher electronegativity than sp^3 carbons and thus a greater attraction for the electrons of the bond. As seen previously (Sec. 8.F, category 7), an $sp\text{-H}$ bond has a higher acidity than an $sp^3\text{-H}$ bond, with that of an $sp^2\text{-H}$ bond in between. This is reasonable; the carbon retains the electrons when the proton is lost and an sp carbon, which has the greatest hold on the electrons, loses the proton most easily. But in nucleophilic substitution, the leaving group *carries off* the electron pair, so the situation is reversed and it is the sp^3 carbon that loses the leaving group and the electron pair most easily. Recall (Sec. 1.J) that bond distances decrease with increasing s character. Thus the bond length for a vinylic or aryl C—Cl bond is 1.73 Å compared with 1.78 Å for a saturated C—Cl bond. Other things being equal, a shorter bond is a stronger bond.

Of course, it has been seen (Sec. 10.F) that S_N1 reactions at vinylic substrates can be accelerated by α substituents that stabilize that cation, and that reactions by the tetrahedral mechanism can be accelerated by β substituents that stabilize the carbanion. Also, reactions at vinylic substrates can in certain cases proceed by addition–elimination or elimination–addition sequences (Sec. 10.F).

²⁹⁸ See Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2004**, *126*, 5174; Kevill, D.N. in Charton, M. *Advances in Quantitative Structure–Property Relationships*, Vol. 1, JAI Press, Greenwich, CT, **1996**, pp 81–115; Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1976**, *98*, 7667.

²⁹⁹ Dafforn, G.A.; Streitwieser, Jr., A. *Tetrahedron Lett.* **1970**, 3159.

³⁰⁰ Cafferata, L.F.R.; Desvard, O.E.; Sicre, J.E. *J. Chem. Soc. Perkin Trans. 2* **1981**, 940.

³⁰¹ Kornblum, N.; Cheng, L.; Davies, T.M.; Earl, G.W.; Holy, N.L.; Kerber, R.C.; Kestner, M.M.; Manthey, J.W.; Musser, M.T.; Pinnick, H.W.; Snow, D.H.; Stuchal, F.W.; Swiger, R.T. *J. Org. Chem.* **1987**, *52*, 196.

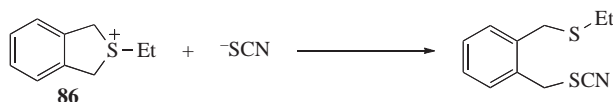
³⁰² See Miller, S.I.; Dickstein, J.I. *Acc. Chem. Res.* **1976**, *9*, 358.

In contrast to such systems, substrates of the type RCOX are usually much *more* reactive than the corresponding RCH_2X . Of course, the mechanism here is almost always the tetrahedral one. Three reasons can be given for the enhanced reactivity of RCOX : (1) The carbonyl carbon has a sizable partial positive charge that makes it very attractive to nucleophiles. (2) In an $\text{S}_{\text{N}}2$ reaction, a σ bond must break in the rate-determining step, which requires more energy than the shift of a pair of π electrons, which is what happens in a tetrahedral mechanism. (3) A trigonal carbon offers less steric hindrance to a nucleophile than a tetrahedral carbon.

For reactivity in aryl systems, see Chapter 13.

3. *Unsaturation at the β Carbon.* The $\text{S}_{\text{N}}1$ rates are increased when there is a double bond in the β position, so that allylic and benzylic substrates react rapidly (allylic tosylates react more than 30 times faster than ethyl tosylate).³⁰³ The reason is that allylic (Sec. 5.A.ii) and benzylic³⁰⁴ (Sec. 5.A.ii) cations are stabilized by resonance. The presence of a second or a third phenyl group increases the rate still more (10^5 and 10^{10} times faster, respectively), because these carbocations are more stable yet.³⁰³ Remember that allylic rearrangements are possible with allylic systems.

In general, $\text{S}_{\text{N}}1$ rates at an allylic substrate are increased by any substituent in the 1 or 3 position that can stabilize the carbocation by resonance or hyperconjugation.³⁰⁵ Among these are alkyl, aryl, and halo groups.



The $\text{S}_{\text{N}}2$ rates for allylic and benzylic systems are also increased (see above), probably owing to resonance possibilities in the transition state. Evidence for this in benzylic systems is that the rate of the reaction was 8000 times slower than the rate with $(\text{PhCH}_2)_2\text{SEt}^+$.³⁰⁶ The cyclic **86** does not have the proper geometry for conjugation in the transition state.

Triple bonds in the β position (in propargyl systems) have about the same effect as double bonds.³⁰⁷ Alkyl, aryl, halo, and cyano groups, among others, in the 3 position of allylic substrates increase $\text{S}_{\text{N}}2$ rates, owing to increased resonance in the transition state, but alkyl and halo groups in the 1 position decrease the rates because of steric hindrance.

4. *α Substitution.* Compounds of the formula 2X , where $\text{Z} = \text{RO}$, RS , or R_2N undergo $\text{S}_{\text{N}}1$ reactions very rapidly,³⁰⁸ because of the increased resonance in the carbocation.

³⁰³ Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, **1962**, p. 75.

³⁰⁴ For a Grunwald–Winstein correlation analysis of the solvolysis of benzyl bromide see Liu, K.-T.; Hou, I.-J. *Tetrahedron* **2001**, *57*, 3343.

³⁰⁵ See DeWolfe, R.H.; Young, W.G. in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, **1964**, pp. 683–688, 695–697.

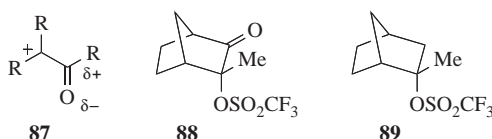
³⁰⁶ King, J.F.; Tsang, G.T.Y.; Abdel-Malik, M.M.; Payne, N.C. *J. Am. Chem. Soc.* **1985**, *107*, 3224.

³⁰⁷ Jacobs, T.L.; Brill, W.F. *J. Am. Chem. Soc.* **1953**, *75*, 1314.

³⁰⁸ See Gross, H.; Höft, E. *Angew. Chem. Int. Ed.* **1967**, *6*, 335.

These groups have an unshared pair on an atom directly attached to the positive carbon, which stabilizes the carbocation (Sec. 5.A.ii). The field effects of these groups would be expected to decrease S_N1 rates (see Sec. 10.G.i, category 6), so the resonance effect is far more important.

When Z in $2X$ is RCO ,³⁰⁹ HCO , $ROCO$, NH_2CO , NC , or F_3C ,³¹⁰ S_N1 rates are decreased compared to CH_3X , owing to the electron-withdrawing field effects of these groups. Furthermore, carbocations³¹¹ with a CO or CN group are greatly destabilized because of the partial positive charge on the adjacent carbon (**87**). The S_N1 reactions have been carried out on such compounds,³¹² but the rates are very low. For example, from a comparison of the solvolysis rates of **88** and **89**, a rate-retarding effect of 10^{76}



was estimated for the $C=O$ group.³¹³ However, when a different kind of comparison is made: $RCOCR'_2X$ versus HCR'_2X (where X = a leaving group), the RCO had only a small or negligible rate-retarding effect, indicating that resonance³¹⁴ may be offsetting the inductive destabilization for this group.³¹⁵ For a CN group also, the rate-retarding effect is reduced by this kind of resonance.³¹⁶ A carbocation with a COR group has been isolated.³¹⁷ When S_N2 reactions are carried out on these substrates, rates are greatly increased for certain nucleophiles (e.g., halide or halide-like ions), but decreased or essentially unaffected by others.³¹⁸ For example, α -chloroacetophenone ($PhCOCH_2Cl$) reacts with KI in acetone at $75^\circ C \sim 32,000$ times faster than 1-chlorobutane,³¹⁹ but α -bromoacetophenone reacts with the nucleophile triethylamine 0.14 times as fast as iodomethane.³¹⁸ The reasons

³⁰⁹ See De Kimpe, N.; Verhé, R. *The Chemistry of α -Haloketones, α -Haloaldehydes, and α -Haloimines*, Wiley, NY, **1988**, pp. 225–368.

³¹⁰ Allen, A.D.; Kanagasabapathy, V.M.; Richard, J.P. *J. Am. Chem. Soc.* **1989**, *111*, 1455.

³¹¹ For reviews of such carbocations, see Bégué, J.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* **1974**, 343.

³¹² For reviews, see Creary, X. *Acc. Chem. Res.* **1985**, *18*, 3; Creary, X.; Hopkinson, A.C.; Lee-Ruff, E. *Adv. Carbocation Chem.* **1989**, *1*, 45; Charpentier-Morize, M.; Bonnet-Delpon, D. *Adv. Carbocation Chem.* **1989**, *1*, 219.

³¹³ Creary, X. *J. Org. Chem.* **1979**, *44*, 3938.

³¹⁴ The resonance contributor that has the positive charge on the more electronegative atom is less stable, according to rule c in Section 2.E, but it nevertheless seems to be contributing in this case.

³¹⁵ Creary, X. *J. Am. Chem. Soc.* **1984**, *106*, 5568. See, however, Takeuchi, K.; Yoshida, M.; Ohga, Y.; Tsugenno, A.; Kitagawa, T. *J. Org. Chem.* **1990**, *55*, 6063.

³¹⁶ Gassman, P.G.; Saito, K.; Talley, J.J. *J. Am. Chem. Soc.* **1980**, *102*, 7613.

³¹⁷ Takeuchi, K.; Kitagawa, T.; Okamoto, K. *J. Chem. Soc., Chem. Commun.* **1983**, 7. See also, Dao, L.H.; Maleki, M.; Hopkinson, A.C.; Lee-Ruff, E. *J. Am. Chem. Soc.* **1986**, *108*, 5237.

³¹⁸ Halvorsen, A.; Songstad, J. *J. Chem. Soc., Chem. Commun.* **1978**, 327.

³¹⁹ Bordwell, F.G.; Brannen, Jr., W.T. *J. Am. Chem. Soc.* **1964**, *86*, 4645. Sisti, A.J.; Lowell, S. *Can. J. Chem.* **1964**, *42*, 1896.

for this varying behavior are not clear, but those nucleophiles that form a “tight” transition state (one in which bond making and breaking have proceeded to about the same extent) are more likely to accelerate the reaction.³²⁰

When Z is SOR or SO₂R (e.g., α-halo sulfoxides and sulfones), nucleophilic substitution is retarded.³²¹ The S_N1 mechanism is slowed by the electron-withdrawing effect of the SOR or SO₂R group,³²² and the S_N2 mechanism presumably by the steric effect.

5. *β Substitution.* For compounds of the type ZCH₂CH₂X, where Z is any of the groups listed in Section 10.F, as well as halogen³²³ or phenyl, S_N1 rates are lower than for unsubstituted systems, because the resonance effects mentioned in item 4 are absent, but the field effects are still there, although smaller. These groups in the β position do not have much effect on S_N2 rates unless they behave as neighboring groups and enhance the rate through anchimeric assistance,³²⁴ or unless their size causes the rates to decrease for steric reasons.³²⁵ It has been shown that silicon exerts a β-effect, and that tin exerts a γ-effect.³²⁶ Silicon also exerts a γ-effect.³²⁷
6. *The Effect of Electron-Donating and Electron-Withdrawing Groups.* If substitution rates for a series of compounds *p*-ZC₆H₄CH₂X are measured, it is possible to study the electronic effects of groups Z on the reaction. Steric effects of Z are minimized or eliminated, because Z is so far from the reaction site. For S_N1 reactions, electron-withdrawing Z decrease the rate and electron-donating Z increase it,³²⁸ because the latter decrease the energy of the transition state (and of the carbocation) by spreading the positive charge, for example,



while electron-withdrawing groups concentrate the charge. The Hammett σ relationship³²⁹ (Sec. 9.C) fairly successfully correlates the rates of many of these reactions (with σ^+ instead of σ). The ρ values are generally about -4 , which is expected for a reaction where a positive charge is created in the transition state.

For S_N2 reactions, no such simple correlations are found.³³⁰ In this mechanism, bond breaking is about as important as bond making in the rate-determining step,

³²⁰ See McLLee, I.; Shim, C.S.; Chung, S.Y.; Lee, I. *J. Chem. Soc. Perkin Trans. 2* **1988**, 975; Yoh, S.; Lee, H.W. *Tetrahedron Lett.* **1988**, 29, 4431.

³²¹ Cinquini, M.; Colonna, S.; Landini, D.; Maia, A.M. *J. Chem. Soc. Perkin Trans. 2* **1976**, 996.

³²² See Creary, X.; Mehrsheikh-Mohammadi, M.E.; Eggers, M.D. *J. Am. Chem. Soc.* **1987**, 109, 2435.

³²³ See Gronert, S.; Pratt, L.M.; Mogali, S. *J. Am. Chem. Soc.* **2001**, 123, 3081.

³²⁴ See Sedaghat-Herati, M.R.; McManus, S.P.; Harris, J.M. *J. Org. Chem.* **1988**, 53, 2539.

³²⁵ See, for example, Okamoto, K.; Kita, T.; Araki, K.; Shingu, H. *Bull. Chem. Soc. Jpn.* **1967**, 40, 1913.

³²⁶ Sugawara, M.; Yoshida, J.-i. *Bull. Chem. Soc. Jpn.* **2000**, 73, 1253.

³²⁷ Nakashima, T.; Fujiyama, R.; Kim, H.-J.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **2000**, 73, 429.

³²⁸ Jorge, J.A.L.; Kiyan, N.Z.; Miyata, Y.; Miller, J. *J. Chem. Soc. Perkin Trans. 2* **1981**, 100; Vitullo, V.P.; Grabowski, J.; Sridharan, S. *J. Chem. Soc., Chem. Commun.* **1981**, 737.

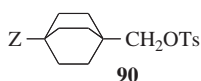
³²⁹ See Fernández, I.; Frenking, G. *J. Org. Chem.* **2006**, 71, 2251.

³³⁰ See Sugden, S.; Willis, J.B. *J. Chem. Soc.* **1951**, 1360; Baker, J.W.; Nathan, W.S. *J. Chem. Soc.* **1935**, 1840; Lee, I.; Sohn, S.C.; Oh, Y.J.; Lee, B.C. *Tetrahedron* **1986**, 42, 4713.

and substituents have an effect on both processes, often in opposite directions. The unsubstituted benzyl chloride and bromide solvolyze by the S_N2 mechanism.³²²

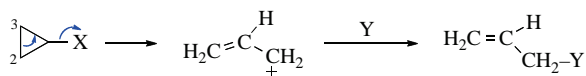
For $Z = \text{alkyl}$, the *Baker–Nathan order* (Sec. 2.M) is usually observed both for S_N1 and S_N2 reactions.

In para-substituted benzyl systems, steric effects have been removed, but resonance and field effects are still present. However, Holtz and Stock³³¹ studied a system that removes not only steric effects, but also resonance effects. This is the 4-substituted bicyclo[2.2.2]octylmethyl tosylate system (**90**). In this system, steric effects are completely absent owing to the rigidity of the molecules, and only field effects operate. By this means, Holtz and Stock showed that electron-withdrawing groups increase the rate of S_N2 reactions. This can be ascribed to stabilization of the transition state by withdrawal of some of the electron density.



For substrates that react by the tetrahedral mechanism, electron-withdrawing groups increase the rate and electron-donating groups decrease it.

7. *Cyclic Substrates.* Cyclopropyl substrates are extremely resistant to nucleophilic attack.³³² For example, cyclopropyl tosylate solvolyzes $\sim 10^6$ times more slowly than cyclobutyl tosylate in acetic acid at 60°C .³³³ When such attack does take place, the result is generally not normal substitution (though exceptions are known,³³⁴ especially when a stabilizing group, e.g., aryl or alkoxy, is present), but ring opening:³²⁶



There is much evidence that the ring opening is usually concerted with the departure of the leaving group³³⁵ (as in the similar case of cyclobutyl substrates, Sec. 10.C.i, category 4.b.iv), from which we can conclude that if the 2,3-bond of the cyclopropane ring did not assist, the rates would be lower still. Strain plays a role in the ring-opening process.³³⁶ It has been estimated³³⁷ that without this

³³¹ Holtz, H.D.; Stock, L.M. *J. Am. Chem. Soc.* **1965**, 87, 2404.

³³² See Friedrich, E.C. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, **1987**, pp. 633–700; Aksenov, V.S.; Terent'eva, G.A.; Savinykh, Yu.V. *Russ. Chem. Rev.* **1980**, 49, 549.

³³³ Roberts, J.D.; Chambers, V.C. *J. Am. Chem. Soc.* **1951**, 73, 5034.

³³⁴ See Banert, K. *Chem. Ber.* **1985**, 118, 1564; Vilsmaier, E.; Weber, S.; Weidner, J. *J. Org. Chem.* **1987**, 52, 4921.

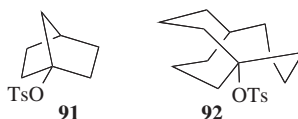
³³⁵ See Jefford, C.W.; Wojnarowski, W. *Tetrahedron* **1969**, 25, 2089; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* **1972**, 37, 4087.

³³⁶ See Wolk, J. L.; Hoz, T.; Basch, H.; Hoz, S. *J. Org. Chem.* **2001**, 66, 915.

³³⁷ Brown, H.C.; Rao, C.G.; Ravindranathan, M. *J. Am. Chem. Soc.* **1978**, 100, 7946.

assistance the rates of these already slow reactions would be further reduced by a factor of perhaps 10^{12} . For a discussion of the stereochemistry of the ring opening, see Reaction **18-27**, Section B. For larger rings, we have seen (Sec. 9.A) that, because of I strain, cyclohexyl substrates solvolyze slower than analogous compounds in which the leaving group is attached to a ring of 5 or of from 7 to 11 members.

8. *Bridgeheads*.¹⁴ The S_N2 mechanism is impossible at most bridgehead compounds (Sec. 10.A.i). Nucleophilic attack in [1.1.1]propellane has been reported, however.³³⁸ In general, a relatively large ring is required for an S_N1 reaction to take place (Sec. 10.A.ii).³³⁹ The S_N1 reactions have been claimed to occur for 1-iodobicyclo[1.1.1]pentane via the bicyclo[1.1.1]pentyl cation,³⁴⁰ but this has been disputed and the bicyclo[1.1.0]butylcarbiny cation was calculated to be the real intermediate.³⁴¹ Solvolytic reactivity at



bridgehead positions spans a wide range; for example, from $k = 4 \times 10^{-17} \text{ s}^{-1}$ for **91** (very slow) to $3 \times 10^6 \text{ s}^{-1}$ for the [3.3.3] compound **92** (very fast);³⁴² a range of 22 orders of magnitude. Molecular mechanics calculations show that S_N1 bridgehead reactivity is determined by strain changes between the substrate and the carbocation intermediate.³⁴³

9. *Deuterium Substitution*. Both α and β secondary isotope effects affect the rate in various ways (Sec. 6.J.vii). The measurement of a secondary isotope effect provides a means of distinguishing between S_N1 and S_N2 mechanisms, since for S_N2 reactions the values range from 0.95 to 1.06 per α D, while for S_N1 reactions the values are higher.³⁴⁴ This method is especially good because it provides the minimum of perturbation of the system under study; changing from α H to α D hardly affects the reaction, while other probes (e.g., changing a substituent or the polarity of the solvent) may have a much more complex effect.

Table 10.3 is an approximate listing of groups in order of S_N1 and S_N2 reactivity. Table 10.4 shows the main reactions that proceed by the S_N2 mechanism (if R = primary or, often, secondary alkyl).

³³⁶ See Wolk, J. L.; Hoz, T.; Basch, H.; Hoz, S. *J. Org. Chem.* **2001**, 66, 915.

³³⁷ Brown, H.C.; Rao, C.G.; Ravindranathan, M. *J. Am. Chem. Soc.* **1978**, 100, 7946.

³³⁸ Sella, A.; Basch, H.; Hoz, S. *Tetrahedron Lett.* **1996**, 37, 5573.

³³⁹ See Kraus, G.A.; Hon, Y.; Thomas, P.J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev.* **1989**, 89, 1591.

³⁴⁰ Adcock, J.L.; Gakh, A.A. *Tetrahedron Lett.* **1992**, 33, 4875.

³⁴¹ Wiberg, K.B.; McMurdie, N. *J. Org. Chem.* **1993**, 58, 5603.

³⁴² Bentley, T.W.; Roberts, K. *J. Org. Chem.* **1988**, 50, 5852.

³⁴³ Bentley, T.W.; Roberts, K. *J. Org. Chem.* **1988**, 50, 5852.

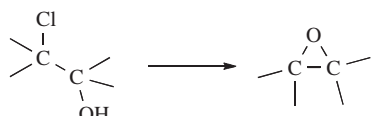
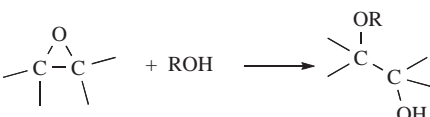
³⁴⁴ Shiner, Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* **1971**, 93, 2553. For a review of secondary isotope effects in S_N2 reactions, see Westaway, K.C. *Isot. Org. Chem.* **1987**, 7, 275.

TABLE 10.3 List of Groups in Approximately Descending Order of Reactivity Toward S_N1 and S_N2 Reactions^a

S _N 1 Reactivity	S _N 2 Reactivity
Ar ₃ CX	Ar ₃ CX
Ar ₂ CHX	Ar ₂ CHX
ROCH ₂ X, RSCH ₂ X, R ₂ NCH ₂ X	ArCH ₂ X
R ₃ CX	ZCH ₂ X
ArCH ₂ X	—C=C—CH ₂ X
—C=C—CH ₂ X	RCH ₂ X ~ RCHDX ~ RCHDCH ₂ X
R ₂ CHX	R ₂ CHX
RCH ₂ X ~ R ₃ CCH ₂ X	R ₃ CX
RCHDX	ZCH ₂ CH ₂ X
RCHDCH ₂ X	R ₃ CCH ₂ X
—C=C—C—X	—C=C—C—X
ZCH ₂ X	
ZCH ₂ CH ₂ X	
ArX	ArX
[2.2.1] Bridgehead-X	Bridgehead-X

^aHere Z is RCO, HCO, ROCO, NH₂CO, NC, or a similar group.

TABLE 10.4 The More Important Synthetic Reactions of Chapter 10 That Take Place by an S_N2 Mechanism.^{a,b}

Reaction Number	Reactions
10-1	$RX + OH^- \longrightarrow ROH$
10-8	$RX + OR' \longrightarrow ROR'$
10-9	
10-10	$R-OSO_2OR'' + OR' \longrightarrow ROR'$
10-12	$2 ROH \longrightarrow ROR$
10-14	
10-15	$R_3O^+ + R'OH \longrightarrow ROR'$
10-17	$RX + R'COO^- \longrightarrow R'COOR$
10-21	$RX + OOH^- \longrightarrow ROOH$
10-25	$RX + SH^- \longrightarrow RSH$
10-26	$RX + R'S^- \longrightarrow RSR'$
10-27	$RX + S_2^{2-} \longrightarrow RSSR$
10-30	$RX + SCN^- \longrightarrow RSCN$
10-31	$RX + R'_2NH \longrightarrow RR'_2N$
10-31	$RX + R'_3N \longrightarrow RR'_3N^+X^-$

(continued)

TABLE 10.4 (Continued)

Reaction Number	Reactions
10-35	$ \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{C} - \text{C} \\ \diagdown \quad \diagup \end{array} + \text{RNH}_2 \longrightarrow \begin{array}{c} \text{NHR} \\ \\ \text{C} - \text{C} \\ \diagdown \quad \diagup \\ \text{OH} \end{array} $
10-41	$\text{RX} + \text{R}'\text{CONH}^- \longrightarrow \text{RNHCOR}'$
10-42	$\text{RX} + \text{NO}_2^- \longrightarrow \text{RNO}_2 + \text{RONO}$
10-43	$\text{RX} + \text{N}_3^- \longrightarrow \text{RN}_3$
10-44	$\text{RX} + \text{NCO}^- \longrightarrow \text{RNCO}$
10-46	$\text{RX} + \text{X}'^- \longrightarrow \text{RX}'$
10-47	$\text{R}-\text{OSO}_2\text{OR}' + \text{X}^- \longrightarrow \text{RX}$
10-48	$\text{ROH} + \text{PCl}_5 \longrightarrow \text{RCl}$
10-49	$\text{ROR}' + 2 \text{HI} \longrightarrow \text{RI} + \text{R}'\text{I}$
10-50	$ \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{C} - \text{C} \\ \diagdown \quad \diagup \end{array} + \text{HX} \longrightarrow \begin{array}{c} \text{X} \\ \\ \text{C} - \text{C} \\ \diagdown \quad \diagup \\ \text{OH} \end{array} $
10-51	$\text{R}-\text{O}-\text{COR}' + \text{LiI} \longrightarrow \text{RI} + \text{R}'\text{COO}^-$
10-57	$\text{RX} + \text{R}'_2\text{CuLi} \longrightarrow \text{RR}'$
10-65	$ \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{C} - \text{C} \\ \diagdown \quad \diagup \end{array} + \text{RMgX} \longrightarrow \begin{array}{c} \text{R} \\ \\ \text{C} - \text{C} \\ \diagdown \quad \diagup \\ \text{OH} \end{array} $
10-67	$\text{RX} + \text{H}^-\text{C}(\text{CO}_2\text{R}')_2 \longrightarrow \text{RCH}(\text{CO}_2\text{R}')_2$
10-68	$\text{RX} + \text{R}''\text{CH}-\text{COR}' \longrightarrow \text{RCR}''-\text{COR}'$
10-70	$\text{RX} + \text{R}'\text{CHCOO}^- \longrightarrow \text{RR}'\text{CHCOO}^-$
10-71	$ \text{R-X} + \text{H} - \begin{array}{c} \text{S} \\ \\ \text{C} \\ \\ \text{S} \end{array} \longrightarrow \begin{array}{c} \text{R} \\ \\ \text{C} \\ \\ \text{S} \end{array} $
10-74	$\text{RX} + \text{R}'\text{C}\equiv\text{C}^- \longrightarrow \text{RC}\equiv\text{CR}'$
10-75	$\text{RX} + \text{CN}^- \longrightarrow \text{RCN}$

^aHere R = primary, often secondary, alkyl.

^bCatalysts are not shown. This is a schematic list only. Some of these reactions may also take place by other mechanisms and the scope may vary greatly. See the discussion of each reaction for details.

10.G.ii The Effect of the Attacking Nucleophile³⁴⁵

Any species that has an unshared pair (i.e., any Lewis base) can, in principle, be a nucleophile, whether it is neutral or has a negative charge. The rates of S_N1 reactions

³⁴⁵ Harris, J.M.; McManus, S.P. *Nucleophilicity*, American Chemical Society, Washington, **1987**; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, **1982**, pp. 145–167, 181–186; Hudson, R.F. in Klopman, G. *Chemical Reactivity and Reaction Paths*, Wiley, NY, **1974**, pp. 167–252.

are independent of the identity of the nucleophile, since it does not appear in the rate-determining step.³⁴⁶ This may be illustrated by the effect of changing the nucleophile from H_2O to OH^- for a primary and a tertiary substrate. For methyl bromide, which reacts by an $\text{S}_{\text{N}}2$ mechanism, the rate is multiplied > 5000 by the change to the more powerful nucleophile OH^- , but for *tert*-butylbromide, which reacts by an $\text{S}_{\text{N}}1$ mechanism, the rate is unaffected.³⁴⁷ A change in nucleophile can, however, change the *product* of an $\text{S}_{\text{N}}1$ reaction. Thus solvolysis of benzyl tosylate in methanol gives benzyl methyl ether (the nucleophile is the solvent methanol). If the more powerful nucleophile Br^- is added, the rate is unchanged, but the product is now benzyl bromide.

Note that the so-called *cation affinity* is used to measure the ability of a cation to interact with an electron-donating species. While this is not formally used to describe $\text{S}_{\text{N}}1$ reactions, it is important for catalytic activity due to different ligands.³⁴⁸

For $\text{S}_{\text{N}}2$ reactions in solution, there are four main principles that govern the effect of the nucleophile on the rate. The nucleophilicity order is not invariant, but depends on substrate, solvent, leaving group, and so on.

1. A nucleophile with a negative charge is always a more powerful nucleophile than its conjugate acid (assuming the latter is also a nucleophile). Thus OH^- is more powerful than H_2O , NH_2^- is more powerful than NH_3 , and so on
2. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately the same as the order of basicity,³⁴⁹ although *basicity is thermodynamically controlled and nucleophilicity is kinetically controlled*. So an approximate order of nucleophilicity is $\text{NH}_2^- > \text{RO}^- > \text{OH}^- > \text{R}_2\text{NH} > \text{ArO}^- > \text{NH}_3 > \text{pyridine} > \text{F}^- > \text{H}_2\text{O} > \text{ClO}_4^-$, and another is $\text{R}_3\text{C}^- > \text{R}_2\text{N}^- > \text{RO}^- > \text{F}^-$ (see Table 8.1). This type of correlation works best when the structures of the nucleophiles being compared are similar, as with a set of substituted phenoxides. Within such a series, linear relationships can often be established between nucleophilic rates and $\text{p}K$ values.³⁵⁰
3. Going down the periodic table, nucleophilicity increases, although basicity decreases. Thus the usual order of halide nucleophilicity is $\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$ (as seen below, this order is solvent dependent). Similarly, any sulfur nucleophile is more powerful than its oxygen analogue. The same is true for phosphorus versus nitrogen. The main reason for this distinction between basicity and nucleophilic power is that the smaller negatively charged nucleophiles are more solvated by the usual polar protic solvents; that is, because the negative charge of Cl^- is more concentrated than the charge of I^- , the former is more tightly surrounded by a shell of solvent molecules that constitute a barrier between it and the substrate. This finding is most important for protic polar solvents in which the solvent may be hydrogen bonded to small nucleophiles. Evidence for this is that many nucleophilic substitutions with small negatively charged nucleophiles are much more rapid in aprotic polar solvents than in protic ones.³⁵¹ Also, in DMF, an aprotic solvent, the

³⁴⁶ See Ritchie, C.D.; Minasz, R.J.; Kamego, A.A.; Sawada, M. *J. Am. Chem. Soc.* **1977**, *99*, 3747; McClelland, R.A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* **1986**, *108*, 7023.

³⁴⁷ Bateman, L.C.; Cooper, K.A.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* **1940**, 925.

³⁴⁸ See Wei, Y.; Sastry, G.N.; Zipse, H. *J. Am. Chem. Soc.* **2008**, *130*, 3473.

³⁴⁹ Uggerud, E. *Chem. Eur. J.* **2006**, *12*, 1127.

³⁵⁰ See Bordwell, F.G.; Hughes, D.L. *J. Am. Chem. Soc.* **1984**, *106*, 3234.

³⁵¹ Parker, A.J. *J. Chem. Soc.* **1961**, 1328 has a list of ~ 20 such reactions.

order of nucleophilicity was $\text{Cl}^- > \text{Br}^- > \text{I}^-$.³⁵² Another experiment was the use of $\text{Bu}_4\text{N}^+ \text{X}^-$ and LiX as nucleophiles in acetone, where X^- was a halide ion. The halide ion in the former salt is much less associated than in LiX . The relative rates with LiX were Cl^- , 1; Br^- , 5.7; I^- , 6.2, which is in the normal order, while with $\text{Bu}_4\text{N}^+ \text{X}^-$, where X^- is much freer, the relative rates were Cl^- , 68; Br^- , 18; I^- , 3.7.³⁵³ In a further experiment, halide ions were allowed to react with the molten salt $(n\text{-C}_5\text{H}_{11})_4\text{N}^+ \text{X}^-$ at 180°C in the absence of a solvent.³⁵⁴ Under these conditions, where the ions are unsolvated and unassociated, the relative rates were Cl^- , 620; Br^- , 7.7; I^- , 1. In the gas phase (no solvent), an approximate order of nucleophilicity was found to be $^-\text{OH} > \text{F}^- \sim \text{MeO}^- > \text{MeS}^- \gg \text{Cl}^- > ^-\text{CN} > \text{Br}^-$,³⁵⁵ providing further evidence that solvation³⁵⁶ is responsible for the effect in solution.

However, solvation is not the entire answer since, even for *uncharged* nucleophiles, nucleophilicity increases going down a column in the periodic table. These nucleophiles are not so greatly solvated and changes in solvent do not greatly affect their nucleophilicity.³⁵⁷ To explain these cases, the principle of hard and soft acids and bases (Sec. 8.E) may be used.³⁵⁸ The proton is a hard acid, but an alkyl substrate (which may be considered to act as a Lewis acid toward the nucleophile considered as a base) is a good deal softer. According to the principle given in Section 8.F, an alkyl group is expected to prefer softer nucleophiles than the proton. Thus the larger, more polarizable (softer) nucleophiles have a greater (relative) attraction toward an alkyl carbon than toward a proton.

4. The freer the nucleophile, the greater the rate.³⁵⁹ One instance of this has already been discussed.³⁵³ Another is that the rate of attack by $(\text{EtOOC})_2\text{CBu}^- \text{Na}^+$ in benzene was increased by the addition of substances (e.g., 1,2-dimethoxyethane, adipamide) that specifically solvated the Na^+ and thus left the anion freer.³⁶⁰ In a nonpolar solvent (e.g., benzene), salts, [e.g., $(\text{EtOOC})_2\text{CBu}^- \text{Na}^+$], usually exist as ion-pair aggregations of large molecular weights.³⁶¹ Similarly, it was shown that the half-life of the reaction between $\text{C}_6\text{H}_5\text{COCHEt}^-$ and ethyl bromide depended on the positive ion: K^+ , 4.5×10^{-3} ; Na^+ , 3.9×10^{-5} ; Li^+ , 3.1×10^{-7} .³⁶² Presumably, the potassium ion leaves

³⁵² Weaver, W.M.; Hutchison, J.D. *J. Am. Chem. Soc.* **1964**, *86*, 261; See also, Bordwell, F.G.; Hughes, D.L. *J. Org. Chem.* **1981**, *46*, 3570. For a contrary result in liquid sulfur dioxide, see Lichtin, N.N.; Puar, M.S.; Wasserman, B. *J. Am. Chem. Soc.* **1967**, *89*, 6677.

³⁵³ Winstein, S.; Savedoff, L.G.; Smith, S.G.; Stevens, I.D.R.; Gall, J.S. *Tetrahedron Lett.* **1960**, no. 9, 24.

³⁵⁴ Gordon, J.E.; Varughese, P. *Chem. Commun.* **1971**, 1160. See also, Ford, W.T.; Hauri, R.J.; Smith, S.G. *J. Am. Chem. Soc.* **1974**, *96*, 4316.

³⁵⁵ Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* **1977**, *99*, 4219. See also, Tanaka, K.; Mackay, G.I.; Payzant, J.D.; Bohme, D.K. *Can. J. Chem.* **1976**, *54*, 1643.

³⁵⁶ See Kormos, B.L.; Cramer, C.J. *J. Org. Chem.* **2003**, *68*, 6375.

³⁵⁷ Parker, A.J. *J. Chem. Soc.* **1961**, 4398.

³⁵⁸ Pearson, R.G. *Surv. Prog. Chem.* **1969**, *5*, 1, pp. 21-38.

³⁵⁹ See Guibe, F.; Bram, G. *Bull. Soc. Chim. Fr.* **1975**, 933.

³⁶⁰ Zaugg, H.E.; Leonard, J.E. *J. Org. Chem.* **1972**, *37*, 2253. See also, Solov'yanyov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* **1987**, *23*, 1243; Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* **1981**, *103*, 4494.

³⁶¹ See, for example Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* **1986**, *108*, 462.

³⁶² Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* **1960**, *82*, 1386. See also, Cacciapaglia, R.; Mandolini, L. *J. Org. Chem.* **1988**, *53*, 2579.

the negative ion freest to attack most rapidly. Further evidence is that in the gas phase,³⁶³ where nucleophilic ions are completely free, without solvent or counterion, reactions take place orders of magnitude faster than the same reactions in solution.³⁶⁴ It has proven possible to measure the rates of reaction of ^-OH with methyl bromide in the gas phase, with ^-OH either unsolvated or solvated with one, two, or three molecules of water.³⁶⁵ The rates were, with the number of water molecules in parentheses: (0) 1.0×10^{-9} ; (1) 6.3×10^{-10} ; (2) 2×10^{-12} ; (3) $2 \times 10^{-13} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$, evidence that solvation of the nucleophile decreases the rate. The rate of this reaction in aqueous solution is $2.3 \times 10^{-25} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. Similar results were found for other nucleophiles and other solvents.³⁶⁶ Also, solution studies have been made of the effect of solvation of the nucleophile by a specific number of water molecules. Indeed, hydrogen bonding lowers the intrinsic nucleophilicity.³⁶⁷ When the salt $(n\text{-C}_6\text{H}_{13})_4\text{N}^+\text{F}^-$ reacted with n -octyl methanesulfonate, the relative rate fell from 822 for no water molecules to 96 for 1.5 water molecules to 1 for 6 water molecules.³⁶⁸

In Chapter 3, cryptands were seen to specifically solvate the alkali metal portion of salts like KF, KOAc, and so on. Synthetic advantage can be taken of this fact to allow anions to be freer, thus increasing the rates of nucleophilic substitutions and other reactions (see Sec. 10.G.v).

However, the four rules given above do not always hold. One reason is that steric influences often play a part. For example, the *tert*-butoxide ion Me_3CO^- is a stronger base than ^-OH or ^-OEt , but a much poorer nucleophile because its large bulk hinders it from closely approaching a substrate.

The following overall nucleophilicity order for $\text{S}_{\text{N}}2$ mechanisms (in protic solvents) was given by Edwards and Pearson³⁶⁹: $\text{RS}^- > \text{ArS}^- > \text{I}^- > \text{CN}^- > ^-\text{OH} > \text{N}_3^- > \text{Br}^- > \text{ArO}^- > \text{Cl}^- > \text{pyridine} > \text{AcO}^- > \text{H}_2\text{O}$. A quantitative relationship³⁷⁰ (the *Swain-Scott equation*, which can be derived from *Marcus theory*³⁷¹) has been worked out similar to the linear free-energy equations considered in Chapter 9:³⁷²

$$\log(k, k_0) = sn$$

where n is the nucleophilicity of a given group, s is the sensitivity of a substrate to nucleophilic attack, and k_0 is the rate for H_2O , which is taken as the standard and for which n is assigned a value of zero. The parameter s is defined as 1.0 for bromomethane.

³⁶³ See Barlow, S.E.; Van Doren, J.M.; Bierbaum, V.M. *J. Am. Chem. Soc.* **1988**, *110*, 7240; Merkel, A.; Havlas, Z.; Zahradník, R. *J. Am. Chem. Soc.* **1988**, *110*, 8355.

³⁶⁴ Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* **1977**, *99*, 4219.

³⁶⁵ Bohme, D.K.; Raksit, A.B. *J. Am. Chem. Soc.* **1984**, *106*, 3447. See also, Hierl, P.M.; Ahrens, A.F.; Henchman, M.; Viggiano, A.A.; Paulson, J.F.; Clary, D.C. *J. Am. Chem. Soc.* **1986**, *108*, 3142.

³⁶⁶ Bohme, D.K.; Raksit, A.B. *Can. J. Chem.* **1985**, *63*, 3007.

³⁶⁷ Chen, X.; Brauman, J.I. *J. Am. Chem. Soc.* **2008**, *130*, 15038.

³⁶⁸ Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1989**, *54*, 328.

³⁶⁹ Edwards, J.O.; Pearson, R.G. *J. Am. Chem. Soc.* **1962**, *84*, 16.

³⁷⁰ Swain, C.G.; Scott, C.B. *J. Am. Chem. Soc.* **1953**, *75*, 141.

³⁷¹ Alberty, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* **1978**, *16*, 87, pp. 113–115.

³⁷² Also see Ritchie, C.D. *Pure Appl. Chem.* **1978**, *50*, 1281; Duboc, C. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry, Recent Advances*, Plenum, NY, **1978**, pp. 313–355; Ibne-Rasa, K.M. *J. Chem. Educ.* **1967**, *44*, 89; Kawazoe, Y.; Ninomiya, S.; Kohda, K.; Kimoto, H. *Tetrahedron Lett.* **1986**, *27*, 2897; Kevill, D.N.; Fujimoto, E.K. *J. Chem. Res. (S)* **1988**, 408.

TABLE 10.5 Nucleophilicities of Some Common Reagents^a

Nucleophile	<i>n</i>	Nucleophile	<i>n</i>
SH	5.1	Br [−]	3.5
CN [−]	5.1	PhO [−]	3.5
I [−]	5.0	AcO [−]	2.7
PhNH ₂	4.5	Cl [−]	2.7
OH	4.2	F [−]	2.0
N ₃ [−]	4.0	NO ₃ [−]	1.0
Pyridine	3.6	H ₂ O	0.0

Reprinted with permission Wells, P.R. *Chem. Rev.* **1963**, 63, 171. Copyright © 1963 American Chemical Society.

^aSee Ref. 373.

Table 10.5 contains values of *n* for some common nucleophiles.³⁷³ The order is similar to that of Edwards and Pearson.

It is now evident that there is *no* absolute order of either nucleophilicity³⁷⁴ or leaving-group ability, even in the gas phase where solvation is not a factor because they have an effect on each other. When the nucleophile and leaving group are both hard or both soft, the reaction rates are relatively high, but when one is hard and the other soft, rates are reduced.³⁶³ Although this effect is smaller than the effects in paragraphs one and four above, it still prevents an absolute scale of either nucleophilicity or leaving-group ability.³⁷⁵ There has been controversy as to whether the selectivity of a reaction should increase with decreasing reactivity of a series of nucleophiles, or whether the opposite holds. There is evidence for both views.³⁷⁶

For substitution at a carbonyl carbon, the nucleophilicity order is not the same as it is at a saturated carbon, but follows the basicity order more closely. The reason is presumably that the carbonyl carbon has a partial positive charge. That is, a carbonyl carbon is a much harder acid than a saturated carbon. The following nucleophilicity order for these substrates has been determined:³⁷⁷ Me₂C=NO[−] > EtO[−] > MeO[−] > [−]OH > [−]OAr > N₃[−] > F[−] > H₂O > Br[−] ~ I[−]. Soft bases are ineffective at a carbonyl carbon.³⁷⁸ In a reaction carried out in the gas phase with alkoxide nucleophiles OR[−] solvated by only one molecule of an alcohol R'OH, it was found that both RO[−] and R'O[−] attacked the formate substrate (HCO₂R'') about equally, although in the unsolvated case, the more basic alkoxide is the better nucleophile.³⁷⁹ In this study, the product ion R²O[−] was also solvated by one molecule of ROH or R'OH.

If an atom containing one or more unshared pairs is adjacent to the attacking atom on the nucleophile, the nucleophilicity is enhanced.³⁸⁰ Examples of such nucleophiles are HO₂[−],

³⁷³ From Wells, P.R. *Chem. Rev.* **1963**, 63, 171, p. 212. See also, Koskikallio, J. *Acta Chem. Scand.* **1969**, 23, 1477, 1490.

³⁷⁴ See Pellerite, M.J.; Brauman, J.I. *J. Am. Chem. Soc.* **1983**, 105, 2672.

³⁷⁵ For reference scales for the characterization of cationic electrophiles and neutral nucleophiles see Mayr, H.; Bug, T.; Gotta, M.F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A.R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, 123, 9500.

³⁷⁶ For discussions, see Dietze, P.; Jencks, W.P. *J. Am. Chem. Soc.* **1989**, 111, 5880.

³⁷⁷ Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, 90, 2622.

³⁷⁸ For theoretical treatments of nucleophilicity at a carbonyl carbon, see Buncl, E.; Shaik, S.S.; Um, I.; Wolfe, S. *J. Am. Chem. Soc.* **1988**, 110, 1275, and references cited therein.

³⁷⁹ Baer, S.; Stoutland, P.O.; Brauman, J.I. *J. Am. Chem. Soc.* **1989**, 111, 4097.

³⁸⁰ Definition in the *Glossary of Terms used in Physical Organic Chemistry*, *Pure Appl. Chem.* **1979**, 51, 1731.

$\text{Me}_2\text{C}=\text{NO}^-$, NH_2NH_2 , and so on. This is called the *alpha effect* (α -effect),³⁸¹ and a broader definition is a positive deviation exhibited by an α -nucleophile from a Brønsted-type nucleophilicity plot,³⁸² where the reference (or normal) nucleophile is one that possesses the same basicity as the α -nucleophile, but does not deviate from the Brønsted-type plot. Several reviews of the α -effect have been published previously.^{72,383} Several possible explanations have been offered.³⁸⁴ One is that the ground state of the nucleophile is destabilized by repulsion between the adjacent pairs of electrons;³⁸⁵ another is that the transition state is stabilized by the extra pair of electrons;³⁸⁶ a third is that the adjacent electron pair reduces solvation of the nucleophile.³⁸⁷ Evidence supporting the third explanation is that there was no alpha effect in the reaction of HO_2^- with methyl formate in the gas phase,³⁸⁸ although HO_2^- shows a strong alpha effect in solution. The α -effect has been demonstrated to be remarkably dependent on the nature of the solvent.³⁸⁹ The α -effect is substantial for substitution at a carbonyl or other unsaturated carbon, at some inorganic atoms,³⁹⁰ and for reactions of a nucleophile with a carbocation,³⁹¹ but is generally smaller or absent entirely for substitution at a saturated carbon.³⁹²

Attempts have been made to establish a general scale of nucleophilicity,³⁹³ and the nucleophilic reactivity of other moieties have been determined, including alcohols and alkoxides,³⁹⁴ carbanions,³⁹⁵ amines,³⁹⁶ pyridines,³⁹⁷ pyrroles,³⁹⁸ indoles,³⁹⁹ imides and amides,⁴⁰⁰ amino acids and peptides,⁴⁰¹ and sulfur ylids.⁴⁰²

³⁸¹ See Ren, Y.; Yamataka, H. *J. Org. Chem.* **2007**, *72*, 5660; *Org. Lett.* **2006**, *8*, 119; *Chemistry: European J.* **2007**, *13*, 677.

³⁸² Hoz, S.; Buncel, E. *Israel J. Chem.* **1985**, *26*, 313.

³⁸³ Grekov, A.P.; Veselov, V.Ya. *Russ. Chem. Rev.* **1978**, *47*, 631; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, **1969**; pp 107–111.

³⁸⁴ See Ho, S.; Buncel, E. *Isr. J. Chem.* **1985**, *26*, 313.

³⁸⁵ Buncel, E.; Hoz, S. *Tetrahedron Lett.* **1983**, *24*, 4777. For evidence that this is not the sole cause, see Oae, S.; Kadoma, Y. *Can. J. Chem.* **1986**, *64*, 1184.

³⁸⁶ See Hoz, S. *J. Org. Chem.* **1982**, *47*, 3545; Laloi-Diard, M.; Verchere, J.; Gosselin, P.; Terrier, F. *Tetrahedron Lett.* **1984**, *25*, 1267.

³⁸⁷ Also see Hudson, R.F.; Hansell, D.P.; Wolfe, S.; Mitchell, D.J. *J. Chem. Soc., Chem. Commun.* **1985**, 1406. For a discussion, see Herschlag, D.; Jencks, W.P. *J. Am. Chem. Soc.* **1990**, *112*, 1951.

³⁸⁸ Buncel, E.; Um, I. *J. Chem. Soc., Chem. Commun.* **1986**, 595; Terrier, F.; Degorre, F.; Kiffer, D.; Laloi, M. *Bull. Soc. Chim. Fr.* **1988**, 415. For some evidence against this explanation, see Moss, R.A.; Swarup, S.; Ganguli, S. *J. Chem. Soc., Chem. Commun.* **1987**, 860.

³⁸⁹ Buncel, E.; Um, I.-H. *Tetrahedron* **2004**, *60*, 7801.

³⁹⁰ For example, see Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* **1973**, *95*, 3912.

³⁹¹ Dixon, J.E.; Bruice, T.C. *J. Am. Chem. Soc.* **1971**, *93*, 3248, 6592.

³⁹² McIsaac, Jr., J.E.; Subbaraman, L.R.; Subbaraman, J.; Mulhausen, H.A.; Behrman, E.J. *J. Org. Chem.* **1972**, *37*, 1037. See, however, Buncel, E.; Wilson, H.; Chuaqui, C. *J. Am. Chem. Soc.* **1982**, *104*, 4896; *Int. J. Chem. Kinet.* **1982**, *14*, 823.

³⁹³ Phan, T.B.; Breugst, M.; Mayr, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3869.

³⁹⁴ Phan, T.B.; Mayr, H. *Can. J. Chem.* **2005**, *83*, 1554.

³⁹⁵ Phan, T.B.; Mayr, H. *Eur. J. Org. Chem.* **2006**, 2530.

³⁹⁶ Brotzel, F.; Chu, Y.C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679; Korzhenevskaya, N.G. *Russ. J. Org. Chem.* **2008**, *44*, 1255.

³⁹⁷ Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chemistry: European J.* **2007**, *13*, 336.

³⁹⁸ Nigst, T.A.; Westermaier, M.; Ofial, A.R.; Mayr, H. *Eur. J. Org. Chem.* **2008**, 2369.

³⁹⁹ Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A.R.; Mayr, H. *J. Org. Chem.* **2006**, *71*, 9088.

⁴⁰⁰ Breugst, M.; Tokuyasu, T.; Mayr, H. *J. Org. Chem.* **2010**, *75*, 5250.

⁴⁰¹ Brotzel, F.; Mayr, H. *Org. Biomol. Chem.* **2007**, *5*, 3814.

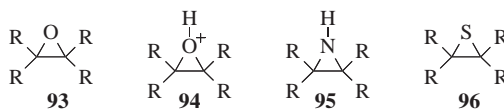
⁴⁰² Appel, R.; Mayr, H. *Chemistry: Eur. J.* **2010**, *16*, 8610.

10.G.iii. The Effect of the Leaving Group

The leaving group at the saturated carbon comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides and fluoride is the poorest. Since XH is always a weaker base than X^- , nucleophilic substitution is always easier at a substrate RXH^+ than at RX . An example of this effect is that OH and OR are not leaving groups from ordinary alcohols and ethers, but can come off when the groups are protonated (i.e., converted to ROH_2^+ or RORH^+).⁴⁰³ Reactions in which the leaving group does not come off until it has been protonated have been called $\text{S}_{\text{N}}1\text{cA}$ or $\text{S}_{\text{N}}2\text{cA}$, depending on whether after protonation the reaction is an $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ process (these designations are often shortened to $\text{A}1$ and $\text{A}2$). The cA stands for conjugate acid, since the substitution takes place on the conjugate acid of the substrate. The IUPAC designations for these mechanisms are, respectively, $\text{A}_{\text{h}} + \text{D}_{\text{N}} + \text{A}_{\text{N}}$ and $\text{A}_{\text{h}} + \text{A}_{\text{N}}\text{D}_{\text{N}}$; that is, the same designations as $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$, with A_{h} to show the preliminary step. When another electrophile assumes the role of the proton, the symbol A_{e} is used instead. The ions ROH_2^+ and RORH^+ can be observed as stable entities at low temperatures in superacid solutions.⁴⁰⁴ At higher temperatures, they cleave to give carbocations.

It is obvious that the best nucleophiles (e.g., NH_2^- , $^- \text{OH}$) cannot take part in $\text{S}_{\text{N}}1\text{cA}$ or $\text{S}_{\text{N}}2\text{cA}$ processes, because they would be converted to their conjugate acids under the acidic conditions necessary to protonate the leaving groups.⁴⁰⁵ Because $\text{S}_{\text{N}}1$ reactions do not require powerful nucleophiles, but do require good leaving groups, most of them take place under acidic conditions. In contrast, $\text{S}_{\text{N}}2$ reactions, which do require powerful nucleophiles, which are generally strong bases, most often take place under basic or neutral conditions.

Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all and protonated ethers only under strenuous conditions, but epoxides⁴⁰⁶ (**93**) are cleaved quite easily and protonated epoxides (**94**) even more easily. Aziridines (**95**)⁴⁰⁷ and episulfides (**96**) are also easily cleaved (see Sec. 10.G.viii).⁴⁰⁸



Although halides are common leaving groups in nucleophilic substitution for synthetic purposes, it is often more convenient to use alcohols. Since OH does not leave from ordinary alcohols, it must be converted to a group that does leave. One way is protonation, mentioned above. Another is conversion to a reactive ester, most commonly a sulfonic ester. The sulfonic ester groups *tosylate*, *brosylate*, *nosylate*, and *mesylate* are better

⁴⁰³ See Staude, E.; Patat, F. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, **1967**, pp. 22–46.

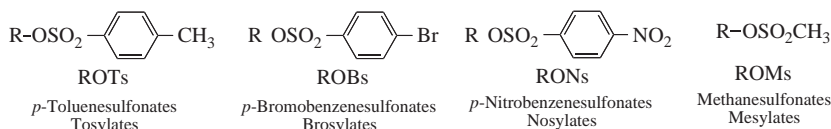
⁴⁰⁴ Olah, G.A.; O'Brien, D.H. *J. Am. Chem. Soc.* **1967**, 89, 1725; Olah, G.A.; Sommer, J.; Namanworth, E. *J. Am. Chem. Soc.* **1967**, 89, 3576; Olah, J.A.; Olah, G.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, pp. 743–747.

⁴⁰⁵ See Okada, S.; Abe, Y.; Taniguchi, S.; Yamabe, S. *J. Chem. Soc., Chem. Commun.* **1989**, 610.

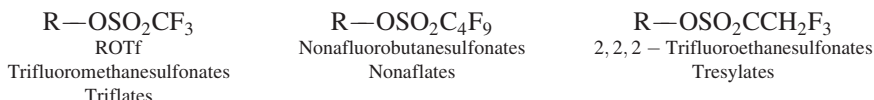
⁴⁰⁶ See Smith, J.G. *Synthesis* **1984**, 629; Bartók, M.; Láng, K.L. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, **1980**, pp. 609–681.

⁴⁰⁷ See Hu, X.E. *Tetrahedron* **2004**, 60, 2701.

⁴⁰⁸ See Di Vona, M.L.; Illuminati, G.; Lillocci, C. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1943; Bury, A.; Earl, H.A.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* **1985**, 393.



leaving groups than halides and are frequently used.⁴⁰⁹ Other leaving groups are still better, and compounds containing these groups make powerful alkylating agents. Among them are oxonium ions (ROR_2^+),⁴¹⁰ and the



fluorinated compounds *triflates*⁴¹¹ and *nonaflates*.⁴¹¹ *Tresylates* are ~ 400 times less reactive than triflates, but still ~ 100 times more reactive than tosylates.⁴¹² Halonium ions (RCIR^+ , RBrR^+ , RIR^+), which can be prepared in superacid solutions (Sec. 5.A.ii) and isolated as solid SbF_6^- salts, are also extremely reactive in nucleophilic substitution.⁴¹³ Of the above types of compound, the most important in organic synthesis are tosylates, mesylates, oxonium ions, and triflates. The others have been used mostly for mechanistic purposes.

The leaving group ability of NH_2 , NHR , and NR_2 are extremely poor,⁴¹⁴ but the leaving-group ability of NH_2 can be greatly improved by converting a primary amine (RNH_2) to the ditosylate (RNTs_2). The NTs_2 group has been successfully replaced by a number of nucleophiles.⁴¹⁵ Another way of converting NH_2 into a good leaving group has been extensively developed by Katritzky et al.⁴¹⁶ In this method, the amine is converted to a pyridinium compound (**98**) by treatment with a pyrylium salt (frequently a 2,4,6-triphenylpyrylium salt, **97**).⁴¹⁷ When the salt is heated, the counterion acts as a nucleophile. In some cases, a non-nucleophilic ion (e.g., BF_4^-), is used as the counterion for the conversion **97** \rightarrow **98**, and then Y^- is added to **98**. Among the nucleophiles that have been used successfully in this reaction are I^- , Br^- , Cl^- , F^- , OAc^- , N_3^- , NHR_2 , and H^- . Ordinary NR_2 groups are good leaving groups when the substrate is a *Mannich base* (these are compounds of the form $\text{RCOCH}_2\text{CH}_2\text{NR}_2$; see Reaction 16-19).⁴¹⁸ The elimination-addition mechanism applies in this case.

⁴⁰⁹ Bentley, T.W.; Christl, M.; Kemmer, R.; Llewellyn, G.; Oakley, J.E. *J. Chem. Soc. Perkin Trans. 2* **1994**, 2531.

⁴¹⁰ Perst, H. *Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, **1971**, pp. 100–127; Perst, H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, **1976**, pp. 1961–2047; Granik, V.G.; Pyatin, B.M.; Glushkov, R.G. *Russ. Chem. Rev.* **1971**, 40, 747; See Curphey, T.J. *Org. Synth.* **VI**, 1021.

⁴¹¹ See Stang, P.J.; Hanack, M.; Subramanian, L.R. *Synthesis* **1982**, 85; Howells, R.D.; McCown, J.D. *Chem. Rev.* **1977**, 77, 69, pp. 85–87.

⁴¹² Crossland, R.K.; Wells, W.E.; Shiner, Jr., V.J. *J. Am. Chem. Soc.* **1971**, 93, 4217.

⁴¹³ Olah, G.A.; Mo, Y.K. *J. Am. Chem. Soc.* **1974**, 96, 3560.

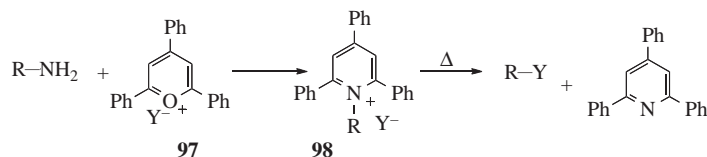
⁴¹⁴ See Baumgarten, R.J.; Curtis, V.A. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, **1982**, pp. 929–997.

⁴¹⁵ See Müller, P.; Thi, M.P.N. *Helv. Chim. Acta* **1980**, 63, 2168; Curtis, V.A.; Knutson, F.J.; Baumgarten, R.J. *Tetrahedron Lett.* **1981**, 22, 199.

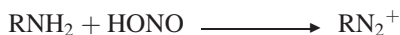
⁴¹⁶ See Katritzky, A.R.; Marson, C.M. *Angew. Chem. Int. Ed.* **1984**, 23, 420; Katritzky, A.R.; Sakizadeh, K.; Musumarra, G. *Heterocycles* **1985**, 23, 1765; Katritzky, A.R.; Musumarra, G. *Chem. Soc. Rev.* **1984**, 13, 47.

⁴¹⁷ See Katritzky, A.R.; Brycki, B. *J. Am. Chem. Soc.* **1986**, 108, 7295, and other papers in this series.

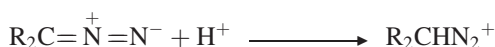
⁴¹⁸ For a review of *Mannich bases*, see Tramontini, M. *Synthesis* **1973**, 703.



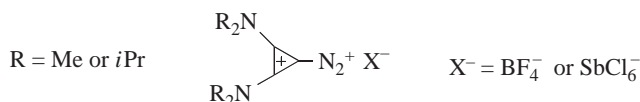
Probably the best leaving group is N_2 from the species RN_2^+ , which can be generated in several ways,⁴¹⁹ of which the two most important are the treatment of primary amines with nitrous acid (see Reaction **13-19**)



and the protonation of diazo compounds⁴²⁰



No matter how produced, RN_2^+ are usually too unstable to be isolable,⁴²¹ reacting presumably by the $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism.⁴²² The simplest aliphatic diazonium ion (CH_2N_2^+) has been prepared at -120°C in superacid solution, where it lived long enough for an NMR spectrum to be taken.⁴²³ Actually, the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.⁴²⁴ If there are free carbocations they should give the same ratio of substitution to elimination to rearrangements, and so on, as carbocations generated in other $\text{S}_{\text{N}}1$ reactions, but they often do not. "Hot" carbocations (unsolvated and/or chemically activated) that can hold their configuration have been postulated,⁴²⁵ as have ion pairs, in which ^-OH (or ^-OAc , etc., depending on how the diazonium ion is generated) is the counterion.⁴²⁶ One class of aliphatic diazonium salts of which several members have been isolated as stable salts are the cyclopropenyldiazonium salts:⁴²⁷



⁴¹⁹ See Kirmse, W. *Angew. Chem. Int. Ed.* **1976**, 15, 251; Collins, C.J. *Acc. Chem. Res.* **1971**, 4, 315.

⁴²⁰ See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, **1986**; Hegarty, A.F. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, 1978, pp. 511–591, pp. 571–575; More O'Ferrall, R.A. *Adv. Phys. Org. Chem.* **1967**, 5, 331; Studzinskii, O.P.; Korobitsyna, I.K. *Russ. Chem. Rev.* **1970**, 39, 834.

⁴²¹ For aromatic diazoium salts, see Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* **1985**, 107, 4491; Laali, K.; Olah, G.A. *Rev. Chem. Intermed.* **1985**, 6, 237; Bott, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, **1983**, pp. 671–697.

⁴²² See Mohrig, J.R.; Keegstra, K.; Maverick, A.; Roberts, R.; Wells, S. *J. Chem. Soc., Chem. Commun.* **1974**, 780.

⁴²³ Berner, D.; McGarrity, J.F. *J. Am. Chem. Soc.* **1979**, 101, 3135

⁴²⁴ See Manuilov, A.V.; Barkhash, V.A. *Russ. Chem. Rev.* **1990**, 59, 179; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**, pp. 280–317.

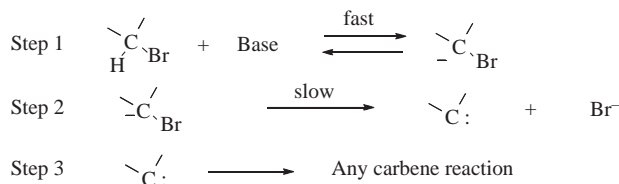
⁴²⁵ Semenow, D.; Shih, C.; Young, W.G. *J. Am. Chem. Soc.* **1958**, 80, 5472. See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, the articles by Keating, J.T.; Skell, P.S. pp. 573–653.

⁴²⁶ Maskill, H.; Thompson, J.T.; Wilson, A.A. *J. Chem. Soc. Perkin Trans. 2* **1984**, 1693; Connor, J.K.; Maskill, H. *Bull. Soc. Chim. Fr.* **1988**, 342.

⁴²⁷ Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* **1985**, 107, 4491.

Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% 1-butanol, 5.2% 1-chlorobutane, 13.2% 2-butanol, 36.5% butenes (consisting of 71% 1-butene, 20% *trans*-2-butene, and 9% *cis*-2-butene), and traces of butyl nitrites.⁴²⁸

In the S_N1cA and S_N2cA mechanisms (see above) there is a preliminary step, the addition of a proton, before the normal S_N1 or S_N2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions, there is a carbene intermediate.



Once formed by this process, the carbene may undergo any of the normal carbene reactions (see Sec. 5.D.ii). When the net result is substitution, this mechanism has been called the S_N1cB (for conjugate base) mechanism.⁴²⁹ Although the slow step is an S_N1 step, the reaction is second order; first order in substrate and first order in base.

Table 10.6 lists some leaving groups in approximate order of ability to leave.^{430–432} The order of leaving-group ability is about the same for S_N1 and S_N2 reactions.

10.G.iv. The Effect of the Reaction Medium⁴³³

The effect of solvent polarity⁴³⁴ on the rate of S_N1 reactions depends on whether the substrate is neutral or positively charged.⁴³⁵ For neutral substrates, which constitute the majority of cases, the more polar the solvent, the faster the reaction, since there is a greater charge in the transition state than in the starting compound (Table 10.7⁴³⁶) and the energy of an ionic transition state is reduced by polar solvents. However, when the substrate is positively charged, the charge is more spread out in the transition state than in the starting ion, and a greater solvent polarity slows the reaction. Even for solvents with about the same

⁴²⁸ Streitwieser, Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* **1957**, 79, 2888.

⁴²⁹ Pearson, R.G.; Edgington, D.N. *J. Am. Chem. Soc.* **1962**, 84, 4607.

⁴³⁰ See Knipe, A.C. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, **1981**, pp. 313–385. See also, Badet, B.; Julia, M.; Lefebvre, C. *Bull. Soc. Chim. Fr.* **1984**, II-431.

⁴³¹ See McMurry, J.E. *Org. React.* **1976**, 24, 187.

⁴³² For the effect of nitro substitution, see Sinnott, M.L.; Whiting, M.C. *J. Chem. Soc. B* **1971**, 965. See also, Page, I.D.; Pritt, J.R.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* **1972**, 906.

⁴³³ See Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, **1988**; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, **1982**, pp. 186–203; Bentley, T.W.; Schleyer, P.v.R. *Adv. Phys. Org. Chem.* **1977**, 14, 1.

⁴³⁴ Mu, L.; Drago, R.S.; Richardson, D.E. *J. Chem. Soc. Perkin Trans. 2*, **1998**, 159; Fujio, M.; Saeki, Y.; Nakamoto, K.; Kim, S.H.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1996**, 69, 751.

⁴³⁵ Bentley, T.W.; Llewellyn, G.; Ryu, Z.H. *J. Org. Chem.* **1998**, 63, 4654.

⁴³⁶ This analysis is due to Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2d ed., Cornell University Press, Ithaca, NY, **1969**, pp. 457–463.

TABLE 10.6 Leaving Groups Listed in Approximate Order of Decreasing Ability to Leave.^a

Substrate RX	Common leaving groups	
	At Saturated Carbon	At Carbonyl Carbon
RN ₂ ⁺	x	
ROR' ₂ ⁺		
ROSO ₂ C ₄ F ₉		
ROSO ₂ CF ₃	x	
ROSO ₂ F		
ROTs, etc. ^b	x	
RI	x	
RBr	x	
ROH ₂ ⁺	x (conjugate acid of alcohol)	
RCI	x	x (acyl halides)
RORH ⁺	x (conjugate acid of ether)	
RONO ₂ , etc. ^b		
RSR' ₂ ^{++c}		
RNR' ₂ ⁺	x	
RF		
ROCOR' ^d	x	x (anhydrides)
RNH ₃ ⁺		
ROAr ^e		x (aryl esters)
ROH		x (carboxylic acids)
ROR		x (alkyl esters)
RH		
RNH ₂		x (amides)
RAr		
RR		

^aGroups that are common leaving groups at saturated and carbonyl carbons are indicated;

^bThe ROTs, and so on, includes esters of sulfuric and sulfonic acids in general, for example, ROSO₂OH, ROSO₂OR, ROSO₂R, and so on, RONO₂, and so on, includes inorganic ester leaving groups, such as ROPO(OH)₂ and ROB(OH)₂.

^cSee Ref. 430.

^dSee Ref. 431.

^eSee Ref. 432.

polarity, there is a difference between protic and aprotic solvents.⁴³⁷ The S_N1 reactions of un-ionized substrates are more rapid in protic solvents, which can form hydrogen bonds with the leaving group. Examples of protic solvents are water,⁴³⁸ alcohols, and carboxylic acids, while some polar aprotic solvents are DMF, DMSO,⁴³⁹ acetonitrile, acetone, sulfur dioxide, and HMPA [(Me₂N)₃PO].⁴⁴⁰ An algorithm has been developed to accurately

⁴³⁷ See Ponomareva, E.A.; Dvorko, G.F.; Kulik, N.I.; Evtushenko, N.Yu. *Doklad. Chem.* **1983**, 272, 291.

⁴³⁸ See Bug, T.; Mayr, H. *J. Am. Chem. Soc.* **2003**, 125, 12980; Brinchi, L.; DiProfio, P.; Germani, R.; Savelli, G.; Spreti, N.; Bunton, L.A. *Eur. J. Org. Chem.* **2000**, 3849.

⁴³⁹ See Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, 14, 133; Martin, D.; Weise, A.; Niclas, H. *Angew. Chem. Int. Ed.* **1967**, 6, 318.

⁴⁴⁰ See Normant, H. *Russ. Chem. Rev.* **1970**, 39, 457; *Angew. Chem. Int. Ed.* **1967**, 6, 1046.

TABLE 10.7 Transition States for S_N1 Reactions of Charged and Uncharged Substrates, and for S_N2 Reactions of the Four Charge Types^a

Reactants and Transition States		Charge in the Transition State Relative to Starting Materials	How an Increase in Solvent Polarity Affects the Rate
Type I	$RX + Y^- \rightarrow Y^{\delta-} \cdots R \cdots X^{\delta-}$	Dispersed	Small decrease
Type II	$RX + Y^- \rightarrow Y^{\delta+} \cdots R \cdots X^{\delta-}$	Increased	Large increase
S _N 2			
Type III	$RX + Y^- \rightarrow Y^{\delta-} \cdots R \cdots X^{\delta+}$	Decreased	Large decrease
Type IV	$RX + Y^- \rightarrow Y^{\delta-} \cdots R \cdots X^{\delta+}$	Dispersed	Small decrease
	$RX \rightarrow R^{\delta+} \cdots X^{\delta-}$	Increased	Large increase
S _N 1			
	$RX^- \rightarrow R^{\delta-} \cdots X^{\delta-}$	Dispersed	Small decrease

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^aSee Ref. 436.

calculate dielectric screening effects in solvents.⁴⁴¹ The S_N2 reactions have been done in ionic liquids (see Sec. 9.D.iii)⁴⁴² and in supercritical carbon dioxide (see Sec. 9.D.ii).⁴⁴³

For S_N2 reactions, the effect of the solvent⁴⁴⁴ depends on which of the four charge types the reaction belongs to (preceding Sec. 10.A). In types I and IV, an initial charge is dispersed in the transition state, so the reaction is hindered by polar solvents. In type III, initial charges are *decreased* in the transition state, so that the reaction is even more hindered by polar solvents. Only type II, where the reactants are uncharged but the transition state has built up a charge, is aided by polar solvents. These effects are summarized in Table 10.7.⁴³⁶ Westaway⁴⁴⁵ proposed a “solvation rule” for S_N2 reactions, which states that changing the solvent will not change the structure of the transition state for type I reactions, but will change it for type II reactions. The difference between protic and aprotic solvents must be considered for S_N2 reactions as well.⁴⁴⁶ For reactions of types I and III the transition state is more solvated in polar aprotic solvents than in protic ones,⁴⁴⁷ while (as seen in Sec. 10.G.ii) the original charged nucleophile is less solvated in aprotic solvents⁴⁴⁸ (the second factor is generally much greater than the first⁴⁴⁹). So the change from, say, methanol to DMSO should greatly increase the rate. As an example, the relative rates at 25 °C for the reaction between MeI and Cl[−] were in MeOH, 1;³⁵¹ in HCONH₂ (still protic although a weaker acid), 12.5; in HCONHMe, 45.3; and HCONMe₂, 1.2×10^6 . The change in rate in going from a protic to an aprotic solvent is also related to the *size* of the

⁴⁴¹ Klamt, A.; Schüürmann, G. *J. Chem. Soc. Perkin Trans. 2* **1993**, 799.

⁴⁴² Kim, D.W.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* **2003**, 68, 4281; Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* **2003**, 68, 6710.

⁴⁴³ DeSimone, J.; Selva, M.; Tundo, P. *J. Org. Chem.* **2001**, 66, 4047.

⁴⁴⁴ See Craig, S.L.; Brauman, J.I. *J. Am. Chem. Soc.* **1999**, 121, 6690.

⁴⁴⁵ Westaway, K.C.; Lai, Z. *Can. J. Chem.* **1989**, 67, 345.

⁴⁴⁶ For reviews of the effects of protic and aprotic solvents, see Parker, A.J. *Chem. Rev.* **1969**, 69, 1; Madaule-Aubry, F. *Bull. Soc. Chim. Fr.* **1966**, 1456.

⁴⁴⁷ See Magnera, T.F.; Caldwell, G.; Sunner, J.; Ikuta, S.; Kebarle, P. *J. Am. Chem. Soc.* **1984**, 106, 6140.

⁴⁴⁸ See, for example, Fuchs, R.; Cole, L.L. *J. Am. Chem. Soc.* **1973**, 95, 3194.

⁴⁴⁹ See, however, Haberfield, P.; Clayman, L.; Cooper, J.S. *J. Am. Chem. Soc.* **1969**, 91, 787.

TABLE 10.8 Relative Rates of Ionization of *p*-Methoxyneophyl Toluenesulfonate in Various Solvents^a

Solvent	Relative Rate	Solvent	Relative Rate
HCOOH	153	Ac ₂ O	0.020
H ₂ O	39	Pyridine	0.013
80% EtOH—H ₂ O	1.85	Acetone	0.0051
AcOH	1.00	EtOAc	6.7×10^{-4}
MeOH	0.947	THF	5.0×10^{-4}
EtOH	0.370	Et ₂ O	3×10^{-5}
Me ₂ SO	0.108	CHCl ₃	Lower still
Octanoic acid	0.043	Benzene	Lower still
MeCN	0.036	Alkanes	Lower still
HCONMe ₂	0.029		

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^aSee Ref. 450.

attacking anion. Small ions are solvated best in protic solvents, since hydrogen bonding is most important for them, while large anions are solvated best in aprotic solvents (protic solvents have highly developed structures held together by hydrogen bonds; aprotic solvents have much looser structures, and it is easier for a large anion to be fitted in). So the rate of attack by small anions is most greatly increased by the change from a protic to an aprotic solvent. This may have preparative significance. The review articles in Ref. 431 have lists of several dozen reactions of charge types I and III in which yields are improved and reaction times reduced in polar aprotic solvents. Reaction types II and IV are much less susceptible to the difference between protic and aprotic solvents.

Since for most reactions S_N1 rates go up and S_N2 rates go down in solvents of increasing polarity, it is quite possible for the same reaction to go by the S_N1 mechanism in one solvent and the S_N2 in another. Table 10.8 is a list of solvents in order of ionizing power;⁴⁵⁰ a solvent high on the list is a good solvent for S_N1 reactions. Trifluoroacetic acid, which was not studied by Smith et al.,⁴⁵⁰ has greater ionizing power⁴⁵¹ than any solvent listed in Table 10.8. Because it also has very low nucleophilicity, it is an excellent solvent for S_N1 solvolyses. Other good solvents for this purpose are 1,1,1-trifluoroethanol (CF₃CH₂OH), and 1,1,1,3,3,3-hexafluoro-2-propanol [(F₃C)₂CHOH].⁴⁵²

Previously, the influence of the polarity of the solvent on the rates of S_N1 and S_N2 reactions was discussed. The ionic strength of the medium has similar effects. In general, the addition of an external salt affects the rates of S_N1 and S_N2 reactions in the same way as an increase in solvent polarity, although this is not quantitative; different salts have different effects.⁴⁵³ However, there are exceptions: Although the rates of S_N1 reactions are usually increased by the addition of salts (this is called the *salt effect*), addition of the leaving-group ion often decreases the rate (the common-ion effect, Sec. 10.A.ii). There is also the special salt effect of LiClO₄, mentioned on Section 10.A.iii, category 2. In addition

⁴⁵⁰ Smith, S.G.; Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* **1961**, 83, 618.

⁴⁵¹ Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1, Plenum, NY, **1976**; Haywood-Farmer, J. *Chem. Rev.* **1974**, 74, 315.

⁴⁵² Schadt, F.L.; Schleyer, P.v.R.; Bentley, T.W. *Tetrahedron Lett.* **1974**, 2335.

⁴⁵³ See Bunton, C.A.; Robinson, L. *J. Am. Chem. Soc.* **1968**, 90, 5965.

to these effects, S_N1 rates are also greatly accelerated when there are ions present that specifically help in pulling off the leaving group.⁴⁵⁴ Especially important are Ag^+ , Hg^{2+} , and Hg_2^{2+} , but H^+ helps to pull off F (hydrogen bonding).⁴⁵⁵ Even primary halides have been reported to undergo S_N1 reactions when assisted by metal ions.⁴⁵⁶ This does not mean, however, that reactions in the presence of metallic ions invariably proceed by the S_N1 mechanism. It has been shown that alkyl halides can react with $AgNO_2$ and $AgNO_3$ by the S_N1 or S_N2 mechanism, depending on the reaction conditions.⁴⁵⁷

The effect of solvent has been treated quantitatively (for S_N1 mechanisms, in which the solvent pulls off the leaving group) by a linear free energy relationship⁴⁵⁸

$$\log(k, k_0) = m Y$$

where m is characteristic of the substrate (defined as 1.00 for t -BuCl) and is usually near unity, Y is characteristic of the solvent and measures its “ionizing power”, and k_0 is the rate in a standard solvent, 80% aq ethanol at 25 °C. This is known as the *Grunwald–Winstein equation*, and its utility is at best limited. The Y values can of course be measured for solvent mixtures as well. This is one of the principal advantages of the treatment, since it is not easy otherwise to assign a polarity arbitrarily to a given mixture of solvents.⁴⁵⁹ The treatment is most satisfactory for different proportions of a given solvent pair. For wider comparisons, the treatment is not so good quantitatively, although the Y values do give a reasonably good idea of solvolyzing power.⁴⁶⁰ Table 10.9 contains a list of some Y values.⁴⁶¹

Ideally, Y should measure only the ionizing power of the solvent, and should not reflect any backside attack by a solvent molecule in helping the nucleofuge to leave (nucleophilic assistance; k_s , Sec. 10.C.i, category 3). Actually, there is evidence that many solvents do

⁴⁵⁴ See Kevill, D.N. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, **1983**, pp. 933–984.

⁴⁵⁵ See Rudakov, E.S.; Kozhevnikov, I.V.; Zamashchikov, V.V. *Russ. Chem. Rev.* **1974**, *43*, 305. For an example of assistance in removal of F by H^+ , see Coverdale, A.K.; Kohnstam, G. *J. Chem. Soc.* **1960**, 3906.

⁴⁵⁶ Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* **1984**, *20*, 424. See, however, Kevill, D.N.; Fujimoto, E.K. *J. Chem. Soc., Chem. Commun.* **1983**, 1149.

⁴⁵⁷ Kornblum, N.; Jones, W.J.; Hardies, D.E. *J. Am. Chem. Soc.* **1966**, *88*, 1704; Kornblum, N.; Hardies, D.E. *J. Am. Chem. Soc.* **1966**, *88*, 1707.

⁴⁵⁸ Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846.

⁴⁵⁹ See Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, **1988**, pp. 339–405; Langhals, H. *Angew. Chem. Int. Ed.* **1982**, *21*, 724.

⁴⁶⁰ For a criticism of the Y scale, see Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J.M.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1097.

⁴⁶¹ Y values are from Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* **1956**, *78*, 2770, except for the value for CF_3CH_2OH which is from Shiner, Jr., V.J.; Dowd, W.; Fisher, R.D.; Hartshorn, S.R.; Kessick, M.A.; Milakofsky, L.; Rapp, M.W. *J. Am. Chem. Soc.* **1969**, *91*, 4838. Y_{OTs} values are from Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* **1990**, *17*, pp. 143–144. Z values are from Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* **1961**, *83*, 3147. See also, Larsen, J.W.; Edwards, A.G.; Dobi, P. *J. Am. Chem. Soc.* **1980**, *102*, 6780. $E_T(30)$ values are from Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* **1969**, *11*, 1; Reichardt, C. *Angew. Chem. Int. Ed.* **1979**, *18*, 98; Laurence, C.; Nicolet, P.; Reichardt, C. *Bull. Soc. Chim. Fr.* **1987**, 125; Laurence, C.; Nicolet, P.; Lucon, M.; Reichardt, C. *Bull. Soc. Chim. Fr.* **1987**, 1001; Reichardt, C.; Eschner, M.; Schäfer, G. *Liebigs Ann. Chem.* **1990**, 57. Also see Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, **1988**.

TABLE 10.9 The Y , Y_{OTs} , Z , and E_{T} (30) Values for Some Solvents^a

Solvent	Y	Y_{OTs}	Z	E_{T} (30)
CF ₃ CO ₂ H		4.57		
H ₂ O	3.5	4.1	94.6	63.1
(CF ₃) ₂ CHOH		3.82		65.3
HCO ₂ H	2.1	3.04		
H ₂ O—EtOH (1:1)	1.7	1.29	90	55.6
CF ₃ CH ₂ OH	1.0	1.77		59.8
HCONH ₂	0.6		83.3	56.6
80% EtOH	0.0	0.0	84.8	53.7
MeOH	−1.1	−0.92	83.6	55.4
AcOH	−1.6	−0.9	79.2	51.7
EtOH	−2.0	−1.96	79.6	51.9
90% dioxane	−2.0	−2.41	76.7	46.7
<i>i</i> PrOH	−2.7	−2.83	76.3	48.4
95% Acetone	−2.8	−2.95	72.9	48.3
<i>t</i> -BuOH	−3.3	−3.74	71.3	43.9
MeCN		−3.21	71.3	45.6
Me ₂ SO			71.1	45.1
HCONMe ₂		−4.14	68.5	43.8
Acetone			65.7	42.2
HMPA				40.9
CH ₂ Cl ₂				40.7
Pyridine			64.0	40.5
CHCl ₃			63.2	39.1
PhCl				37.5
THF				37.4
Dioxane				36.0
Et ₂ O				34.5
C ₆ H ₆			54	34.3
PhMe				33.9
CCl ₄				32.4
<i>n</i> -Octane				31.1
<i>n</i> -Hexane				31.0
Cyclohexane				30.9

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^aSee Ref. 461.

lend some nucleophilic assistance,⁴⁶² even with tertiary substrates.⁴⁶³ It was proposed that a better measure of solvent “ionizing power” would be a relationship based on 2-adamantyl substrates, rather than *t*-BuCl, since the structure of this system completely prevents backside nucleophilic assistance (Sec. 10.G.i). Such a scale, called Y_{OTs} , was developed,

⁴⁶² A scale of solvent nucleophilicity (as opposed to ionizing power), called the N_{T} scale, has been developed: Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* **1991**, 56, 1845.

⁴⁶³ See Kevill, D.N.; Anderson, S.W. *J. Am. Chem. Soc.* **1986**, 108, 1579; McManus, S.P.; Neamati-Mazreah, N.; Karaman, R.; Harris, J.M. *J. Org. Chem.* **1986**, 51, 4876; Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J. M.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* **1987**, 913.

with m defined as 1.00 for 2-adamantyl tosylate.⁴⁶⁴ Some values of Y_{OTs} are given in Table 10.9. These values, which are actually based on both 1- and 2-adamantyl tosylates (both are equally impervious to nucleophilic assistance and show almost identical responses to solvent ionizing power⁴⁶⁵) are called Y_{OTs} because they apply only to tosylates. It has been found that solvent “ionizing power” depends on the leaving group, so separate scales⁴⁶⁶ have been set up for OTf,⁴⁶⁷ Cl,⁴³³ Br,⁴⁶⁸ I,⁴⁶⁹ and other nucleofuges,⁴⁷⁰ all based on the corresponding adamantyl compounds. A new Y scale has been established based on benzylic bromides.⁴⁷¹ In part, this was done because benzylic tosylates did not give a linear correlation with the 2-adamantyl Y_{OTs} parameter.⁴⁷² This is substrate dependent, since solvolysis of 2,2-dimethyl-1-phenyl-1-propanol tosylate showed no nucleophilic solvent participation.⁴⁷³

In order to include a wider range of solvents than those in which any of the Y values can be conveniently measured, other attempts have been made at correlating solvent polarities.⁴⁷⁴ Kosower et al.⁴⁷⁵ found that the position of the charge-transfer peak (see Sec. 3.C.i) in the UV spectrum of the complex (**99**) between iodide ion and 1-methyl- or 1-ethyl-4-carbomethoxypyridinium ion was dependent on the polarity of the solvent.⁴⁷⁵ From these peaks, which are very easy to measure, Kosower et al.⁴⁷⁵ calculated transition energies that he called Z values. These values are thus measures of solvent polarity analogous to Y values. Another scale is based on the position of electronic spectra peaks of the pyridinium- N -phenolbetaine (**100**) in various solvents.⁴⁷⁶ Solvent polarity values on this scale are called $E_{\text{T}}(30)$ ⁴⁷⁷ values. The $E_{\text{T}}(30)$ values are related to Z values by the expression⁴⁷⁸

$$Z = 1.41 E_{\text{T}}(30) + 6.92$$

⁴⁶⁴ Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1976**, *98*, 7667.

⁴⁶⁵ Bentley, T.W.; Carter, G.E. *J. Org. Chem.* **1983**, *48*, 579.

⁴⁶⁶ For a review of these scales, see Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* **1990**, *17*, 121.

⁴⁶⁷ Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* **1985**, *50*, 3330. See also, Creary, X.; McDonald, S.R. *J. Org. Chem.* **1985**, *50*, 474.

⁴⁶⁸ Bentley, T.W.; Carter, G.E. *J. Am. Chem. Soc.* **1982**, *104*, 5741. See also, Liu, K.; Sheu, H. *J. Org. Chem.* **1991**, *56*, 3021.

⁴⁶⁹ Bentley, T.W.; Carter, G.E.; Roberts, K. *J. Org. Chem.* **1984**, *49*, 5183.

⁴⁷⁰ See Kevill, D.N.; Hawkinson, D.C. *J. Org. Chem.* **1990**, *55*, 5394 and references cited therein.

⁴⁷¹ Fujio, M.; Saeki, Y.; Nakamoto, K.; Yatsugi, K.-i.; Goto, N.; Kim, S.H.; Tsuji, Y.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2603; Liu, K.-T.; Chin, C.-P.; Lin, Y.-S.; Tsao, M.-L. *J. Chem. Res. (S)* **1997**, *18*.

⁴⁷² Fujio, M.; Susuki, T.; Goto, M.; Tsuji, Y.; Yatsugi, K.; Saeki, Y.; Kim, S.H.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2233.

⁴⁷³ Tsuji, Y.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* **1992**, *33*, 349.

⁴⁷⁴ See Abraham, M.H.; Grellier, P.L.; Abboud, J.M.; Doherty, R.M.; Taft, R.W. *Can. J. Chem.* **1988**, *66*, 2673; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, **1982**, pp. 127–172; Reichardt, C. *Angew. Chem. Int. Ed.* **1979**, *18*, 98; Abraham, M.H. *Prog. Phys. Org. Chem.* **1974**, *11*, 1. See also, Chastrette, M.; Rajzmann, M.; Chanon, M.; Purcell, K.F. *J. Am. Chem. Soc.* **1985**, *107*, 1.

⁴⁷⁵ Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* **1961**, *83*, 3147. See also, Larsen, J.W.; Edwards, A. G.; Dobi, P. *J. Am. Chem. Soc.* **1980**, *102*, 6780.

⁴⁷⁶ Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* **1969**, *727*, 93. See also, Haak, J.R.; Engberts, J.B.F.N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 307.

⁴⁷⁷ The symbol E_{T} comes from *energy, transition*. The (30) is used because the ion **100** bore this number in Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* **1969**, *727*, 93. Values based on other ions have also been reported: See, for example, Reichardt, C.; Harbusch-Görnert, E.; Schäfer, G. *Liebigs Ann. Chem.* **1988**, *839*.

⁴⁷⁸ Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* **1969**, *11*, p. 32.

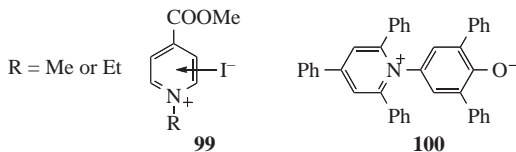


Table 10.9 shows that Z and $E_T(30)$ values are generally in the same order as Y values. Other scales, the π^* scale,⁴⁷⁹ the π^*_{azo} scale,⁴⁸⁰ and the Py scale,⁴⁸¹ are also based on spectral data.⁴⁸²

Carbon dioxide can be liquefied under high pressure (supercritical CO_2). Several reactions have been done using supercritical CO_2 as the medium (Sec. 9.D.ii), but special apparatus is required. This medium offers many advantages,⁴⁸³ and some disadvantages, but is an interesting new area of research.

The effect of solvent on nucleophilicity has already been discussed (Sec. 10.G.ii).

10.G.v. Phase-Transfer Catalysis

A difficulty that occasionally arises when carrying out nucleophilic substitution reactions is that the reactants do not mix. For a reaction to take place, the reacting molecules must collide. In nucleophilic substitutions, the substrate is usually insoluble in water and other polar solvents, while the nucleophile is often an anion, which is soluble in water, but not in the substrate or other organic solvents. Consequently, when the two reactants are brought together, their concentrations in the same phase are too low for convenient reaction rates. One way to overcome this difficulty is to use a solvent that will dissolve both species. As seen in Section 10.G.iv, a dipolar aprotic solvent may serve this purpose. Another way, which is used very often, is *phase-transfer catalysis*.⁴⁸⁴

In this method, a catalyst is used to carry the nucleophile from the aqueous into the organic phase. As an example, simply heating and stirring a two-phase mixture of 1-chlorooctane for several days with aq. NaCN gives essentially no yield of 1-cyanooctane. But if a small amount of an appropriate quaternary ammonium salt is added, the product is quantitatively formed in ~ 2 h.⁴⁸⁵ There are two principal types of phase-transfer catalyst, although the action of the two types is somewhat different, the effects are the same. Both get the anion into the organic phase and allow it to be relatively free to react with the substrate.

1. *Quaternary Ammonium or Phosphonium Salts*. In the above-mentioned case of NaCN, the uncatalyzed reaction does not take place because the ^-CN ions

⁴⁷⁹ Doherty, R.M.; Abraham, M.H.; Harris, J.M.; Taft, R.W.; Kamlet, M.J. *J. Org. Chem.* **1986**, *51*, 4872. See also, Bekárek, V. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1425; Abe, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2328.

⁴⁸⁰ Buncl, E.; Rajagopal, S. *J. Org. Chem.* **1989**, *54*, 798.

⁴⁸¹ Dong, D.C.; Winnik, M.A. *Can. J. Chem.* **1984**, *62*, 2560.

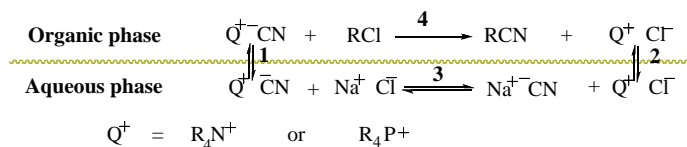
⁴⁸² For a review of such scales, see Buncl, E.; Rajagopal, S. *Acc. Chem. Res.* **1990**, *23*, 226.

⁴⁸³ Kaupp, G. *Angew. Chem. Int. Ed.* **1994**, *33*, 1452.

⁴⁸⁴ Dehmlow, E.V.; Dehmlow, S.S. *Phase Transfer Catalysis*, 2nd ed., Verlag Chemie, Deerfield Beach, FL, **1983**; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, **1978**; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, **1977**; Makosza, M. *Pure Appl. Chem.* **2000**, *72*, 1399; Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* **1982**, *101*, 147; Alper, H. *Adv. Organomet. Chem.* **1981**, *19*, 183; Sjöberg, K. *Aldrichimica Acta* **1980**, *13*, 55.

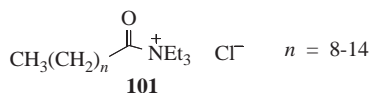
⁴⁸⁵ Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, **1978**, p. 2.

cannot cross the interface between the two phases, except in very low concentration. The reason is that the Na^+ ions are solvated by the water, and this solvation energy would not be present in the organic phase. The CN^- ions cannot cross without the Na^+ ions because that would destroy the electrical neutrality of each phase. In contrast to Na^+ ions, quaternary ammonium (R_4N^+)⁴⁸⁶ and phosphonium (R_4P^+) ions with sufficiently large R groups are poorly solvated in water and prefer organic solvents. If a small amount of such a salt is added, three equilibria are set up:



The Na^+ ions remain in the aqueous phase; they cannot cross. The Q^+ ions do cross the interface and carry an anion with them. At the beginning of the reaction, the chief anion present is CN^- . This gets carried into the organic phase (equilibrium 1) where it reacts with RCl to produce RCN and Cl^- . The Cl^- then gets carried into the aqueous phase (equilibrium 2). Equilibrium 3, taking place entirely in the aqueous phase, allows Q^+CN^- to be regenerated. All the equilibria are normally reached much faster than the actual conversion of RCl to RCN , so the latter is the rate-determining step.

In some cases, the Q^+ ions have such a low solubility in water that virtually all remain in the organic phase.⁴⁸⁷ In such cases, the exchange of ions (equilibrium 3) takes place across the interface. Still another mechanism (*the interfacial mechanism*) can operate where OH^- extracts a proton from an organic substrate.⁴⁸⁸ In this mechanism, the OH^- ions remain in the aqueous phase and the substrate in the organic phase; the deprotonation takes place at the interface.⁴⁸⁹ Thermal stability of the quaternary ammonium salt is a problem, limiting the use of some catalysts. The trialkylacetyl ammonium halide (**101**) is thermally stable, however, even at high reaction temperatures.⁴⁹⁰ The use of molten quaternary ammonium salts as ionic reaction media for substitution reactions has also been reported.⁴⁹¹



2. *Crown Ethers and Other Cryptands*.⁴⁹² As seen in Section 3.C.ii, certain cryptands are able to surround certain cations. In effect, a salt like KCN is converted by

⁴⁸⁶ See Lissel, M.; Feldman, D.; Nir, M.; Rabinovitz, M. *Tetrahedron Lett.* **1989**, 30, 1683.

⁴⁸⁷ Landini, D.; Maia, A.; Montanari, F.J. *Am. Chem. Soc.* **1978**, 100, 2796.

⁴⁸⁸ For a review, see Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem. Int. Ed.* **1986**, 25, 960.

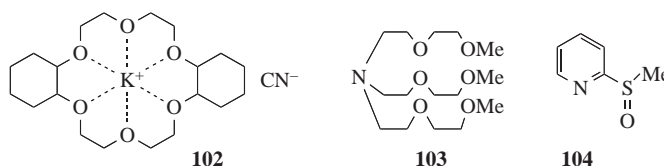
⁴⁸⁹ See Makosza, M. *Pure Appl. Chem.* **1975**, 43, 439. See also, Dehmlow, E.V.; Thieser, R.; Sasson, Y.; Pross, E. *Tetrahedron* **1985**, 41, 2927; Mason, D.; Magdassi, S.; Sasson, Y. *J. Org. Chem.* **1990**, 55, 2714.

⁴⁹⁰ Bhalerao, U.T.; Mathur, S.N.; Rao, S.N. *Synth. Commun.* **1992**, 22, 1645.

⁴⁹¹ Badri, M.; Brunet, J.-J.; Perron, R. *Tetrahedron Lett.* **1992**, 33, 4435.

⁴⁹² See Liotta, C. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, **1980**, pp. 157–174.

dicyclohexano-18-crown-6 into a new salt (**102**) whose anion is the same, but whose cation is now a much larger species with the positive charge spread over a large volume, and hence much less concentrated. This larger cation is much less solubilized by water than K^+ and much more attracted to organic solvents. Although KCN is generally insoluble in organic solvents, the cryptate salt is soluble in many of them. In these cases, we do not need an aqueous phase at all but simply add the salt to the organic phase. Suitable cryptands have been used to increase the rates of reactions where F^- , Br^- , I^- , ^-OAc , and ^-CN are nucleophiles.⁴⁹³ Certain compounds that are not cryptands can act in a similar manner. One example is the podand tris(3,6-dioxaheptyl)amine (**103**), also called TDA-1.⁴⁹⁴ Another, not related to the crown ethers, is the pyridyl sulfoxide (**104**).⁴⁹⁵



Both of the above-mentioned catalyst types get the anions into the organic phase, but there is another factor as well. There is evidence that sodium and potassium salts of many anions, even if they could be dissolved in organic solvents, would undergo reactions very slowly (dipolar aprotic solvents are exceptions) because in these solvents the anions exist as ion pairs with Na^+ or K^+ and are not free to react with the substrate (Sec. 10.G.ii, category 4). Fortunately, ion pairing is usually much less with the quaternary ions and with the positive cryptate ions, so the anions in these cases are quite free to attack. Such anions are sometimes referred to as “naked” anions.

Not all quaternary salts and cryptands work equally well in all situations. Some experimentation is often required to find the optimum catalyst.

Although phase-transfer catalysis has been most often used for nucleophilic substitutions, it is not confined to these reactions. Any reaction that needs an insoluble anion dissolved in an organic solvent can be accelerated by an appropriate phase-transfer catalyst. Some examples will be seen in later chapters. In fact, in principle, the method is not even limited to anions, and a small amount of work has been done in transferring cations,⁴⁹⁶ radicals, and molecules.⁴⁹⁷ The reverse type of phase-transfer catalysis has also been reported: transport into the aqueous phase of a reactant that is soluble in organic solvents.⁴⁹⁸ Microwave activated phase-transfer catalysis has been reported.⁴⁹⁹

⁴⁹³ See Liotta, C.; Harris, H.P.; McDermott, M.; Gonzalez, T.; Smith, K. *Tetrahedron Lett.* **1974**, 2417; Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* **1974**, 96, 2252; Durst, H.D. *Tetrahedron Lett.* **1974**, 2421.

⁴⁹⁴ Soula, G. *J. Org. Chem.* **1985**, 50, 3717.

⁴⁹⁵ Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1833. See also, Fujihara, H.; Imaoka, K.; Furukawa, N.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* **1986**, 333.

⁴⁹⁶ See Iwamoto, H.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1983**, 56, 796.

⁴⁹⁷ See, for example, Dehmlow, E.V.; Slopianka, M. *Chem. Ber.* **1979**, 112, 2765.

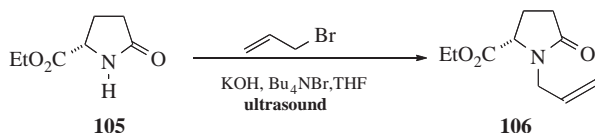
⁴⁹⁸ Fife, W.K.; Xin, Y. *J. Am. Chem. Soc.* **1987**, 109, 1278.

⁴⁹⁹ Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* **1999**, 55, 10851.

The catalysts mentioned above are soluble. Certain cross-linked polystyrene resins, as well as alumina⁵⁰⁰ and silica gel, have been used as insoluble phase-transfer catalysts. These, called *triphasic catalysts*,⁵⁰¹ have the advantage of simplified product work up and easy and quantitative catalyst recovery, since the catalyst can easily be separated from the product by filtration.

10.G.vi. Influencing Reactivity by External Means

In many cases, reactions are slow. This is sometimes due to poor mixing or the aggregation state of one or more reactants. A powerful technique used to increase reaction rates is *ultrasound* (see Sec. 7.B). In this technique, the reaction mixture is subjected to high-energy sound waves, most often 20 KHz, but sometimes higher (a frequency of 20 KHz is about the upper limit of human hearing). When these waves are passed through a mixture, small bubbles form (*cavitation*). Collapse of these bubbles produces powerful shock waves that greatly increase the temperatures and pressures within these tiny regions, resulting in an increased reaction rate.⁵⁰² In an instance where a metal, as a reactant or catalyst, is in contact with a liquid phase, a further effect is that the surface of the metal is cleaned and/or eroded by the ultrasound, allowing the liquid-phase molecules to come into closer contact with the metal atoms. Among the advantages of ultrasound is that it may increase yields, reduce side reactions, and permit the use of lower temperatures and/or pressures. The reaction of pyrrolidinone (**105**) with allyl bromide, under phase-transfer conditions, gave < 10% of the *N*-allyl product, (**106**). When the reaction was done under identical conditions, but with exposure to ultrasound (in an ultrasonic bath), the yield of **106** was 78%.⁵⁰³ It has been postulated that ultrasound has its best results with reactions that proceed, at least partially, through free radical intermediates.⁵⁰⁴



As noted in Chapter 7 (see Sec. 7.C), microwave irradiation is used extensively. Reaction times are greatly accelerated in many reactions, and reactions that took hours to be complete in refluxing solvents are done in minutes. Benzyl alcohol was converted to benzyl bromide, for example, using microwave irradiation (650 W) in only 9 min on a doped K-10 Montmorillonite clay.⁵⁰⁵ This technique is growing and very useful.

⁵⁰⁰ Quici, S.; Regen, S.L. *J. Org. Chem.* **1979**, *44*, 3436.

⁵⁰¹ See Regen, S.L. *Nouv. J. Chim.* **1982**, *6*, 629; *Angew. Chem. Int. Ed.* **1979**, *18*, 421. See also, Bogatskii, A.V.; Luk'yanenko, N.G.; Pastushok, V.N.; Parfenova, M.N. *Doklad. Chem.* **1985**, *283*, 210; Pugia, M.J.; Czech, B.P.; Czech, B.P.; Bartsch, R.A. *J. Org. Chem.* **1986**, *51*, 2945.

⁵⁰² See Mingos, D.M.P.; Baghurst, D.R. *Chem. Soc. Rev.* **1991**, *20*, 1; Giguere, R.J. *Org. Synth. Theory Appl.* **1989**, *1*, 103.

⁵⁰³ Keusenkothen, P.F.; Smith, M.B. *Tetrahedron Lett.* **1989**, *30*, 3369.

⁵⁰⁴ See Einhorn, C.; Einhorn, J.; Dickens, M.J.; Luche, J. *Tetrahedron Lett.* **1990**, *31*, 4129.

⁵⁰⁵ Kad, G.-L.; Singh, V.; Kuar, K.P.; Singh, J. *Tetrahedron Lett.* **1997**, *38*, 1079.

The rate of many reactions can be increased by application of high pressure.⁵⁰⁶ In solution, the rate of a reaction can be expressed in terms of the activation volume (ΔV^\ddagger).⁵⁰⁷

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^\ddagger}{RT}$$

The value of ΔV^\ddagger is the difference in partial molal volume between the transition state and the initial state, but it can be approximated by the molar volume.⁵⁰⁷ Increasing pressure decreases the value of ΔV^\ddagger and ΔV^\ddagger is negative as the reaction rate is accelerated. This equation is not strictly obeyed > 10 kbar. If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. Cleavage of a bond, dispersal of charge, neutralization of the transition state, and diffusion control lead to a positive volume of activation. Reactions for which rate enhancement is expected at high pressure include⁵⁰⁷:

1. Reactions in which the number of molecules decreases when starting materials are converted to products: cycloadditions [e.g., the *Diels–Alder* (Reaction **15-60**)] and condensations, [e.g., the *Knoevenagel condensation* (**16-38**)].
2. Reactions that proceed via cyclic transition states: *Claisen* (Reaction **18-33**) and *Cope* (Reaction **18-32**) rearrangements.
3. Reactions that take place through dipolar transition states: *Menshutkin reaction* (Reaction **10-31**), electrophilic aromatic substitution.
4. Reactions with steric hindrance.

Many high-pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, which influences the viscosity of the medium (viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important.⁵⁰⁸ In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place.

10.G.vii. Ambident (Bidentant) Nucleophiles: Regioselectivity

Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair. In these cases, the nucleophile may attack in two or more different ways to give different products. Such reagents are called *ambident nucleophiles*.⁵⁰⁹ In most cases, a nucleophile with two potentially attacking atoms can attack with either of them, depending on conditions, and mixtures are often obtained, although this is not always the case. For example, the

⁵⁰⁶ Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, NY, **1991**; Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1, 999.

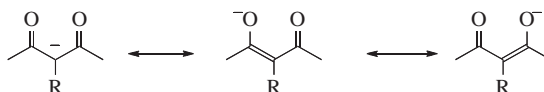
⁵⁰⁷ Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, **1981**; Asano, T.; le Noble, W.J. *Chem. Rev.* **1978**, 78, 407.

⁵⁰⁸ Firestone, R.A.; Vitale, M.A. *J. Org. Chem.* **1981**, 46, 2160.

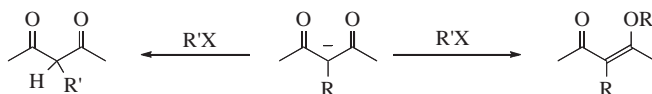
⁵⁰⁹ See Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, **1983**. For a review, see Black, T.H. *Org. Prep. Proced. Int.* **1989**, 21, 179.

nucleophile (NCO^-) usually gives only isocyanates (RNCO) and not the isomeric cyanates (ROCN).⁵¹⁰ When a reaction can potentially give rise to two or more structural isomers (e.g., ROCN or RNCO), but actually produces only one, the reaction is said to be *regioselective*⁵¹¹ (cf. the definitions of stereoselective, Sec. 4.N and enantioselective, Sec. 4.H., category 2). Some important ambident nucleophiles follow:

1. *Ions of the Type* $-\text{CO}-\text{CR}^--\text{CO}-$. These ions, which are derived by removal of a proton from malonic esters, β -keto esters, β -diketones, and so on, are resonance hybrids:

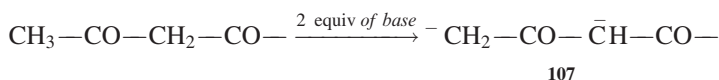


Attack is therefore possible at a saturated carbon via the carbon atoms (*C*-alkylation) or the oxygen atoms (*O*-alkylation):



With unsymmetrical ions, three products are possible, since either oxygen can attack. With a carbonyl substrate the ion can analogously undergo *C*- or *O*-acylation.

2. *Compounds of the Type* $\text{CH}_3\text{CH}-\text{CH}_2-\text{CO}-$. *Can Give Up Two Protons*, if treated with 2 molar equivalents of a strong enough base, to give dicarbanions:



Such ions are ambident nucleophiles, since they have two possible attacking carbon atoms, aside from the possibility of attack by oxygen. In such cases, the attack is virtually always by the more basic carbon.⁵¹² Since the hydrogen of a carbon bonded to two carbonyl groups is more acidic than that of a carbon bonded to just one (see Chap 8), the CH group of **107** is less basic than the CH_2 group, so the latter attacks the substrate. This gives rise to a useful general principle: Whenever the goal is to remove a proton at a given position for use as a nucleophile, but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position since it is the ion of the weaker acid. On the other hand, if the goal is to attack with the more acidic position, all that is necessary is to remove just one proton.⁵¹³ For example, ethyl acetoacetate can be

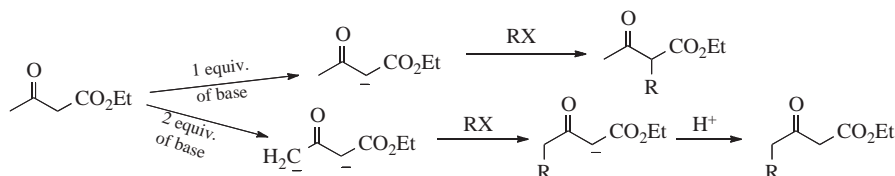
⁵¹⁰ See Holm, A.; Wentrup, C. *Acta Chem. Scand.* **1966**, 20, 2123.

⁵¹¹ This term was introduced by Hassner, A. *J. Org. Chem.* **1968**, 33, 2684.

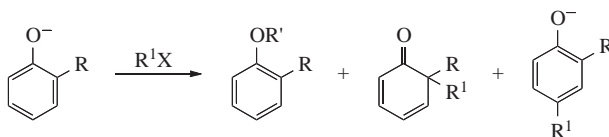
⁵¹² For an exception, see Trimitsis, G.B.; Hinkley, J.M.; TenBrink, R.; Faburada, A.L.; Anderson, R.; Poli, M.; Christian, B.; Gustafson, G.; Erdman, J.; Rop, D. *J. Org. Chem.* **1983**, 48, 2957.

⁵¹³ See Hauser, C.R.; Harris, C.M. *J. Am. Chem. Soc.* **1958**, 80, 6360. For reviews, see Thompson, C.M.; Green, D. L.C. *Tetrahedron* **1991**, 47, 4223; Harris, T.M.; Harris, C.M. *Org. React.* **1969**, 17, 155.

alkylated at either the methyl or the methylene group (Reaction 10-67):



3. *The CN^- Ion.* This nucleophile can give nitriles (RCN , Reaction 10-75) or isocyanides ($\text{RN}\equiv\text{C}$).
4. *The Nitrite Ion.* This ion can give nitrite esters $\text{R}-\text{O}-\text{N}=\text{O}$ (Reaction 10-22) or nitro compounds RNO_2 (Reaction 10-76), which are not esters.
5. *Phenoxide ions.* These ions, (which are analogous to enolate anions) can undergo C- or O-alkylation:



6. *Removal of a Proton from an Aliphatic Nitro Compound.* This reaction gives a carbanion ($\text{R}_2\text{C}^- - \text{NO}_2$) that can be alkylated at oxygen or carbon.⁵¹⁴ O-Alkylation gives a nitronic ester, and such compounds are generally unstable to heat and break down to give an oxime and an aldehyde or ketone.



There are many other ambident nucleophiles.

It would be useful to have general rules as to which atom of an ambident nucleophile will attack a given substrate under a given set of conditions.⁵¹⁵ Unfortunately, the situation is complicated by the large number of variables. It might be expected that the more electronegative atom would always attack, but this is often not the case. Where the products are determined by thermodynamic control (Sec. 6.F), the principal product is usually the one in which the atom of higher basicity has attacked (i.e., $\text{C} > \text{N} > \text{O} > \text{S}$).⁵¹⁶ However, in most reactions, the products are kinetically controlled and matters are much less simple. Nevertheless, the following generalizations can be made, while recognizing that there are many exceptions and unexplained results. As in the discussion of nucleophilicity in general (Sec. 10.G.ii), there are two major factors: the polarizability (hard-soft character) of the nucleophile and solvation effects.

1. The principle of hard and soft acids and bases states that hard acids prefer hard bases and soft acids prefer soft bases (Sec. 8.E.i). In an $\text{S}_{\text{N}}1$ mechanism, the nucleophile attacks a carbocation, which is a hard acid. In an $\text{S}_{\text{N}}2$ mechanism, the nucleophile

⁵¹⁴ For a review, see Erashko, V.I.; Shevelev, S.A.; Fainzil'berg, A.A. *Russ. Chem. Rev.* **1966**, 35, 719.

⁵¹⁵ See Jackman, L.M.; Lange, B.C. *Tetrahedron* **1977**, 33, 2737; Reutov, O.A.; Kurts, A.L. *Russ. Chem. Rev.* **1977**, 46, 1040; Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* **1976**, 15, 321.

⁵¹⁶ See Bégué, J.; Charpentier-Morize, M.; Née, G. *J. Chem. Soc., Chem. Commun.* **1989**, 83.

attacks the carbon atom of a molecule, which is a softer acid. The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom. Therefore, as the character of a given reaction changes from S_N1 to S_N2 like, an ambident nucleophile becomes more likely to attack with its less electronegative atom.⁵¹⁷ Thus, changing from S_N1 to S_N2 conditions should favor C attack by ^-CN , N attack by NO_2^- , C attack by enolate or phenoxide ions, and so on. As an example, primary alkyl halides are attacked (in protic solvents) by the carbon atom of the anion of $CH_3COCH_2CO_2Et$, while α -chloro ethers, which react by the S_N1 mechanism, are attacked by the oxygen atom. However, this does not mean that attack is by the less electronegative atom in all S_N2 reactions and by the more electronegative atom in all S_N1 reactions. The position of attack also depends on the nature of the nucleophile, the solvent, the leaving group, and other conditions. The rule merely states that increasing the S_N2 character of the transition state makes attack by the less electronegative atom more likely.

2. All negatively charged nucleophiles must of course have a positive counterion. If this ion is Ag^+ (or some other ion that specifically helps in removing the leaving group, Sec. 10.G.iv), rather than the more usual Na^+ or K^+ , then the transition state is more S_N1 like. Therefore the use of Ag^+ promotes attack at the more electronegative atom. For example, alkyl halides treated with $NaCN$ generally give mostly RCN , but the use of $AgCN$ increases the yield of isocyanides (RNC).⁵¹⁸
3. In many cases, the solvent influences the position of attack. The freer the nucleophile, the more likely it is to attack with its more electronegative atom, but the more this atom is encumbered by either solvent molecules or positive counterions, the more likely it is to attack by the less electronegative atom. In protic solvents, the more electronegative atom is better solvated by hydrogen bonds than the less electronegative atom. In polar aprotic solvents, neither atom of the nucleophile is greatly solvated, but these solvents are very effective in solvating cations. Thus in a polar aprotic solvent the more electronegative end of the nucleophile is freer from entanglement by both the solvent and the cation, so that a change from a protic to a polar aprotic solvent often increases the extent of attack by the more electronegative atom. An example is attack by sodium β -naphthoxide on benzyl bromide, which resulted in 95% O-alkylation in DMSO and 85% C-alkylation in 2,2,2-trifluoroethanol.⁵¹⁹ Changing the cation from Li^+ to Na^+ to K^+ (in nonpolar solvents) also favors O- over C-alkylation⁵²⁰ for similar reasons (K^+ leaves the nucleophile much freer than Li^+), as does the use of crown ethers, which are good at solvating cations (Sec. 3.C.ii).⁵²¹ Alkylation of the enolate anion of cyclohexanone in the gas phase,

⁵¹⁷ This principle, sometimes called *Kornblum's rule*, was first stated by Kornblum, N.; Smiley, R.A.; Blackwood, R.K.; Iffland, D.C. *J. Am. Chem. Soc.* **1955**, 77, 6269.

⁵¹⁸ See Austad, T.; Songstad, J.; Stangeland, L.J. *Acta Chem. Scand.* **1971**, 25, 2327; Carretero, J.C.; García Ruano, J.L. *Tetrahedron Lett.* **1985**, 26, 3381.

⁵¹⁹ Kornblum, N.; Berrigan, P.J.; le Noble, W.J. *J. Chem. Soc.* **1963**, 85, 1141; Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* **1963**, 85, 1148. For other examples, see le Noble, W.J.; Puerta, J.E. *Tetrahedron Lett.* **1966**, 1087; Schick, H.; Schwarz, H.; Finger, A.; Schwarz, S. *Tetrahedron* **1982**, 38, 1279.

⁵²⁰ Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* **1963**, 85, 1148; Kurts, A.L.; Beletskaya, I.P.; Masias, A.; Reutov, O.A. *Tetrahedron Lett.* **1968**, 3679. See, however, Sarthou, P.; Bram, G.; Guibe, F. *Can. J. Chem.* **1980**, 58, 786.

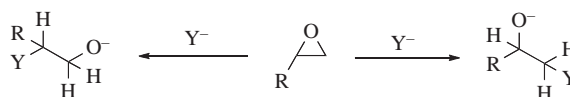
⁵²¹ Smith, S.G.; Hanson, M.P. *J. Org. Chem.* **1971**, 36, 1931; Akabori, S.; Tuji, H. *Bull. Chem. Soc. Jpn.* **1978**, 51, 1197. See also, le Noble, W.J.; Palit, S.K. *Tetrahedron Lett.* **1972**, 493.

where the nucleophile is completely free, showed only O-alkylation and no C-alkylation.⁵²²

4. In extreme cases, steric effects can govern the regioselectivity.⁵²³

10.G.viii. Ambident Substrates

Some substrates (e.g., 1,3-dichlorobutane) can be attacked at two or more positions, and these may be called *ambident substrates*. In the example given, there happen to be two leaving groups in the molecule. Apart from dichlorobutane, and in general, there are two kinds of substrates that are inherently ambident (unless symmetrical). One of these, the allylic type, has already been discussed (Sec. 10.E). The other is the epoxy (or the similar aziridine⁵²⁴ or episulfide) substrate.⁵²⁵ Selectivity for one or the other position is usually called regioselectivity.



Substitution of the free epoxide, which generally occurs under basic or neutral conditions, usually involves an S_N2 mechanism. Since primary substrates undergo S_N2 attack more readily than secondary, unsymmetrical epoxides are attacked in neutral or basic solution at the less highly substituted carbon, and stereospecifically, with inversion at that carbon. Under acidic conditions, it is the protonated epoxide that undergoes the reaction. Under these conditions the mechanism can be either S_N1 or S_N2 . In S_N1 mechanisms, which favor tertiary carbons, attack may be expected to be at the more highly substituted carbon, and this is indeed the case. However, even when protonated epoxides react by what is expected to be an S_N2 mechanism, attack is usually at the more highly substituted position.⁵²⁶ This result probably indicates significant carbocation character at the carbon (ion pairing, for example). Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic or vice versa. In the ring opening of 2,3-epoxy alcohols, the presence of $Ti(OiPr)_4$ increases both the rate and the regioselectivity, favoring attack at C-3 rather than C-2.⁵²⁷ When an epoxide ring is fused to a cyclohexane ring, S_N2 ring opening invariably gives diaxial rather than diequatorial ring opening.⁵²⁸

⁵²² Jones, M.E.; Kass, S.R.; Filley, J.; Barkley, R.M.; Ellison, G.B. *J. Am. Chem. Soc.* **1985**, *107*, 109.

⁵²³ See, for example O'Neill, P.; Hegarty, A.F. *J. Org. Chem.* **1987**, *52*, 2113.

⁵²⁴ Chechik, V.O.; Bobylev, V.A. *Acta Chem. Scand. B*, **1994**, *48*, 837.

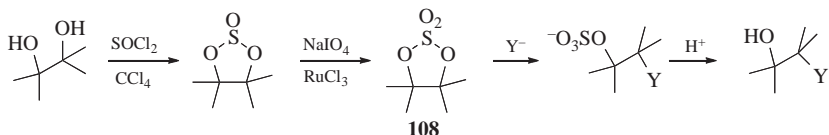
⁵²⁵ Rao, A.S.; Paknikar, S.K.; Kirtane, J.G. *Tetrahedron* **1983**, *39*, 2323; Behrens, C.H.; Sharpless, K.B. *Aldrichimica Acta* **1983**, *16*, 67; Enikolopyan, N.S. *Pure Appl. Chem.* **1976**, *48*, 317; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, **1969**, pp. 206–273.

⁵²⁶ Biggs, J.; Chapman, N.B.; Finch, A.F.; Wray, V. *J. Chem. Soc. B* **1971**, 55.

⁵²⁷ Caron M.; Sharpless, K.B. *J. Org. Chem.* **1985**, *50*, 1557. See also, Chong, J.M.; Sharpless, K.B. *J. Org. Chem.* **1985**, *50*, 1560; Behrens, C.H.; Sharpless, K.B. *J. Org. Chem.* **1985**, *50*, 5696.

⁵²⁸ Murphy, D.K.; Alumbaugh, R.L.; Rickborn, B. *J. Am. Chem. Soc.* **1969**, *91*, 2649. For a method of overriding this preference, see McKittrick, B.A.; Ganem, B. *J. Org. Chem.* **1985**, *50*, 5897.

Cyclic sulfates (**108**), prepared from 1,2-diols, react in the same manner as epoxides, but usually more rapidly.⁵²⁹



10.H. REACTIONS

The reactions in this chapter are classified according to the attacking atom of the nucleophile in the order O, S, N, halogen, H, C. For a given nucleophile, reactions are classified by the substrate and leaving group. For the most part, only alkyl substrates are considered, since acyl substrates are considered in Chapter 16. Nucleophilic substitutions at a sulfur atom are treated at the end.

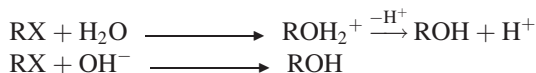
Not all the reactions in this chapter are actually nucleophilic substitutions. In some cases, the mechanisms are not known with enough certainty even to decide whether a nucleophile, an electrophile, or a free radical is attacking. In other cases, conversion of one compound to another can occur by two or even all three of these possibilities, depending on the reagent and reaction conditions. However, one or more of the nucleophilic mechanisms previously discussed do hold for the overwhelming majority of the reactions in this chapter. For the alkylations, the S_N2 is by far the most common mechanism, as long as R is primary or secondary alkyl. For the acylations, the tetrahedral mechanism is the most common.

10.H.i. Oxygen Nucleophiles

A. Attack by OH at an Alkyl Carbon

10-1 Hydrolysis of Alkyl Halides

Hydroxy-de-halogenation



Alkyl halides can be converted to alcohols. Hydroxide ion is usually required, although particularly active substrates (e.g., allylic or benzylic alcohols) can be hydrolyzed by water. Ordinary halides can be hydrolyzed by water,⁵³⁰ if the solvent is HMPA or *N*-methyl-2-pyrrolidinone,⁵³¹ or if the reaction is done in an ionic solvent.⁵³² If the hydrolysis (solvolysis) reaction proceeds via ionization, by an S_N1 type mechanism, this reaction can be performed on tertiary substrates without significant interference from elimination side reactions. Tertiary alkyl α -halocarbonyl compounds can be converted to the corresponding alcohol with silver oxide in aq acetonitrile.⁵³³ The reaction is not frequently used for synthetic purposes, because alkyl halides are usually obtained from alcohols.

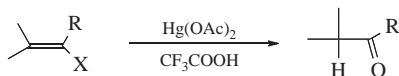
⁵²⁹ Gao, Y.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *110*, 7538; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* **1989**, *30*, 655.

⁵³⁰ See, however, Kurz, J.L.; Lee, J.; Love, M.E.; Rhodes, S. *J. Am. Chem. Soc.* **1986**, *108*, 2960.

⁵³¹ Hutchins, R.O.; Taffer, I.M. *J. Org. Chem.* **1983**, *48*, 1360.

⁵³² Kim, D.W.; Hong, D.J.; Seo, J.W.; Kim, H.S.; Kim, H.K.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* **2004**, *69*, 3186.

⁵³³ Cavicchioni, G. *Synth. Commun.* **1994**, *24*, 2223.

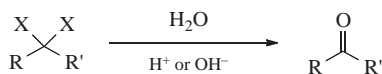


Vinyl halides are unreactive (Sec. 10.F), but they can be hydrolyzed to ketones at room temperature with mercuric trifluoroacetate, or with mercuric acetate in either trifluoroacetic acid or acetic acid containing BF_3 etherate.⁵³⁴ Primary bromides and iodides give alcohols when treated with bis(tributyltin)oxide ($\text{Bu}_3\text{Sn}-\text{O}-\text{SnBu}_3$) in the presence of silver salts.⁵³⁵

OS **II**, 408; **III**, 434; **IV**, 128; **VI**, 142, 1037.

10-2 Hydrolysis of gem-Dihalides

Oxo-de-dihalo-bisubstitution

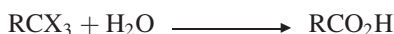


gem-Dihalides can be hydrolyzed using either acid or basic catalysis to give aldehydes or ketones.⁵³⁶ Formally, the reaction may be regarded as giving $\text{R}-\text{C}(\text{OH})\text{XR}'$, which is unstable and loses HX to give the carbonyl compound. For aldehydes derived from RCHX_2 , strong bases cannot be used, because the product undergoes the *aldol reaction* (**16-34**) or the *Cannizzaro reaction* (**19-81**). A mixture of calcium carbonate and sodium acetate is effective,⁵³⁷ and heating to 100°C in DMSO gives good yields.⁵³⁸ A simple method heats a *gem*-dibromide with pyridine, and subsequent treatment with water gives the aldehyde.⁵³⁹ Heating 1,1-dihaloalkenes ($\text{C}=\text{CX}_2$) with zinc and water leads to the corresponding methyl ketone.⁵⁴⁰

OS **I**, 95; **II**, 89, 133, 244, 549; **III**, 538, 788; **IV**, 110, 423, 807. Also see, OS **III**, 737.

10-3 Hydrolysis of 1,1,1-Trihalides

Hydroxy,oxo-de-trihalo-tersubstitution



This reaction is similar to **10-2**. The utility of the method is limited by the lack of availability of trihalides, although these compounds can be prepared by addition of CCl_4 and similar compounds to double bonds (Reaction **15-38**) and by the free radical halogenation of methyl groups on aromatic rings (Reaction **14-1**). When the reaction is carried out in the presence of an alcohol, a carboxylic ester can be obtained directly.⁵⁴¹ 1,1-Dichloroalkenes

⁵³⁴ Martin, S.F.; Chou, T. *Tetrahedron Lett.* **1978**, 1943; Yoshioka, H.; Takasaki, K.; Kobayashi, M.; Matsumoto, T. *Tetrahedron Lett.* **1979**, 3489.

⁵³⁵ Gingras, M.; Chan, T.H. *Tetrahedron Lett.* **1989**, 30, 279.

⁵³⁶ Salomaa, P. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 177–210.

⁵³⁷ Mataka, S.; Liu, G.-B.; Sawada, T.; Tori-i, A.; Tashiro, M. *J. Chem. Res. (S)* **1995**, 410.

⁵³⁸ Li, W.; Li, J.; DeVincentis, D.; Masour, T.S. *Tetrahedron Lett.* **2004**, 45, 1071.

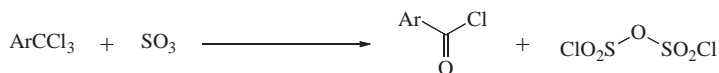
⁵³⁹ Augustine, J.K.; Naik, Y.A.; Mandal, A.B.; Chowdappa, N.; Praveen, V.B. *Tetrahedron* **2008**, 64, 688.

⁵⁴⁰ Wang, L.; Li, P.; Yan, J.; Wu, Z. *Tetrahedron Lett.* **2003**, 44, 4685.

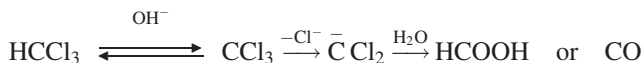
⁵⁴¹ See, for example, Le Fave, G.M.; Scheurer, P.G. *J. Am. Chem. Soc.* **1950**, 72, 2464.

can also be hydrolyzed to carboxylic acids, by treatment with aq H_2SO_4 . In general 1,1,1-trifluorides do not undergo this reaction,⁵⁴² although exceptions are known.⁵⁴³

Aryl 1,1,1-trihalomethanes can be converted to acyl halides by treatment with sulfur trioxide.⁵⁴⁴ Hydrolysis of the acid chloride gives the carboxylic acid (Reaction 16-57).



Chloroform is more rapidly hydrolyzed with base than dichloromethane or carbon tetrachloride and gives not only formic acid, but also carbon monoxide.⁵⁴⁵ Hine⁵⁴⁶ showed that the mechanism of chloroform hydrolysis is quite different from that of dichloromethane or carbon tetrachloride, although superficially the three reactions appear similar. The first step is the loss of a proton to give CCl_3^- , which then loses Cl^- to give dichlorocarbene (CCl_2), which is hydrolyzed to formic acid or carbon monoxide.

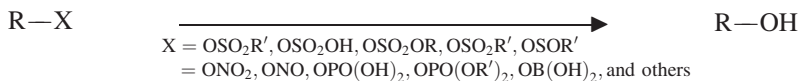


This is an example of an $\text{S}_{\text{N}}1\text{CB}$ mechanism (Sec. 10.G.iii, category 1). The other two compounds react by the normal mechanisms. Carbon tetrachloride cannot give up a proton and dichloromethane is not acidic enough.

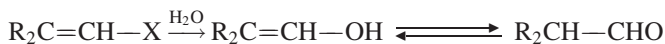
OS III, 270; V, 93. Also see, OS I, 327.

10-4 Hydrolysis of Alkyl Esters of Inorganic Acids

Hydroxy-de-sulfonyloxy-substitution, and so on



Esters of inorganic acids, including those given above and others, can be hydrolyzed to alcohols. The reactions are most successful when the ester is that of a strong acid, but it can be done for esters of weaker acids by the use of hydroxide ion (a more powerful nucleophile) or acidic conditions (which make the leaving group come off more easily). When vinylic substrates are hydrolyzed, the products are enols, which tautomerize to aldehydes or ketones (Sec. 2.N), as shown.



These reactions are all considered at one place because they are formally similar. Although some of them involve $\text{R}-\text{O}$ cleavage and are thus nucleophilic substitutions at

⁵⁴² Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, **1969**, pp. 410–411; Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, **1976**, pp. 273–274.

⁵⁴³ See, for example, Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* **1978**, *11*, 197.

⁵⁴⁴ Rondestvedt, Jr., C.S. *J. Org. Chem.* **1976**, *41*, 3569, 3574, 3576. For another method, see Nakano, T.; Ohkawa, K.; Matsumoto, H.; Nagai, Y. *J. Chem. Soc., Chem. Commun.* **1977**, 808.

⁵⁴⁵ See Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, **1971**, pp. 129–141.

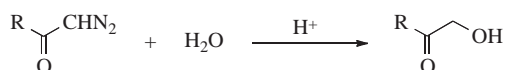
⁵⁴⁶ Hine, J. *J. Am. Chem. Soc.* **1950**, *72*, 2438. Also see, le Noble, W.J. *J. Am. Chem. Soc.* **1965**, *87*, 2434.

a saturated carbon, others involve cleavage of the bond between the inorganic atom and oxygen and are thus nucleophilic substitutions at a sulfur, nitrogen, and so on. It is even possible for the same ester to be cleaved at either position, depending on the conditions. Thus benzhydryl *p*-toluenesulfate ($\text{Ph}_2\text{CHOSOC}_6\text{H}_4\text{CH}_3$) was found to undergo C—O cleavage in HClO_4 solutions and S—O cleavage in alkaline media.⁵⁴⁷ In general, the weaker the corresponding acid, the less likely is C—O cleavage. Thus, sulfonic acid esters ($\text{ROSO}_2\text{R}'$) generally give C—O cleavage,⁵⁴⁸ while nitrous acid esters (RONO) usually give N—O cleavage.⁵⁴⁹ Esters of sulfonic acids that are frequently hydrolyzed are mentioned in Section 10.G.iii. For hydrolysis of sulfonic acid esters (see also, Reaction 16-100).

OS VI, 852. See also, VIII, 50.

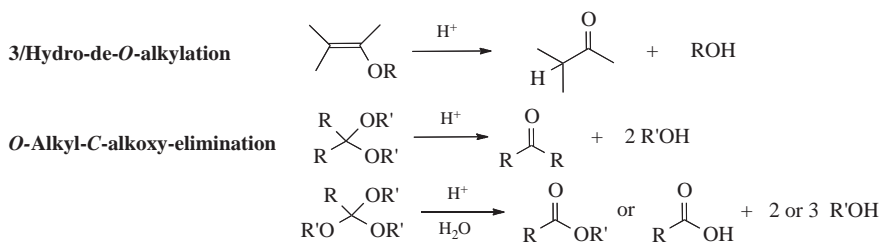
10-5 Hydrolysis of Diazoketones

Hydro, hydroxy-de-diazo-bisubstitution



Diazoketones are relatively easy to prepare (see Reaction 16-89). When treated with acid, they add a proton to give α -keto diazonium salts, which are hydrolyzed to the alcohols by the $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism.⁵⁵⁰ Relatively good yields of α -hydroxy ketones can be prepared in this way, since the diazonium ion is somewhat stabilized by the presence of the carbonyl group, which discourages N_2 from leaving because that would result in an unstable α -carbonyl carbocation.

10-6 Hydrolysis of Acetals, Enol Ethers, and Similar Compounds⁵⁵¹



The alkoxyl group (OR) is not a leaving group in these reactions, so these compounds must be converted to the conjugate acids before they can be hydrolyzed. Although 100% sulfuric acid and other concentrated strong acids readily cleave simple ethers,⁵⁵² the only

⁵⁴⁷ Batts, B.D. *J. Chem. Soc. B* **1966**, 551.

⁵⁴⁸ Barnard, P.W.C.; Robertson, R.E. *Can. J. Chem.* **1961**, 39, 881. See also, Drabicky, M.J.; Myhre, P.C.; Reich, C.J.; Schmittou, E.R. *J. Org. Chem.* **1976**, 41, 1472.

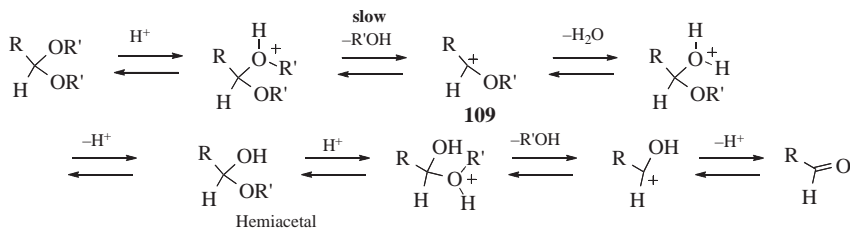
⁵⁴⁹ See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, **1988**, pp. 162–163.

⁵⁵⁰ Dahn, H.; Gold, H. *Helv. Chim. Acta* **1963**, 46, 983; Thomas, C.W.; Leveson, L.L. *Int. J. Chem. Kinet.* **1983**, 15, 25. See Smith, III, A.B.; Dieter, R.K. *Tetrahedron* **1981**, 37, 2407.

⁵⁵¹ Bergstrom, R.G. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, **1980**, pp. 881–902; Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups, Supplement A*, pt. 1, Wiley, NY, **1977**, pp. 149–329; Cordes, E.H.; Bull, H.G. *Chem. Rev.* **1974**, 74, 581; Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* **1987**, 16, 75 (ortho esters); DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, **1970**, pp. 134–146 (ortho esters); Rekasheva, A.F. *Russ. Chem. Rev.* **1968**, 37, 1009 (enol ethers).

⁵⁵² Jaques, D.; Leisten, J.A. *J. Chem. Soc.* **1964**, 2683. See also, Olah, G.A.; O'Brien, D.H. *J. Am. Chem. Soc.* **1967**, 89, 1725.

acids used preparatively for this purpose are HBr and HI (Reaction 10-49). However, acetals, ketals, and ortho esters⁵⁵³ are easily cleaved by dilute acids. These compounds are hydrolyzed with greater facility because carbocations of type $R_2(RO)C^+$ are greatly stabilized by resonance (Sec. 5.A.ii). The reactions therefore proceed by the S_N1 mechanism,⁵⁵⁴ as shown for acetals:⁵⁵⁵



This mechanism, which is an S_N1 or $A1$ mechanism, is the reverse of that for acetal formation by reaction of an aldehyde and an alcohol (Reaction 16-5). Among the facts supporting the mechanism are⁵⁵⁶ (1) The reaction proceeds with *specific* H_3O^+ catalysis (see Sec. 8.D). (2) It is faster in D_2O . (3) Optically active ROH are not racemized. (4) Even with *tert*-butyl alcohol the R—O bond does not cleave, as shown by ^{18}O labeling.⁵⁵⁷ (5) In the case of acetophenone ketals, the intermediate corresponding to **109** [$\text{ArCMe}(\text{OR})_2$] could be trapped with sulfite ions (SO_3^{2-}).⁵⁵⁸ (6) Trapping of this ion did not affect the hydrolysis rate,⁵⁵⁸ so the rate-determining step must come earlier. (7) In the case of 1,1-dialkoxyalkanes, intermediates corresponding to **109** were isolated as stable ions in superacid solution at -75°C , where their spectra could be studied.⁵⁵⁹ (8) Hydrolysis rates greatly increase in the order $\text{CH}_2(\text{OR}')_2 < \text{RCH}(\text{OR}')_2 < \text{R}_2\text{C}(\text{OR}')_2 < \text{RC}(\text{OR}')_3$, as would be expected for a carbocation intermediate.⁵⁶⁰ Formation of **109** is usually the rate-determining step (as marked above), but there is evidence that at least in some cases this step is fast, and the rate-determining step is loss of R'OH from the protonated hemiacetal.⁵⁶¹ Rate-determining addition of water to **109** has also been reported.⁵⁶²

While the $A1$ mechanism shown above operates in most acetal hydrolyses, it has been shown that at least two other mechanisms can take place with suitable substrates.⁵⁶³ In one of these mechanisms, the second and third of the above steps are concerted, so that the

⁵⁵³ See Pavlova, L.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* **1986**, 55, 1026.

⁵⁵⁴ See Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* **1990**, 19, 55.

⁵⁵⁵ Kreevoy, M.M.; Taft, R.W. *J. Am. Chem. Soc.* **1955**, 77, 3146, 5590.

⁵⁵⁶ For a discussion of these, and of other evidence, see Cordes, E.H. *Prog. Phys. Org. Chem.* **1967**, 4, 1.

⁵⁵⁷ Cawley, J.J.; Westheimer, F.H. *Chem. Ind. (London)* **1960**, 656.

⁵⁵⁸ Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* **1977**, 99, 8238. See also, Jencks, W.P. *Acc. Chem. Res.* **1980**, 13, 161; Young, P.R.; Bogseth, R.C.; Rietz, E.G. *J. Am. Chem. Soc.* **1980**, 102, 6268. However, see Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* **1988**, 110, 3677.

⁵⁵⁹ See White, A.M.; Olah, G.A. *J. Am. Chem. Soc.* **1969**, 91, 2943; Akhmatdinov, R.T.; Kantor, E.A.; Imashev, U.B.; Yasman, Ya.B.; Rakhmankulov, D.L. *J. Org. Chem. USSR* **1981**, 17, 626.

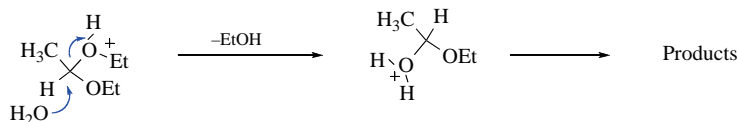
⁵⁶⁰ See Belarmino, A.T.N.; Froehner, S.; Zanette, D.; Farah, J.P.S.; Bunton, C.A.; Romsted, L.S. *J. Org. Chem.* **2003**, 68, 706.

⁵⁶¹ Fife, T.H.; Natarajan, R. *J. Am. Chem. Soc.* **1986**, 108, 2425, 8050; McClelland, R.A.; Sørensen, P.E. *Acta Chem. Scand.* **1990**, 44, 1082.

⁵⁶² Fife, T.H.; Natarajan, R. *J. Am. Chem. Soc.* **1986**, 108, 2425, 8050.

⁵⁶³ See Fife, T.H. *Acc. Chem. Res.* **1972**, 5, 264; Wann, S.R.; Kreevoy, M.M. *J. Org. Chem.* **1981**, 46, 419.

mechanism is S_N2cA (or $A2$). This has been shown, for example, in the hydrolysis of 1,1-diethoxyethane, by isotope effect studies:⁵⁶⁴



In the second mechanism, the first and second steps are concerted. In the case of hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran, *general* acid catalysis was shown⁵⁶⁵ demonstrating that the substrate is protonated in the rate-determining step (Sec. 8.D). Reactions in which a substrate is protonated in the rate-determining step are called $A-S_E2$ reactions.⁵⁶⁶ However, if protonation of the substrate were all that happens in the slow step, then the proton in the transition state would be expected to lie closer to the weaker base (Sec. 8.D). Because the substrate is a much weaker base than water, the proton should be largely transferred. Since the Brønsted coefficient was found to be 0.5, the proton was actually transferred only about halfway. This can be explained if the basicity of the substrate is increased by partial breaking of the C—O bond. The conclusion drawn is that steps 1 and 2 are concerted. The hydrolysis of ortho esters in most cases is also subject to general acid catalysis.⁵⁶⁷

The hydrolysis of acetals and ortho esters is governed by the stereoelectronic control factor discussed in Section 16.A.i, category 4,⁵⁶⁸ although the effect can generally be seen only in systems where conformational mobility is limited, especially in cyclic systems. There is evidence for synplanar stereoselection in the acid hydrolysis of acetals.⁵⁶⁹ The mechanism of Lewis acid mediated cleavage of chiral acetals is also known.⁵⁷⁰

Convenient reagents for the hydrolysis of acetals are wet silica gel⁵⁷¹ and Amberlyst-15 (a sulfonic acid based polystyrene cation exchange resin).⁵⁷² Both cyclic and acyclic acetals and ketals can be converted to aldehydes or ketones under nonaqueous conditions by treatment with TESOTf-2,6-lutidine (or 2,4,6-collidine) in dichloromethane followed by treatment with water,⁵⁷³ with Lewis acids e.g., 0.8% $\text{In}(\text{OTf})_3$ in acetone,⁵⁷⁴ ceric ammonium nitrate in aq acetonitrile,⁵⁷⁵ or $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$.⁵⁷⁶

⁵⁶⁴ Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* **1984**, *106*, 7140. See also, Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* **1989**, *111*, 7888, 7900.

⁵⁶⁵ Fife, T.H.; Brod, L.H. *J. Am. Chem. Soc.* **1970**, *92*, 1681; Jensen, J.L.; Herold, L.R.; Lenz, P.A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* **1979**, *101*, 4672.

⁵⁶⁶ See Williams Jr., J.M.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* **1968**, *6*, 63.

⁵⁶⁷ Chiang, Y.; Kresge, A.J.; Lahti, M.O.; Weeks, D.P. *J. Am. Chem. Soc.* **1983**, *105*, 6852 and references cited therein; Fife, T.H.; Przystas, T.J. *J. Chem. Soc. Perkin Trans. 2* **1987**, 143.

⁵⁶⁸ See, for example, Kirby, A.J. *Acc. Chem. Res.* **1984**, *17*, 305; Bouab, O.; Lamaty, G.; Moreau, C. *Can. J. Chem.* **1985**, *63*, 816. See, however, Ratcliffe, A.J.; Mootoo, D.R.; Andrews, C.W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 7661.

⁵⁶⁹ Li, S.; Kirby, A.J.; Deslongchamps, P. *Tetrahedron Lett.* **1993**, *34*, 7757.

⁵⁷⁰ Sammakia, T.; Smith, R.S. *J. Org. Chem.* **1992**, *57*, 2997.

⁵⁷¹ Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J.M. *Synthesis* **1978**, 63. See Caballero, G.M.; Gros, E.G. *Synth. Commun.* **1995**, *25*, 395.

⁵⁷² Coppola, G.M. *Synthesis* **1984**, 1021.

⁵⁷³ Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930.

⁵⁷⁴ Gregg, B.T.; Golden, K.C.; Quinn, J.F. *J. Org. Chem.* **2007**, *72*, 5890.

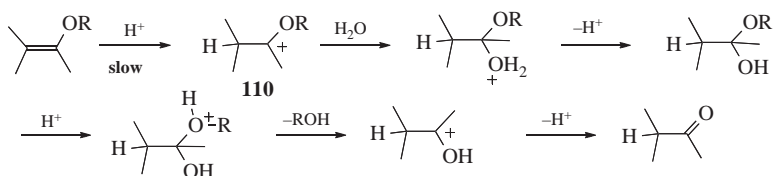
⁵⁷⁵ Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.M.; Quesnel, Y.; Markó, I.E. *Tetrahedron Lett.* **1999**, *40*, 1799.

⁵⁷⁶ Carrigan, M.D.; Sarapa, D.; Smith, R.C.; Wieland, L.C.; Mohan, R.S. *J. Org. Chem.* **2002**, *67*, 1027.

Although acetals, ketals, and ortho esters are easily hydrolyzed by acids, they are extremely resistant to hydrolysis by bases. An aldehyde or ketone can therefore be protected from attack by a base by conversion to the acetal or ketal (Reaction 16-5), and then can be cleaved with acid. Pyridine–HF has also been used for this conversion.⁵⁷⁷

Thioacetals, thioketals, *gem*-diamines, and other compounds that contain any two of the groups OR, OCOR, NR₂, NHCOR, SR, and halogen on the same carbon can also be hydrolyzed to aldehydes or ketones, in most cases, by acid treatment. Thioacetals [RCH(SR')₂] and thioketals [R₂C(SR')₂] are among those compounds generally resistant to acid hydrolysis.⁵⁷⁸ Because conversion to these compounds (Reaction 16-11) serves as an important method for protection of aldehydes and ketones, many methods have been devised to cleave them to the parent carbonyl compounds. Among reagents⁵⁷⁹ used for this purpose are HgCl₂,⁵⁸⁰ FeCl₂•6 H₂O,⁵⁸¹ cetyltrimethylammonium tribromide in dichloromethane,⁵⁸² *m*-chloroperoxybenzoic acid, the *Dess–Martin periodinane*⁵⁸³ (see Reaction 19-03), and sodium nitrite in aqueous acetyl chloride.⁵⁸⁴ Mixed acetals and ketals (RO—C—SR) can be hydrolyzed with most of the reagents mentioned above, including *N*-bromosuccinimide (NBS) in aq acetone,⁵⁸⁵ and glyoxylic acid on Amberlyst-15 with microwave irradiation.⁵⁸⁶

Enol ethers (vinyl ethers) are readily hydrolyzed by acids; the rate-determining step is protonation of the substrate.⁵⁸⁷ However, protonation does not take place at the oxygen, but at the β carbon,⁵⁸⁸ because that gives rise to the stable carbocation (110).⁵⁸⁹ After that, the mechanism is similar to the A1 mechanism given above for the hydrolysis of acetals.



Among the facts supporting this mechanism, which is an A-S_E2 mechanism because the substrate is protonated in the rate-determining step, are (1) the ¹⁸O labeling shows that in ROCH=CH₂ it is the vinyl–oxygen bond and not the RO bond that cleaves;⁵⁹⁰ (2) the

⁵⁷⁷ Watanabe, Y.; Kiyosawa, Y.; Tatsukawa, A.; Hayashi, M. *Tetrahedron Lett.* **2001**, 42, 4641.

⁵⁷⁸ Ali, M.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* **1992**, 219; **1993**, 1825; Ali, M.; Satchell, D.P.N.; Le, V.T. *J. Chem. Soc. Perkin Trans. 2* **1993**, 917.

⁵⁷⁹ See Gröbel, B.; Seebach, D. *Synthesis* **1977**, 357, see pp. 359–367; Cussans, N.J.; Ley, S.V.; Barton, D.H.R. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1654.

⁵⁸⁰ Corey, E.J.; Erickson, B.W. *J. Org. Chem.* **1971**, 36, 3553; Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* **1987**, 513.

⁵⁸¹ Kamal, A.; Laxman, E.; Reddy, P.S.M.M. *Synlett* **2000**, 1476.

⁵⁸² Mondal, E.; Bose, G.; Khan, A.T. *Synlett* **2001**, 785.

⁵⁸³ Langille, N.F.; Dakin, L.A.; Panek, J.S. *Org. Lett.* **2003**, 5, 575. See also, Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, 30, 287.

⁵⁸⁴ Khan, A.T.; Mondal, E.; Sahu, P.R. *Synlett* **2003**, 377.

⁵⁸⁵ Karimi, B.; Seradj, H.; Tabaei, M.H. *Synlett* **2000**, 1798.

⁵⁸⁶ Chavan, S.P.; Soni, P.; Kamat, S.K. *Synlett* **2001**, 1251.

⁵⁸⁷ Jones, J.; Kresge, A.J. *Can. J. Chem.* **1993**, 71, 38.

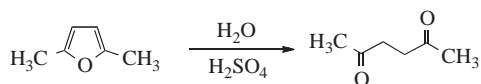
⁵⁸⁸ See Burt, R.A.; Chiang, Y.; Kresge, A.J.; Szilagyi, S. *Can. J. Chem.* **1984**, 62, 74.

⁵⁸⁹ See Chwang, W.K.; Kresge, A.J.; Wiseman, J.R. *J. Am. Chem. Soc.* **1979**, 101, 6972.

⁵⁹⁰ Kiprianova, L.A.; Rekasheva, A.F. *Dokl. Akad. Nauk SSSR*, **1962**, 142, 589.

reaction is subject to general acid catalysis;⁵⁹¹ (3) there is a solvent isotope effect when D₂O is used.⁵⁹¹ A method has been developed to determine primary kinetic isotope effects relating to proton transfer in the hydrolysis of enol ethers.⁵⁹² Enantioselective protonation is possible in some cases. Cyclic silyl enol ethers are converted to chiral α -substituted ketones, for example, with high enantioselectivity using a chiral Brønsted acid.⁵⁹³

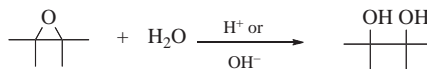
Enamines are also hydrolyzed by acids (see Reaction 16-2); the mechanism is similar. Ketene dithioacetals [R₂C=C(SR')₂] also hydrolyze by a similar mechanism, except that the initial protonation step is partially reversible.⁵⁹⁴ Furans represent a special case of enol ethers that are cleaved by acid to give 1,4-diones.⁵⁹⁵ Thus oxonium ions are cleaved by water to give an alcohol and an ether:



OS I, 67, 205; II, 302, 305, 323; III, 37, 127, 465, 470, 536, 541, 641, 701, 731, 800; IV, 302, 499, 660, 816, 903; V, 91, 292, 294, 703, 716, 937, 967, 1088; VI, 64, 109, 312, 316, 361, 448, 496, 683, 869, 893, 905, 996; VII, 12, 162, 241, 249, 251, 263, 271, 287, 381, 495; VIII, 19, 155, 241, 353, 373

10-7 Hydrolysis of Epoxides

(3) *OC-seco*-hydroxy-de-alkoxy substitution



The hydrolysis of epoxides is a convenient method for the preparation of *vic*-diols. The reaction is catalyzed by acids or bases. A basic reagent will attack the polarized carbon of the epoxide unit to open the ring, whereas an acid-catalyzed reaction leads to a protonated epoxide (an oxonium ion),⁵⁹⁶ which is opened by nucleophilic attack at an adjacent carbon. Among acid catalysts, perchloric acid leads to minimal side reactions,⁵⁹⁷ and 10% Bu₄NHSO₄ in water is effective.⁵⁹⁸ However, water reacts directly with epoxides at 60 °C.⁵⁹⁹ Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.⁶⁰⁰

Cobalt salen [salen = bis(salicylidene)ethylenediamine] catalysts, in the presence of water, open epoxides with high stereoselectivity.⁶⁰¹ The enzyme *epoxide hydrolase* opens epoxides with high enantioselectivity.⁶⁰²

OS V, 414.

⁵⁹¹ Fife, T.H. *J. Am. Chem. Soc.* **1965**, 87, 1084; Kresge, A.J.; Yin, Y. *Can. J. Chem.* **1987**, 65, 1753.

⁵⁹² Tsang, W.-Y.; Richard, J.P. *J. Am. Chem. Soc.* **2007**, 129, 10330.

⁵⁹³ Cheon, C.H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, 130, 9246. For a different example, see Nakashima, D.; Yamamoto, H. *Synlett* **2006**, 150.

⁵⁹⁴ For a review, see Okuyama, T. *Acc. Chem. Res.* **1986**, 19, 370.

⁵⁹⁵ See Finlay, J.; McKervey, M.A.; Gunaratne, H.Q.N. *Tetrahedron Lett.* **1998**, 39, 5651.

⁵⁹⁶ For a density functional analysis of this ion, see Zhao, Y.; Truhlar, D.G. *J. Org. Chem.* **2007**, 72, 295.

⁵⁹⁷ Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1, Wiley, NY, **1967**, p. 796.

⁵⁹⁸ Fan, R.-H.; Hou, X.-L. *Org. Biomol. Chem.* **2003**, 1, 1565. For a reaction with NaHSO₄, see Cavdar, H.; Saracoglu, N. *Tetrahedron* **2009**, 65, 985.

⁵⁹⁹ Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, 73, 2270.

⁶⁰⁰ Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron Lett.* **1965**, 3421.

⁶⁰¹ Ready, J.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2001**, 123, 2687.

⁶⁰² See Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D.S.; Zhu, Z.; Milan, A.; Robertson, D.E.; Weiner, D.P.; Burk, M. J. *J. Am. Chem. Soc.* **2004**, 126, 11156.

10.H.ii Attack by OR at an Alkyl Carbon

10-8 Alkylation with Alkyl Halides: The Williamson Reaction

Alkoxy-de-halogenation



The *Williamson reaction* (*Williamson ether synthesis*), discovered in 1850, is still the best general method for the preparation of unsymmetrical or symmetrical ethers.⁶⁰³ The reaction can also be carried out with aromatic R', although C-alkylation is sometimes a side reaction (see Sec. 10.G.vii).⁶⁰⁴ The normal method involves treatment of a primary or secondary alkyl halide with alkoxide or aroxide ion prepared from an alcohol or phenol by reaction with a suitable base, although methylation using dimethyl carbonate has been reported.⁶⁰⁵ The solvent is usually an aprotic solvent (THF, ether, etc.) rather than an alcohol solvent, which typically promotes elimination reactions in the presence of alkoxides (see Chap. 17). It is also possible to mix the halide and alcohol or phenol directly with Cs₂CO₃ in acetonitrile,⁶⁰⁶ or with NaH in the presence of DMF.⁶⁰⁷ The reaction can also be carried out in a dry medium,⁶⁰⁸ neat,⁶⁰⁹ or in solvents using microwave irradiation.⁶¹⁰ Williamson ether synthesis in ionic liquids has also been reported.⁶¹¹ The reaction is *not* successful for tertiary R (elimination predominates), and low yields are often obtained with secondary R. Monoethers can be formed from diols and alkyl halides.⁶¹² It is possible to selectively alkylate the primary hydroxyl in a diol [HOCH₂CH(OH)R] using a tin complex.⁶¹³

Many other functional groups can be present in the molecule without interference. Ethers with one tertiary group *can* be prepared by treatment of an alkyl halide or sulfate ester (Reaction 10-10) with a tertiary alkoxide (R'O⁻). Di-*tert*-butylether was prepared in high yield by direct attack by *t*-BuOH on reaction with the *tert*-butyl cation (at -80 °C in SO₂ClF).⁶¹⁴ Di-*tert*-alkyl ethers in general have proved difficult to make, but they can be prepared in low-to-moderate yields by treatment of a tertiary halide with Ag₂CO₃ or Ag₂O.⁶¹⁵ Alcohols react with Mg(ClO₄)₂ and an excess of Boc (Boc = *t*-butoxycarbonyl) anhydride (Boc₂O) to give the *tert*-butyl ether.⁶¹⁶

⁶⁰³ See Feuer, H.; Hooz, J. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, **1967**, pp. 446–450, 460–468.

⁶⁰⁴ For a list of reagents used to convert alcohols and phenols to ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 890–893.

⁶⁰⁵ Ouk, S.; Thiebaud, S.; Borredon, E.; Legars, P.; Lecomte, L. *Tetrahedron Lett.* **2002**, 43, 2661.

⁶⁰⁶ Lee, J.C.; Yuk, J.Y.; Cho, S.H. *Synth. Commun.* **1995**, 25, 1367.

⁶⁰⁷ Jin, C.H.; Lee, H.Y.; Lee, S.H.; Kim, I.S.; Jung, Y.H. *Synlett* **2007**, 2695.

⁶⁰⁸ Bogdal, D.; Pielichowski, J.; Jaskot, K. *Org. Prep. Proceed. Int.* **1998**, 30, 427.

⁶⁰⁹ Yuncheng, Y.; Yulin, J.; Jun, P.; Xiaohui, Z.; Conggui, Y. *Gazz. Chim. Ital.* **1993**, 123, 519.

⁶¹⁰ Paul, S.; Gupta, M. *Tetrahedron Lett.* **2004**, 45, 8825.

⁶¹¹ Xu, Z.Y.; Xu, D.Q.; Liu, B.Y. *Org. Prep. Proceed. Int.* **2004**, 36, 156. Also see More, S.V.; Ardhapure, S.S.;

Naik, N.H.; Bhusare, S.R.; Jadhav, W.N.; Pawar, R.P. *Synth. Commun.* **2005**, 35, 3113.

⁶¹² See Jha, S.C.; Joshi, N.N. *J. Org. Chem.* **2002**, 67, 3897.

⁶¹³ Boons, G.-J.; Castle, G.H.; Clase, J.A.; Grice, P.; Ley, S.V.; Pinel, C. *Synlett*, **1993**, 913.

⁶¹⁴ Olah, G.A.; Halpern, Y.; Lin, H.C. *Synthesis* **1975**, 315. Also see Masada, H.; Yonemitsu, T.; Hirota, K. *Tetrahedron Lett.* **1979**, 1315.

⁶¹⁵ Masada, H.; Sakajiri, T. *Bull. Chem. Soc. Jpn.* **1978**, 51, 866.

⁶¹⁶ Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, 7, 427.

Active halides (e.g., Ar_3CX) may react directly with the alcohol.⁶¹⁷ Hindered alcohols may react as well.⁶¹⁸ The mechanism for these cases is of course $\text{S}_{\text{N}}1$. *tert*-Butyl halides can be converted to aryl *tert*-butyl ethers by treatment with phenols and an amine (e.g., pyridine).⁶¹⁹ Aryl alkyl ethers can be prepared from alkyl halides by treatment with an aryl acetate (instead of a phenol) in the presence of K_2CO_3 and a crown ether.⁶²⁰ The Pd-catalyzed displacement of allylic acetates with aliphatic alcohols has been shown to give the corresponding alkyl allyl ether.⁶²¹ A Rh-catalyst⁶²² Ir catalyst,⁶²³ and an In-Si combined Lewis acid catalyst⁶²⁴ have been used in ether forming reactions. Aryl ethers have been prepared using *Mitsunobu conditions* (see Reaction 10-17).⁶²⁵

Vinyl ethers have been formed by coupling tetravinyl tin with phenols, in the presence of cupric acetate and oxygen.⁶²⁶ The Pd-catalyzed coupling of vinyl triflates and phenols has also been reported.⁶²⁷

Both aryl alkyl and dialkyl ethers can be efficiently prepared with the use of phase-transfer catalysis (Sec. 10.G.v)⁶²⁸ and with micellar catalysis.⁶²⁹ Symmetrical benzylic ethers have been prepared by reaction of benzylic alcohols with Mg/I_2 followed by triflic anhydride.⁶³⁰

A slight variation of the *Williamson ether synthesis* has been used for the protection of hydroxy groups⁶³¹ by reaction of their salts with chloromethyl methyl ether.



This protecting group is known as MOM (methoxymethyl) and such compounds are called MOM ethers. The resulting acetals are stable to bases and are easily cleaved with mild acid treatment (Reaction 10-7). Another protecting group, the 2-methoxyethoxymethyl group (the MEM group), is formed in a similar manner. Both MOM and MEM groups can be cleaved with dialkyl- and diarylboron halides (e.g., Me_2BBr).⁶³²

⁶¹⁷ See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, pp. 454–466. Also see Biordi, J.; Moelwyn-Hughes, E.A. *J. Chem. Soc.* **1962**, 4291.

⁶¹⁸ Aspinal, H.C.; Greeves, N.; Lee, W.-M.; McIver, E.G.; Smith, P.M. *Tetrahedron Lett.* **1997**, 38, 4679.

⁶¹⁹ Masada, H.; Oishi, Y. *Chem. Lett.* **1978**, 57; Camps, F.; Coll, J.; Moretó, J.M. *Synthesis* **1982**, 186.

⁶²⁰ Banerjee, S.K.; Gupta, B.D.; Singh, K. *J. Chem. Soc., Chem. Commun.* **1982**, 815.

⁶²¹ Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, 69, 3474; Haight, A.R.; Stoner, E.J.; Peterson, M.J.; Grover, V.K. *J. Org. Chem.* **2003**, 68, 8092.

⁶²² Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* **2002**, 124, 7882.

⁶²³ Ueno, S.; Hartwig, J.F. *Angew. Chem. Int. Ed.* **2008**, 47, 1928.

⁶²⁴ Saito, T.; Yasuda, M.; Baba, A. *Synlett* **2005**, 1737.

⁶²⁵ Lepore, S.D.; He, Y. *J. Org. Chem.* **2003**, 68, 8261.

⁶²⁶ Blouin, M.; Frenette, R. *J. Org. Chem.* **2001**, 66, 9043.

⁶²⁷ Willis, M.C.; Taylor, D.; Gillmore, A.T. *Chem. Commun.* **2003**, 2222.

⁶²⁸ Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Springer, NY, **1978**, pp. 128–138; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, **1977**, pp. 73–84. See also, Eynde, J.J.V.; Maillieux, I. *Synth. Commun.* **2001**, 31, 1; de la Zerda, J.; Barak, G.; Sasson, Y. *Tetrahedron* **1989**, 45, 1533.

⁶²⁹ Jursic, B. *Tetrahedron* **1988**, 44, 6677.

⁶³⁰ Nishiyama, T.; Kameyama, H.; Maekawa, H.; Watanuki, K. *Can. J. Chem.* **1999**, 77, 258.

⁶³¹ See Greene, T.W. *Protective Groups in Organic Synthesis* Wiley, New York, **1980**; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis* 2nd ed., Wiley, New York, **1991**; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis* 3rd ed., Wiley, New York, **1999**; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis* 4th ed., Wiley, New Jersey, **2006**.

⁶³² Guindon, Y.; Yoakim, C.; Morton, H.E. *J. Org. Chem.* **1984**, 49, 3912. For other methods, see Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, 25, 2515; Rigby, J.H.; Wilson, J.Z. *Tetrahedron Lett.* **1984**, 25, 1429.

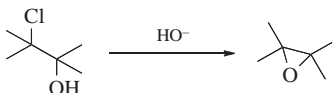
Another common method for the protection of alcohols is conversion to the silyl ether ($R-O-SiR'_3$). The alcohol is generally treated with a base (e.g., trimethylamine or imidazole) and then with a chlorotrialkylsilane (R_3SiCl), or the analogous bromide.⁶²⁹ There are many variations of this basic procedure. Iodine promotes the reaction, for example.⁶³³ There are also many ways to remove the silyl group to regenerate the alcohol, although fluoride ion, including tetrabutylammonium fluoride in THF, is probably the most common method.⁶²⁹

Most Williamson reactions proceed by the S_N2 mechanism, but there is evidence (see Sec. 10.C) that in some cases the SET mechanism can take place, especially with alkyl iodides.⁶³⁴ Secondary alcohols have been converted to the corresponding methyl ether by reaction with methanol in the presence of ferric nitrate nonahydrate.⁶³⁵

OS **I**, 75, 205, 258, 296, 435; **II**, 260; **III**, 127, 140, 209, 418, 432, 544; **IV**, 427, 457, 558, 590, 836; **V**, 251, 258, 266, 403, 424, 684; **VI**, 301, 361, 395, 683; **VII**, 34, 386, 435; **VIII**, 26, 161, 155, 373; **80**, 227.

10-9 Epoxide Formation (Internal Williamson Ether Synthesis)

(3)OC-cyclo-Alkoxy-de-halogenation



This is a special case of Reaction 10-8. The base removes the proton from the OH group of a halohydrin (chlorohydrin or bromohydrin), and the resulting alkoxide subsequently attacks in an internal S_N2 reaction.⁶³⁶ Many epoxides have been made in this way.⁶³⁷ The course of the reaction can be influenced by neighboring group effects.⁶³⁸ Enantioselective epoxide-forming reactions are known, using chiral additives (e.g., dihydrocinchonidines).⁶³⁹ Epoxidation of alkenes has also been accomplished using HOF—MeCN in a continuous flow system.⁶⁴⁰

Larger cyclic ethers can be prepared, including five- and six-membered rings (tetrahydrofurans and tetrahydropyrans, respectively).⁶⁴¹ Additional treatment with base yields the glycol (Reaction 10-7). Thiiranes can be prepared by the reaction of α -chloro ketones with $(EtO)_2P(=O)-SH$ and $NaBH_4-Al_2O_3$ with microwave irradiation.⁶⁴²

1,2-Diols can be converted to epoxides by treatment with DMF dimethyl acetal, $[(MeO)_2CHNMe_2]$,⁶⁴³ with diethyl azodicarboxylate ($Et_2OCN=NCO_2Et$),

⁶³³ Bartoszewicz, A.; Kalek, M.; Stawinski, J. *Tetrahedron* **2008**, 64, 8843.

⁶³⁴ Ashby, E.C.; Bae, D.; Park, W.; Depriest, R.N.; Su, W. *Tetrahedron Lett.* **1984**, 25, 5107.

⁶³⁵ Namboodiri, V.V.; Varma, R.S. *Tetrahedron Lett.* **2002**, 43, 4593.

⁶³⁶ See Knipe, A.C. *J. Chem. Soc. Perkin Trans. 2* **1973**, 589.

⁶³⁷ See Berti, G. *Top. Stereochem.* **1973**, 7, 93, pp. 187.

⁶³⁸ Lang, F.; Kassab, D.J.; Ganem, B. *Tetrahedron Lett.* **1998**, 39, 5903.

⁶³⁹ Lygo, B.; Gardiner, S.D.; McLeod, M.C.; To, D.C.M. *Org. Biomol. Chem.* **2007**, 5, 2283.

⁶⁴⁰ McPake, C.B.; Murray, C.B.; Sandford, G. *Tetrahedron Lett.* **2009**, 50, 1674.

⁶⁴¹ See Kim, K.M.; Jeon, D.J.; Ryu, E.K. *Synthesis* **1998**, 835. Also see Marek, I.; Lefrancois, J.-M.; Normant, J.-F. *Tetrahedron Lett.* **1992**, 33, 1747.

⁶⁴² Yadav, L.D.S.; Kapoor, R. *Synthesis* **2002**, 2344.

⁶⁴³ Neumann, H. *Chimia*, **1969**, 23, 267.

and Ph_3P ,⁶⁴⁴ with a dialkoxytriphenylphosphorane,⁶⁴⁵ or with $\text{TsCl}^-\text{Na}^+\text{OHPHCH}_2\text{NEt}_2^+$
 Cl^- .⁶⁴⁶

OS **I**, 185, 233; **II**, 256; **III**, 835; **VI**, 560; **VII**, 164, 356; **VIII**, 434.

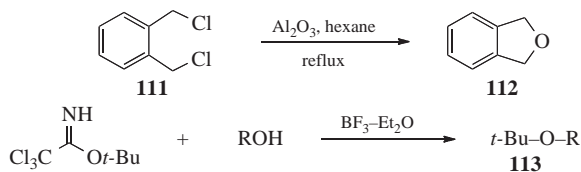
10-10 Alkylation with Inorganic Esters

Alkoxy-de-sulfonyloxy substitution



The reaction of alkyl sulfates with alkoxide ions is quite similar to Reaction **10-8** in mechanism and scope. Other inorganic esters can also be used. Methyl ethers of alcohols and phenols are commonly formed by treatment of alkoxides or aroxides with methyl sulfate. The alcohol or phenol can be methylated directly with dimethyl sulfate under various conditions.⁶⁴⁷ Carboxylic esters sometimes give ethers when treated with alkoxides ($\text{B}_{\text{AL}}2$ mechanism, Reaction **16-59**) in a very similar process (see also, Reaction **16-64**). A related reaction heated **111** with alumina to give the corresponding benzofuran, (**112**).⁶⁴⁸ The reaction of aliphatic alcohols and potassium organotrifluoroborate salts also gives ethers.⁶⁴⁹

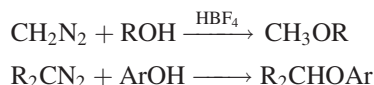
tert-Butyl ethers (**113**) can be prepared by treating the compound *tert*-butyl-2,2,2-trichloroacetimidate with an alcohol or phenol in the presence of boron trifluoride etherate.⁶⁵⁰ Trichloroimidates can be used to prepare other ethers as well.⁶⁵¹ *tert*-Butyl ethers can be cleaved by acid-catalyzed hydrolysis.⁶⁵²



OS **I**, 58, 537; **II**, 387, 619; **III**, 127, 564, 800; **IV**, 588; **VI**, 737, 859; **VII**, 41. Also see, OS **V**, 431.

10-11 Alkylation with Diazo Compounds

Hydro, alkoxy-de-diazo-bisubstitution



⁶⁴⁴ Guthrie, R.D.; Jenkins, I.D.; Yamasaki, R.; Skelton, B.W.; White, A.H. *J. Chem. Soc. Perkin Trans. 1* **1981**, 2328 and references cited therein. For a review of diethyl azodicarboxylate- Ph_3P , see Mitsunobu, O. *Synthesis* **1981**, 1.

⁶⁴⁵ Kelly, J.W.; Evans, Jr., S.A. *J. Org. Chem.* **1986**, 51, 5490. See also, Hendrickson, J.B.; Hussoin, M.S. *Synlett*, **1990**, 423.

⁶⁴⁶ Szeja, W. *Synthesis* **1985**, 983.

⁶⁴⁷ Cao, Y.-Q.; Pei, B.-G. *Synth. Commun.* **2000**, 30, 1759.

⁶⁴⁸ Mihara, M.; Ishino, Y.; Minakata, S.; Komatsu, M. *Synlett* **2002**, 1526.

⁶⁴⁹ Quach, T.D.; Batey, R.A. *Org. Lett.* **2003**, 5, 1381.

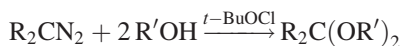
⁶⁵⁰ Armstrong, A.; Brackenridge, I.; Jackson, R.F.W.; Kirk, J.M. *Tetrahedron Lett.* **1988**, 29, 2483.

⁶⁵¹ Rai, A.N.; Basu, A. *Tetrahedron Lett.* **2003**, 44, 2267.

⁶⁵² Lajunen, M.; Ianskanen-Lehti, K. *Acta Chem. Scand. B*, **1994**, 48, 861.

Alcohols react with diazo compounds to form ethers, but diazomethane and diazo ketones are most readily available, giving methyl ethers or α -keto ethers,⁶⁵³ respectively. With diazomethane⁶⁵⁴ the method is expensive and requires great caution, but the conditions are mild and high yields are obtained. Diazomethane is used chiefly to methylate alcohols and phenols that are expensive or available in small amounts. Hydroxy compounds react better as their acidity increases; ordinary alcohols do not react at all unless a catalyst (e.g., HBF_4 ⁶⁵⁵ or silica gel)⁶⁵⁶ is present. The more acidic phenols react very well in the absence of a catalyst. The reaction of oximes, and ketones that have substantial enolic contributions, give O-alkylation to form, respectively, O-alkyl oximes and enol ethers. The mechanism⁶⁵⁷ is as in Reaction 10-5. Note that O-aryloximes are prepared from oximes and aryl halides, mediated by CuI .⁶⁵⁸

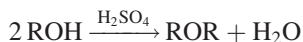
Diazoalkanes can also be converted to ethers by thermal or photochemical cleavage in the presence of an alcohol. These are carbene or carbenoid reactions.⁶⁵⁹ Enantioselective insertion into phenolic O—H bond leads to highly substituted ethers.⁶⁶⁰ Similar intermediates are involved when diazoalkanes react with alcohols in the presence of *t*-BuOCl to give acetals.⁶⁶¹



OS V, 245. Also see, OS V, 1099.

10-12 Dehydration of Alcohols

Alkoxy-de-hydroxylation



The dehydration of alcohols to form symmetrical ethers⁶⁶² is analogous to Reactions 10-8 and 10-10, but the species from which the leaving group departs is ROH_2^+ or ROSO_2OH . The former is obtained directly on treatment of alcohols with sulfuric acid and may go, by an $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ pathway, directly to the ether if attacked by another molecule of alcohol. On the other hand, it may, again by either an $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ route, be attacked by the nucleophile HSO_4^- , in which case it is converted to ROSO_2OH , which in turn may be attacked by an alcohol molecule to give ROR. Elimination is always a side reaction and, in the case of tertiary alkyl substrates, completely predominates. Good yields of ethers were obtained by heating diarylcarbinols [$\text{ArAr}'\text{CHOH} \rightarrow (\text{ArAr}'\text{CH})_2\text{O}$] with TsOH in the solid

⁶⁵³ Pansare, S.V.; Jain, R.P.; Bhattacharyya, A. *Tetrahedron Lett.* **1999**, 40, 5255.

⁶⁵⁴ For a review of diazomethane, see Pizey, J.S. *Synthetic Reagents*, Vol. 2; Wiley, NY, **1974**, pp. 65–142.

⁶⁵⁵ Neeman, M.; Caserio, M.C.; Roberts, J.D.; Johnson, W.S. *Tetrahedron* **1959**, 6, 36.

⁶⁵⁶ Ogawa, H.; Hagiwara, H.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn.* **1987**, 60, 627.

⁶⁵⁷ Kreevoy, M.M.; Thomas, S.J. *J. Org. Chem.* **1977**, 42, 3979. See also, McGarrity, J.F.; Smyth, T. *J. Am. Chem. Soc.* **1980**, 102, 7303.

⁶⁵⁸ De, P.; Nonappa; Pandurangan, K.; Maitra, U.; Wailes, S. *Org. Lett.* **2007**, 9, 2767.

⁶⁵⁹ Noels, A.F.; Demonceau, A.; Petiniot, N.; Hubert, A.J.; Teyssié, P. *Tetrahedron* **1982**, 38, 2733.

⁶⁶⁰ Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, 129, 12616.

⁶⁶¹ Baganz, H.; May, H. *Angew. Chem. Int. Ed.* **1966**, 5, 420.

⁶⁶² See Feuer, H.; Hooz, J. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, **1967**, pp.457–460, 468–470.

state.⁶⁶³ Acids (e.g., Nafion-H with silyl ethers)⁶⁶⁴ can be used in this transformation, and Lewis acids can be used with alcohols in some cases.⁶⁶⁵

Mixed (unsymmetrical) ethers can be prepared if one group is tertiary alkyl and the other primary or secondary, since the latter group is not likely to compete with the tertiary group in the formation of the carbocation, while a tertiary alcohol is a very poor nucleophile.⁶⁶⁶ If one group is not tertiary, the reaction of a mixture of two alcohols leads to all three possible ethers. Unsymmetrical ethers have been formed by treatment of two different alcohols with MeReO_3 ⁶⁶⁷ or with BiBr_3 .⁶⁶⁸ Unsymmetrical ethers have been prepared under *Mitsunobu conditions* (Reaction **10-17**) with a polymer-supported phosphine and diethyl azadicarboxylate (DEAD).⁶⁶⁹ Symmetrical ethers are formed by heating benzylic alcohols with the polymer poly(3,4-ethylenedioxythiophene) in toluene or heptane (a two-phase system), with no other additives.⁶⁷⁰ Diols can be converted to cyclic ethers,⁶⁷¹ although the reaction is most successful for five-membered rings, but five-, six-, and seven-membered rings have been prepared.⁶⁷² Thus, 1,6-hexanediol gives mostly 2-ethyltetrahydrofuran. This reaction is also important in preparing furfural derivatives from aldoses, with concurrent elimination.

Phenols and primary alcohols form ethers when heated with dicyclohexylcarbodiimide⁶⁷³ (see Reaction **16-63**).

OS **I**, 280; **II**, 126; **IV**, 25, 72, 266, 350, 393, 534; **V**, 539, 1024; **VI**, 887; **VIII**, 116. Also see, OS **V**, 721.

10-13 Transesterification

Hydroxy-de-alkoxylation and Alkoxy-de-hydroxylation



The exchange of one alkoxy group for another is rare for *ethers* without a reactive R group (e.g., diphenylmethyl),⁶⁷⁴ or by treatment of alkyl aryl ethers with alkoxide ions: $\text{ROAr} + \text{R}'\text{O}^- \rightarrow \text{ROR}' + \text{ArO}^-$.⁶⁷⁵ 3-(2-Benzyloxyethyl)-3-methyl-oxetane was transformed into 3-benzyloxymethyl-3-methyltetrahydrofuran by an internal transesterification catalyzed by $\text{BF}_3 \cdot \text{OEt}_2$.⁶⁷⁶

⁶⁶³ Toda, F.; Takumi, H.; Akehi, M. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1270.

⁶⁶⁴ Zolfigol, M.A.; Mohammadpoor-Baltork, I.; Habibi, D.; Mirjalili, B.B.F.; Bamoniri, A. *Tetrahedron Lett.* **2003**, *44*, 8165.

⁶⁶⁵ See Ooi, T.; Ichikawa, H.; Itagaki, Y.; Maruoka, K. *Heterocycles* **2000**, *52*, 575.

⁶⁶⁶ See, for example, Jenner, G. *Tetrahedron Lett.* **1988**, *29*, 2445.

⁶⁶⁷ Zhu, Z.; Espenson, J.H. *J. Org. Chem.* **1996**, *61*, 324.

⁶⁶⁸ Boyer, B.; Keramane, E.-M.; Roque, J.-P.; Pavia, A.A. *Tetrahedron Lett.* **2000**, *41*, 2891.

⁶⁶⁹ Lizarzaburu, M.E.; Shuttleworth, S. *Tetrahedron Lett.* **2002**, *43*, 2157.

⁶⁷⁰ D'Angelo, J.G.; Sawyer, R.; Kumar, A.; Onorato, A.; McCluskey, C.; Delude, C.; Vollenweider, L.; Reyes, N.; French, R.; Warner, S.; Chou, J.; Stenzel, J.; Sotzing, G.A.; Smith, M.B. *J. Polymer Sci., Part A* **2007**, *45*, 2328.

⁶⁷¹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 893–894.

⁶⁷² See Olah, G.A.; Fung, A.P.; Malhotra, R. *Synthesis* **1981**, 474.

⁶⁷³ Vowinkel, E. *Chem. Ber.* **1962**, *95*, 2997; **1963**, *96*, 1702; **1966**, *99*, 42.

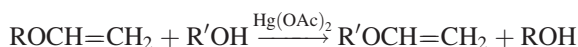
⁶⁷⁴ Pratt, E.F.; Draper, J.D. *J. Am. Chem. Soc.* **1949**, *71*, 2846. See Salehi, P.; Irandoost, M.; Seddighi, B.; Behbahani, F.K.; Tahmasebi, D.P. *Synth. Commun.* **2000**, *30*, 1743.

⁶⁷⁵ Zoltewicz, J.A.; Sale, A.A. *J. Org. Chem.* **1970**, *35*, 3462.

⁶⁷⁶ Itoh, A.; Hirose, Y.; Kashiwagi, H.; Masaki, Y. *Heterocycles* **1994**, *38*, 2165.



Acetals and ortho esters undergo transesterification readily,⁶⁷⁷ as with the transformation of **114** to **115**.⁶⁷⁸ As seen in Reaction **10-6**, departure of the leaving group from an acetal gives a particularly stable carbocation. It is also possible to convert a dimethylketal directly to a dithiane by reaction with butane 1,4-dithiol on clay.⁶⁷⁹ These are equilibrium reactions, and most often the equilibrium is shifted by removing the lower-boiling alcohol by distillation. Enol ethers can be prepared by treating an alcohol with an enol ester or a different enol ether, with mercuric acetate as a catalyst,⁶⁸⁰ as shown in the example. *N,N*-Diethylaminoethylthiol reacts with aryl ethers to give the phenol derivative and the corresponding sulfide in what is effectively a transesterification.⁶⁸¹

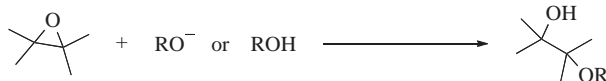


1,2-Diketones can be converted to α -keto enol ethers by treatment with an alkoxytrimethylsilane (ROSiMe_3).⁶⁸²

OS **VI**, 298, 491, 584, 606, 869; **VII**, 334; **VIII**, 155, 173. Also see, OS **V**, 1080, 1096.

10-14 Alcoholysis of Epoxides

(3)*OC-seco-alkoxy-de-alkoxylation*



This reaction is analogous to **10-7**. It may be acid (including Lewis acid⁶⁸³), base, or alumina⁶⁸⁴ catalyzed, and may occur by either an $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism. Catalysts (e.g., mesoporous aluminosilicate,⁶⁸⁵ $\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$,⁶⁸⁶ $\text{Al}(\text{OTf})_3$,⁶⁸⁷ or BiCl_3),⁶⁸⁸ have been used. β -Cyclodextrin has been used to promote the reaction with phenoxides in aqueous

⁶⁷⁷ See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, pp. 458–463; DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, **1970**, pp. 18–29, 146–148.

⁶⁷⁸ McElvain, S.M.; Curry, M.J. *J. Am. Chem. Soc.* **1948**, 70, 3781.

⁶⁷⁹ Jnaneshwara, G.K.; Barahate, N.B.; Sudalai, A.; Deshpande, V.H.; Wakharkar, R.D.; Gajare, A.S.; Shingare, M.S.; Sukumar, R. *J. Chem. Soc. Perkin Trans. 1* **1998**, 965.

⁶⁸⁰ Watanabe, W.H.; Conlon, L.E. *J. Am. Chem. Soc.* **1957**, 79, 2828; Shostakovskii, M.F.; Trofimov, B.A.; Atavin, A.S.; Lavrov, V.I. *Russ. Chem. Rev.* **1968**, 37, 907; Gareev, G.A. *J. Org. Chem. USSR* **1982**, 18, 36.

⁶⁸¹ Magano, J.; Chen, M.H.; Clark, J.D.; Nussbaumer, T. *J. Org. Chem.* **2006**, 71, 7103.

⁶⁸² Ponaras, A.A.; Meah, M.Y. *Tetrahedron Lett.* **1986**, 27, 4953.

⁶⁸³ Iranpoor, N.; Tarrian, T.; Movahedi, Z. *Synthesis* **1996**, 1473. See Moberg, C.; Rákos, L.; Tottie, L. *Tetrahedron Lett.* **1992**, 33, 2191 for an example that generates a hydroxy ether with high enantioselectivity. Also see, Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett*, **1992**, 673.

⁶⁸⁴ See Posner, G.H.; Rogers, D.Z. *J. Am. Chem. Soc.* **1977**, 99, 8208, 8214.

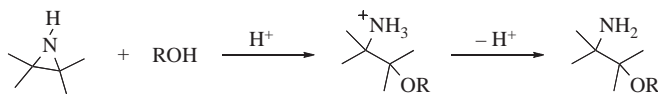
⁶⁸⁵ Robinson, M.W.C.; Buckle, R.; Mabbett, I.; Grant, G.M.; Graham, A.E. *Tetrahedron Lett.* **2007**, 48, 4723.

⁶⁸⁶ Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J.M. *Org. Lett.* **2002**, 4, 2817.

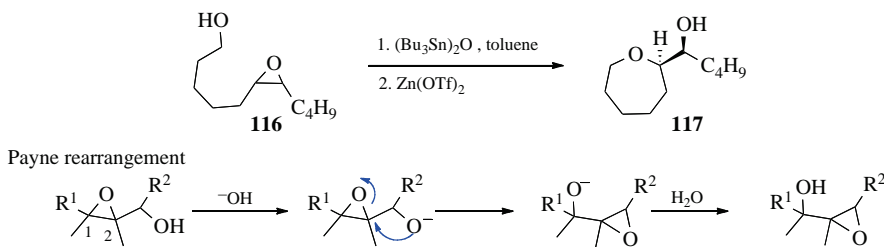
⁶⁸⁷ Williams, D.B.G.; Lawton, M. *Org. Biomol. Chem.* **2005**, 3, 3269.

⁶⁸⁸ Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Aliyan, H.; Mirkhani, V. *Synth. Commun.*, **2000**, 30, 2365.

media.⁶⁸⁹ Many of the β -hydroxy ethers produced in this way are valuable solvents, [e.g., diethylene glycol and Cellosolve (2-ethoxyethanol)]. Reaction with thiols leads to hydroxy thioethers.⁶⁹⁰ Other nucleophilic oxygen or sulfur species have been shown to open epoxides, including thiols⁶⁹¹ (catalyzed by Sc⁶⁹² or In⁶⁹³). (Phenylseleno)silanes react with epoxides to give β -hydroxy selenides.⁶⁹⁴



Opening an epoxide by an alkoxide moiety can be done intramolecularly, and a new cyclic ether is generated. Ethers of various ring sizes can be produced depending on the length of the tether between the alkoxide unit and the epoxide. Specialized conditions are common, as in the conversion of **116** to **117**.⁶⁹⁵ Another variant of this transformation used a Co-salen catalyst.⁶⁹⁶ A specialized version has the alkoxide moiety on the carbon adjacent to the epoxide, leading to the *Payne rearrangement* where a 2,3-epoxy alcohol is converted to an isomeric one, by treatment with aqueous base, as shown in the example.⁶⁹⁷



The reaction results in inverted configuration at C-2. Of course, the product can also revert to the starting material by the same pathway, so a mixture of epoxy alcohols is generally obtained.

The reaction of alcohols with aziridines leads to β -amino ethers,⁶⁹⁸ and reaction with thiols gives β -amino thioethers.⁶⁹⁹ It has been shown that ring opening of aziridines by

⁶⁸⁹ Surendra, K.; Krishnaveni, N.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* **2003**, 68, 4994.

⁶⁹⁰ Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* **2003**, 68, 8248; Amantini, D.; Friguelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Synlett* **2003**, 2292.

⁶⁹¹ See also Degl'Innocenti, A.; Capperucci, A.; Cerreti, A.; Pollicino, S.; Scapecchi, S.; Malesci, I.; Castagnoli, G. *Synlett* **2005**, 3063.

⁶⁹² Ogawa, C.; Wang, N.; Kobayashi, S. *Chem. Lett.* **2007**, 36, 34.

⁶⁹³ Nandakumar, M.V.; Tschöp, A.; Krautscheid, H.; Schneider, C. *Chem. Commun.* **2007**, 2756.

⁶⁹⁴ Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Del Verme, F.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron* **2008**, 64, 3337.

⁶⁹⁵ Matsumura, R.; Suzuki, T.; Sato, K.; Oku, K.-i.; Hagiwara, H.; Hoshi, T.; Ando, M.; Kamat, V.P. *Tetrahedron Lett.* **2000**, 41, 7701. See also, Karikomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* **2002**, 43, 1495.

⁶⁹⁶ Wu, M.H.; Hansen, K.B.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* **1999**, 38, 2012.

⁶⁹⁷ Behrens, C.H.; Ko, S.Y.; Sharpless, K.B.; Walker, F.J. *J. Org. Chem.* **1985**, 50, 5687. See Yamazaki, T.; Ichige, T.; Kitazume, T. *Org. Lett.* **2004**, 6, 4073.

⁶⁹⁸ See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, **1969**, pp. 224–227, 256–257.

⁶⁹⁹ Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1314.

phenols is promoted by tributylphosphine.⁷⁰⁰ Aldehydes open aziridines when catalyzed by nucleophilic carbenes.⁷⁰¹ Metal catalysts [e.g., Cu(OTf)₂] mediate the ring opening of *N*-tosylaziridines by alcohols.⁷⁰² The reaction of *N*-tosyl aziridines with 10% ceric ammonium nitrate in aq methanol leads to *N*-tosylamino alcohols,⁷⁰³ and reaction with ethanol and 10% BF₃•OEt₂ gives *N*-tosyl ethers.⁷⁰⁴ In addition, *N*-tosylaziridines are opened by acetic acid in the presence of In(OTf)₃ to give *N*-tosylamino acetates.⁷⁰⁵ In the presence of Amberlyst-15, *N*-Boc (Boc = *tert*-butoxycarbonyl, —CO₂*t*-Bu) aziridines react with LiBr to give the corresponding bromo amide.⁷⁰⁶ Aziridines are opened by potassium thiocyanate, catalyzed by LiClO₄.⁷⁰⁷ Catalytic enantioselective ring opening of *N*-acyl aziridines with TMSCN and a Gd catalyst leads to amino-nitriles.⁷⁰⁸ *aza-Payne rearrangements* are known, based on reactions of aziridines rather than epoxides (see above).⁷⁰⁹

10-15 Alkylation with Onium Salts

Alkoxy-de-hydroxylation

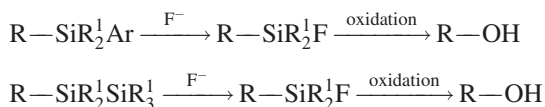


Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.⁷¹⁰ Quaternary ammonium salts can sometimes also be used.⁷¹¹

OS VIII, 536.

10-16 Hydroxylation via Silanes

Hydroxy-de-silylalkylation



Alkylsilanes can be oxidized, with the silyl unit converted to a hydroxy unit. This usually requires either an aryl group⁷¹² or another silyl group⁷¹³ attached to silicon. It has

⁷⁰⁰ Hou, X.-L.; Fan, R.-H.; Dai, L.-X. *J. Org. Chem.* **2002**, 67, 5295.

⁷⁰¹ Liu, Y.-K.; Li, R.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. *Org. Lett.* **2006**, 8, 1521.

⁷⁰² Ghorai, M.K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, 72, 5859.

⁷⁰³ Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S.S. *Tetrahedron Lett.* **2002**, 43, 7361.

⁷⁰⁴ Prasad, B.A.B.; Sekar, G.; Singh, V.K. *Tetrahedron Lett.* **2000**, 41, 4677.

⁷⁰⁵ Yadav, J.S.; Reddy, B.V.S.; Sadashiv, K.; Harikishan, K. *Tetrahedron Lett.* **2002**, 43, 2099.

⁷⁰⁶ Righi, G.; Potini, C.; Bovicelli, P. *Tetrahedron Lett.* **2002**, 43, 5867.

⁷⁰⁷ Yadav, J.S.; Subba Reddy, B.V.; Jyothirmmai, B.; Murty, M.S.R. *Tetrahedron Lett.* **2005**, 46, 6385. Also in water, with β-cyclodextrin, see Reddy, M.S.; Narendra, M.; Nageswar, Y.V.D.; Rao, K.R. *Tetrahedron Lett.* **2005**, 46, 6437.

⁷⁰⁸ Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, 127, 11252.

⁷⁰⁹ Xichun, F.; Guofu, Q.; Shucai, L.; Hanbing, T.; Lamei, W.; Xianming, H. *Tetrahedron Asymmetry* **2006**, 17, 1394.

⁷¹⁰ Granik, V.G.; Pyatin, B.M.; Glushkov, R.G. *Russ. Chem. Rev.* **1971**, 40, 747, see p. 749.

⁷¹¹ See Vogel, D.E.; Büchi, G.H. *Org. Synth.*, **66**, 29. With pyridinium salts, see Poon, K.W.C.; Dudley, G.B. *J. Org. Chem.* **2006**, 71, 3923. See also Saitoh, T.; Ichikawa, J. *J. Am. Chem. Soc.* **2005**, 127, 9696.

⁷¹² Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, 39, 983; Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. For the protodesilylation step see Häbich, D.; Effenberger, F. *Synthesis* **1979**, 841. Also see Buncel, E.; Davies, A.G. *J. Chem. Soc.* **1958**, 1550.

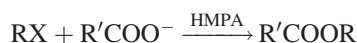
⁷¹³ Sugimoto, M.; Matsunaga, S.; Ito, Y. *Synlett*, **1995**, 941.

been shown that a strained four-membered ring silane (a siletane) also gives the corresponding alcohol upon oxidation.⁷¹⁴ Treatment with a fluorinating agent (e.g., tetrabutylammonium fluoride or CsF) replaces Ar or SiR₃ with F, which is oxidized with hydrogen peroxide or a peroxyacid to give the alcohol. This sequence is often called the *Tamao–Fleming oxidation*.⁷¹² There are several variations in substrate that allow versatility in the initial incorporation of the silyl unit.⁷¹⁵ Hydroperoxide oxidation of a cyclic silane leads to a diol.⁷¹⁶

C. Attack by OCOR at an Alkyl Carbon

10-17 Alkylation of Carboxylic Acid Salts

Acyloxy-de-halogenation



Sodium salts of carboxylic acids, including hindered acids (e.g., mesitoic), rapidly react with primary and secondary bromides and iodides at room temperature in dipolar aprotic solvents, especially HMPA, to give high yields of carboxylic esters.⁷¹⁷ The mechanism is S_N2. Several bases or basic media have been used to generate the carboxylate salt.⁷¹⁸ Sodium salts are often used, but K, Ag, Cs,⁷¹⁹ and substituted ammonium salts have also been used. An important variation uses phase transfer catalysis,⁷²⁰ and good yields of esters have been obtained from primary, secondary, benzylic, allylic, and phenacyl halides.⁷²¹ Without phase-transfer catalysts and in protic solvents, the reaction is useful only for fairly active R [e.g., benzylic and allylic (S_N1 mechanism)], but not for tertiary alkyl, since elimination occurs instead.⁷²² Solid-state procedures are available. Addition of the dry carboxylate salt and the halide to alumina as a solid support, and microwave irradiation gives the ester in a procedure that is applicable to long-chain primary halides.⁷²³ A similar reaction of hexanoic acid and benzyl bromide on solid benzyltributylammonium chloride

⁷¹⁴ Sunderhaus, J.D.; Lam, H.; Dudley, G.B. *Org. Lett.* **2003**, 5, 4571.

⁷¹⁵ See Matsumoto, Y.; Hayashi, T.; Ito, Y. *Tetrahedron* **1994**, 50, 335; Uozumi, Y.; Kitayama, K.; Hayashi, T.; Yanagi, K.; Fukuyo, E. *Bull. Chem. Soc. Jpn.* **1995**, 68, 713.

⁷¹⁶ Liu, D.; Kozmin, S.A. *Angew. Chem. Int. Ed.* **2001**, 40, 4757.

⁷¹⁷ Shaw, J.E.; Kunerth, D.C. *J. Org. Chem.* **1974**, 39, 1968; Larock, R.C. *J. Org. Chem.* **1974**, 39, 3721; Pfeffer, P.E.; Silbert, L.S. *J. Org. Chem.* **1976**, 41, 1373.

⁷¹⁸ Bases include DBU (see Reaction 17-13): See Mal, D. *Synth. Commun.* **1986**, 16, 331. Cs₂CO₃: Lee, J.C.; Oh, Y.S.; Cho, S.H.; Lee, J.I. *Org. Prep. Proceed. Int.* **1996**, 28, 480. CsF–Celite: Lee, J.C.; Choi, Y. *Synth. Commun.* **1998**, 28, 2021.

⁷¹⁹ See Dijkstra, G.; Kruizinga, W.H.; Kellogg, R.M. *J. Org. Chem.* **1987**, 52, 4230.

⁷²⁰ See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, **1978**, pp. 140–155; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, **1977**, pp. 85–95.

⁷²¹ See Clark, J.H.; Miller, J.M. *Tetrahedron Lett.* **1977**, 599.

⁷²² See, however, Moore, G.G.; Foglia, T.A.; McGahan, T.J. *J. Org. Chem.* **1979**, 44, 2425.

⁷²³ Bram, G.; Loupy, A.; Majdoub, M.; Gutierrez, E.; Ruiz-Hitzky, E. *Tetrahedron* **1990**, 46, 5167. See Arrad, O.; Sasson, Y. *J. Am. Chem. Soc.* **1988**, 110, 185; Dakka, J.; Sasson, Y.; Khawaled, K.; Bram, G.; Loupy, A. *J. Chem. Soc., Chem. Commun.* **1991**, 853.

gave the ester with microwave irradiation.⁷²⁴ Ionic liquid solvents have been shown to facilitate this alkylation reaction.⁷²⁵

The reaction of an alcohol and a carboxylate anion with diethyl azodicarboxylate ($\text{EtOOCN}=\text{NCOOEt}$) and Ph_3P ⁷²⁶ is called the *Mitsunobu reaction*.⁷²⁷ Other azocarboxylates may be used in this reaction, including diisopropyl azodicarboxylate (DIAD), and di-2-methoxyethyl azodicarboxylate (DMEAD).⁷²⁸ Other Mitsunobu catalysts are available,⁷²⁹ including organocatalysts,⁷³⁰ and polymer-supported reagents have been used.⁷³¹ A renewable phosphine ligand has been developed.⁷³² Note that other functional groups, including azides⁷³³ and thiocyanates⁷³⁴ can be generated from alcohols using Mitsunobu conditions. This reaction can also be considered as an $\text{S}_{\text{N}}2$ mechanism. Phenol esters can also be formed.⁷³⁵ Mitsunobu cyclodehydration of 1,2-diols leads to epoxides.⁷³⁶

Lactones can be prepared from halo acids by treatment with base (see Reaction 16-63). This has most often been accomplished with γ and δ lactones, but macrocyclic lactones (e.g., 11-17-members) have also been prepared in this way.⁷³⁷ An interesting variation treated 2-ethylbenzoic acid with hypervalent iodine and then $\text{I}_2/h\nu$ to give the five-membered ring lactone.⁷³⁸

Copper(I) carboxylates give esters with primary (including neopentyl without rearrangement), secondary, and tertiary alkyl, allylic, and vinylic halides.⁷³⁹ A simple S_{N} mechanism is obviously precluded in this case. Vinylic halides can be converted to vinylic acetates by treatment with sodium acetate if palladium(II) chloride is present.⁷⁴⁰

A carboxylic acid (not the salt) can be the nucleophile if F^- is present.⁷⁴¹ Mesylates are readily displaced, for example, by benzoic acid/ CsF .⁷⁴² Dihalides have been converted to

⁷²⁴ Yuncheng, Y.; Yulin, J.; Dabin, G. *Synth. Commun.* **1992**, 22, 3109.

⁷²⁵ Brinchi, L.; Germani, R.; Savelli, G. *Tetrahedron Lett.* **2003**, 44, 2027, 6583; Liu, Z.; Chen, Z.-C.; Zheng, Q.-G. *Synthesis* **2004**, 33.

⁷²⁶ Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, 40, 2380; Camp, D.; Jenkins, I.D. *Aust. J. Chem.* **1988**, 41, 1835.

⁷²⁷ But, T.Y.S.; Toy, P.H. *Chemistry: Asian J.* **2007**, 2, 1340. See Ahn, C.; Correia, R.; DeShong, P. J. *Org. Chem.* **2002**, 67, 1751 and references cited therein. See also, Hughes, D.L. *Org. Prep. Proceed. Int.* **1996**, 28, 127; Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763; Dandapani, S.; Curran, D.P. *Chem. Eur. J.* **2004**, 10, 3131. Also see Steinreiber, A.; Stadler, A.; Mayer, S.F.; Faber, K.; Kappe, C.O. *Tetrahedron Lett.* **2001**, 42, 6283. For a chromatography-free product separation, see Proctor, A.J.; Beaument, K.; Clough, J.M.; Knight, D.W.; Li, Y. *Tetrahedron Lett.* **2006**, 47, 5151.

⁷²⁸ Sugimura, T.; Hagiya, K. *Chem. Lett.* **2007**, 36, 566.

⁷²⁹ See Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Itô, S. *Tetrahedron Lett.* **1995**, 36, 2529; Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Itô, S. *Tetrahedron Lett.* **1995**, 36, 2531. For fluororous reactions and reagents see Dandapani, S.; Curran, D.P. *Tetrahedron* **2002**, 58, 3855.

⁷³⁰ But, T.Y.S.; Toy, P.H. *J. Am. Chem. Soc.* **2006**, 128, 9636.

⁷³¹ Hamed, A.M.; He, H.S.; Toy, P.H.; Flynn, D.L.; Hanson, P.R. *J. Am. Chem. Soc.* **2005**, 127, 52.

⁷³² Yoakim, C.; Guse, I.; O'Meara, J.A.; Thavonokham, B. *Synlett* **2003**, 473.

⁷³³ See Papeo, G.; Poster, H.; Vianello, P.; Varasi, M. *Synthesis* **2004**, 2886.

⁷³⁴ Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Azadi, R. *Synthesis* **2004**, 92.

⁷³⁵ Fitzjarrald, V.P.; Pongdee, R. *Tetrahedron Lett.* **2007**, 48, 3553.

⁷³⁶ García-Delgado, N.; Riera, A.; Verdaguer, X. *Org. Lett.* **2007**, 9, 635.

⁷³⁷ See Galli, C.; Mandolini, L. *Org. Synth.* **VI**, 698; Kimura, Y.; Regen, S.L. *J. Org. Chem.* **1983**, 48, 1533.

⁷³⁸ Togo, H.; Muraki, T.; Yokoyama, M. *Tetrahedron Lett.* **1995**, 36, 7089.

⁷³⁹ Klumpp, G.W.; Bos, H.; Schakel, M.; Schmitz, R.F.; Vrielink, J.J. *Tetrahedron Lett.* **1975**, 3429.

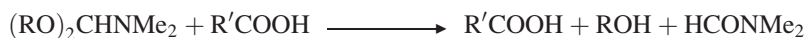
⁷⁴⁰ Yamaji, M.; Fujiwara, Y.; Asano, R.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1973**, 46, 90.

⁷⁴¹ Ooi, T.; Sugimoto, H.; Doda, K.; Maruoka, K. *Tetrahedron Lett.* **2001**, 42, 9245.

⁷⁴² Sato, T.; Otera, J. *Synlett*, **1995**, 336.

diesters by this method.⁷⁴¹ A COOH group can be conveniently protected by reaction of its ion with a phenacyl bromide (ArCOCH₂Br).⁷⁴³ The resulting ester is easily cleaved when desired with zinc and acetic acid. Dialkyl carbonates can be prepared without phosgene (see Reaction **16-61**) by phase-transfer catalyzed treatment of primary alkyl halides with dry KHCO₃ and K₂CO₃.⁷⁴⁴

Other leaving groups can also be replaced by OCOR. Alkyl chlorosulfites (ROSOCI) and other derivatives of sulfuric, sulfonic, and other inorganic acids can be treated with carboxylate ions to give the corresponding esters. Treatment with oxalyl chloride allows displacement by carboxylate salts.⁷⁴⁵ The use of dimethyl sulfate⁷⁴⁶ or trimethyl phosphate⁷⁴⁷ allows sterically hindered COOH groups to be methylated. The reaction of benzoic acid with aq lithium hydroxide, and then dimethyl sulfate gave methyl benzoate.⁷⁴⁸ Dimethyl carbonate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, see Reaction **17-13**) has been used to prepare methyl esters.⁷⁴⁹ With certain substrates, carboxylic acids are strong enough nucleophiles for the reaction. Examples of such substrates are trialkyl phosphites [P(OR)₃]⁷⁵⁰ and acetals of DMF.⁷⁵¹



This is an S_N2 process, since inversion is found at R. Another good leaving group is NTs₂ and ditosylamines react quite well with acetate ion in dipolar aprotic solvents:⁷⁵² RNTs₂ + OAc[−] → ROAc. Ordinary primary amines have been converted to acetates and benzoates by the *Katritzky pyrylium–pyridinium method* (Sec. 10.G.iii).⁷⁵³ Quaternary ammonium salts can be cleaved by heating with AcO[−] in an aprotic solvent.⁷⁵⁴ Oxonium ions can also be used as substrates:⁷⁵⁵ R₃O⁺ + R'COO[−] → R'COOR + R₂O. The reaction of potassium thioacetate with alkyl halides give dithiocarboxylic esters.⁷⁵⁶

In a variation of this reaction, alkyl halides can be converted to carbamates, by treatment with a secondary amine and K₂CO₃ under phase transfer conditions.⁷⁵⁷ The reaction of alcohols and alkyl halides can lead to carbonates.⁷⁵⁸

⁷⁴³ Hendrickson, J.B.; Kandall, L.C. *Tetrahedron Lett.* **1970**, 343.

⁷⁴⁴ Verdecchia, M.; Frochi, M.; Palombi, L.; Rossi, L. *J. Org. Chem.* **2002**, *67*, 8287. See also, Kadokawa, J.-i.; Habu, H.; Fukamachi, S.; Karasu, M.; Tagaya, H.; Chiba, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2205.

⁷⁴⁵ Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Koike, N.; Procopiou, P.A. *J. Org. Chem.* **1998**, *63*, 6273.

⁷⁴⁶ Grundy, J.; James, B.G.; Pattenden, G. *Tetrahedron Lett.* **1972**, 757.

⁷⁴⁷ Harris, M.M.; Patel, P.K. *Chem. Ind. (London)* **1973**, 1002.

⁷⁴⁸ Chakraborti, A.K.; Basak, A.; Grover, V. *J. Org. Chem.* **1999**, *64*, 8014. See also, Avila-Zárraga, J.G.; Martínez, R. *Synth. Commun.* **2001**, *31*, 2177.

⁷⁴⁹ Shieh, W.-C.; Dell, S.; Repic, O. *Tetrahedron Lett.* **2002**, *43*, 5607.

⁷⁵⁰ Szmuszkovicz, J. *J. Org. Prep. Proceed. Int.* **1972**, *4*, 51.

⁷⁵¹ Vorbrüggen, H. *Angew. Chem. Int. Ed.* **1963**, *2*, 211; Brechbühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Angew. Chem. Int. Ed.* **1963**, *2*, 212.

⁷⁵² Curtis, V.A.; Schwartz, H.S.; Hartman, A.F.; Pick, R.M.; Kolar, L.W.; Baumgarten, R.J. *Tetrahedron Lett.* **1977**, 1969.

⁷⁵³ See Katritzky, A.R.; Gruntz, U.; Kenny, D.H.; Rezende, M.C.; Sheikh, H. *J. Chem. Soc. Perkin Trans. 1* **1979**, 430.

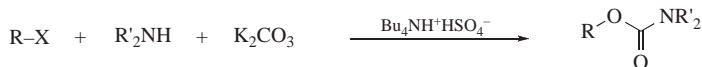
⁷⁵⁴ Wilson, N.D.V.; Joule, J.A. *Tetrahedron* **1968**, *24*, 5493.

⁷⁵⁵ Raber, D.J.; Gariano, Jr., P.; Brod, A.O.; Gariano, A.; Guida, W.C.; Guida, A.R.; Herbst, M.D. *J. Org. Chem.* **1979**, *44*, 1149.

⁷⁵⁶ Zheng, T.-C.; Burkart, M.; Richardson, D.E. *Tetrahedron Lett.* **1999**, *40*, 603.

⁷⁵⁷ Gómez-Parra, V.; Sánchez, F.; Torres, T. *J. Chem. Soc. Perkin Trans. 2* **1987**, 695.

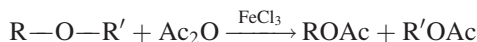
⁷⁵⁸ Dueno, E.E.; Chu, F.; Kim, S.-I.; Jung, K.W. *Tetrahedron Lett.* **1999**, *40*, 1843. Also see Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874.



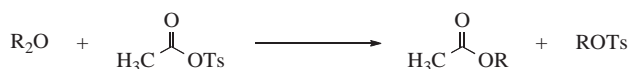
OS II, 5; III, 650; IV, 582; V, 580; VI, 273, 576, 698.

10-18 Cleavage of Ethers with Acetic Anhydride or Acid Halides

Acyloxy-de-alkoxylation



Dialkyl ethers can be cleaved by treatment with anhydrous ferric chloride in acetic anhydride,⁷⁵⁹ or with Me_3SiOTf in acetic anhydride.⁷⁶⁰ In this reaction, both R groups are converted to acetates and yields are moderate to high. Ethers can also be cleaved by the mixed, anhydride acetyl tosylate.⁷⁶¹



Epoxides give β -hydroxyalkyl carboxylates when treated with a carboxylic acid or a carboxylate ion and a suitable catalyst.⁷⁶² Tetrahydrofuran was opened to give *O*-acetyl-4-iodo-1-butanol by treatment with acid chlorides and samarium halides⁷⁶³ or BCl_3 .⁷⁶⁴ In a highly specialized transformation, the reaction of an epoxide with CO_2 and ZnCl_2 in an ionic liquid leads to a cyclic carbonate.⁷⁶⁵ Epoxides react with CO and CH_3OH in the presence of 10% of 3-hydroxypyridine and 5% of $\text{Co}_2(\text{CO})_8$ to give a β -hydroxy methyl ester.⁷⁶⁶

OS VIII, 13.

10-19 Alkylation of Carboxylic Acids with Diazo Compounds

Hydro, acyloxy-de-diazo-bisubstitution



Carboxylic acids can be converted to esters with diazo compounds in a reaction essentially the same as 10-11. In contrast to alcohols, carboxylic acids undergo the reaction quite well at room temperature, since the reactivity of the reagent increases with acidity. The reaction is used where high yields are important or where the acid is sensitive to higher temperatures. Because of availability, diazomethane (CH_2N_2)⁶⁵⁴ is commonly used to prepare methyl esters, and diazo ketones are common. The mechanism is as shown in Reaction 10-11.

OS V, 797.

⁷⁵⁹ Ganem, B.; Small, Jr., V.M. *J. Org. Chem.* **1974**, 39, 3728.

⁷⁶⁰ Procopiou, P.A.; Baugh, S.P.D.; Flack, S.S.; Inglis, G.G.A. *Chem. Commun.* **1996**, 2625.

⁷⁶¹ Karger, M.H.; Mazur, Y. *J. Am. Chem. Soc.* **1968**, 90, 3878. See also, Coffi-Nketsia, S.; Kergomard, A.; Tautou, H. *Bull. Soc. Chim. Fr.* **1967**, 2788.

⁷⁶² See Otera, J.; Matsuzaki, S. *Synthesis* **1986**, 1019; Deardorff, D.R.; Myles, D.C. *Org. Synth.*, **67**, 114.

⁷⁶³ Kwon, D.W.; Kim, Y.H.; Lee, K. *J. Org. Chem.* **2002**, 67, 9488.

⁷⁶⁴ Malladi, R.R.; Kabalka, G.W. *Synth. Commun.* **2002**, 32, 1997.

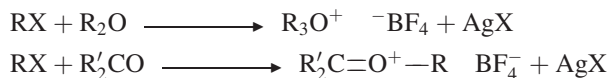
⁷⁶⁵ Li, F.; Xiao, L.; Xia, C.; Hu, B. *Tetrahedron Lett.* **2004**, 45, 8307.

⁷⁶⁶ Denmark, S.E.; Ahmad, M. *J. Org. Chem.* **2007**, 72, 9630.

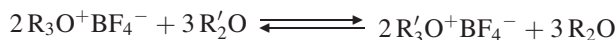
D. Other Oxygen Nucleophiles

10-20 Formation of Oxonium Salts

Dialkyloxonio-de-halogenation



Alkyl halides can be alkylated by ethers or ketones to give oxonium salts, if a very weak, negatively charged nucleophile is present to serve as a counterion and a Lewis acid is present to combine with X^- .⁷⁶⁷ A typical procedure consists of treating the halide with the ether or the ketone in the presence of AgBF_4 or AgSbF_6 . The Ag^+ serves to remove X^- and the BF_4^- or SbF_6^- acts as the counterion. Another method involves treatment of the halide with a complex formed between the oxygen compound and a Lewis acid (e.g., $\text{R}_2\text{O} \cdot \text{BF}_3 + \text{RX} \rightarrow \text{R}_3\text{O}^+ \text{ } ^-\text{BF}_4^-$), although this method is most satisfactory when the oxygen and halogen atoms are in the same molecule so that a cyclic oxonium ion is obtained. Ethers and oxonium ions also undergo exchange reactions:



OS V, 1080, 1096, 1099; VI, 1019.

10-21 Preparation of Peroxides and Hydroperoxides

Hydroperoxy-de-halogenation



Hydroperoxides can be prepared by treatment of alkyl halides, esters of sulfuric or sulfonic acids, or alcohols with hydrogen peroxide in basic solution, where it is actually HO_2^- .⁷⁶⁸ Sodium peroxide is similarly used to prepare dialkyl peroxides ($2\text{RX} + \text{Na}_2\text{O}_2 \rightarrow \text{ROOR}$). Another method, which gives primary, secondary, or tertiary hydroperoxides and peroxides, involves treatment of the halide with H_2O_2 or a peroxide in the presence of silver trifluoroacetate.⁷⁶⁹ Peroxides can also be prepared⁷⁷⁰ by treatment of alkyl bromides or tosylates with potassium superoxide (KO_2) in the presence of crown ethers (though alcohols may be side products⁷⁷¹) and by the reaction between alkyl triflates and germanium or tin peroxide.⁷⁷²

Diacyl peroxides and acyl hydroperoxides can similarly be prepared⁷⁷³ from acyl halides or anhydrides and from carboxylic acids.⁷⁷⁴ Diacyl peroxides can also be prepared by the

⁷⁶⁷ Meerwein, H.; Hederich, V.; Wunderlich, K. *Arch. Pharm.* **1958**, 291/63, 541. See Perst, H. *Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, **1971**, pp. 22–39.

⁷⁶⁸ See Hiatt, R. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, **1971**, pp. 1–151; Pandiarajan, K. in Pizey, J. S. *Synthetic Reagents*, Vol. 6, Wiley, NY, **1985**, pp. 60–155.

⁷⁶⁹ Cookson, P.G.; Davies, A.G.; Roberts, B.P. *J. Chem. Soc., Chem. Commun.* **1976**, 1022. Also see Bourgeois, M.; Montaudon, E.; Maillard, B. *Synthesis* **1989**, 700.

⁷⁷⁰ Johnson, R.A.; Nidy, E.G.; Merritt, M.V. *J. Am. Chem. Soc.* **1978**, 100, 7960.

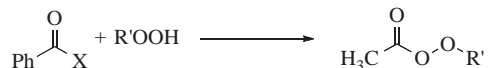
⁷⁷¹ See San Filippo, Jr., J.; Chern, C.; Valentine, J.S. *J. Org. Chem.* **1975**, 40, 1678; Corey, E.J.; Nicolaou, K.C.; Shibasaki, M.; Machida, Y.; Shiner, C.S. *Tetrahedron Lett.* **1975**, 3183.

⁷⁷² Salomon, M.F.; Salomon, R.G. *J. Am. Chem. Soc.* **1979**, 101, 4290.

⁷⁷³ See Bouillon, G.; Lick, C.; Schank, K. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, **1983**, pp. 279–309; Hiatt, R.; Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, **1971**, pp. 799–929.

⁷⁷⁴ See Silbert, L.S.; Siegel, E.; Swern, D. *J. Org. Chem.* **1962**, 27, 1336.

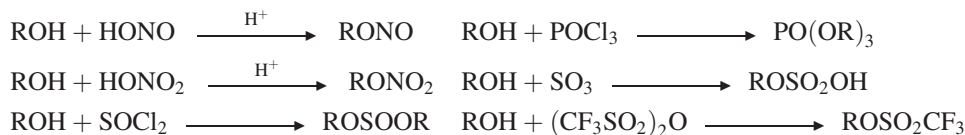
treatment of carboxylic acids with hydrogen peroxide in the presence of dicyclohexylcarbodiimide,⁷⁷⁵ Sulfuric acid, methanesulfonic acid, or some other dehydrating agent. Mixed alkyl–acyl peroxides (peresters) can be made from acyl halides and hydroperoxides.



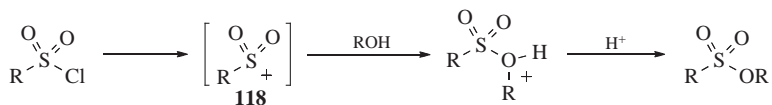
OS III, 619, 649; V, 805, 904; VI, 276.

10-22 Preparation of Inorganic Esters

Nitrosooxy-de-hydroxylation, and so on.



The above transformations show a few of the many inorganic esters that can be prepared by the reaction of an alcohol with an inorganic acid or, better, its acid halide or anhydride⁷⁷⁶ These similar reactions are grouped together for convenience, but not all involve nucleophilic substitutions at R. The other possible pathway is nucleophilic substitution at the inorganic central atom, such as the attack of the alcohol oxygen at the electrophilic sulfur atom in **118**,⁷⁷⁷ or a corresponding S_N2 type process (see Sec. 16.B.v). In such cases, there



is no alkyl–O cleavage. Mono esters of sulfuric acid (alkylsulfuric acids), which are important industrially because their salts are used as detergents, can be prepared by treating alcohols with SO₃, H₂SO₄, ClSO₂OH, or SO₃ complexes.⁷⁷⁸ It is possible to prepare a primary sulfonate ester (e.g., tosylate), in the presence of a secondary alcohol unit when tosic acid reacts with a 1,2-diol in the presence of Fe³⁺-Montmorillonite.⁷⁷⁹ Polymer-bound reagents have been used to prepare sulfonate esters.⁷⁸⁰ Phenolic triflates have been prepared using *N,N*-ditriflylaniline and K₂CO₃ under microwave irradiation.⁷⁸¹ Sulfinic esters are readily prepared from alcohols and sulfinyl chlorides, and in the presence of Cinchona alkaloids the reaction is enantioselective.⁷⁸²

⁷⁷⁵ Greene, F.D.; Kazan, J. *J. Org. Chem.* **1963**, 28, 2168.

⁷⁷⁶ See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, pp. 481–497.

⁷⁷⁷ See Aldred, S.E.; Williams, D.L.H.; Garley, M. *J. Chem. Soc. Perkin Trans. 2* **1982**, 777.

⁷⁷⁸ Sandler, S.R.; Karo, W. *Organic Functional Group Preparations*, 2nd ed., Vol 3, Academic Press, NY, **1989**, pp. 129–151.

⁷⁷⁹ Choudary, B.M.; Chowdari, N.S.; Kantam, M.L. *Tetrahedron* **2000**, 56, 7291.

⁷⁸⁰ Vignola, N.; Dahmen, S.; Enders, D.; Bräse, S. *Tetrahedron Lett.* **2001**, 42, 7833.

⁷⁸¹ Bengtson, A.; Hallberg, A.; Larhed, M. *Org. Lett.* **2002**, 4, 1231.

⁷⁸² Shibata, N.; Matsunaga, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *Synlett* **2005**, 1699.

Alkyl nitrites⁷⁸³ can be conveniently prepared by an exchange reaction $\text{ROH} + \text{R}'\text{ONO} \rightarrow \text{RONO} + \text{R}'\text{OH}$, where $\text{R} = t\text{-Bu}$.⁷⁸⁴ Primary amines can be converted to alkyl nitrates ($\text{RNH}_2 \rightarrow \text{RONO}_2$) by treatment with N_2O_4 at -78°C in the presence of an excess of amidine base.⁷⁸⁵ *Mitsunobu* conditions (Reaction **10-17**) can be used to prepare phosphate ester or phosphonate esters. The reaction can be done intramolecularly for prepare cyclic phosphonate esters.⁷⁸⁶

Alkyl halides are often used as substrates instead of alcohols. In such cases, the *salt* of the inorganic acid is usually used and the mechanism is nucleophilic substitution at the carbon atom. An important example is the treatment of alkyl halides with silver nitrate to form alkyl nitrates. This is used as a test for alkyl halides. In some cases, there is competition from the central atom. Thus nitrite ion is an ambident nucleophile that can give nitrites or nitro compounds (see Reaction **10-42**).⁷⁸⁷ Dialkyl or aryl alkyl ethers can be cleaved with anhydrous sulfonic acids.⁷⁸⁸



Here R'' may be alkyl or aryl. For dialkyl ethers, the reaction does not end as indicated above, since $\text{R}'\text{OH}$ is rapidly converted to $\text{R}'\text{OR}'$ by the sulfonic acid (Reaction **10-12**), which in turn is further cleaved to $\text{R}'\text{OSO}_2\text{R}''$ so that the product is a mixture of the two sulfonates. For aryl alkyl ethers, cleavage always takes place to give the phenol, which is not converted to the aryl ether under these conditions. Ethers can also be cleaved in a similar manner by mixed anhydrides of sulfonic and carboxylic acids⁷⁸⁹ (prepared as in Reaction **16-68**). β -Hydroxyalkyl perchlorates⁷⁹⁰ and sulfonates can be obtained from epoxides.⁷⁹¹ Epoxides and oxetanes give α,ω -dinitrates when treated with N_2O_5 .⁷⁹² Aziridines and azetidines react similarly, giving nitramine nitrates (e.g., *N*-butylazetidine gave $\text{NO}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{Bu})\text{NO}_2$).⁷⁹²

Phosphinate esters are prepared by transesterification-type reactions (**16-64**) from alcohols and other phosphinates.⁷⁹³

OS II, 106, 108, 109, 112, 204, 412; III, 148, 471; IV, 955; V, 839; VIII, 46, 50, 616. Also see, OS II, 111.

10-23 Alcohols from Amines

Hydroxy-de-amination



This transformation is rare. A rather direct method was reported whereby a primary amine reacted with KOH in diethylene glycol at 210°C .⁷⁹⁴ The reaction of

⁷⁸³ See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, **1988**, pp. 150–172.

⁷⁸⁴ Doyle, M.P.; Terpstra, J.W.; Pickering, R.A.; LePoire, D.M. *J. Org. Chem.* **1983**, *48*, 3379. See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, **1988**, pp. 150–156.

⁷⁸⁵ Barton, D.H.R.; Narang, S.C. *J. Chem. Soc. Perkin Trans. 1* **1977**, 1114.

⁷⁸⁶ Pungente, M.D.; Weiler, L. *Org. Lett.* **2001**, *3*, 643.

⁷⁸⁷ See Boguslavskaya, L.S.; Chuvatkin, N.N.; Kartashov, A.V. *Russ. Chem. Rev.* **1988**, *57*, 760.

⁷⁸⁸ Klamann, D.; Weyerstahl, P. *Chem. Ber.* **1965**, *98*, 2070.

⁷⁸⁹ Karger, M.H.; Mazur, Y. *J. Org. Chem.* **1971**, *36*, 532, 540.

⁷⁹⁰ See Zefirov, N.S.; Zhdankin, V.V.; Koz'min, A.S. *Russ. Chem. Rev.* **1988**, *57*, 1041.

⁷⁹¹ Zefirov, N.S.; Kirin, V.N.; Yur'eva, N.M.; Zhdankin, V.V.; Kozmin, A.S. *J. Org. Chem. USSR* **1987**, *23*, 1264.

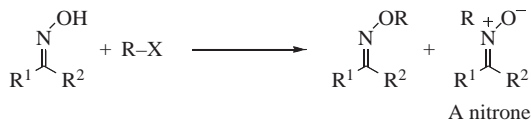
⁷⁹² Golding, P.; Millar, R.W.; Paul, N.C.; Richards, D.H. *Tetrahedron Lett.* **1988**, *29*, 2731, 2735.

⁷⁹³ Han, L.-B.; Zhao, C.-Q. *J. Org. Chem.* **2005**, *70*, 10121.

⁷⁹⁴ Rahman, S.M.A.; Ohno, H.; Tanaka, T. *Tetrahedron Lett.* **2001**, *42*, 8007.

(*S*)-phenethylamine and the bis-(sulfonyl chloride) of 1,2-benzenesulfonic acid, followed by KNO_2 and 18-crown-6 gave (*R*)-phenethyl alcohol in 70% yield and 40% enantiomeric excess (ee).⁷⁹⁵

10-24 Alkylation of Oximes⁷⁹⁶



Oximes can be alkylated by alkyl halides or sulfates. *N*-Alkylation is a side reaction, yielding a nitron.⁷⁹⁷ The relative yield of oxime ether and nitron depends on the nature of the reagents, including the configuration of the oxime, and on the reaction conditions.⁷⁹⁸ For example, *anti*-benzaloximes give nitrones, while the *syn* isomers give oxime ethers.⁷⁹⁹

OS III, 172; V, 1031. Also see, OS V, 269; VI, 199.

10.H.iii. Sulfur Nucleophiles

Sulfur compounds⁸⁰⁰ are better nucleophiles than their oxygen analogues (Sec. 10.G.ii), so in most cases these reactions take place faster and more smoothly than the corresponding reactions with oxygen nucleophiles. There is evidence that some of these reactions take place by SET mechanisms.⁸⁰¹

10-25 Attack by SH at an Alkyl Carbon: Formation of Thiols⁸⁰²

Mercapto-de-halogenation



Sodium sulfhydryde (NaSH) is a much better reagent for the formation of thiols (mercaptans) from alkyl halides than H_2S and is used much more often. It is easily prepared by bubbling H_2S into an alkaline solution, but hydrosulfide on a supported polymer resin has also been used.⁸⁰³ The reaction is most useful for primary halides. Secondary substrates give much lower yields, and the reaction fails completely for tertiary

⁷⁹⁵ Sørbye, K.; Tautermann, C.; Carlsen, P.; Fiksdahl, A. *Tetrahedron Asymmetry*, **1998**, 9, 681.

⁷⁹⁶ See Abele, E.; Lukevics, E. *Org. Prep. Proceed. Int.* **2000**, 32, 235.

⁷⁹⁷ See Torrsell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, **1988**, pp. 75–93; Katritzky, A.R.; Cui, X.; Long, Q.; Yanga, B.; Wilcox, A.L.; Zhang, Y.-K. *Org. Prep. Proceed. Int.* **2000**, 32, 175.

⁷⁹⁸ See Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, **1983**, pp. 262–272.

⁷⁹⁹ Buehler, E. *J. Org. Chem.* **1967**, 32, 261.

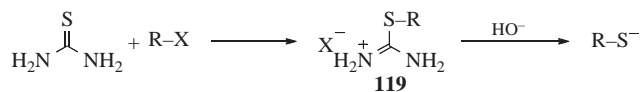
⁸⁰⁰ See Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, **1985**; Oae, S. *Organic Chemistry of Sulfur*, Plenum, NY, **1977**. For selenium compounds, see Krief, A.; Hevesi, L. *Organoselenium Chemistry I*, Springer, NY, **1988**; Liotta, D. *Organoselenium Chemistry*, Wiley, NY, **1987**.

⁸⁰¹ See Ashby, E.C.; Park, W.S.; Goel, A.B.; Su, W. *J. Org. Chem.* **1985**, 50, 5184.

⁸⁰² See Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, **1974**, pp. 179–211.

⁸⁰³ Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Chem. Lett.* **2000**, 1304.

halides because elimination predominates. Sulfuric and sulfonic esters can be used instead of halides. Thioethers (RSR) are often side products.⁸⁰⁴ The conversion can also be accomplished under neutral conditions by treatment of a primary halide with F^- and a tin sulfide (e.g., $Ph_3SnSSnPh_3$).⁸⁰⁵ An indirect method for the preparation of a thiol is the reaction of an alkyl halide with thiourea to give an isothiuronium salt (**119**), and subsequent treatment with alkali or a high-molecular-weight amine gives cleavage to the thiol.



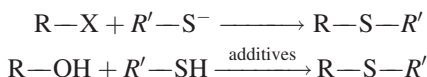
Other indirect methods are treatment of the halide with silyl-thiols and KH, followed by treatment with fluoride ion and water,⁸⁰⁶ and hydrolysis of *Bunte salts* (see Reaction **10-28**) is another method.

Thiols have also been prepared from alcohols. One method involves treatment with H_2S and a catalyst (e.g., Al_2O_3),⁸⁰⁷ but this is limited to primary alcohols. Another method involves treatment with *Lawesson's reagent* (see Reaction **16-10**).⁸⁰⁸ Tertiary nitro compounds give thiols ($RNO_2 \rightarrow RSH$) when treated with sulfur and sodium sulfide, followed by amalgamated aluminum.⁸⁰⁹

OS **III**, 363, 440; **IV**, 401, 491; **V**, 1046; **VIII**, 592. Also see, OS **II**, 345, 411, 573; **IV**, 232; **V**, 223; **VI**, 620.

10-26 Attack by S at an Alkyl Carbon: Formation of Thioethers

Alkylthio-de-halogenation; Alkylthio-de-hydroxylation



Thioethers (sulfides) can be prepared by treatment of alkyl halides with salts of thiols (thiolate anions).⁸¹⁰ The R' group may be alkyl or aryl and organolithium bases can be used to deprotonate the thiol.⁸¹¹ As in Reaction **10-25**, RX cannot be a tertiary halide, and sulfuric and sulfonic esters can be used instead of halides. As in the *Williamson Reaction* (**10-8**), yields are often improved by phase-transfer catalysis.⁸¹² Thiols react directly with alkyl halides in the presence of bases (e.g., DBU; see Reaction **17-13**)⁸¹³ or CsF .⁸¹⁴ Leaving groups other than chloride can be used, as in the Ru catalyzed reaction of thiols

⁸⁰⁴ See Vasil'tsov, A.M.; Trofimov, B.A.; Amosova, S.V. *J. Org. Chem. USSR* **1983**, 19, 1197.

⁸⁰⁵ Gingras, M.; Harpp, D.N. *Tetrahedron Lett.* **1990**, 31, 1397.

⁸⁰⁶ Miranda, E.I.; Díaz, M.J.; Rosado, I.; Soderquist, J.A. *Tetrahedron Lett.* **1994**, 35, 3221; Rane, A.M.; Miranda, E.I.; Soderquist, J. *Tetrahedron Lett.* **1994**, 35, 3225.

⁸⁰⁷ Lucien, J.; Barrault, J.; Guisnet, M.; Maurel, R. *Nouv. J. Chim.* **1979**, 3, 15.

⁸⁰⁸ Nishio, T. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1113.

⁸⁰⁹ Kornblum, N.; Widmer, J. *J. Am. Chem. Soc.* **1978**, 100, 7086.

⁸¹⁰ See Peach, M.E. in Patai, S. *The Chemistry of the Thiol Groups*, pt. 2, Wiley, NY, **1974**, pp. 721-735.

⁸¹¹ Yin, J.; Pidgeon, C. *Tetrahedron Lett.* **1997**, 38, 5953.

⁸¹² See Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, **1977**, pp. 221-233. Also see Salvatore, R.N.; Smith, R.A.; Nischwitz, A.K.; Gavi, T. *Tetrahedron Lett.* **2005**, 46, 8931.

⁸¹³ Ono, N.; Miyake, H.; Saito, T.; Kaji, A. *Synthesis* **1980**, 952. See also, Ferreira, J.T.B.; Comasseto, J.V.; Braga, A.L. *Synth. Commun.* **1982**, 12, 595; Ando, W.; Furuhashi, T.; Tsumaki, H.; Sekiguchi, A. *Synth. Commun.* **1982**, 12, 627.

⁸¹⁴ Shah, S.T.A.; Khan, K.M.; Heinich, A.M.; Voelter, W. *Tetrahedron Lett.* **2002**, 43, 8281.

with propargylic carbonates.⁸¹⁵ Vinylic sulfides can be prepared by treating vinylic bromides with PhS^- in the presence of a Ni complex,⁸¹⁶ or in the presence of $\text{Pd}(\text{PPh}_3)_4$. Alternatively, the Ag salt of an enethiol reacts with iodomethane to give the corresponding methyl vinyl sulfide.⁸¹⁷

In some cases, alcohols can be converted to thioethers by reaction with thiols. Tertiary alcohols react with thiols in the presence of sulfuric acid to give thioethers, and the reaction works best with tertiary substrates.⁸¹⁸ This reaction is analogous to Reaction 10-12. Thiophenol reacts with propargylic alcohols in the presence of a Ru catalyst to give propargylic thioethers.⁸¹⁹ Primary and secondary alcohols can be converted to alkyl aryl sulfides ($\text{ROH} \rightarrow \text{RSAr}$) in high yields by treatment with Bu_3P and an *N*-(arylthio)succinimide in benzene.⁸²⁰ Iodine catalyzes the allylic alkylation of thiols.⁸²¹ Thioethers (RSR') can be prepared from an alcohol ROH and a halide $\text{R}'\text{Cl}$ by treatment with tetramethylthiourea $\text{Me}_2\text{NC}(=\text{S})\text{NMe}_2$ followed by NaH .⁸²²

Thiolate ions are also useful for the demethylation of certain ethers,⁸²³ esters, amines, and quaternary ammonium salts. Aryl methyl ethers⁸²⁴ can be cleaved by heating with EtS^- in the dipolar aprotic solvent DMF: $\text{ROAr} + \text{EtS}^- \rightarrow \text{ArO}^- + \text{EtSR}$.⁸²⁵ Allylic sulfides have been prepared by treating allylic carbonates ROCO_2Me (R = an allylic group) with a thiol and a $\text{Pd}(0)$ catalyst.⁸²⁶ A good method for the demethylation of quaternary ammonium salts consists of refluxing them with PhS^- in 2-butanone to give the amine and methyl phenyl sulfide.⁸²⁷

A methyl group is cleaved more readily than other simple alkyl groups (e.g., ethyl), although loss of these groups competes. Benzylic and allylic groups cleave even more easily, and this is a useful procedure for the cleavage of benzylic and allylic groups from quaternary ammonium salts, even if methyl groups are also present.⁸²⁸

Symmetrical thioethers ($\text{R}-\text{S}-\text{R}$) can also be prepared by treatment of an alkyl halide ($\text{R}-\text{X}$) with sodium sulfide (Na_2S).⁸²⁹ Symmetrical thioethers have also been prepared by the reaction of $\text{S}(\text{MgBr})_2$ with allylic halides.⁸³⁰ This reaction can be carried out internally, by treatment of sulfide ions with 1,4-, 1,5-, or 1,6-dihalides, to prepare five-, six-, and

⁸¹⁵ Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T.-a. *J. Am. Chem. Soc.* **2002**, *124*, 12960.

⁸¹⁶ Cristau, H.J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *J. Org. Chem.* **1986**, *51*, 875.

⁸¹⁷ Ochiai, M.; Hirobe, M.; Miyamoto, K. *J. Am. Chem. Soc.* **2006**, *128*, 9046.

⁸¹⁸ See Cain, M.E.; Evans, M.B.; Lee, D.F. *J. Chem. Soc.* **1962**, 1694.

⁸¹⁹ Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 15172.

⁸²⁰ Walker, K.A.M. *Tetrahedron Lett.* **1977**, 4475. See the references in this paper for other methods of converting alcohols to sulfides. See also, Cleary, D.G. *Synth. Commun.* **1989**, *19*, 737.

⁸²¹ Zhang, X.; Rao, W.; Chan, P.W.H. *Synlett* **2008**, 2204.

⁸²² Fujisaki, S.; Fujiwara, I.; Norisue, Y.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2429.

⁸²³ See Evers, M. *Chem. Scr.* **1986**, *26*, 585.

⁸²⁴ Also see Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* **1980**, *21*, 2305; Williard, P.G.; Fryhle, C.B. *Tetrahedron Lett.* **1980**, *21*, 3731; Node, M.; Nishide, K.; Fujii, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275; Evers, M.; Christiaens, L. *Tetrahedron Lett.* **1983**, *24*, 377; Tiecco, M. *Synthesis* **1988**, 749.

⁸²⁵ Feutrill, G.I.; Mirrington, R.N. *Tetrahedron Lett.* **1970**, 1327; *Aust. J. Chem.* **1972**, *25*, 1719, 1731.

⁸²⁶ Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1994**, *50*, 10321.

⁸²⁷ Shamma, M.; Deno, N.C.; Remar, J.F. *Tetrahedron Lett.* **1966**, 1375. For alternative procedures, see Hutchins, R.O.; Dux, F.J. *J. Org. Chem.* **1973**, *38*, 1961; Posner, G.H.; Ting, J. *Synth. Commun.* **1974**, *4*, 355.

⁸²⁸ Kametani, T.; Kigasawa, T.; Hiiragi, M.; Wagatsuma, N.; Wakisaka, K. *Tetrahedron Lett.* **1969**, 635.

⁸²⁹ For another reagent, see Harpp, D.N.; Gingras, M.; Aida, T.; Chan, T.H. *Synthesis* **1987**, 1122.

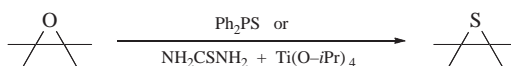
⁸³⁰ Nedugov, A.N.; Pavlova, N.N. *Zhur. Org. Khim.*, **1992**, *28*, 1401 (Engl. 1103).

seven-membered⁸³¹ sulfur-containing heterocyclic rings. Certain larger rings have also been closed in this way.⁸³²

gem-Dihalides can be converted to dithioacetals $[RCH(SR')_2]$,⁸³³ and acetals have been converted to monothioacetals $[R_2C(OR')(SR')]$,⁸³⁴ and to dithioacetals.⁸³⁵ The combination of carbon disulfide and $NaBH_4$ converted 1,3-dibromopropane to 1,3-dithiane.⁸³⁶

When epoxides are substrates,⁸³⁷ reaction with $PhSeSnBu_3/BF_3 \cdot OEt_2$ ⁸³⁸ gives the corresponding β -hydroxy selenide in a manner analogous to that mentioned in Reaction 10-25. Reaction of an epoxide with Ph_3SiSH followed by treatment with Bu_4NF gives hydroxy-thiols.⁸³⁹

Epoxides can also be directly converted to episulfides (thiiranes)⁸⁴⁰ by treatment with a phosphine sulfide (e.g., Ph_3PS),⁸⁴¹ with thiourea and titanium tetraisopropoxide⁸⁴² or thiourea and $LiBF_4$ in acetonitrile,⁸⁴³ with NH_4SCN and $TiO(tfa)_2$ ($tfa = trifluoroacetyl$),⁸⁴⁴ with $(EtO)_2P(=O)H/S/Al_2O_3$,⁸⁴⁵ with $KSCN$ and $InBr_3$,⁸⁴⁶ and with $KSCN$ in ionic liquids (Sec. 9.D.iii).⁸⁴⁷ 2,4,6-Trichloro-1,3,5-triazine catalyzes this conversion under solvent-free conditions.⁸⁴⁸



Selenides (selenoethers) and tellurides can be prepared via RSe^- and RTe^- species,⁸⁴⁹ and Se and borohydride exchange resin followed by the halide give the selenoether.⁸⁵⁰ The La/I_2 catalyzed reaction of diphenyl diselenide with primary alkyl iodides gave arylalkyl

⁸³¹ Tan, L.C.; Pagni, R.M.; Kabalka, G.W.; Hillmyer, M.; Woosley, J. *Tetrahedron Lett.* **1992**, 33, 7709.

⁸³² See Singh, A.; Mehrotra, A.; Regen, S.L. *Synth. Commun.* **1981**, 11, 409.

⁸³³ See, for example Wähälä, K.; Ojanperä, I.; Häyri, L.; Hase, T.A. *Synth. Commun.* **1987**, 17, 137.

⁸³⁴ Sato, T.; Kobayashi, T.; Gojo, T.; Yoshida, E.; Otera, J.; Nozaki, H. *Chem. Lett.* **1987**, 1661.

⁸³⁵ Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, 66, 7527 and references cited therein; Ranu, B.C.; Das, A.; Samanta, S. *Synlett.* **2002**, 727.

⁸³⁶ Wan, Y.; Kurchan, A.N.; Barnhurst, L.A.; Kutateladze, A.G. *Org. Lett.* **2000**, 2, 1133.

⁸³⁷ Chini, M.; Crotti, P.; Giovani, E.; Macchia, F.; Pineschi, M. *Synlett*, **1992**, 303.

⁸³⁸ Nishiyama, Y.; Ohashi, H.; Itoh, K.; Sonoda, N. *Chem. Lett.* **1998**, 159.

⁸³⁹ Brittain, J.; Gareau, Y. *Tetrahedron Lett.* **1993**, 34, 3363.

⁸⁴⁰ See Fokin, A.V.; Kolomiets, A.F. *Russ. Chem. Rev.* **1975**, 44, 138. Key intermediates have been isolated: Kleiner, C.M.; Horst, L.; Würtele, C.; Wende, R.; Schreiner, P.R. *Org. Biomol. Chem.* **2009**, 7, 1397. See Das, B.; Reddy, V.S.; Krishnaiah, M. *Tetrahedron Lett.* **2006**, 47, 8471.

⁸⁴¹ Chan, T.H.; Finkenbine, J.R. *J. Am. Chem. Soc.* **1972**, 94, 2880.

⁸⁴² Gao, Y.; Sharpless, K.B. *J. Org. Chem.* **1988**, 53, 4114. Also see Bouda, H.; Borredon, M.E.; Delmas, M.; Gaset, A. *Synth. Commun.* **1987**, 17, 943; **1989**, 19, 491.

⁸⁴³ Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* **2003**, 33, 595.

⁸⁴⁴ Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* **1998**, 28, 3913. See also, Tamami, B.; Kolahdoozan, M. *Tetrahedron Lett.* **2004**, 45, 1535.

⁸⁴⁵ Kaboudin, B.; Norouzi, H. *Tetrahedron Lett.* **2004**, 45, 1283.

⁸⁴⁶ Yadav, J.S.; Reddy, B.V.S.; Baishya, G. *Synlett.* **2003**, 396.

⁸⁴⁷ Yadav, J.S.; Reddy, B.V.S.; Reddy, Ch.S.; Rajasekhar, K. *J. Org. Chem.* **2003**, 68, 2525.

⁸⁴⁸ Bandgar, B.P.; Joshi, N.S.; Kamble, V.T. *Tetrahedron Lett.* **2006**, 47, 4775.

⁸⁴⁹ Cohen, R.J.; Fox, D.L.; Salvatore, R.N. *J. Org. Chem.* **2004**, 69, 4265. Also see Monahan, R.; Brown, D.; Waykole, L.; Liotta, D. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, **1987**, pp. 207–241.

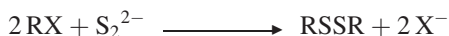
⁸⁵⁰ Yanada, K.; Fujita, T.; Yanada, R. *Synlett*, **1998**, 971.

selenides,⁸⁵¹ Indium has been used with alkyl halides.⁸⁵² A Zn mediated synthesis of tertiary alkyl selenides from tertiary alkyl halides is known.⁸⁵³ Diaryl selenides (Ar—Se—Ar') have been prepared by coupling aryl iodides with tin reagents (ArSeSnR₃) with a Pd catalyst.⁸⁵⁴ α -Seleno aldehydes are prepared by the reaction of an aldehyde with PhSe(N(phthalimide)).⁸⁵⁵

OS II, 31, 345, 547, 576; III, 332, 751, 763; IV, 396, 667, 892, 967; V, 562, 780, 1046; VI, 5, 31, 268, 364, 403, 482, 556, 601, 683, 704, 737, 833, 859; VII, 453; VIII, 592. See also, OS VI, 776.

10-27 Formation of Disulfides⁸⁵⁶

Dithio-de-dihalo- *aggre* -substitution

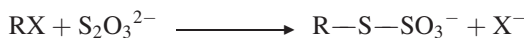


Disulfides can be prepared by treatment of alkyl halides with disulfide ions and also indirectly by the reaction of *Bunte salts* (see Reaction 10-28) with acid solutions of iodide, thiocyanate ion, or thiourea,⁸⁵⁷ or by pyrolysis or treatment with hydrogen peroxide. Alkyl halides also give disulfides when heated to reflux with sulfur and NaOH.⁸⁵⁸ Some molybdenum compounds convert alkyl halides to disulfides, including (BnNEt₃)₆Mo₇S₂₄.⁸⁵⁹

There are no OS references, but a similar preparation of a polysulfide may be found in OS IV, 295.

10-28 Formation of Bunte Salts

Sulfonatothio-de-halogenation



Primary and secondary, but not tertiary, alkyl halides are easily converted to *Bunte salts* (RSSO₃[−]) by treatment with thiosulfate ion.⁸⁶⁰ Bunte salts can be hydrolyzed with acids to give the corresponding thiols⁸⁶¹ or converted to disulfides, tetrasulfides, or pentasulfides.⁸⁶²

OS VI, 235.

⁸⁵¹ Nishino, T.; Okada, M.; Kuroki, T.; Watanabe, T.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* **2002**, 67, 8696. Zinc in aqueous media has also been used: see Bieber, L.W.; de Sá, A.C.P.F.; Menezes, P.H.; Goncalves, S.M.C. *Tetrahedron Lett.* **2001**, 42, 4597.

⁸⁵² Munbunjong, W.; Lee, E.H.; Chavasiri, W.; Jang, D.O. *Tetrahedron Lett.* **2005**, 46, 8769.

⁸⁵³ Krief, A.; Derock, M.; Lacroix, D. *Synlett* **2005**, 2832.

⁸⁵⁴ Nishiyama, Y.; Tokunaga, K.; Sonoda, N. *Org. Lett.* **1999**, 1, 1725.

⁸⁵⁵ Wang, J.; Li, H.; Mei, Y.; Lou, B.; Xu, D.; Xie, D.; Guo, H.; Wang, W. *J. Org. Chem.* **2005**, 70, 5678.

⁸⁵⁶ See Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2004**, 125, 6624.

⁸⁵⁷ Milligan, B.; Swan, J.M. *J. Chem. Soc.* **1962**, 2712.

⁸⁵⁸ Chorbadjiev, S.; Roumian, C.; Markov, P. *J. Prakt. Chem.* **1977**, 319, 1036. For an example using microwave irradiation, see Wang, J.-X.; Gao, L.; Huang, D. *Synth. Commun.* **2002**, 32, 963.

⁸⁵⁹ See Polshettiwar, V.; Nivsarkar, M.; Acharya, J.; Kaushik, M.P. *Tetrahedron Lett.* **2003**, 44, 887.

⁸⁶⁰ For a review of Bunte salts, see Distler, H. *Angew. Chem. Int. Ed.* **1967**, 6, 544–553.

⁸⁶¹ Kice, J.L. *J. Org. Chem.* **1963**, 28, 957.

⁸⁶² Milligan, B.; Saville, B.; Swan, J.M. *J. Chem. Soc.* **1963**, 3608.

10-29 Alkylation of Sulfinic Acid Salts**Alkylsulfonyl-de-halogenation**

Alkyl halides or alkyl sulfates, treated with the salts of sulfinic acids, give sulfones.⁸⁶³ A Pd catalyzed reaction with a chiral complexing agent led to sulfones with modest asymmetric induction.⁸⁶⁴ Alkyl sulfinates ($\text{R}'\text{SO}-\text{OR}$) may be side products.⁸⁶⁵ Sodium tosylsulfinate reacted with allylic acetates in the presence of a Pd catalyst to give the corresponding sulfone.⁸⁶⁶ Sulfonic acids themselves can be used, if DBU (see Reaction 17-13) is present.⁸⁶⁷ Sulfonyl halides react with allylic halides in the presence of AlCl_3-Fe ⁸⁶⁸ and with benzyl halides in the presence of Sm/HgCl_2 .⁸⁶⁹ Sulfones have also been prepared by treatment of alkyl halides with tosylhydrazide.⁸⁷⁰ The copper(II)-catalyzed cross-coupling of organoboronic acids and sulfinic acid salts leads to sulfones.⁸⁷¹ Vinyl sulfones were prepared from PhSO_2Na and vinyl iodonium salts $\text{C}=\text{C}-\text{I}^+\text{Ph BF}_4^-$.⁸⁷² OS IV, 674; IX, 497. See also, OS VI, 1016.

10-30 Formation of Alkyl Thiocyanates**Thiocyanato-de-halogenation**

Alkyl halides⁸⁷³ or sulfuric or sulfonic esters can be heated with sodium or potassium thiocyanate to give alkyl thiocyanates,⁸⁷⁴ although the attack by the analogous cyanate ion (Reaction 10-44) gives exclusive *N*-alkylation. Primary amines can be converted to thiocyanates by the *Katritzky pyrylium-pyridinium method* (Sec. 10.G.iii).⁸⁷⁵ Tertiary chlorides are converted to tertiary thiocyanates with $\text{Zn}(\text{SCN})_2$ in pyridine and ultrasound.⁸⁷⁶

OS II, 366.

⁸⁶³ See Schank, K. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, **1988**, pp. 165–231, pp. 177–188. For a reaction using the MgBr salt of an aryl sulfinic acid, see Wu, J.-P.; Emeigh, J.; Su, X.-P. *Org. Lett.* **2005**, 7, 1223.

⁸⁶⁴ Eichelmann, H.; Gais, H.-J. *Tetrahedron Asymmetry*, **1995**, 6, 643.

⁸⁶⁵ See Kielbasinski, P.; Zurawinski, R.; Drabowicz, J.; Mikolajczyk, M. *Tetrahedron* **1988**, 44, 6687.

⁸⁶⁶ Felpin, F.-X.; Landais, Y. *J. Org. Chem.* **2005**, 70, 6441. Also see Chandrasekhar, S.; Jagadeshwar, V.; Saritha, B.; Narsihmulu, C. *J. Org. Chem.* **2005**, 70, 6506.

⁸⁶⁷ Biswas, G.; Mal, D. *J. Chem. Res. (S)* **1988**, 308.

⁸⁶⁸ Saikia, P.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* **2001**, 512.

⁸⁶⁹ Zhang, J.; Zhang, Y. *J. Chem. Res. (S)* **2001**, 516.

⁸⁷⁰ Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron* **1989**, 45, 6791.

⁸⁷¹ Huang, F.; Batey, R.A. *Tetrahedron* **2007**, 63, 7667.

⁸⁷² Ochiai, M.; Oshima, K.; Masaki, Y.; Kunishima, M.; Tani, S. *Tetrahedron Lett.* **1993**, 34, 4829.

⁸⁷³ Renard, P.-Y.; Schwebel, H.; Vayron, P.; Leclerc, E.; Dias, S.; Mioskowski, C. *Tetrahedron Lett.* **2001**, 42, 8479. The reagent $\text{Ph}_3\text{P}(\text{SCN})_2$ has also been used: see Iranpoor, N.; Firouzabadi, H.; Shaterian, H.R. *Tetrahedron Lett.* **2002**, 43, 3439. Also see Mohanazadeh, F.; Aghvami, M. *Tetrahedron Lett.* **2007**, 48, 7240.

⁸⁷⁴ See Guy, R.G. in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2, pp. 819–886, Wiley, NY, **1977**, pp. 819–886.

⁸⁷⁵ Katritzky, A.R.; Gruntz, U.; Mongelli, N.; Rezende, M.C. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1953. See Tamura, Y.; Kawasaki, T.; Adachi, M.; Tanio, M.; Kita, Y. *Tetrahedron Lett.* **1977**, 4417.

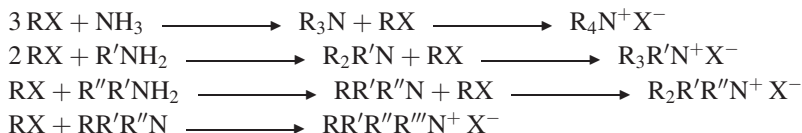
⁸⁷⁶ Bettadaiah, B.K.; Gurudutt, K.N.; Srinivas, P. *Synth. Commun.* **2003**, 33, 2293.

10.H.iv. Nitrogen Nucleophiles

A. Attack by NH₂, NHR, or NR₂ at an Alkyl Carbon

10-31 Alkylation of Amines

Amino-de-halogenation (alkyl)



The reaction between alkyl halides and ammonia or primary amines is not usually a feasible method for the preparation of primary or secondary amines, since they are stronger bases than ammonia and preferentially attack the substrate. However, the reaction is very useful for the preparation of tertiary amines⁸⁷⁷ and quaternary ammonium salts. If ammonia is the nucleophile,⁸⁷⁸ the three or four alkyl groups on the nitrogen of the product must be identical. If a primary, secondary, or tertiary amine is used, then different alkyl groups can be placed on the same nitrogen atom. The conversion of tertiary amines to quaternary salts is called the *Menshutkin reaction*.⁸⁷⁹ It is sometimes possible to use this method for the preparation of a primary amine by the use of a large excess of ammonia or a secondary amine by the use of a large excess of primary amine. Metal-catalyzed methods are available to convert primary amines to secondary amines,⁸⁸⁰ and secondary amines can be converted to tertiary amines.⁸⁸¹ Ionic liquids have been used to facilitate amination reactions.⁸⁸² The use of ammonia in methanol with microwave irradiation has also been effective.⁸⁸³ Microwave irradiation has also been used in reactions of aniline with allyl iodides.⁸⁸⁴ Bromides react faster than chlorides, and secondary amines reaction with 3-chloro-1-bromopropane via the bromide, in the presence of Zn and THF.⁸⁸⁵ N-Alkylation has been accomplished using alkyl halides in aqueous media.⁸⁸⁶

Bases other than amine can be used. Both sodium carbonate⁸⁸⁷ and lithium hydroxide⁸⁸⁸ have been used. Cesium hydroxide was successfully used as a base in the presence of

⁸⁷⁷ See Gibson, M.S. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, **1968**, pp. 45–55; Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, **1965**, pp. 14–29.

⁸⁷⁸ See Jeyaraman, R. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, **1983**, pp. 9–83.

⁸⁷⁹ For a discussion of solvent effects see Sola, M.; Lledos, A.; Duran, M.; Bertran, J.; Abboud, J.L.M. *J. Am. Chem. Soc.* **1991**, *113*, 2873. For other parameters, see Bottini, A.T. *Sel. Org. Transform.* **1970**, *1*, 89; Persson, J.; Berg, U.; Matsson, O. *J. Org. Chem.* **1995**, *60*, 5037; Zoltewicz, J.A.; Dedy, L.W. *Adv. Heterocycl. Chem.* **1978**, *22*, 71; Shaik, S.; Ioffe, A.; Reddy, A.C.; Pross, A. *J. Am. Chem. Soc.* **1994**, *116*, 262.

⁸⁸⁰ Lorentz-Petersen, L.L.R.; Jensen, P.; Madsen, R. *Synthesis* **2009**, 4110.

⁸⁸¹ Kurosu, M.; Dey, S.S.; Crick, D.C. *Tetrahedron Lett.* **2006**, *47*, 4871.

⁸⁸² Lyubimov, S.E.; Davankov, V.A.; Gavrilov, K.N. *Tetrahedron Lett.* **2006**, *47*, 2721.

⁸⁸³ Saulnier, M.G.; Zimmermann, K.; Struzynski, C.P.; Sang, X.; Velaparthi, U.; Wittman, M.; Frennesson, D.B. *Tetrahedron Lett.* **2004**, *45*, 397.

⁸⁸⁴ Romera, J.L.; Cid, J.M.; Trabanco, A.A. *Tetrahedron Lett.* **2004**, *45*, 8797.

⁸⁸⁵ Murty, M.S.R.; Jyothirmai, B.; Krishna, P.R.; Yadav, J.S. *Synth. Commun.* **2003**, *33*, 2483.

⁸⁸⁶ Singh, C.B.; Kavala, V.; Samal, A.K.; Patel, B.K. *Eur. J. Org. Chem.* **2007**, 1369; Simion, A.M.; Arimura, T.; Miyazawa, A.; Simion, C.; Prakash, G.K.S.; Olah, G.A.; Tashiro, M. *Synth. Commun.* **2009**, *39*, 2859.

⁸⁸⁷ Faul, M.M.; Kobierski, M.E.; Kopach, M.E. *J. Org. Chem.* **2003**, *68*, 5739.

⁸⁸⁸ Cho, J.H.; Kim, B.M. *Tetrahedron Lett.* **2002**, *43*, 1273.

molecular sieve 4 Å,⁸⁸⁹ and cesium fluoride has been used with benzylic halides.⁸⁹⁰ Potassium carbonate in DMSO has been used for the alkylation of aniline.⁸⁹¹

The limitations of this approach can be seen in the reaction of a saturated solution of ammonia in 90% ethanol with ethyl bromide in a 16:1 molar ratio, which gave 34.2% of the primary amine (at a 1:1 ratio the yield was 11.3%).⁸⁹² α -Halo acids are one type of substrate that give reasonable yields of primary amine (provided a large excess of NH_3 is used) and are subsequently converted to amino acids. *N*-Chloromethyl lactams also react with amines to give good yields to the *N*-aminomethyl lactam.⁸⁹³ An indirect method to prepare primary amines from alkyl halides uses Reaction **10-43**, followed by reduction of the azide (**19-32**),⁸⁹⁴ and the *Gabriel synthesis* (**10-41**) is effective.

The immediate product in any particular step is the protonated amine, but it rapidly loses a proton to another molecule of ammonia or amine in an equilibrium process, for example,



When a primary or secondary amine must be converted directly to the quaternary salt (*exhaustive alkylation*), the rate can be increased by the addition of a non-nucleophilic strong base that serves to remove the proton from $\text{RR}'\text{NH}_2^+$ or $\text{RR}'\text{R}^2\text{NH}^+$ and thus liberates the amine to attack another molecule of RX .⁸⁹⁵

The conjugate bases of ammonia and of primary and secondary amines (NH_2^- , RNH^- , R_2N^-) are generically known as *amide bases*, and are sometimes used as nucleophiles,⁸⁹⁶ including amide bases generated from organolithium reagents and amines (R_2NLi).⁸⁹⁷ This is in contrast to analogous methods **10-1**, **10-8**, **10-25**, and **10-26**. Primary alkyl, allylic, and benzylic bromides, iodides, and tosylates react with sodium bis(trimethylsilyl)amide to give derivatives that are easily hydrolyzed to produce amine salts in high overall yields.⁸⁹⁸ Primary arylamines are easily alkylated, but diaryl- and triaryl amines are very poor nucleophiles. However, the reaction has been carried out with diarylamines.⁸⁹⁹ Sulfates or sulfonates can be used instead of halides. *N*-Alkylation of heterocycles is sometimes problematic, but pyrrole is converted to *N*-methylpyrrole with KOH, iodomethane in ionic liquids.⁹⁰⁰

The reaction can be carried out intramolecularly to give cyclic amines, with three-, five-, and six-membered (but not four-membered) rings being easily prepared. Thus, 4-chloro-1-aminobutane treated with base gives pyrrolidine, and 2-chloroethylamine gives

⁸⁸⁹ Salvatore, R.N.; Schmidt, S.E.; Shin, S.I.; Nagle, A.S.; Worrell, J.H.; Jung, K.W. *Tetrahedron Lett.* **2000**, *41*, 9705.

⁸⁹⁰ Hayat, S.; Rahman, A.-u.; Choudhary, M.I.; Khan, K.M.; Schumann, W.; Bayer, E. *Tetrahedron* **2001**, *57*, 9951.

⁸⁹¹ Salvatore, R.N.; Nagle, A.S.; Jung, K.W. *J. Org. Chem.* **2002**, *67*, 674.

⁸⁹² Werner, E.A. *J. Chem. Soc.* **1918**, *113*, 899.

⁸⁹³ Chen, P.; Suh, D.J.; Smith, M.B. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1317; Deskus, J.; Fan, D.-p.; Smith, M.B. *Synth. Commun.* **1998**, *28*, 1649.

⁸⁹⁴ See Kumar, H.M.S.; Anjaneyulu, S.; Reddy, B.V.S.; Yadav, J.S. *Synlett.* **1999**, 551.

⁸⁹⁵ Sommer, H.Z.; Lipp, H.I.; Jackson, L.L. *J. Org. Chem.* **1971**, *36*, 824. See also, Chuang, T.-H.; Sharpless, K.B. *Org. Lett.* **2000**, *2*, 3555.

⁸⁹⁶ See DePue, J.S.; Collum, D.B. *J. Am. Chem. Soc.* **1988**, *110*, 5524.

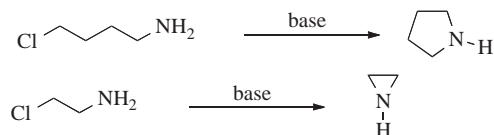
⁸⁹⁷ Vitale, A.A.; Chioconci, A.A. *J. Chem. Res. (S)* **1996**, 336.

⁸⁹⁸ Bestmann, H.J.; Wölfel, G. *Chem. Ber.* **1984**, *117*, 1250.

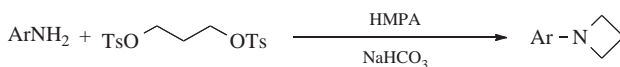
⁸⁹⁹ Patai, S.; Weiss, S. *J. Chem. Soc.* **1959**, 1035.

⁹⁰⁰ Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* **2004**, 1951.

aziridine⁹⁰¹ (analogous to Reaction 10-9):



Reduction of *N*-(3-bromopropyl) imines gives a bromoamine *in situ*, which cyclizes to the aziridine.⁹⁰² Five-membered ring amines (pyrrolidines) can be prepared from alkenyl amines via treatment with *N*-chlorosuccinimide (NCS) and then Bu₃SnH.⁹⁰³ The Pd catalyzed internal addition of amine to allylic acetates leads to cyclic products via a S_N2' reaction.⁹⁰⁴ Three-membered cyclic amines (aziridines) can be prepared from chiral conjugated amides via bromination and reaction with an amine.⁹⁰⁵ Four-membered cyclic amines (azetidines) have been prepared from the ditosylate of 1,3-propanediol⁹⁰⁶ and from 1,3-dichloropropane.⁹⁰⁷ This reaction was also used to close five-, six-, and seven-membered rings.



As usual, tertiary substrates do not give the reaction at all, but undergo preferential elimination upon treatment with a basic amine. However, tertiary (but not primary or secondary) halides (e.g., R₃CCl) can be converted to primary amines (R₃CNH₂) by treatment with NCl₃ and AlCl₃⁹⁰⁸ in a reaction related to Reaction 10-39. Ruthenium(II) complexes have been used for the alkylation of aryl amines.⁹⁰⁹

Primary amines can be prepared from alkyl halides by the use of hexamethylenetetramine⁹¹⁰ followed by cleavage of the resulting salt with ethanolic HCl. The method called the *Delépine reaction* is most successful for active halides (e.g., allylic and benzylic halides and α-halo ketones).

A convenient way of obtaining secondary amines without contamination by primary or tertiary amines involves treatment of alkyl halides with the sodium or calcium salt of cyanamide (NH₂—CN) to give disubstituted cyanamides, which are then hydrolyzed and decarboxylated to secondary amines. Good yields are obtained when the reaction is carried out under phase-transfer conditions.⁹¹¹ The R group may be primary, secondary, allylic, or benzylic. 1,ω-Dihalides give cyclic secondary amines. Aminoboranes react with sulfonate esters to give a derivative that can be hydrolyzed to a tertiary amine.⁹¹² An aminyl-radical

⁹⁰¹ See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, **1969**, pp. 1–59.

⁹⁰² DeKimpe, N.; DeSmaele, D. *Tetrahedron Lett.* **1994**, 35, 8023. Also see, De Kimpe, N.; Boelens, M.; Piqueur, J.; Baele, J. *Tetrahedron Lett.* **1994**, 35, 1925.

⁹⁰³ Tokuda, M.; Fujita, H.; Sugimoto, H. *J. Chem. Soc. Perkin Trans. 1* **1994**, 777.

⁹⁰⁴ Grellier, M.; Pfeffer, M.; van Koten, G. *Tetrahedron Lett.* **1994**, 35, 2877.

⁹⁰⁵ Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett.* **1994**, 35, 1653.

⁹⁰⁶ Juaristi, E.; Madrigal, D. *Tetrahedron* **1989**, 45, 629.

⁹⁰⁷ Ju, Y.; Varma, R.S. *J. Org. Chem.* **2006**, 71, 135.

⁹⁰⁸ Strand, J.W.; Kovacic, M.K. *J. Am. Chem. Soc.* **1973**, 95, 2977.

⁹⁰⁹ Naskar, S.; Bhattacharjee, M. *Tetrahedron Lett.* **2007**, 48, 3367; Hollmann, D.; Bähn, S.; Tillack, A.; Parton, R.; Altink, R.; Beller, M. *Tetrahedron Lett.* **2008**, 49, 5742.

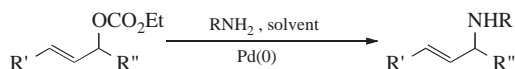
⁹¹⁰ See Blazevec, N.; Kolbah, D.; Belin, B.; Sunjic, V.; Kajfez, F. *Synthesis* **1979**, 161.

⁹¹¹ Jonczyk, A.; Ochal, Z.; Makosza, M. *Synthesis* **1978**, 882.

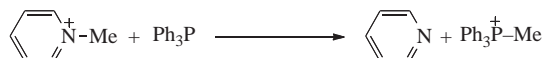
⁹¹² Thomas, S.; Huynh, T.; Enriquez-Rios, V.; Singaram, B. *Org. Lett.* **2001**, 3, 3915.

cyclization process was used to prepare cyclic amines.⁹¹³ *N*-Silylalkyl amines are formed from amines by reaction with halotrialkylsilanes and a suitable base.⁹¹⁴ Amines react directly with triarylsilanes in the presence of Yb catalysts.⁹¹⁵

Palladium compounds react with allylic halides, acetates, or carbonate derivatives to generate π -allyl Pd intermediates that react with amines to give an allylic amine (see the reaction below).⁹¹⁶ The same reaction is discussed in Reaction 10-60 with other nucleophiles. Propargylic amines can be prepared by similar methodology.⁹¹⁷ Boronic acid derivatives leads to methylation of aniline derivatives in the presence of cupric acetate.⁹¹⁸ *tert*-Butylamines can be prepared from isobutylene, HBr, and the amine by heating a sealed tube.⁹¹⁹



Phosphines behave similarly to amines, and compounds, such as R_3P and $\text{R}_4\text{P}^+ \text{X}^-$, can be prepared.⁹²⁰ The reaction between triphenylphosphine and quaternary salts of nitrogen heterocycles in an aprotic solvent is probably the best way of dealkylating the heterocycles, for example,⁹²¹



Other phosphorus compounds can be alkylated. Phosphinate esters, for example, react with a suitable base and then an alkyl halide to give the P-substituted product.⁹²²

OS I, 23, 48, 102, 300, 488; II, 85, 183, 290, 328, 374, 397, 419, 563; III, 50, 148, 254, 256, 495, 504, 523, 705, 753, 774, 813, 848; IV, 84, 98, 383, 433, 466, 582, 585, 980; V, 88, 124, 306, 361, 434, 499, 541, 555, 608, 736, 751, 758, 769, 825, 883, 985, 989, 1018, 1085, 1145; VI, 56, 75, 104, 106, 175, 552, 652, 704, 818, 967; VIII, 9, 152, 231, 358. Also see, OS II, 395; IV, 950; OS V, 121; OS I, 203.

For *N*-arylation of amines see Reaction 13-5.

⁹¹³ Crich, D.; Shirai, M.; Rumthao, S. *Org. Lett.* **2003**, 5, 3767.

⁹¹⁴ Greene, T.W. *Protective Groups in Organic Synthesis* Wiley, New York, **1980**; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis* 2nd ed., Wiley, New York, **1991**; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis* 3rd ed., Wiley, New York, **1999**; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis* 4th ed., Wiley, New Jersey, **2006**.

⁹¹⁵ Takaki, K.; Kamata, T.; Miura, Y.; Shishido, T.; Takehira, K. *J. Org. Chem.* **1999**, 64, 3891.

⁹¹⁶ Faller, J.W.; Wilt, J.C. *Org. Lett.* **2005**, 7, 633; Nagano, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2009**, 131, 4200; Watson, I.D.G.; Styler, S.A.; Yudin, A.K. *J. Am. Chem. Soc.* **2004**, 126, 5086. See also, Evans, P.A.; Robinson, J.E.; Moffett, K.K. *Org. Lett.* **2001**, 3, 3269; Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **2001**, 42, 1655. For mechanistic insights, see Watson, I.D.G.; Yudin, A.K. *J. Am. Chem. Soc.* **2005**, 127, 17516.

⁹¹⁷ Detz, R.J.; Delville, M.M.E.; Hiemstra, H.; van Maarseveen, J.H. *Angew. Chem. Int. Ed.* **2008**, 47, 3777. A Cu(I) mediated reaction in ionic liquids is known, see Park, S.B.; Alper, H. *Chem. Commun.* **2005**, 1315.

⁹¹⁸ González, I.; Mosquera, J.; Guerrero, C.; Rodríguez, R.; Cruces, J. *Org. Lett.* **2009**, 11, 1677. See also, Bariwal, J.B.; Ermolat'ev, D.S.; Van der Eycken, E.V. *Chemistry: Eur. J.* **2010**, 16, 3281.

⁹¹⁹ Gage, J.R.; Wagner, J.M. *J. Org. Chem.* **1995**, 60, 2613.

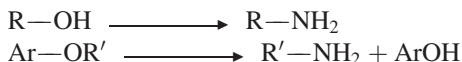
⁹²⁰ See Honaker, M.T.; Sandefur, B.J.; Hargett, J.L.; McDaniel, A.L.; Salvatore, R.N. *Tetrahedron Lett.* **2003**, 44, 8373.

⁹²¹ See Deady, L.W.; Finlayson, W.L.; Korytsky, O.L. *Aust. J. Chem.* **1979**, 32, 1735.

⁹²² Abrunhosa-Thomas, I.; Sellers, C.E.; Montchamp, J.-L. *J. Org. Chem.* **2007**, 72, 2851.

10-32 Replacement of a Hydroxy or Alkoxy by an Amino Group

Amino-de-hydroxylation and Amino-de-alkoxylation



Alcohols can be converted to alkyl halides, which then react with amines (Reaction 10-43). Alcohols react with various amine reagents that give products convertible to the amine.⁹²³ The conversion $\text{ROH} \rightarrow \text{RNH}_2$ can be accomplished for primary and secondary alcohols by treatment with hydrazoic acid (HN_3), diisopropyl azodicarboxylate ($i\text{Pr}-\text{OOCN}=\text{NCOO}-i\text{Pr}$), and excess Ph_3P in THF, followed by water or aq acid.⁹²⁴ This is a type of *Mitsunobu Reaction* (see 10-17).⁹²⁵ Primary and secondary alcohols (ROH , but not methanol) can be converted to tertiary amines.⁹²⁶ Primary amines can be generated directly from primary alcohols and ammonia.⁹²⁷ Formation of $\text{R}'_2\text{NR}$ required treatment with the secondary amine ($\text{R}'_2\text{NH}$) with the $(t\text{-BuO})_3\text{Al}$ compound in the presence of Raney nickel.⁹²⁸

Allylic alcohols (ROH) react with amines in the presence of Pt^{929} or Pd^{930} complexes, to give allylic amines.⁹³¹ Amines can be *N*-alkylated by reaction with alcohols, in a sealed tube with microwave irradiation,⁹³² and also by Ru -,⁹³³ Ir -,⁹³⁴ or Au catalyzed⁹³⁵ reactions, or by Ti mediated⁹³⁶ reactions. Copper–aluminum hydrotalcite can also be used to generate amines from alcohols.⁹³⁷ The use of aniline gives secondary amines (PhNHR). Phenols can be converted to aniline derivatives.^{938,939} Heating indoles with benzylic alcohols in the presence of $\text{Me}_3\text{P}=\text{CH}(\text{CN})$ gives the *N*-benzylindole.⁹⁴⁰ Heating an alcohol on $\gamma\text{-Al}_2\text{O}_3$

⁹²³ See Katritzky, A.R.; Huang, T.-B.; Voronkov, M.V. *J. Org. Chem.* **2001**, 66, 1043; Cami-Kobeci, G.; Williams, J.M.J. *Chem. Commun.* **2004**, 1072. See also, Salehi, P.; Motlagh, A.R. *Synth. Commun.* **2000**, 30, 671; Lakouraj, M.M.; Movassagh, B.; Fasihi, J. *Synth. Commun.* **2000**, 30, 821.

⁹²⁴ Fabiano, E.; Golding, B.T.; Sadeghi, M.M. *Synthesis* **1987**, 190. See also, Klepacz, A.; Zwierzak, A. *Synth. Commun.* **2001**, 31, 1683.

⁹²⁵ See Edwards, M.L.; Stemerick, D.M.; McCarthy, J.R. *Tetrahedron Lett.* **1990**, 31, 3417.

⁹²⁶ See Arcelli, A.; Evans, Jr., S.A. *J. Org. Chem.* **1986**, 51, 95; Huh, K.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* **1988**, 449.

⁹²⁷ Gunanathan, C.; Milstein, D. *Angew. Chem. Int. Ed.* **2008**, 47, 8661. For a Ru -catalyzed reaction of primary and secondary alcohols with ammonia, see Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, 49, 8126.

⁹²⁸ Botta, M.; De Angelis, F.; Nicoletti, R. *Synthesis* **1977**, 722.

⁹²⁹ Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett.* **2007**, 9, 3371.

⁹³⁰ Yamashita, Y.; Gopalarathnam, A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2007**, 129, 7508; Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H. *Tetrahedron* **2006**, 62, 3949.

⁹³¹ Tsuji, Y.; Takeuchi, R.; Ogawa, H.; Watanabe, Y. *Chem. Lett.* **1986**, 293.

⁹³² Jiang, Y.-L.; Hu, Y.-Q.; Feng, S.-Q.; Wu, J.-S.; Wu, Z.-W.; Yuan, Y.-C.; Liu, J.-M.; Hao, Q.-S.; Li, D.-P. *Synth. Commun.* **1996**, 26, 161.

⁹³³ Hamid, M.H.S.A.; Williams, J.M.J. *Tetrahedron Lett.* **2007**, 48, 8263; Malai Haniti S.A.; Hamid, M.H.S.A.; Williams, J.M.J. *Chem. Commun.* **2007**, 725; Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4745.

⁹³⁴ Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, 64, 1943; Defieber, C.; Ariger, M.A.; Moriel, P.; Carreira, E.M. *Angew. Chem. Int. Ed.* **2007**, 46, 3139.

⁹³⁵ Guo, S.; Song, F.; Liu, Y. *Synlett* **2007**, 964.

⁹³⁶ Ramanathan, B.; Odom, A.L. *J. Am. Chem. Soc.* **2006**, 128, 9344.

⁹³⁷ Likhar, P.R.; Arundhati, R.; Kantam, M.L.; Prathima, P.S. *Eur. J. Org. Chem.* **2009**, 5383.

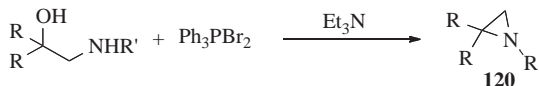
⁹³⁸ Mizuno, M.; Yamano, M. *Org. Lett.* **2005**, 7, 3629.

⁹³⁹ Kaboudin, B. *Tetrahedron Lett.* **2003**, 44, 1051.

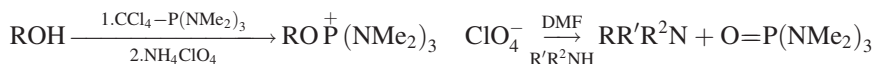
⁹⁴⁰ Bombrun, A.; Cusi, G. *Tetrahedron Lett.* **2002**, 43, 2187.

leads to an amine,⁹⁴¹ as does treatment with the amine, SnCl₂, and Pd(PPh₃)₄.⁹⁴² The Ru catalyzed reaction of amines and diols leads to cyclic amines.⁹⁴³

β-Amino alcohols give aziridines (**120**) when treated with triphenylphosphine dibromide in the presence of triethylamine.⁹⁴⁴ The fact that inversion takes place at the OH carbon indicates that an S_N2 mechanism is involved, with OPPh₃ as the leaving group.

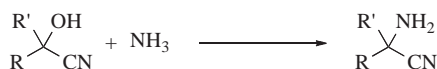


Alcohols can be converted to amines in an indirect manner.⁹⁴⁵ The alcohols are converted to alkylphosphonium perchlorates, which in DMF successfully *monoalkylate* not only secondary but also primary amines.⁹⁴⁶



Thus by this means secondary as well as tertiary amines, can be prepared in good yields. Benzylic alcohols can be converted to an azide and then treated with triphenylphosphine to give the amine (Reaction **19-50**).⁹⁴⁷

Cyanohydrins can be converted to amines by treatment with ammonia. The use of primary or secondary amines instead of ammonia leads to secondary and tertiary cyanoamines, respectively. It is more common to perform the conversion of an aldehyde or ketone directly to the cyanoamine without isolation of the cyanohydrin (see Reaction **16-52**). α-Hydroxy ketones (acyloins and benzoin)s behave similarly.⁹⁴⁸



A solution of the sodium salt of *N*-methylaniline in HMPA can be used to cleave the methyl group from aryl methyl ethers.⁹⁴⁹ ArOMe + PhNMe[−] → ArO[−] + PhNMe₂. This reagent also cleaves benzylic groups. In a similar reaction, methyl groups of aryl methyl ethers can be cleaved with lithium diphenylphosphide (Ph₂PLi).⁹⁵⁰ This reaction is specific for methyl ethers and can be carried out in the presence of ethyl ethers with

⁹⁴¹ Valot, F.; Fache, F.; Jacquot, R.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* **1999**, 40, 3689. See Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2003**, 68, 7374.

⁹⁴² Masuyama, Y.; Kagawa, M.; Kurusu, Y. *Chem. Lett.* **1995**, 1121.

⁹⁴³ Fujita, K.-i.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, 6, 3525.

⁹⁴⁴ Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* **1970**, 43, 1185. See also, Pfister, J.R. *Synthesis* **1984**, 969; Suzuki, H.; Tani, H. *Chem. Lett.* **1984**, 2129; Marsella, J.A. *J. Org. Chem.* **1987**, 52, 467.

⁹⁴⁵ Also see Hendrickson, J.B.; Joffe, I. *J. Am. Chem. Soc.* **1973**, 95, 4083; Trost, B.M.; Keinan, E. *J. Org. Chem.* **1979**, 44, 3451; Koziara, A.; Osowska-Pacewicz, K.; Zawadzki, S.; Zwierzak, A. *Synthesis* **1985**, 202; **1987**, 487.

⁹⁴⁶ Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* **1971**, 4368. For a similar method, see Tanigawa, Y.; Murahashi, S.; Moritani, I. *Tetrahedron Lett.* **1975**, 471.

⁹⁴⁷ Reddy, G.V.S.; Rao, G.V.; Subramanyam, R.V.K.; Iyengar, D.S. *Synth. Commun.* **2000**, 30, 2233.

⁹⁴⁸ See Klemmensen, P.; Schroll, G.; Lawesson, S. *Ark. Kemi*, **1968**, 28, 405.

⁹⁴⁹ Loubinoux, B.; Coudert, G.; Guillaumet, G. *Synthesis* **1980**, 638.

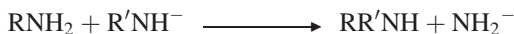
⁹⁵⁰ Ireland, R.E.; Walba, D.M. *Org. Synth.* **VI**, 567.

high selectivity. Phenyl allyl ethers react with secondary amines in the presence of a Pd catalyst to give phenol and the tertiary allyl amine.⁹⁵¹

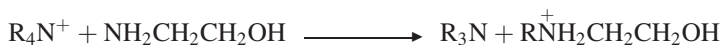
OS II, 29, 231; IV, 91, 283; VI, 567, 788; VII, 501. Also see, OS I, 473; III, 272, 471.

10-33 Transamination

Alkylamino-de-amination



Where the nucleophile is the conjugate base of a primary amine, NH_2 can be a leaving group. The method has been used to prepare secondary amines.⁹⁵² In another process, primary amines are converted to secondary amines in which both R groups are the same ($2 \text{RNH}_2 \rightarrow \text{R}_2\text{NH} + \text{NH}_3$)⁹⁵³ by refluxing in xylene in the presence of Raney nickel.⁹⁵⁴ Quaternary salts can be dealkylated with ethanolamine.⁹⁵⁵



In this reaction, methyl groups are cleaved in preference to other saturated alkyl groups. A similar reaction takes place between a *Mannich base* (see Reaction 16-19) and a secondary amine, where the mechanism is elimination–addition (see Sec. 10.F). Transamination has been accomplished using yeast alcohol dehydrogenase.⁹⁵⁶

See also, Reaction 19-5.

OS V, 1018.

10-34 Alkylation of Amines With Diazo Compounds

Hydro, dialkylamino-de-diazo-bisubstitution



The reaction of diazo compounds with amines is similar to Reaction 10-11.⁹⁵⁷ The acidity of amines is not great enough for the reaction to proceed without a catalyst, but BF_3 , which converts the amine to the $\text{F}_3\text{B}-\text{NHR}'_2$ complex, enables the reaction to take place. Cuprous cyanide can also be used as a catalyst.⁹⁵⁸ Ammonia has been used rather than an amine but, as in the case of Reaction 10-31, mixtures of primary, secondary, and tertiary amines are obtained. However, a highly chemoselective reaction of amines in water has been reported.⁹⁵⁹ Primary aliphatic amines give mixtures of secondary and tertiary amines. Secondary amines give successful alkylation. Primary aromatic amines also give the reaction, but diaryl or arylalkylamines react very poorly.

⁹⁵¹ Widehem, R.; Lacroix, T.; Bricout, H.; Monflier, E. *Synlett* **2000**, 722.

⁹⁵² Baltzly, R.; Blackman, S.W. *J. Org. Chem.* **1963**, 28, 1158.

⁹⁵³ See Geller, B.A. *Russ. Chem. Rev.* **1978**, 47, 297.

⁹⁵⁴ De Angelis, F.; Grgurina, I.; Nicoletti, R. *Synthesis* **1979**, 70; See also, Tsuji, Y.; Shida, J.; Takeuchi, R.; Watanabe, Y. *Chem. Lett.* **1984**, 889; Bank, S.; Jewett, R. *Tetrahedron Lett.* **1991**, 32, 303.

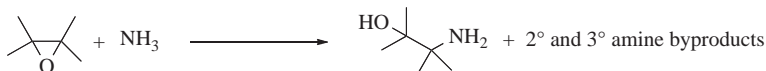
⁹⁵⁵ Hünig, S.; Baron W. *Chem. Ber.* **1957**, 90, 395, 403.

⁹⁵⁶ Cassimjee, K.E.; Branneby, C.; Abedi, V.; Wells, A.; Berglund, P. *Chem. Commun.* **2010**, 5569.

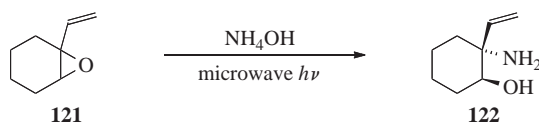
⁹⁵⁷ Müller, E.; Huber-Emden, H.; Rundel, W. *Liebigs Ann. Chem.* **1959**, 623, 34.

⁹⁵⁸ Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. *Tetrahedron Lett.* **1966**, 6131.

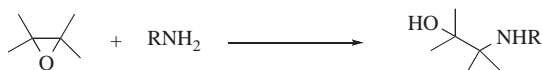
⁹⁵⁹ Azizi, N.; Saidi, M.R. *Org. Lett.* **2005**, 7, 3649.

10-35 Reaction of Epoxides with Nitrogen Reagents⁹⁶⁰(3) *OC-seco-Amino-de-alkoxylation*

The reaction between epoxides and ammonia⁹⁶¹ (or ammonium hydroxide)⁹⁶² is a general and useful method for the preparation of β -hydroxyamines. With epoxides derived from terminal alkenes, the reaction with ammonia gives largely the primary amine, but secondary and tertiary amine products are possible from the appropriate epoxide. The reaction of **121** with ammonium hydroxide with microwave irradiation, for example,



gave **122**.⁹⁶³ Ethanolamines, which are useful solvents, as well as synthetic precursors, are prepared by this reaction. Similar ring-opening occurs with alkyl and aromatic amines.⁹⁶⁴ For another way of accomplishing this conversion, see Reaction 10-40. Ring opening has been accomplished with aniline on silica gel,⁹⁶⁵ and with aromatic amines in the presence of heteropoly acids in water.⁹⁶⁶



Primary and secondary amines give, respectively, secondary and tertiary amines (**121**). Aniline reacts with epoxides in the presence of aq β -cyclodextrin⁹⁶⁷ in 5 M LiClO₄ in ether,⁹⁶⁸ or in fluoro-alcohol solvents.⁹⁶⁹ Aniline reacts with epoxides in the presence of a VCl₃ catalyst⁹⁷⁰ or a Cu(II) catalyst.⁹⁷¹ *N*-Boc-amine (H₂N—CO₂*t*-Bu) reacted with epoxides in the presence of a cobalt–salen catalyst to give the amido alcohol.⁹⁷² Solvent-free reactions using a catalytic amount of SnCl₄ are known.⁹⁷³ Other metal-catalyzed

⁹⁶⁰ Lu, P. *Tetrahedron* **2010**, 66, 2549.

⁹⁶¹ See Charrada, B.; Hedhli, A.; Baklouti, A. *Tetrahedron Lett.* **2000**, 41, 7347.

⁹⁶² Pastó, M.; Rodríguez, B.; Riera, A.; Pericàs, M.A. *Tetrahedron Lett.* **2003**, 44, 8369.

⁹⁶³ Lindström, U.M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* **1999**, 40, 9273.

⁹⁶⁴ See Harrack, Y.; Pujol, M.D. *Tetrahedron Lett.* **2002**, 43, 819; Steiner, D.; Sethofer, S.G.; Goralski, C.T.; Singaram, B. *Tetrahedron Asymmetry* **2002**, 13, 1477. For a reaction catalyzed by LiBr, see Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* **2004**, 3597.

⁹⁶⁵ Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Org. Biomol. Chem.* **2004**, 2, 1277.

⁹⁶⁶ Azizi, N.; Saidi, M.R. *Tetrahedron* **2007**, 63, 888.

⁹⁶⁷ Reddy, L.R.; Reddy, M.A.; Chanumathi, N.; Rao, K.R. *Synlett* **2000**, 339.

⁹⁶⁸ Heydari, A.; Mehrdad, M.; Malecki, A.; Ahmadi, N. *Synthesis* **2004**, 1563.

⁹⁶⁹ Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégue, J.P. *J. Org. Chem.* **2000**, 65, 6749.

⁹⁷⁰ Sabitha, G.; Reddy, G.S.K.K.; Reddy, K.B.; Yadav, J.S. *Synthesis* **2003**, 2298.

⁹⁷¹ Kamal, A.; Ramu, R.; Azhar, M.A.; Khanna, G.B.R. *Tetrahedron Lett.* **2005**, 46, 2675.

⁹⁷² Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mechiorre, P.; Sambri, L. *Org. Lett.* **2004**, 6, 3973.

⁹⁷³ Zhao, P.-Q.; Xu, L.-W.; Xia, C.-G. *Synlett* **2004**, 846.

ring-opening reactions of epoxides with amines have been reported,⁹⁷⁴ often with high enantioselectivity.

Enantioselective ring-opening reactions typically use a metal catalyst in the presence of a chiral additive. Amines react with epoxides using a catalytic amount of a Nb complex, in the presence of a 1,1-bi-2-naphthol (BINOL) derivative, to give chiral amino alcohols.⁹⁷⁵ Other enantioselective ring-opening reactions include a V–salen-catalyzed reaction,⁹⁷⁶ and a Mg–BINOL complex.⁹⁷⁷

Tetrahydropyrimidones can be used to mediate the addition of indole to epoxides.⁹⁷⁸ Amide bases react differently with epoxides. Lithium 2,2,6,6-tetramethylpiperidide (LTMP), for example, reacted with epoxides, but the product was the corresponding enamine.⁹⁷⁹ This latter reaction follows a very different mechanism. Initial formation of the lithio-epoxide is followed by rearrangement to give the aldehyde,⁹⁸⁰ and subsequent reaction with the amine byproduct of the lithiation leads to the enamine.

An indirect method for generating an amino alcohol (**124**) is to open an epoxide with azide to give the azido-alcohol (**123**),⁹⁸¹ and subsequent reduction (Reaction **19-50**) gives the amine group.⁹⁸² The cerium ammonium nitrate catalyzed reaction of epoxides and sodium azide, for example, gave the azido alcohol with selectivity for the azide group on the more substituted position.⁹⁸³ Cerium chloride has also been used, giving the azide on the less substituted carbon.⁹⁸⁴ Under *Mitsunobu conditions* (Reaction **10-17**), epoxides are converted to 1,2-diazides with HN₃.⁹⁸⁵ The reaction of trimethylsilyl azide and an epoxide was reported using an ionic solvent.⁹⁸⁶ In the presence of AlCl₃ in water at pH 4, sodium azide reacts with epoxy acids to give the β -azido- α -hydroxycarboxylic acid.⁹⁸⁷ Silylazides can be used as well.⁹⁸⁸

⁹⁷⁴ Examples include **Al compounds**: Williams, D.B.G.; Lawton, M. *Tetrahedron Lett.* **2006**, 47, 6557; Robinson, M.W.C.; Timms, D.A.; Williams, S.M.; Graham, A.E. *Tetrahedron Lett.* **2007**, 48, 6249. **Bi compounds**: McCluskey, A.; Leitch, S.K.; Garner, J.; Caden, C.E.; Hill, T.A.; Odell, L.R.; Stewart, S.G. *Tetrahedron Lett.* **2005**, 46, 8229; Ollevier, T.; Nadeau, E. *Tetrahedron Lett.* **2008**, 49, 1546. **Ce compounds**: Reddy, L.R.; Reddy, M.A.; Bhanumathi, N.; Rao, K.R. *Synthesis* **2001**, 831. **Co compounds**: Sundararajan, G.; Viyayakrishna, K.; Varghese, B. *Tetrahedron Lett.* **2004**, 45, 8253. **Er compounds**: Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Rosati, O. *Tetrahedron Lett.* **2008**, 49, 2289. **In compounds**: Rodríguez, J.R.; Navarro, A. *Tetrahedron Lett.* **2004**, 45, 7495. **Sc compounds**: Azoulay, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2005**, 7, 4593; Placzek, A.T.; Donelson, J.L.; Trivedi, R.; Gibbs, R.A.; De, S.K. *Tetrahedron Lett.* **2005**, 46, 9029. **Sm compounds**: Carrée, F.; Gil, R.; Collin, J. *Org. Lett.* **2005**, 7, 1023. **Sn compounds**: Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, 64, 287. **Zn compounds**: Bonollo, S.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synlett* **2008**, 1574. **Zr compounds**: Charkraborti, A.K.; Kondaskar, A. *Tetrahedron Lett.* **2003**, 44, 8315.

⁹⁷⁵ Arai, K.; Lucarini, S.; Salter, M.M.; Ohta, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, 129, 8103; Arai, K.; Salter, K.M.; Yamashita, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2007**, 46, 955.

⁹⁷⁶ Sun, J.; Dai, Z.; Yang, M.; Pan, X.; Zhu, C. *Synthesis* **2008**, 2100.

⁹⁷⁷ Bao, H.; Wu, J.; Li, H.; Wang, Z.; You, T.; Ding, K. *Eur. J. Org. Chem.* **2010**, 6722.

⁹⁷⁸ Fink, D.M. *Synlett* **2004**, 2394.

⁹⁷⁹ Hodgson, D.M.; Bray, C.D.; Kindon, N.D. *J. Am. Chem. Soc.* **2004**, 126, 6870. For a similar reaction with LiNTf₂, see Cossy, J.; Bellosta, V.; Hamoir, C.; Desmurs, J.-R. *Tetrahedron Lett.* **2002**, 43, 7083.

⁹⁸⁰ Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1994**, 2103.

⁹⁸¹ Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* **2003**, 33, 999. For a reaction done under phase transfer conditions, see Tamami, B.; Mahdavi, H. *Tetrahedron Lett.* **2001**, 42, 8721.

⁹⁸² Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, p. 815.

⁹⁸³ Iranpoor, N.; Kazemi, F. *Synth. Commun.* **1999**, 29, 561.

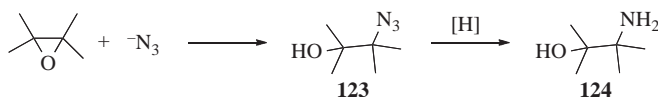
⁹⁸⁴ Sabitha, G.; Babu, R.S.; Rajkumar, M.; Yadav, J.S. *Org. Lett.* **2002**, 4, 343.

⁹⁸⁵ Göksu, S.; Socen, H.; Sütbeyaz, Y. *Synthesis* **2002**, 2373.

⁹⁸⁶ Song, C.E.; Oh, C.R.; Roh, E.J.; Choo, D.J. *Chem. Commun.* **2000**, 1743.

⁹⁸⁷ Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Tetrahedron Lett.* **2001**, 42, 1131.

⁹⁸⁸ Schneider, C. *Synlett* **2000**, 1840.



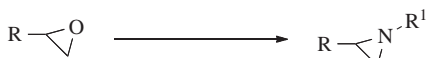
Sodium nitrate (NaNO_2) reacts with epoxides in the presence of MgSO_4 to give the nitro alcohol.⁹⁸⁹ The nitro group can also be reduced to give the amine (Reaction **19-45**).⁹⁹⁰

Episulfides (thiiranes), which can be generated *in situ* in various ways, react similarly to give β -amino thiols,⁹⁹¹ and aziridines react with amines to give 1,2-diamines (Reaction **10-38**). Triphenylphosphine similarly reacts with epoxides to give an intermediate that undergoes elimination to give alkenes (see the *Wittig Reaction*, **16-44**).

OS X, 29. See OS VI, 652 for a related reaction.

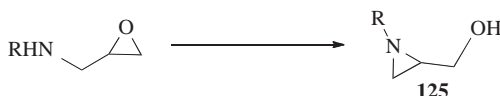
10-36 Formation of Aziridines from Epoxides

Amino-de-alkoxylation



It is possible to prepare aziridines, which are synthetically important molecules, directly from the corresponding epoxide. Reaction of $\text{Ph}_3\text{P}=\text{NPh}$ with an epoxide in the presence of ZnCl_2 gives the *N*-phenyl aziridine.⁹⁹² Guanidines have also been used to prepare aziridines from epoxides.⁹⁹³ Tosylamines react with epoxides to give the *N*-tosylaziridine.⁹⁹⁴

Various methods are available to convert an aminomethyl epoxide to a hydroxymethyl aziridine (**125**).⁹⁹⁵



10-37 Amination of Oxetanes

(4)OC-homoseco-Amino-de-alkoxylation



Oxetanes are significantly less reactive with nucleophiles due to diminished ring strain. Under certain conditions, however, amines can open oxetanes to give amino alcohols. *tert*-Butyl amine reacts with oxetanes in the presence of $\text{Yb}(\text{OTf})_3$, for example, to give 3-hydroxy amines.⁹⁹⁶ Lithium tetrafluoroborate has also been used for this purpose.⁹⁹⁷

⁹⁸⁹ Kalita, B.; Barua, N.C.; Bezbarua, M.; Bez, G. *Synlett* **2001**, 1411.

⁹⁹⁰ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, p. 821.

⁹⁹¹ Dong, Q.; Fang, X.; Schroeder, J.D.; Garvey, D.S. *Synthesis* **1999**, 1106.

⁹⁹² Kühnau, D.; Thomsen, I.; Jørgensen, K.A. *J. Chem. Soc. Perkin Trans. 1*, **1996**, 1167.

⁹⁹³ Tsuchiya, Y.; Kumamoto, T.; Ishikawa, T. *J. Org. Chem.* **2004**, 69, 8504.

⁹⁹⁴ Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Tetrahedron* **1999**, 55, 6387.

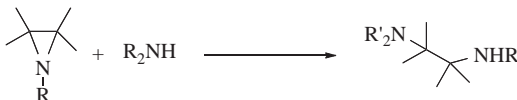
⁹⁹⁵ Najime, R.; Pilard, S.; Vaultier, M. *Tetrahedron Lett.* **1992**, 33, 5351; Moulines, J.; Bats, J.-P.; Hautefaye, P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.* **1993**, 34, 2315.

⁹⁹⁶ Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, 35, 7089.

⁹⁹⁷ Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1994**, 35, 761.

10-38 Reaction of Aziridines with Nitrogen

(3)NC-*seco*-Amino-de-aminoalkylation

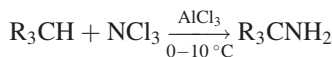


Just as epoxides can be opened by amines to give hydroxy amines, aziridines can be opened to give diamines.⁹⁹⁸ With bicyclic aziridines, the major product is usually the *trans* diamine. *N*-Aryl or *N*-alkyl aziridines react with amines in the presence of T-Binolate,⁹⁹⁹ $\text{Sn}(\text{OTf})_2$ ¹⁰⁰⁰ or $\text{B}(\text{C}_6\text{F}_5)_3$ ¹⁰⁰¹ to give the diamine. Activated aziridines undergo regioselective ring opening with organoalanes.¹⁰⁰² Amines react with *N*-tosylaziridines, in the presence of various catalysts or additives to give the corresponding diamine derivative.¹⁰⁰³ This reaction also takes place on activated silica.¹⁰⁰⁴ The reaction of LiNTf_2 and an amine, in the presence of an *N*-alkyl aziridine gives the diamine.¹⁰⁰⁵

Tosyl-aziridines react with azide ion to generate azido tosylamines,¹⁰⁰⁶ and a clay-catalyzed variation¹⁰⁰⁷ has been reported. Reduction of the azide (Reaction 19-50) gives the diamine. Silylazides (e.g., Me_3SiN_3) also react with aziridine derivatives to give the azido-amine.¹⁰⁰⁸ This latter reaction can be catalyzed by InCl_3 .¹⁰⁰⁹

10-39 Amination of Alkanes

Amino-de-hydrogenation or Amination



Alkanes, arylalkanes, and cycloalkanes can be aminated, at tertiary positions only, by treatment with trichloroamine and aluminum chloride at 0–10 °C.¹⁰¹⁰ For example, *p*- $\text{MeC}_6\text{H}_4\text{CHMe}_2$ gives *p*- $\text{MeC}_6\text{H}_4\text{CMe}_2\text{NH}_2$, methylcyclopentane gives 1-amino-1-methylcyclopentane, and adamantane gives 1-aminoadamantane, all in good yields.

⁹⁹⁸ See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, **1969**, pp. 262–268. See also, Scheuermann, J.E.W.; Ilyashenko, G.; Griffiths, D.V.; Watkinson, M. *Tetrahedron Asymmetry* **2002**, *13*, 269.

⁹⁹⁹ Peruncheralathan, S.; Teller, H.; Schneider, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4849.

¹⁰⁰⁰ Sekar, G.; Singh, V.K. *J. Org. Chem.* **1999**, *64*, 2537.

¹⁰⁰¹ Watson, I.D.G.; Yudin, A.K. *J. Org. Chem.* **2003**, *68*, 5160.

¹⁰⁰² Bertolini, F.; Woodward, S.; Crotti, S.; Pineschi, M. *Tetrahedron Lett.* **2009**, *50*, 4515.

¹⁰⁰³ Examples include **Aqueous media with β -cyclodextrin**: Reddy, M.A.; Reddy, L.R.; Bhanamathi, N.; Rao, K.R. *Chem. Lett.* **2001**, 246. **BiCl_3** : Swamy, N.R.; Venkateswarlu, Y. *Synth. Commun.* **2003**, *33*, 547. **InBr_3** : Yadav, J.S.; Reddy, B.V.S.; Rao, K.; Raj, K.S.; Prasad, A.R. *Synthesis* **2002**, 1061. **InCl_3** : Yadav, J.S.; Reddy, B.V.S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* **2002**, *43*, 1565; **LiClO_4** : Yadav, J.S.; Reddy, B.V.S.; Jyothirmai, B.; Murty, M.S.R. *Synlett* **2002**, 53; Yadav, J.S.; Reddy, B.V.S.; Parimala, G.; Reddy, P.V. *Synthesis* **2002**, 2383. **PBu_3** : Fan, R.-H.; Hou, X.-L. *J. Org. Chem.* **2003**, *68*, 726. **$\text{TaCl}_5/\text{SiO}_2$** : Chandrasekhar, S.; Prakash, S.J.; Shyamsunder, T.; Ramachandar, T. *Synth. Commun.* **2004**, *34*, 3865. **$\text{Yb}(\text{OTf})_3$** : Meguro, M.; Yamamoto, Y. *Heterocycles* **1996**, *43*, 2473.

¹⁰⁰⁴ Kumar, G.D.K.; Baskaran, S. *Synlett* **2004**, 1719.

¹⁰⁰⁵ Cossy, J.; Bellosta, V.; Alauze, V.; Desmurs, J.-R. *Synthesis* **2002**, 2211.

¹⁰⁰⁶ Bisai, A.; Pandey, G.; Pandey, M.K.; Singh, V.K. *Tetrahedron Lett.* **2003**, *44*, 5839.

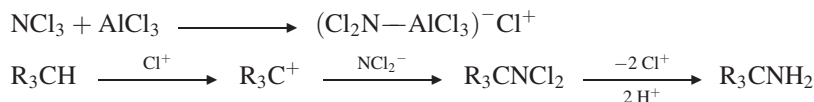
¹⁰⁰⁷ Nadir, U.K.; Singh, A. *Tetrahedron Lett.* **2005**, *46*, 2083.

¹⁰⁰⁸ Rowland, E.B.; Rowland, G.B.; Rivera-Otero, E.; Antilla, J.C. *J. Am. Chem. Soc.* **2007**, *129*, 12084; Chandrasekhar, M.; Sekar, G.; Singh, V.K. *Tetrahedron Lett.* **2000**, *41*, 10079.

¹⁰⁰⁹ Yadav, J.S.; Reddy, B.V.S.; Kumar, G.M.; Murthy, Ch.V.S.R. *Synth. Commun.* **2002**, *32*, 1797.

¹⁰¹⁰ Wnuk, T.A.; Chaudhary, S.S.; Kovacic, P. *J. Am. Chem. Soc.* **1976**, *98*, 5678, and references cited therein.

A Ag catalyzed reaction has also been reported.¹⁰¹¹ There are not many other methods for the preparation of *tert*-alkyl amines. The mechanism has been rationalized as an S_N1 process with H⁺ as the leaving group.¹⁰¹⁰

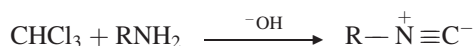


Note that under photochemical conditions, ammonia opens cyclopropane derivatives to give the corresponding alkyl amine.¹⁰¹² See also Reaction, **12-12**.

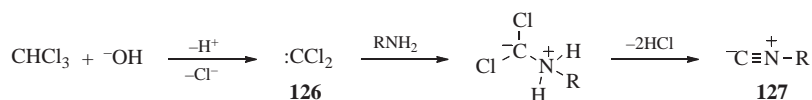
OS V, 35.

10-40 Formation of Isonitriles (Isocyanides)

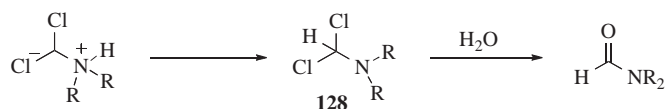
Haloform-isonitrile transformation



There are several methods available for the preparation of isonitriles, otherwise known as isocyanides.¹⁰¹³ Reaction with chloroform under basic conditions is a common test for primary amines, both aliphatic and aromatic, since isonitriles (**126**) have very strong bad odors. The reaction probably proceeds by an S_N1cB mechanism with dichlorocarbene (**127**) as an intermediate.



Yields are generally not high,¹⁰¹⁴ but an improved procedure has been reported.¹⁰¹⁵ When secondary amines are involved, the adduct **128** cannot lose two molar equivalents of HCl. Instead it is hydrolyzed to an *N,N*-disubstituted formamide.¹⁰¹⁶



A completely different way of preparing isocyanides involves the reaction of epoxides or oxetanes with trimethylsilyl cyanide and zinc iodide to give the isocyanide **129**.¹⁰¹⁷

¹⁰¹¹ Li, Z.; Capretto, D.A.; Rahaman, R.; He, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 5184.

¹⁰¹² Yasuda, M.; Kojima, R.; Tsutsui, H.; Utsunomiya, D.; Ishii, K.; Jinnouchi, K.; Shiragami, T.; Yamashita, T. *J. Org. Chem.* **2003**, *68*, 7618.

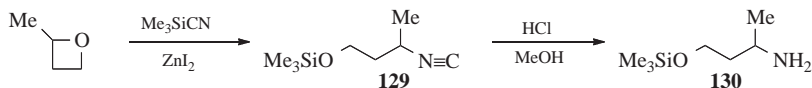
¹⁰¹³ For a method for the preparation of benzyl isocyanides, see Kitano, Y.; Manoda, T.; Miura, T.; Chiba, K.; Tada, M. *Synthesis* **2006**, 405.

¹⁰¹⁴ See Periasamy, M.P.; Walborsky, H.M. *Org. Prep. Proced. Int.* **1979**, *11*, 293.

¹⁰¹⁵ Weber, W.P.; Gokel, G.W. *Tetrahedron Lett.* **1972**, 1637; Weber, W.P.; Gokel, G.W.; Ugi, I. *Angew. Chem. Int. Ed.* **1972**, *11*, 530.

¹⁰¹⁶ Saunders, M.; Murray, R.W. *Tetrahedron* **1959**, *6*, 88; Frankel, M.B.; Feuer, H.; Bank, J. *Tetrahedron Lett.* **1959**, no. 7, 5.

¹⁰¹⁷ Gassman, P.G.; Haberman, L.M. *Tetrahedron Lett.* **1985**, *26*, 4971, and references cited therein.

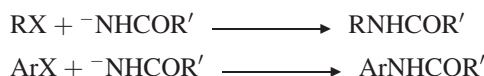


The products can be hydrolyzed to protected hydroxy-amines (e.g., **130**).
OS VI, 232.

B. Attack by NHCOR

10-41 N-Alkylation or N-Arylation of Amides and Imides

Acylamino-de-halogenation



Amides are very weak nucleophiles,¹⁰¹⁸ far too weak to attack alkyl halides, so they first must be converted to their conjugate bases, the anion. By this method, unsubstituted amides can be converted to *N*-substituted, or *N*-substituted to *N,N*-disubstituted, amides.¹⁰¹⁹ Esters of sulfuric or sulfonic acids can also be substrates. Tertiary substrates give elimination and O-Alkylation is at times a side reaction.¹⁰²⁰ Both amides and sulfonamides have been alkylated under phase-transfer conditions.¹⁰²¹ Metal-catalyzed amidations are known, including an Ir(I) catalyzed allylic amidation.¹⁰²²

Lactams can be alkylated using similar procedures. Ethyl pyrrolidone (5-carboethoxy 2-pyrrolidinone) and related lactams were converted to *N*-alkyl derivatives via treatment with NaH (short contact time) followed by addition of the halide.¹⁰²³ Other 2-pyrrolidinone derivatives can be alkylated using a similar procedure.¹⁰²⁴ *N*-Cyclopropyl lactams are prepared using a Bi reagent in the presence of cupric acetate.¹⁰²⁵ *N*-Aryl lactams can be prepared using Ph₃Bi and Cu(OAc)₂.¹⁰²⁶ *N*-Arylation of sulfonamides has been reported using a Pd catalyst,¹⁰²⁷ and this method has been applied to an intramolecular arylation leading to bicyclic lactams.¹⁰²⁸

N-Alkenyl amides have been prepared from vinyl iodides and primary amides, using 10% CuI and two molar equivalents of cesium carbonate.¹⁰²⁹ A related Pd catalyzed vinylation of lactams was repeated using vinyl ethers as a substrate.¹⁰³⁰ Oxazolidin-2-ones (a cyclic carbamate) can be *N*-alkylated using an alkyl halide with KF/Al₂O₃.¹⁰³¹

¹⁰¹⁸ Brace, N.O. *J. Org. Chem.* **1993**, 58, 1804.

¹⁰¹⁹ For procedures, see Yamawaki, J.; Ando, T.; Hanafusa, T. *Chem. Lett.* **1981**, 1143; Sukata, K. *Bull. Chem. Soc. Jpn.* **1985**, 58, 838.

¹⁰²⁰ See Challis, B.C.; Challis, J.A., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 734–754.

¹⁰²¹ Salvatore, R.N.; Shin, S.I.; Flanders, V.L.; Jung, K.w. *Tetrahedron Lett.* **2001**, 42, 1799.

¹⁰²² Singh, O.V.; Han, H. *Tetrahedron Lett.* **2007**, 48, 7094.

¹⁰²³ Simandan, T.; Smith, M.B. *Synth. Commun.* **1996**, 26, 1827.

¹⁰²⁴ Liu, H.; Ko, S.-B.; Josien, H.; Curran, D.P. *Tetrahedron Lett.* **1995**, 36, 8917.

¹⁰²⁵ Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* **2007**, 129, 44.

¹⁰²⁶ Chan, D.M.T. *Tetrahedron Lett.* **1996**, 37, 9013.

¹⁰²⁷ Ikawa, T.; Barder, T.E.; Biscoe, M.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2007**, 129, 13001.

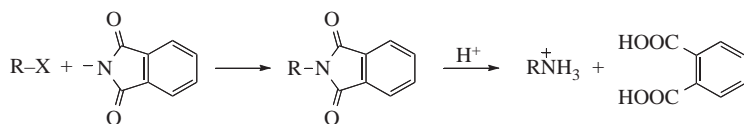
¹⁰²⁸ Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, 130, 14058. See also, Poondra, R.R.; Turner, N.J. *Org. Lett.* **2005**, 7, 863.

¹⁰²⁹ Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, 6, 1809.

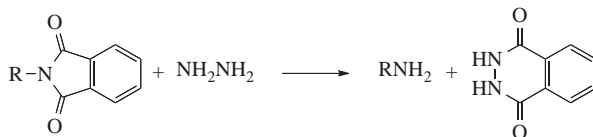
¹⁰³⁰ Brice, J.L.; Meerdink, J.E.; Stahl, S.S. *Org. Lett.* **2004**, 6, 1845.

¹⁰³¹ Blass, B.E.; Drowns, M.; Harris, C.L.; Liu, S.; Portlock, D.E. *Tetrahedron Lett.* **1999**, 40, 6545.

The *Gabriel synthesis*¹⁰³² for converting halides to primary amines is based on this reaction. The halide is treated with potassium phthalimide and the resulting product hydrolyzed (Reaction 16-60)



It is obvious that the primary amines formed in this reaction will be uncontaminated by secondary or tertiary amines (unlike Reaction 10-31). The reaction is usually rather slow, but the rate can be conveniently increased by the use of a dipolar aprotic solvent (e.g., DMF)¹⁰³³ or with a crown ether.¹⁰³⁴ Hydrolysis of the phthalimide, whether acid or base catalyzed (acid catalysis is used far more frequently), is also usually very slow, and better procedures are generally used. A common one is the *Ing-Manske procedure*,¹⁰³⁵ in which the phthalimide is heated with hydrazine in an exchange reaction,¹⁰³⁶ but other methods have been introduced, using Na₂S in aq THF or acetone,¹⁰³⁷ and 40% aq methylamine.¹⁰³⁸ *N*-Aryl imides can be prepared from ArPb(OAc)₃ and NaH.¹⁰³⁹



An alternative to the Gabriel synthesis, in which alkyl halides can be converted to primary amines in good yields, involves treatment of the halide with the strong base guanidine followed by alkaline hydrolysis.¹⁰⁴⁰ There are several other alternative procedures.¹⁰⁴¹

N-Alkyl amides or imides can also be prepared starting from alcohols by treatment of the latter with equimolar amounts of the amide or imide (Ph₃P) and diethyl azodicarboxylate (EtO₂CN=NCO₂Et) at room temperature (the *Mitsunobu Reaction*, 10-17).¹⁰⁴² A related reaction treats an alcohol with ClCH=NMe₂⁺Cl⁻, followed by potassium phthalimide and treatment with hydrazine give the amine.¹⁰⁴³ Metal-catalyzed syntheses of amides via oxidative coupling of alcohols and amines are known. Variations include the use

¹⁰³² For a review, see Gibson, M.S.; Bradshaw, R.W. *Angew. Chem. Int. Ed.* **1968**, 7, 919.

¹⁰³³ See Sheehan, J.C.; Bolhofer, W.A. *J. Am. Chem. Soc.* **1950**, 72, 2786. See also, Landini, D.; Rolla, F. *Synthesis* **1976**, 389.

¹⁰³⁴ Soai, K.; Ookawa, A.; Kato, K. *Bull. Chem. Soc. Jpn.* **1982**, 55, 1671.

¹⁰³⁵ Ing, H.R.; Manske, R.H.F. *J. Chem. Soc.* **1926**, 2348.

¹⁰³⁶ See Khan, M.N. *J. Org. Chem.* **1995**, 60, 4536 for the kinetics of hydrazinolysis of phthalimides.

¹⁰³⁷ Kukolja, S.; Lammert, S.R. *J. Am. Chem. Soc.* **1975**, 97, 5582.

¹⁰³⁸ Wolfe, S.; Hasan, S.K. *Can. J. Chem.* **1970**, 48, 3572.

¹⁰³⁹ López-Alvarado, P.; Avendaño, C.; Menéndez, J.C. *Tetrahedron Lett.* **1992**, 33, 6875.

¹⁰⁴⁰ Hebrard, P.; Olomucki, M. *Bull. Soc. Chim. Fr.* **1970**, 1938.

¹⁰⁴¹ See Grehn, L.; Ragnarsson, U. *Synthesis* **1987**, 275; Dalla Croce, P.; La Rosa, C.; Ritieni, A. *J. Chem. Res. (S)* **1988**, 346; Yinglin, H.; Hongwen, H. *Synthesis* **1990**, 122.

¹⁰⁴² Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, 94, 679; Grunewald, G.L.; Kolasa, T.; Miller, M.J. *J. Org. Chem.* **1987**, 52, 4978; Sammes, P.G.; Thetford, D. *J. Chem. Soc. Perkin Trans. 1* **1989**, 655.

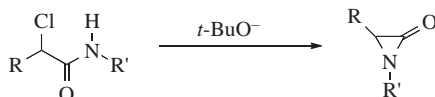
¹⁰⁴³ Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Procopiou, P.A. *Chem. Commun.* **1997**, 433.

of a Ru complex,¹⁰⁴⁴ a RuCl₃ catalyzed reaction,¹⁰⁴⁵ an FeCl₃ catalyzed reaction,¹⁰⁴⁶ an Ir complex catalyzed reaction,¹⁰⁴⁷ and an InCl₃ catalyzed coupling of alcohols with ToSMIC (ToSMIC = toluene sulfonyl methyl cyanide).¹⁰⁴⁸

Amides can also be alkylated with diazo compounds, as in Reaction 10-34. Salts of sulfonamides (ArSO₂NH[−]) can be used to attack alkyl halides to prepare *N*-alkyl sulfonamides (ArSO₂NHR) that can be further alkylated to ArSO₂NRR'. Hydrolysis of the latter is a good method for the preparation of secondary amines. Secondary amines can also be made by crown-ether assisted alkylation of F₃CCONHR (R = alkyl or aryl) and hydrolysis of the resulting F₃CCONRR'.¹⁰⁴⁹

The reaction of a primary amide and benzaldehyde, in the presence of a silane and trifluoroacetic acid, leads to the corresponding *N*-benzylamide.¹⁰⁵⁰ This transformation is a reductive alkylation (Reaction 16-17). *N*-Alkynyl amides have been prepared by the copper-catalyzed reaction of 1-bromoalkynes and secondary amides.¹⁰⁵¹ 1-Haloalkynes are typically prepared by base-induced elimination of 1,1-dihaloalkenes¹⁰⁵² or by direct halogenation of an alkyne with sodium or potassium hypohalite, prepared by reaction of the appropriate base with the halogen.¹⁰⁵³

Internal *N*-alkylation has been used to prepare the highly strained compounds α-lactams.¹⁰⁵⁴



OS I, 119, 203, 271; II, 25, 83, 208; III, 151; IV, 810; V, 1064; VI, 951; VII, 501.

C. Other Nitrogen Nucleophiles

10-42 Formation of Nitro Compounds¹⁰⁵⁵

Nitro-de-halogenation



¹⁰⁴⁴ Nordstrøm, L.U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672. See also, Watson, A.J.A.; Maxwell, A.C.; Williams, J.M.J. *Org. Lett.* **2009**, *11*, 2667; Dam, J.H.; Osztrovsky, G.; Nordstrøm, L.U.; Madsen, R. *Chemistry: Eur. J.* **2010**, *16*, 6820.

¹⁰⁴⁵ Ghosh, S.C.; Hong, S.-H. *Eur. J. Org. Chem.* **2010**, 4266.

¹⁰⁴⁶ Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2008**, *49*, 858.

¹⁰⁴⁷ Fujita, K.; Komatsubara, A.; Yamaguchi, R. *Tetrahedron* **2009**, *65*, 3624.

¹⁰⁴⁸ Krishna, P.R.; Sekhar, E.R.; Prapurna, Y.L. *Tetrahedron Lett.* **2007**, *48*, 9048.

¹⁰⁴⁹ Nordlander, J.E.; Catalane, D.B.; Eberlein, T.H.; Farkas, L.V.; Howe, R.S.; Stevens, R.M.; Tripoulas, N.A. *Tetrahedron Lett.* **1978**, 4987. For other methods, see Briggs, E.M.; Brown, G.W.; Jiricny, J.; Meidine, M.F. *Synthesis* **1980**, 295; Zwierzak, A.; Brylikowska-Piotrowicz, J. *Synthesis* **1982**, 922

¹⁰⁵⁰ Dubé, D.; Scholte, A.A. *Tetrahedron Lett.* **1999**, *40*, 2295.

¹⁰⁵¹ Zhang, Y.; Hsung, R.P.; Tracey, M.R.; Kurtz, K.C.M.; Vera, E.L. *Org. Lett.* **2004**, *6*, 1151; Frederick, M.O.; Mulder, J.A.; Tracey, M.R.; Hsung, R.P.; Huang, J.; Kurtz, K.C.M.; Shen, L.; Douglas, C.J. *J. Am. Chem. Soc.* **2003**, *125*, 2368.

¹⁰⁵² For an example involving bromine see Besstmann, H.-J.; Frey, H. *Liebigs Ann. Chem.* **1980**, *12*, 2061.

¹⁰⁵³ For examples with hypobromite, see Mozuraitis, R.; Buda, V.; Liblikas, I.; Unelius, C.R.; Borg-Karlson, A.-K. *J. Chem. Ecol.* **2002**, *28*, 1191; Barbu, E.; Tsibouklis, J. *Tetrahedron Lett.* **1996**, *37*, 5023.

¹⁰⁵⁴ See Quast, H.; Leybach, H. *Chem. Ber.* **1991**, *124*, 849. For a review of α-lactams, see Lengyel, I.; Sheehan, J.C. *Angew. Chem. Int. Ed.* **1968**, *7*, 25.

¹⁰⁵⁵ See Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, **1969**, pp. 325–339; Kornblum, N. *Org. React.* **1962**, *12*, 101.

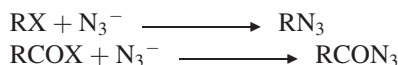
Sodium nitrite can be used to prepare nitro compounds from primary or secondary alkyl bromides or iodides, but the method is of limited scope. Silver nitrite gives nitro compounds only when RX is a primary bromide or iodide.¹⁰⁵⁶ Nitrite esters are an important side product in all these cases (Reaction **10-22**) and become the major product (by an S_N1 mechanism) when secondary or tertiary halides are treated with silver nitrite. Alkyl nitro compounds can be prepared from the alkyl halide via the corresponding azide, by treatment with HOF in acetonitrile.¹⁰⁵⁷

Nitro compounds can be prepared from alcohols using NaNO₂/AcOH/HCl.¹⁰⁵⁸

OS I, 410; IV, 368, 454, 724.

10-43 Formation of Azides

Azido-de-halogenation



Alkyl azides can be prepared by treatment of the appropriate halide with azide ion.¹⁰⁵⁹ Phase-transfer catalysis,¹⁰⁶⁰ ultrasound,¹⁰⁶¹ and the use of reactive clays¹⁰⁶² are important variations. Substrates with leaving groups other than halogen have been used,¹⁰⁶³ including OMs (Ms = methanesulfonyl), OTs (Ts = tosyl),¹⁰⁶⁴ and OAc (Ac = acetyl).¹⁰⁶⁵ There are protocols for the conversion of alcohols to azides.¹⁰⁶⁶ Boronic acids are precursors to azides.¹⁰⁶⁷ Aryl azides are prepared from aryl amines by reaction with *t*-BuONO and moist NaN₃ in *t*-BuOH.¹⁰⁶⁸

Ring-opening reactions of epoxides with nitrogen nucleophiles were discussed in Reaction **10-35**. However, it is appropriate to discuss epoxide-opening reactions involving azides. Epoxides react with NaN₃ (**10-35**), under various conditions and media, including in ionic liquids.¹⁰⁶⁹ Other reagents include TMSN₃ (TMS = trimethylsilyl) and Ph₄SbOH¹⁰⁷⁰ or SmI₂¹⁰⁷¹ or (i-Bu)₂AlHN₃Li¹⁰⁷² to give β-azido alcohols; these are easily converted to aziridines (**131**).¹⁰⁷³

¹⁰⁵⁶ See Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* **2004**, 69, 6907.

¹⁰⁵⁷ Rozen, S.; Carmeli, M. *J. Am. Chem. Soc.* **2003**, 125, 8118.

¹⁰⁵⁸ Baruah, A.; Kalita, B.; Barua, N.C. *Synlett* **2000**, 1064.

¹⁰⁵⁹ See Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* **1988**, 88, 297; Biffin, M.E.C.; Miller, J.; Paul, D.B. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, **1971**, pp. 57–119; Alvarez, S.G.; Alvarez, M.T. *Synthesis* **1997**, 413. Also see Kim, J.-G.; Jang, D.O. *Synlett* **2008**, 2075.

¹⁰⁶⁰ See Reeves, W.P.; Bahr, M.L. *Synthesis* **1979**, 823; Marti, M.J.; Rico, I.; Ader, J.C.; de Savignac, A.; Lattes, A. *Tetrahedron Lett.* **1989**, 30, 1245.

¹⁰⁶¹ Priebe, H. *Acta Chem. Scand. Ser. B*, **1984**, 38, 895.

¹⁰⁶² See, for example, Varma, R.S.; Naicker, K.P.; Aschberger, J. *Synth. Commun.* **1999**, 29, 2823.

¹⁰⁶³ See Murahashi, T.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, 27, 227.

¹⁰⁶⁴ Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* **1988**, 88, 297, see p. 306.

¹⁰⁶⁵ Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, 54, 3292.

¹⁰⁶⁶ Rad, M.N.S.; Behrouz, S.; Khalafi-Nezhad, A. *Tetrahedron Lett.* **2007**, 48, 3445; Hajipour, A.R.; Rajaei, A.; Ruoho, A.E. *Tetrahedron Lett.* **2009**, 50, 708.

¹⁰⁶⁷ Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, 48, 3525.

¹⁰⁶⁸ Das, J.; Patil, S.N.; Awasthi, R.; Narasimhulu, C.P.; Trehan, S. *Synthesis* **2005**, 1801.

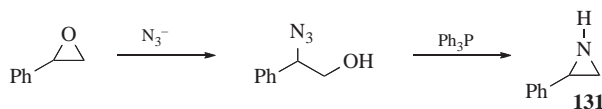
¹⁰⁶⁹ Yadav, J.S.; Reddy, B.V.S.; Jyothirmai, B.; Murty, M.S.R. *Tetrahedron Lett.* **2005**, 46, 6559.

¹⁰⁷⁰ Fujiwara, M.; Tanaka, M.; Baba, A.; Ando, H.; Souma, Y. *Tetrahedron Lett.* **1995**, 36, 4849.

¹⁰⁷¹ Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1995**, 36, 1649.

¹⁰⁷² Youn, Y.S.; Cho, I.S.; Chung, B.Y. *Tetrahedron Lett.* **1998**, 39, 4337.

¹⁰⁷³ See Itah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, 43, 4271. For the mechanism of the conversion to aziridines, see Pöchlauer, P.; Müller, E.P.; Peringer, P. *Helv. Chim. Acta* **1984**, 67, 1238.



This conversion has been used as a key step in the preparation of optically active aziridines from optically active 1,2-diols (prepared by Reaction **15-48**).¹⁰⁷⁴ Even hydrogen can be the leaving group. Benzylic hydrogen atoms have been replaced and N_3 and treatment with HN_3 in CHCl_3 in the presence of DDQ (see Reaction **19-01**).¹⁰⁷⁵

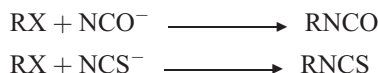
Tertiary alkyl azides can be prepared by stirring tertiary alkyl chlorides with NaN_3 and ZnCl_2 in CS_2 ¹⁰⁷⁶ or by treating tertiary alcohols with NaN_3 and CF_3COOH ¹⁰⁷⁷ or with HN_3 and TiCl_4 ¹⁰⁷⁸ or BF_3 .¹⁰⁷⁹ Aryl azides can be prepared from aniline and aniline derivatives.¹⁰⁸⁰

Acyl azides, which can be used in the *Curtius Reaction* (**18-14**), are generally prepared from acyl halides, anhydrides,¹⁰⁸¹ esters,¹⁰⁸² or other acyl derivatives.¹⁰⁸³ Acyl benzotriazoles are also precursors to acyl azides.¹⁰⁸⁴ Acyl azides also can be prepared from aldehydes using $\text{SiCl}_4/\text{NaN}_3\text{—MnO}_2$,¹⁰⁸⁵ $\text{TMSN}_3/\text{CrO}_3$ ¹⁰⁸⁶ or the *Dess–Martin periodinane* (see Reaction **19-03**, category 5) with NaN_3 .¹⁰⁸⁷

OS **III**, 846; **IV**, 715; **V**, 273, 586; **VI**, 95, 207, 210, 910; **VII**, 433; **VIII**, 116; **IX**, 220; **X**, 378. See also, OS **VII**, 206.

10-44 Formation of Isocyanates and Isothiocyanates

Isocyanato-de-halogenation



When the reagent is the thiocyanate ion, *S*-alkylation is an important side reaction (**10-30**), but the cyanate ion practically always gives exclusive *N*-alkylation.⁵⁰⁹ Primary alkyl halides have been converted to isocyanates by treatment with sodium nitrocyanoamide (NaNCNNO_2) and *m*-chloroperoxybenzoic acid, followed by heating of the initially

¹⁰⁷⁴ Lohray, B.B.; Gao, Y.; Sharpless, K.B. *Tetrahedron Lett.* **1989**, 30, 2623.

¹⁰⁷⁵ Guy, A.; Lemor, A.; Doussot, J.; Lemaire, M. *Synthesis* **1988**, 900.

¹⁰⁷⁶ Miller, J.A. *Tetrahedron Lett.* **1975**, 2959. See also, Koziara, A.; Zwierzak, A. *Tetrahedron Lett.* **1987**, 28, 6513.

¹⁰⁷⁷ Balderman, D.; Kalir, A. *Synthesis* **1978**, 24.

¹⁰⁷⁸ Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, 49, 4237.

¹⁰⁷⁹ See, for example, Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* **1985**, 41, 399.

¹⁰⁸⁰ Liu, Q.; Tor, Y. *Org. Lett.* **2003**, 5, 2571.

¹⁰⁸¹ See Lwowski, W. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, **1971**, pp. 503–554.

¹⁰⁸² Rawal, V.H.; Zhong, H.M. *Tetrahedron Lett.* **1994**, 35, 4947.

¹⁰⁸³ Affandi, H.; Bayquen, A.V.; Read, R.W. *Tetrahedron Lett.* **1994**, 35, 2729. For a preparation using triphosgene see Gumaste, V.K.; Bhawal, B.M.; Deshmukh, A.R.A.S. *Tetrahedron Lett.* **2002**, 43, 1345.

¹⁰⁸⁴ Katritzky, A.R.; Widyan, K.; Kirichenko, K. *J. Org. Chem.* **2007**, 72, 5802.

¹⁰⁸⁵ Elmsory, S.S. *Tetrahedron Lett.* **1995**, 36, 1341.

¹⁰⁸⁶ Lee, J.G.; Kwak, K.H. *Tetrahedron Lett.* **1992**, 33, 3165.

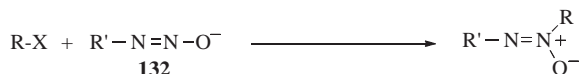
¹⁰⁸⁷ Bose, D.S.; Reddy, A.V.N. *Tetrahedron Lett.* **2003**, 44, 3543.

produced $\text{RN}(\text{NO}_2)\text{CN}$.¹⁰⁸⁸ When alkyl halides are treated with NCO^- in the presence of ethanol, carbamates can be prepared directly (see Reaction **16-8**).¹⁰⁸⁹ Acyl halides give the corresponding acyl isocyanates and isothiocyanates.¹⁰⁹⁰ For the formation of isocyanides (isonitriles), see Reaction **10-75**. Isonitriles, in the presence of sulfur and a Rh catalyst, are converted to isothiocyanate,¹⁰⁹¹ as are amines.¹⁰⁹²

OS **III**, 735.

10-45 Formation of Azoxy Compounds

Alkyl-*NNO*-azoxy-de-halogenation

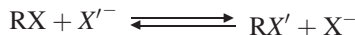


The reaction between alkyl halides and alkanediazotates (**132**) gives azoxyalkanes.¹⁰⁹³ The R and R' groups may be the same or different, but neither may be aryl or tertiary alkyl. The reaction is regioselective; only the isomer shown is obtained.

10.H.v. Halogen Nucleophiles¹⁰⁹⁴

10-46 Halide Exchange

Halo-de-halogenation



Halide exchange, sometimes call the *Finkelstein reaction*, is an equilibrium process, but it is often possible to shift the equilibrium.¹⁰⁹⁵ The reaction is most often applied to the preparation of iodides and fluorides. Iodides can be prepared from chlorides or bromides by taking advantage of the fact that sodium iodide, but not the bromide or chloride, is soluble in acetone. When an alkyl chloride or bromide is treated with a solution of sodium iodide in acetone, the equilibrium is shifted by the precipitation of sodium chloride or bromide. Since the mechanism is $\text{S}_{\text{N}}2$, the reaction is much more successful for primary halides than for secondary or tertiary halides; sodium iodide in acetone can be used as a test for primary bromides or chlorides. Tertiary chlorides can be converted to iodides by treatment with excess NaI in CS_2 , and ZnCl_2 as catalyst.¹⁰⁹⁶ Vinylic bromides give vinylic iodides with

¹⁰⁸⁸ Manimaran, T.; Wolford, L.T.; Boyer, J.H. *J. Chem. Res. (S)* **1989**, 331.

¹⁰⁸⁹ Effenberger, F.; Drauz, K.; Förster, S.; Müller, W. *Chem. Ber.* **1981**, 114, 173.

¹⁰⁹⁰ See Tsuge, O. in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 1, Wiley, NY, **1977**, pp. 445–506; Nuridzhanyan, K.A. *Russ. Chem. Rev.* **1970**, 39, 130; Lozinskii, M.O.; Pel'kis, P.S. *Russ. Chem. Rev.* **1968**, 37, 363.

¹⁰⁹¹ Arisawa, M.; Ashikawa, M.; Suwa, A.; Yamaguchi, M. *Tetrahedron Lett.* **2005**, 46, 1727.

¹⁰⁹² Munch, H.; Hansen, J.S.; Pittelkow, M.; Christensen, J.B.; Boas, U. *Tetrahedron Lett.* **2008**, 49, 3117.

¹⁰⁹³ See Yandovskii, V.N.; Gidasov, B.V.; Tselinskii, I.V. *Russ. Chem. Rev.* **1980**, 49, 237; Moss, R.A. *Acc. Chem. Res.* **1974**, 7, 421.

¹⁰⁹⁴ See Hudlicky, M.; Hudlicky, T. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, **1983**, pp. 1021–1172.

¹⁰⁹⁵ For a list of reagents for alkyl halide interconversion, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 667–671.

¹⁰⁹⁶ Miller, J.A.; Nunn, M.J. *J. Chem. Soc. Perkin Trans. 1* **1976**, 416.

retention of configuration when treated with KI and a nickel bromide-zinc catalyst,¹⁰⁹⁷ or with KI and CuI in hot HMPA.¹⁰⁹⁸

Fluorides¹⁰⁹⁹ are prepared by treatment of other alkyl halides with any of a number of fluorinating agents,¹¹⁰⁰ among them anhydrous HF (which is useful only for reactive substrates, e.g., benzylic or allylic), AgF, KF,¹¹⁰¹ HgF₂, Et₃N·2HF,¹¹⁰² 4-Me—C₆H₄IF₂,¹¹⁰³ and Me₃SiF₂Ph⁺—NBu₄.¹¹⁰⁴ The Pd catalyzed conversion of chlorides to fluorides has also been reported.¹¹⁰⁵ The equilibria in these cases are shifted because the alkyl fluoride once formed has little tendency to react, owing to the extremely poor leaving-group ability of fluorine. Phase-transfer catalysis of the exchange reaction is a particularly effective way of preparing both fluorides and iodides.¹¹⁰⁶

Primary alkyl chlorides can be converted to bromides with ethyl bromide, *N*-methyl-2-pyrrolidinone and a catalytic amount of NaBr,¹¹⁰⁷ with LiBr under phase-transfer conditions,¹¹⁰⁸ and with Bu₄N⁺ Br[−].¹¹⁰⁹ Primary bromides were converted to chlorides with TMSCl/imidazole in hot DMF.¹¹¹⁰ For secondary and tertiary alkyl chlorides, treatment with excess gaseous HBr and an anhydrous FeBr₃ catalyst in CH₂Cl₂ has given high yields¹¹¹¹ (this procedure is also successful for chloride-to-iodide conversions). Alkyl chlorides or bromides can be prepared from iodides by treatment with HCl or HBr in the presence of HNO₃, making use of the fact that the leaving I[−] is oxidized to I₂ by the HNO₃.¹¹¹² Primary iodides give the chlorides when treated with PCl₅ in POCl₃.¹¹¹³ Primary alkyl halides are converted to the corresponding fluoride with tetrabutylammonium fluoride in *tert*-butanol.¹¹¹⁴ Alkyl fluorides and chlorides are converted to the bromides and iodides (and alkyl fluorides to the chlorides) by heating with the corresponding HX in excess amounts.¹¹¹⁵

OS II, 476; IV, 84, 525; VIII, 486; IX, 502.

¹⁰⁹⁷ Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* **1978**, 1435.

¹⁰⁹⁸ Suzuki, H.; Aihara, M.; Yamamoto, H.; Takamoto, Y.; Ogawa, T. *Synthesis* **1988**, 236.

¹⁰⁹⁹ See Mann, J. *Chem. Soc. Rev.* **1987**, 16, 381; Rozen, S.; Filler, R. *Tetrahedron* **1985**, 41, 1111; Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, pt. 2, Ellis Horwood, Chichester, **1976**, pp. 24–169; Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, **1969**, pp. 52–184, 409–430.

¹¹⁰⁰ See Sharts, C.M.; Sheppard, W.A. *Org. React.* **1974**, 21, 125; Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, pt. 2, Ellis Horwood, Chichester, **1976**, pp. 91–136.

¹¹⁰¹ See Makosza, M.; Bujok, R. *Tetrahedron Lett.* **2002**, 43, 2761.

¹¹⁰² Giudicelli, M.B.; Picq, D.; Veyron B. *Tetrahedron Lett.* **1990**, 31, 6527. Also see Sawaguchi, M.; Ayuba, S.; Nakamura, Y.; Fukuhara, J.; Hara, S.; Yoneda, N. *Synlett* **2000**, 999.

¹¹⁰³ Sawaguchi, M.; Hara, S.; Nakamura, Y.; Ayuba, S.; Kukuhara, T.; Yoneda, N. *Tetrahedron* **2001**, 57, 3315.

¹¹⁰⁴ Kvícala, J.; Mysík, P.; Paleta, O. *Synlett* **2001**, 547.

¹¹⁰⁵ Katcher, M.H.; Doyle, A.G. *J. Am. Chem. Soc.* **2010**, 132, 17402.

¹¹⁰⁶ See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, **1978**, pp. 112–125; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*. Springer, NY, **1977**, pp. 117–124. See also, Bram, G.; Loupy, A.; Pigeon, P. *Synth. Commun.* **1988**, 18, 1661.

¹¹⁰⁷ Willy, W.E.; McKean, D.R.; Garcia, B.A. *Bull. Chem. Soc. Jpn.* **1976**, 49, 1989. See also, Babler, J.H.; Spina, K.P. *Synth. Commun.* **1984**, 14, 1313.

¹¹⁰⁸ Loupy, A.; Pardo, C. *Synth. Commun.* **1988**, 18, 1275.

¹¹⁰⁹ Bidd, I.; Whiting, M.C. *Tetrahedron Lett.* **1984**, 25, 5949.

¹¹¹⁰ Peyrat, J.-F.; Figadère, B.; Cavé, A. *Synth. Commun.* **1996**, 26, 4563.

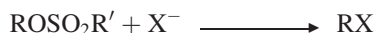
¹¹¹¹ Yoon, K.B.; Kochi, J.K. *J. Org. Chem.* **1989**, 54, 3028.

¹¹¹² Svetlakov, N.V.; Moisaik, I.E.; Averko-Antonovich, I.G. *J. Org. Chem. USSR* **1969**, 5, 971.

¹¹¹³ Bartley, J.P.; Carman, R.M.; Russell-Maynard, J.K.L. *Aust. J. Chem.* **1985**, 38, 1879.

¹¹¹⁴ Kim, D.W.; Jeong, H.-J.; Lim, S.T.; Sohn, M.-H. *Tetrahedron Lett.* **2010**, 51, 432.

¹¹¹⁵ Namavari, M.; Satyamurthy, N.; Phelps, M.E.; Barrio, J.R. *Tetrahedron Lett.* **1990**, 31, 4973.

10-47 Formation of Alkyl Halides from Esters of Sulfuric and Sulfonic Acids**Halo-de-sulfonyloxy-substitution**, and so on

Alkyl sulfates, tosylates, and other esters of sulfuric and sulfonic acids can be converted to alkyl halides with any of the four halide ions.¹¹¹⁶ Neopentyl tosylate, for example, reacts with Cl^- , Br^- , or I^- without rearrangement in HMPA.¹¹¹⁷ Similarly, allylic tosylates can be converted to chlorides without allylic rearrangement by reaction with LiCl in the same solvent.¹¹¹⁸ Inorganic esters are intermediates in the conversion of alcohols to alkyl halides with SOCl_2 , PCl_5 , PCl_3 , and so on (Reaction **10-48**), but those esters are seldom isolated.

OS **I**, 25; **II**, 111, 404; **IV**, 597, 753; **V**, 545.

10-48 Formation of Alkyl Halides from Alcohols**Halo-de-hydroxylation**

Alcohols can be converted to alkyl halides with several reagents,¹¹¹⁹ the most common of which are halogen acids (HX) and inorganic acid halides, (e.g., SOCl_2 ,¹¹²⁰ PCl_5 , PCl_3 , and POCl_3).¹¹²¹ When the reagent is HX, the mechanism is $\text{S}_{\text{N}}1\text{cA}$ or $\text{S}_{\text{N}}2\text{cA}$; that is, the leaving group is not $^- \text{OH}$, but OH_2 (Sec. 10.G.iii). The leaving group is not $^- \text{OH}$ with the other reagents either, since in these cases the alcohol is first converted to an inorganic ester (e.g., ROSOCl) with SOCl_2 (Reaction **10-22**). The leaving group is therefore $^- \text{OSOCl}$ or a similar group (Reaction **10-47**). These may react by the $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism and, in the case of ROSOCl , by the $\text{S}_{\text{N}}\text{i}$ mechanism¹¹²² (Sec. 10.D).

The reagent HBr is usually used for alkyl bromides¹¹²³ and HI for alkyl iodides. These reagents are often generated *in situ* from the halide ion and an acid (e.g., phosphoric or sulfuric). The use of HI sometimes results in reduction of the alkyl iodide to the alkane (Reaction **19-53**) and, if the substrate is unsaturated, can also reduce the double bond.¹¹²⁴ The reaction can be used to prepare primary, secondary, or tertiary halides, but alcohols of the isobutyl or neopentyl type often give large amounts of rearrangement products.¹¹²⁵ Tertiary chlorides are easily made with concentrated HCl, but primary and secondary

¹¹¹⁶ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 697–700.

¹¹¹⁷ Stephenson, B.; Solladié, G.; Mosher, H.S. *J. Am. Chem. Soc.* **1974**, *96*, 3171.

¹¹¹⁸ Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* **1969**, 1393.

¹¹¹⁹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 689–697.

¹¹²⁰ See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, **1974**, pp. 321–357. See Mohanazadeh, F.; Momeni, A.R. *Org. Prep. Proceed. Int.* **1996**, *28*, 492 for the use of SOCl_2 on silica gel.

¹¹²¹ See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, pt. 1, pp. 595–622.

¹¹²² Schreiner, P.R.; Schleyer, P.v.R.; Hill, R.K. *J. Org. Chem.* **1993**, *58*, 2822.

¹¹²³ Chong, J.M.; Heuft, M.A.; Rabbat, P. *J. Org. Chem.* **2000**, *65*, 5837.

¹¹²⁴ Jones, R.; Pattison, J.B. *J. Chem. Soc. C* **1969**, 1046.

¹¹²⁵ See Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M.C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 2830.

alcohols react with HCl so slowly that a catalyst, usually zinc chloride, is required.¹¹²⁶ Primary alcohols give good yields of chlorides upon treatment with HCl in HMPA.¹¹²⁷

The inorganic acid chlorides (SOCl₂,¹¹²⁸ PCl₃, etc.) give primary, secondary, or tertiary alkyl chlorides with much less rearrangement than is observed with HCl. Inorganic bromides and iodides, especially PBr₃, have also been used, but they are more expensive and used less often than HBr or HI, although some of them may also be generated *in situ* (e.g., PBr₃ from phosphorous and bromine). Secondary alcohols always give *some* rearranged bromides if another secondary position is available, even with PBr₃, PBr₅, or SOBr₂; thus 3-pentanol gives both 2- and 3-bromopentane. Such rearrangement can be avoided by converting the alcohol to a sulfonate and then using Reaction 10-47,¹¹²⁹ or by the use of phase-transfer catalysis.¹¹³⁰ Tertiary alcohols can be converted to the bromide with BBr₃ at 0 °C.¹¹³¹ Iodides have been prepared by simply heating the alcohol with iodine.¹¹³² Trichloroisocyanuric acid (1,3,5-trichlorohexahydrotriazin-2,4,6-trione) and triphenylphosphine converts primary alcohols to the corresponding chloride.¹¹³³ Pivaloyl chloride–DMF has been used to convert alcohols to chlorides.¹¹³⁴ Sodium iodide and Amberlyst-15¹¹³⁵ or tosic acid and KI with microwave irradiation¹¹³⁶ converts primary alcohols to the iodide.

The preparation of alkyl fluorides can be problematic, and specialized reagents are usually required. Hydrogen fluoride does not generally convert alcohols to alkyl fluorides.¹¹³⁷ The most important reagent for this purpose is the commercially available diethylaminosulfur trifluoride (Et₂NSF₃, DAST),¹¹³⁸ which converts primary, secondary, tertiary, allylic, and benzylic alcohols to fluorides in high yields under mild conditions.¹¹³⁹ Fluorides have also been prepared from alcohols by treatment with nonaflyl fluoride,¹¹⁴⁰ tetrabutylammonium difluoride,¹¹⁴¹ CsI/BF₃,¹¹⁴² TMSI/ZnCl₂,¹¹⁴³ and indirectly, by conversion to a sulfate or tosylate, and so on (Reaction 10-47). A mixture of IF₅, NEt₃, and excess KF¹¹⁴⁴ or (Cl₃CO)₂C=O [bis(trichloromethyl)carbonate] and KF (which gives COF₂ *in situ*) with 18-crown-6¹¹⁴⁵ also converts primary alcohols to primary fluorides.

¹¹²⁶ Other phase-transfer catalysts have been used: Landini, D.; Montanari, F.; Rolla, F. *Synthesis* **1974**, 37.

¹¹²⁷ Fuchs, R.; Cole, L.L. *Can. J. Chem.* **1975**, 53, 3620.

¹¹²⁸ See Chaudhari, S.S.; Akamanchi, K.G. *Synlett* **1999**, 1763.

¹¹²⁹ Cason, J.; Correia, J.S. *J. Org. Chem.* **1961**, 26, 3645.

¹¹³⁰ Dakka, G.; Sasson, Y. *Tetrahedron Lett.* **1987**, 28, 1223.

¹¹³¹ Pelletier, J.D.; Poirier, D. *Tetrahedron Lett.* **1994**, 35, 1051.

¹¹³² Joseph, R.; Pallan, P.S.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* **1995**, 36, 609.

¹¹³³ Hiegel, G.A.; Rubino, M. *Synth. Commun.* **2002**, 32, 2691.

¹¹³⁴ Dubey, A.; Upadhyay, A.K.; Kumar, P. *Tetrahedron Lett.* **2010**, 51, 744.

¹¹³⁵ Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* **2004**, 635.

¹¹³⁶ Lee, J.C.; Park, J.Y.; Yoo, E.S. *Synth. Commun.* **2004**, 34, 2095.

¹¹³⁷ For an exception, see Hanack, M.; Eggensperger, H.; Hähnle, R. *Liebigs Ann. Chem.* **1962**, 652, 96; See also, Politsanskii, S.F.; Ivanyk, G.D.; Sarancha, V.N.; Shevchuk, V.U. *J. Org. Chem. USSR* **1974**, 10, 697.

¹¹³⁸ See Hudlicky, M. *Org. React.* **1988**, 35, 513.

¹¹³⁹ Middleton, W.J. *J. Org. Chem.* **1975**, 40, 574.

¹¹⁴⁰ Vorbrüggen, H. *Synthesis* **2008**, 1165.

¹¹⁴¹ Kim, K.-Y.; Kim, B.C.; Lee, H.B.; Shin, H. *J. Org. Chem.* **2008**, 73, 8106. See also Zhao, X.; Zhuang, W.; Fang, D.; Xue, X.; Zhou, J. *Synlett* **2009**, 779.

¹¹⁴² Hayat, S.; Atta-ur-Rahman; Khan, K.M.; Choudhary, M.I.; Maharvi, G.M.; Zia-Ullah; Bayer, E. *Synth. Commun.* **2003**, 33, 2531.

¹¹⁴³ Manickam, G.F.; Siddappa, U.; Li, Y. *Tetrahedron Lett.* **2006**, 47, 5867.

¹¹⁴⁴ Yoneda, N.; Fukuhara, T. *Chem. Lett.* **2001**, 222.

¹¹⁴⁵ Flosser, D.A.; Olofson, R.A. *Tetrahedron Lett.* **2002**, 43, 4275.

Primary, secondary, and tertiary alcohols can be converted to any of the four halides by treatment with the appropriate NaX, KX, or NH₄X in polyhydrogen fluoride–pyridine solution.¹¹⁴⁶ This method is even successful for neopentyl halides. Ionic liquids can be used for halogenation, and bmim-Cl (1-*n*-butyl-3-methylimidazolium chloride) generates the chloride directly from the alcohol without any additional reagent.¹¹⁴⁷ Triphenylphosphine and iodine will convert alcohols to iodides in ionic liquids, under solvent-free conditions.¹¹⁴⁸ *tert*-Butyl halides halogenate alcohols in the ionic liquid [pmim]Br with sonication.¹¹⁴⁹

Other reagents¹¹⁵⁰ have also been used, including ZrCl₄/NaI,¹¹⁵¹ Me₃SiCl and BiCl₃,¹¹⁵² or Me₃SiCl and InCl₃¹¹⁵³ or GaCl₃–tartrate,¹¹⁵⁴ or simply Me₃SiCl in DMSO.¹¹⁵⁵ 1,2-Dipyridiniumdibromide ethane is an efficient brominating agent, and simply grinding the reagent and an alcohol in a porcelain mortar at room temperature with no solvent gives the product.¹¹⁵⁶ Other specialized reagents include (RO)₃PRX¹¹⁵⁷ and R₃PX₂¹¹⁵⁸, which give good yields for primary (including neopentyl), secondary, and tertiary halides without rearrangements.¹¹⁵⁹ Similarly, a mixture of PPh₃ and CCl₄¹¹⁶⁰ (or CBr₄¹¹⁶¹) give good results, and PPh₃/Cl₃CCONH₂ is an efficient chlorinating reagent.¹¹⁶² The compound PPh₃—CCl₃CN converts neopentyl alcohol to neopentyl chloride, in 95% yield.¹¹⁶³



¹¹⁴⁶ Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* **1979**, *44*, 3872. See also, Yin, J.; Zarkowsky, D.S.; Thomas, D.W.; Zhao, M.W.; Huffman, M.A. *Org. Lett.* **2004**, *6*, 1465.

¹¹⁴⁷ Ren, R. X.; Wu, J. X. *Org. Lett.* **2001**, *3*, 3727.

¹¹⁴⁸ Hajipour, A.R.; Mostafavi, M.; Ruoho, A.E. *Org. Prep. Proceed. Int.* **2009**, *41*, 87.

¹¹⁴⁹ Ranu, B.C.; Jana, R. *Eur. J. Org. Chem.* **2005**, 755.

¹¹⁵⁰ Also see Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.* **1988**, *53*, 6126; Munyemana, F.; Frisque-Hesbain, A.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* **1989**, *30*, 3077; Ernst, B.; Winkler, T. *Tetrahedron Lett.* **1989**, *30*, 3081.

¹¹⁵¹ Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2004**, *45*, 7451.

¹¹⁵² Labrouillère, M.; LeRoux, C.; Oussaid, A.; Gaspard-Ilouhmane, H.; Dubac, J. *Bull. Soc. Chim. Fr.* **1995**, *132*, 522.

¹¹⁵³ Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 7186.

¹¹⁵⁴ Yasuda, M.; Shimizu, K.; Yamasaki, S.; Baba, A. *Org. Biomol. Chem.* **2008**, *6*, 2790.

¹¹⁵⁵ Snyder, D.C. *J. Org. Chem.* **1995**, *60*, 2638.

¹¹⁵⁶ Kavala, V.; Naik, S.; Patel, B.K. *J. Org. Chem.* **2005**, *70*, 4267.

¹¹⁵⁷ Rydon, H.N. *Org. Synth.* **VI**, 830.

¹¹⁵⁸ Sandri, J.; Viala, J. *Synth. Commun.* **1992**, *22*, 2945.

¹¹⁵⁹ See Castro, B.R. *Org. React.* **1983**, *29*, 1; Mackie, R.K. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, **1979**; pp. 433–466.

¹¹⁶⁰ See Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801; Appel, R.; Halstenberg, M. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, **1979**, pp. 387–431. Also see, Slagle, J.D.; Huang, T.T.; Franzus, B. *J. Org. Chem.* **1981**, *46*, 3526; Pollasatri, M.P.; Sagal, J.F.; Chang, G. *Tetrahedron Lett.* **2001**, *42*, 2459.

¹¹⁶¹ Wagner, A.; Heitz, M.; Mioskowski, C. *Tetrahedron Lett.* **1989**, *30*, 557. See also, Desmaris, L.; Percina, N.; Cottier, L.; Sinou, D. *Tetrahedron Lett.* **2003**, *44*, 7589.

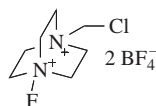
¹¹⁶² Pluempunapat, W.; Chavasiri, W. *Tetrahedron Lett.* **2006**, *47*, 6821. Also see Pluempunapat, W.; Chantarasriwong, O.; Taboonpong, P.; Jang, D.O.; Chavasiri, W. *Tetrahedron Lett.* **2007**, *48*, 223.

¹¹⁶³ Matveeva, E.D.; Yalovskaya, A.I.; Cherepanov, I.A.; Kurts, A.L.; Bundel', Yu.G. *J. Org. Chem. USSR* **1989**, *25*, 587.

The $\text{PPh}_3\text{—CCl}_4$ or CBr_4 method converts allylic alcohols¹¹⁶⁴ to the corresponding halides without allylic rearrangements,¹¹⁶⁵ and also cyclopropylcarbinyl alcohols to the halides without ring opening.¹¹⁶⁶ A mixture of triphenylphosphine and iodine converts alcohols to iodides under solvent-free conditions, using microwave irradiation.¹¹⁶⁷ Hexabromoacetone–ethyltribromoacetate is an efficient brominating reagent.¹¹⁶⁸ *N*-Bromosaccharin and *N*-iodosaccharin in the presence of PPh_3 gives the corresponding bromide or iodide.¹¹⁶⁹

Allylic and benzylic alcohols can also be converted to bromides or iodides with NaX—BF_3 etherate,¹¹⁷⁰ and to iodides with AlI_3 .¹¹⁷¹ A mixture of methanesulfonic acid and NaI also converts benzylic alcohols to benzylic iodides.¹¹⁷² Allylic alcohols are converted to allylic halides in a procedure that uses acetyl halides, but the reaction proceeds with allylic rearrangement.¹¹⁷³ A simple method that is specific for benzylic and allylic alcohols (and does not give allylic rearrangement) involves reaction with NCS or NBS and methyl sulfide.¹¹⁷⁴ A mixture of NBS, $\text{Cu}(\text{OTf})_2$, and diisopropylcarbodiimide converted primary alcohols to the corresponding bromide.¹¹⁷⁵ The use of NCS gave the chloride and *N*-iodosuccinimide (NIS) gave the iodide under identical conditions. Thiols are converted to alkyl bromides by a similar procedure using PPh_3 and NBS.¹¹⁷⁶

Trialkylsilyl ethers (e.g., ROSiMe_3) are converted to the corresponding iodide with $\text{SiO}_2\text{—Cl/NaI}$.¹¹⁷⁷ Hydroxy ketones are converted to the iodide with iodine and iodic acid.¹¹⁷⁸ Propargylic fluorides can be prepared from allenylsilanes by treatment with Selectfluor.¹¹⁷⁹



Selectfluor

OS **I**, 25, 36, 131, 142, 144, 292, 294, 533; **II**, 91, 136, 159, 246, 308, 322, 358, 399, 476; **III**, 11, 227, 370, 446, 698, 793, 841; **IV**, 106, 169, 323, 333, 576, 681; **V**, 1, 249, 608; **VI**, 75, 628, 634, 638, 781, 830, 835; **VII**, 210, 319, 356; **VIII**, 451. Also see, OS **III**, 818; **IV**, 278, 383, 597.

¹¹⁶⁴ See Magid, R.M. *Tetrahedron* **1980**, 36, 1901, pp. 1924–1926.

¹¹⁶⁵ Axelrod, E.H.; Milne, G.M.; van Tamelen, E.E. *J. Am. Chem. Soc.* **1973**, 92, 2139.

¹¹⁶⁶ Hrubiec, R.T.; Smith, M.B. *Synth. Commun.* **1983**, 13, 593.

¹¹⁶⁷ Hajipour, A.R.; Falahati, A.R.; Ruoho, A.E. *Tetrahedron Lett.* **2006**, 47, 4191.

¹¹⁶⁸ Tongkate, P.; Pluempunupat, W.; Chavasiri, W. *Tetrahedron Lett.* **2008**, 49, 1146.

¹¹⁶⁹ Firouzabadi, H.; Iranpoor, N.; Ebrahimzadeh, F. *Tetrahedron Lett.* **2006**, 47, 1771.

¹¹⁷⁰ Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Tetrahedron Lett.* **2001**, 42, 951.

¹¹⁷¹ Sarmah, P.; Barua, N.C. *Tetrahedron* **1989**, 45, 3569.

¹¹⁷² Kamal, A.; Ramesh, G.; Laxman, N. *Synth. Commun.* **2001**, 31, 827.

¹¹⁷³ Kishali, N.; Polat, M.F.; Altundas, R.; Kara, Y. *Helv. Chim. Acta* **2008**, 91, 67.

¹¹⁷⁴ Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

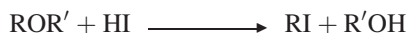
¹¹⁷⁵ Li, Z.; Crosignani, S.; Linclau, B. *Tetrahedron Lett.* **2003**, 44, 8143; Crosignani, S.; Nadal, B.; Li, Z.; Linclau, B. *Chem. Commun.* **2003**, 260.

¹¹⁷⁶ Iranpoor, N.; Firouzabadi, H.; Aghapour, G. *Synlett* **2001**, 1176.

¹¹⁷⁷ Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *Tetrahedron Lett.* **2002**, 43, 7139.

¹¹⁷⁸ Patil, B.R.; Bhusare, S.R.; Pawar, R.P.; Vibhute, Y.R. *Tetrahedron Lett.* **2005**, 46, 7179.

¹¹⁷⁹ Carroll, L.; Pacheco, M.^a C.; Garcia, L.; Gouverneur, V. *Chem. Commun.* **2006**, 4113.

10-49 Formation of Alkyl Halides from Ethers**Halo-de-alkoxylation**

Ethers can be cleaved by heating with concentrated HI or HBr.¹¹⁸⁰ Hydrogen chloride is seldom successful,¹¹⁸¹ and HBr reacts more slowly than HI, but is often a superior reagent, since it causes fewer side reactions. Phase-transfer catalysis has also been used,¹¹⁸² and 47% HBr in ionic liquids has proven effective.¹¹⁸³ Dialkyl ethers and alkyl aryl ethers can be cleaved. In the latter case, the alkyl–oxygen bond is the one broken. As in Reaction **10-48**, the actual leaving group is not OR'^- , but $^-\text{OHR}'$. Although alkyl aryl ethers always cleave so as to give an alkyl halide and a phenol, there is no general rule for dialkyl ethers. Often cleavage occurs from both sides, and a mixture of two alcohols and two alkyl halides is obtained. However, methyl ethers are usually cleaved so that methyl iodide or bromide is a product. An excess of HI or HBr converts the alcohol product into alkyl halide, so that dialkyl ethers (but not alkyl aryl ethers) are converted to 2 equiv of alkyl halide. This procedure is often carried out so that a mixture of only two products is obtained instead of four.

O-Benzyl ethers are readily cleaved to the alcohol and the hydrocarbon via hydrogenolysis, and the most common methods are hydrogenation¹¹⁸⁴ or dissolving metal conditions (Na or K in ammonia).¹¹⁸⁵ Heating in anisole with 3% $\text{Sc}(\text{NTf}_2)_3$ ¹¹⁸⁶ or with In metal in aq ethanol¹¹⁸⁷ also cleaves benzyl ethers. Isoprenyl alkyl ethers are cleaved using iodine in dichloromethane,¹¹⁸⁸ and allyl alkyl ethers are cleaved with Lewis acids under various conditions.¹¹⁸⁹ The $\text{OCH}_2\text{CH}=\text{CHPh}$ unit of mixed allyl ethers ($\text{O}-\text{CH}_2\text{CH}=\text{CH}_2$ and $\text{OCH}_2\text{CH}=\text{CHPh}$) can be cleaved selectively under electrolytic conditions.¹¹⁹⁰

Cyclic ethers (usually THF derivatives) can be similarly cleaved (see Reaction **10-50** for epoxides). Treatment of 2-methyltetrahydrofuran with acetyl chloride and ZnCl_2 gave primarily *O*-acetyl-4-chloro-1-pentanol.¹¹⁹¹ A mixture of $\text{Et}_2\text{NSiMe}_3/2 \text{ MeI}$ cleaved THF to give the *O*-trimethylsilyl ether of 4-iodo-1-butanol.¹¹⁹² Ethers have also been cleaved

¹¹⁸⁰ See Bhatt, M.V.; Kulkarni, S.U. *Synthesis* **1983**, 249; Staude, E.; Patat, F. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, **1967**, p. 22; Tiecco, M. *Synthesis* **1988**, 749.

¹¹⁸¹ Also see Jursic, B. *J. Chem. Res. (S)* **1989**, 284.

¹¹⁸² Landini, D.; Montanari, F.; Rolla, F. *Synthesis* **1978**, 771.

¹¹⁸³ Boovanahalli, S.K.; Kim, D.W.; Chi, D.Y. *J. Org. Chem.* **2004**, 69, 3340.

¹¹⁸⁴ Heathcock, C.H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, 93, 1746.

¹¹⁸⁵ Reist, E.J.; Bartuska, V.J.; Goodman, L. *J. Org. Chem.* **1964**, 29, 3725.

¹¹⁸⁶ Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2000**, 80.

¹¹⁸⁷ Moody, C.J.; Pitts, M.R. *Synlett* **1999**, 1575.

¹¹⁸⁸ Vatile, J.-M. *Synlett* **2001**, 1989. For a procedure using DDQ see Vatile, J.-M. *Synlett* **2002**, 507.

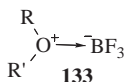
¹¹⁸⁹ See Dahlen, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; Hilmeresson, G. *Org. Lett.* **2003**, 5, 4085; Bartoli, G.; Cupone, G.; Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Marcantoni, E.; Procopio, A. *Synlett* **2001**, 1897; Chandrasekhar, S.; Reddy, Ch.R.; Rao, R.J. *Tetrahedron* **2001**, 57, 3435; Tanaka, S.; Saburi, H.; Ishibashi, Y.; Kitamura, M. *Org. Lett.* **2004**, 6, 1873. See also, Murakami, H.; Minami, T.; Ozawa, F. *J. Org. Chem.* **2004**, 69, 4482.

¹¹⁹⁰ Solis-Oba, A.; Hudlicky, T.; Koroniak, L.; Frey, D. *Tetrahedron Lett.* **2001**, 42, 1241.

¹¹⁹¹ Mimero, P.; Saluzzo, C.; Amouroux, R. *Tetrahedron Lett.* **1994**, 35, 1553.

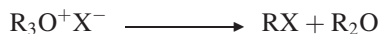
¹¹⁹² Ohshita, J.; Iwata, A.; Kanetani, F.; Kunai, A.; Yamamoto, Y.; Matui, C. *J. Org. Chem.* **1999**, 64, 8024.

with Lewis acids [e.g., BF_3 , $\text{Ce}(\text{OTf})_4$,¹¹⁹³ $\text{SiCl}_4/\text{LiI}/\text{BF}_3$,¹¹⁹⁴ BBr_3 ,¹¹⁹⁵ or AlCl_3].¹¹⁹⁶ In such cases, the departure of the OR is assisted by complex formation with the Lewis acid (see **133**). The reagent $\text{NaI}-\text{BF}_3$ etherate selectively cleaves ethers in the order benzylic ethers > alkyl methyl ethers > aryl methyl ethers.¹¹⁹⁷



Dialkyl and alkyl aryl ethers are cleaved with Me_3SiI ¹¹⁹⁸: $\text{ROR}' + \text{Me}_3\text{SiI} \rightarrow \text{RI} + \text{Me}_3\text{SiOR}$.¹¹⁹⁹ A more convenient and less expensive alternative, which gives the same products, is a mixture of chlorotrimethylsilane and NaI .¹²⁰⁰ Triphenyldibromophosphorane (Ph_3PBr_2) cleaves dialkyl ethers to give 2 molar equivalents of alkyl bromide.¹²⁰¹ Alkyl aryl ethers can also be cleaved with LiI to give alkyl iodides and salts of phenols¹²⁰² in a reaction similar to Reaction **10-51**. Allyl aryl ethers¹²⁰³ are efficiently cleaved with $\text{NaI}/\text{Me}_3\text{SiCl}$,¹²⁰⁴ or NbCl_5 .¹²⁰⁵ Aryl benzyl ethers are cleaved with BCl_3 using pentamethylbenzene as a non-Lewis basic cation scavenger.¹²⁰⁶ Cleavage in ionic liquids is also known.¹²⁰⁷

A closely related reaction is cleavage of oxonium salts.



For these substrates, HX is not required, and X can be any of the four halide ions.

tert-Butyldimethylsilyl ethers ($\text{ROSiMe}_2\text{CMe}_3$) can be converted to bromides (RBr) by treatment with Ph_3PBr_2 ,¹²⁰⁸ $\text{Ph}_3\text{P}-\text{CBr}_4$,¹²⁰⁹ BBr_3 ,¹²¹⁰ and CuBr_2 .¹²¹¹ Alcohols are often protected by conversion to this kind of silyl ether.¹²¹²

OS **I**, 150; **II**, 571; **III**, 187, 432, 586, 692, 753, 774, 813; **IV**, 266, 321; **V**, 412; **VI**, 353. See also, OS **VIII**, 161, 556.

¹¹⁹³ Khalafi-Nezhad, A.; Alamdari, R.F. *Tetrahedron* **2001**, 57, 6805.

¹¹⁹⁴ Zewge, D.; King, A.; Weissman, S.; Tschaen, D. *Tetrahedron Lett.* **2004**, 45, 3729.

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¹¹⁹⁶ Johnson, F. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 4, Wiley, NY, **1965**, pp. 1–109.

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¹¹⁹⁸ See Olah, G.A.; Prakash, G.K.S.; Krishnamurti, R. *Adv. Silicon Chem.* **1991**, 1, 1.

¹¹⁹⁹ Jung, M.E.; Lyster, M.A. *J. Org. Chem.* **1977**, 42, 3761; *Org. Synth.* **VI**, 353.

¹²⁰⁰ Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* **1979**, 44, 1247; Amouroux, R.; Jatczak, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* **1987**, 505.

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¹²⁰² Harrison, I.T. *Chem. Commun.* **1969**, 616.

¹²⁰³ See Ishizaki, M.; Yamada, M.; Watanabe, S.-i.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. *Tetrahedron* **2004**, 60, 7973.

¹²⁰⁴ Kamal, A.; Laxman, E.; Rao, N.V. *Tetrahedron Lett.* **1999**, 40, 371.

¹²⁰⁵ Yadav, J.S.; Ganganna, B.; Bhunia, D.C.; Srihari, P. *Tetrahedron Lett.* **2009**, 50, 4318.

¹²⁰⁶ Okano, K.; Okuyama, K.; Fukuyama, Y.; Tokuyama, H. *Synlett* **2008**, 1977. See also, Konieczny, M.T.; Maciejewski, G.; Konieczny, W. *Synthesis* **2005**, 1575.

¹²⁰⁷ Park, J.; Chae, J. *Synlett* **2010**, 1651; Cheng, L.; Aw, C.; Ong, S.S.; Lu, Y. *Bull. Chem. Soc. Jpn.* **2007**, 80, 2008.

¹²⁰⁸ Aizpurua, J.M.; Cossío, F.P.; Palomo, C. *J. Org. Chem.* **1986**, 51, 4941.

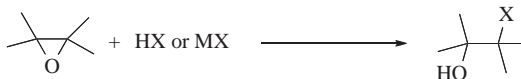
¹²⁰⁹ Mattes, H.; Benezra, C. *Tetrahedron Lett.* **1987**, 28, 1697.

¹²¹⁰ Kim, S.; Park, J.H. *J. Org. Chem.* **1988**, 53, 3111.

¹²¹¹ Bhatt, S.; Nayak, S.K. *Tetrahedron Lett.* **2006**, 47, 8395.

¹²¹² See Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, 94, 6190.

10-50 Formation of Halohydrins from Epoxides

(3) *OC-seco-Halo-de-alkoxylation*

This is a special case of Reaction **10-49** and is frequently used for the preparation of halohydrins.¹²¹³ In contrast to the situation with open-chain ethers and with larger rings, many epoxides react with all four hydrohalic acids, although with HF¹²¹⁴ the reaction is unsuccessful with simple aliphatic and cycloalkyl epoxides.¹²¹⁵ Hydrogen fluoride does react with more rigid epoxides, such as those in steroid systems. The reaction can be applied to simple epoxides¹²¹⁶ if polyhydrogen fluoride–pyridine is the reagent. The reagent $\text{NEt}_3 \cdot 3\text{HF}$ converts epoxides to fluorohydrins with microwave irradiation.¹²¹⁷ Organocatalysts have been used to convert epoxides to fluorohydrins using an acetyl fluoride/fluorous alcohol combination.¹²¹⁸ Chloro-, bromo-, and iodohydrins can also be prepared¹²¹⁹ by treating epoxides with Ph_3P and X_2 ,¹²²⁰ with $3/\text{NaBr}/\text{H}_2\text{O}$,¹²²¹ LiBr on Amberlyst-15 resin,¹²²² ceric ammonium nitrate/ KBr ,¹²²³ I_2 with a SmI_2 catalyst,¹²²⁴ and LiI on silica gel.¹²²⁵ Epoxides can be converted directly to 1,2-dichloro compounds by treatment with SOCl_2 and pyridine,¹²²⁶ or with Ph_3P and CCl_4 .¹²²⁷ These are two-step reactions: a halohydrin is formed first and is then converted by the reagents to the dihalide (Reaction **10-48**). As expected, inversion is found at both carbons. Meso epoxides were cleaved enantioselectively with the chiral B-halodiisopinocampheylboranes (see Reaction **15-16**), where the halogen was Cl, Br, or I.¹²²⁸ Diatomic iodine gives an iodohydrin with a 2,6-bis[2-(*o*-aminophenoxy)methyl]-4-bromo-1-methoxybenzene catalyst.¹²²⁹

¹²¹³ Wang, T.; Ji, W.-H.; Xu, Z.-Y.; Zeng, B.-B. *Synlett* **2009**, 1511.

¹²¹⁴ See Sharts, C.M.; Sheppard, W.A. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, **1969**, pp. 52–184, 409–430. For a related review, see Yoneda, N. *Tetrahedron* **1991**, *47*, 5329.

¹²¹⁵ Shahak, I.; Manor, S.; Bergmann, E.D. *J. Chem. Soc. C* **1968**, 2129.

¹²¹⁶ Olah, G.A.; Meidar, D. *Isr. J. Chem.* **1978**, *17*, 148.

¹²¹⁷ Inagaki, T.; Fukuhara, T.; Hara, S. *Synthesis* **2003**, 1157.

¹²¹⁸ Kalow, J.A.; Doyle, A.G. *J. Am. Chem. Soc.* **2010**, *132*, 3268.

¹²¹⁹ Einhorn, C.; Luche, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1368; Ciaccio, J.A.; Address, K.J.; Bell, T.W. *Tetrahedron Lett.* **1986**, *27*, 3697; Spawn, C.; Drtina, G.J.; Wiemer, D.F. *Synthesis* **1986**, 315. For reviews, see Bonini, C.; Righi, G. *Synthesis* **1994**, 225; Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1992**, *48*, 3805.

¹²²⁰ Palumbo, G.; Ferreri, C.; Caputo, R. *Tetrahedron Lett.* **1983**, *24*, 1307. See Afonso, C.A.M.; Vieira, N.M.L.; Motherwell, W.B. *Synlett* **2000**, 382.

¹²²¹ Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 4463.

¹²²² Bonini, C.; Giuliano, C.; Righi, G.; Rossi, L. *Synth. Commun.* **1992**, *22*, 1863.

¹²²³ Lu, Z.; Wu, W.; Peng, L.; Wu, L. *Can. J. Chem.* **2008**, *86*, 142.

¹²²⁴ Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* **2003**, 959. Thiophenol promotes ring opening by iodine, see Wu, J.; Sun, X.; Sun, W.; Ye, S. *Synlett* **2006**, 2489.

¹²²⁵ Kotsuki, H.; Shimanouchi, T. *Tetrahedron Lett.* **1996**, *37*, 1845.

¹²²⁶ Campbell, J.R.; Jones, J.K.N.; Wolfe, S. *Can. J. Chem.* **1966**, *44*, 2339.

¹²²⁷ Isaacs, N.S.; Kirkpatrick, D. *Tetrahedron Lett.* **1972**, 3869.

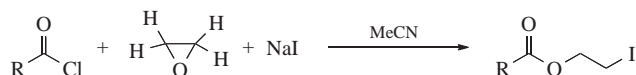
¹²²⁸ Srebnik, M.; Joshi, N.N.; Brown, H.C. *Isr. J. Chem.* **1989**, *29*, 229.

¹²²⁹ Nikam, K.; Nashi, T. *Tetrahedron*, **2002**, *58*, 10259. Also see Sharghi, H.; Niknam, K.; Pooyan, M. *Tetrahedron* **2001**, *57*, 6057; Sharghi, H.; Naeimi, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1525.

Epoxides are converted to the corresponding chlorohydrin upon treatment with the ionic liquid [AcMIm]Cl.¹²³⁰

Bicyclic epoxides are usually opened to the *trans*-halohydrin. Unsymmetrical epoxides are usually opened to give mixtures of regioisomers. In a typical reaction, the halogen is delivered to the less sterically hindered carbon of the epoxide. In the absence of this structural feature, and in the absence of a directing group, relatively equal mixtures of regioisomeric halohydrins are expected. The phenyl is such a group, and in 1-phenyl-2-alkyl epoxides reaction with POCl₃/DMAP (DMAP = 4-dimethylaminopyridine) leads to the chlorohydrin with the chlorine on the carbon bearing the phenyl.¹²³¹ When done in an ionic liquid with Me₃SiCl, styrene epoxide gives 2-chloro-2-phenylethanol.¹²³² The reaction of thionyl chloride and poly(vinylpyrrolidinone) converts epoxides to the corresponding 2-chloro-1-carbinol.¹²³³ Bromine with a phenylhydrazine catalyst, however, converts epoxides to the 1-bromo-2-carbinol.¹²³⁴ An alkenyl group also leads to a halohydrin with the halogen on the carbon bearing the C=C unit.¹²³⁵ Epoxy carboxylic acids are another example. When NaI reacts at pH 4, the major regioisomer is the 2-iodo-3-hydroxy compound, but when InCl₃ is added, the major product is the 3-iodo-2-hydroxy carboxylic acid.¹²³⁶

Acyl chlorides react with ethylene oxide in the presence of NaI to give 2-iodoethyl esters.¹²³⁷



Acyl chlorides react with epoxides in the presence of a Eu(dpm)₃ catalyst¹²³⁸ [dpm = 1,1-bis(diphenylphosphino)methane] or a YCp₂Cl catalyst¹²³⁹ to give chloro esters.

A related reaction with episulfides leads to 2-chlorothio-esters.¹²⁴⁰ Aziridines have been opened with PPh₃ and halogenating agents,¹²⁴¹ and also by MgBr₂ to give 2-haloamides in a related reaction.¹²⁴² *N*-Tosyl aziridines react with KF•2 H₂O to give the 2-fluoro tosylamine product.¹²⁴³ Aziridinium salts are opened by bromide ion.¹²⁴⁴

OS **I**, 117; **VI**, 424; **IX**, 220.

¹²³⁰ Ranu, B.C.; Banerjee, S. *J. Org. Chem.* **2005**, 70, 4517.

¹²³¹ Sartillo-Piscil, F.; Quinero, L.; Villegas, C.; Santacruz-Juárez, E.; de Parrodi, C.A. *Tetrahedron Lett.* **2002**, 43, 15.

¹²³² Xu, L.-W.; Li, L.; Xia, C.-G.; Zhao, P.-Q. *Tetrahedron Lett.* **2004**, 45, 2435.

¹²³³ Tamami, B.; Ghazi, I.; Mahdavi, H. *Synth. Commun.* **2002**, 32, 3725.

¹²³⁴ Sharghi, H.; Eskandari, M.M. *Synthesis* **2002**, 1519.

¹²³⁵ Ha, J.D.; Kim, S.Y.; Lee, S.J.; Kang, S.K.; Ahn, J.H.; Kim, S.S.; Choi, J.-K. *Tetrahedron Lett.* **2004**, 45, 5969.

¹²³⁶ Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, 66, 4719. Also see Concellón, J.M.; Bardales, E.; Concellón, C.; García-Granda, S.; Díaz, M.R. *J. Org. Chem.* **2004**, 69, 6923.

¹²³⁷ Belsner, K.; Hoffmann, H.M.R. *Synthesis* **1982**, 239. See also, Iqbal, J.; Khan, M.A.; Srivastava, R.R. *Tetrahedron Lett.* **1988**, 29, 4985.

¹²³⁸ Taniguchi, Y.; Tanaka, S.; Kitamura, T.; Fujiwara, Y. *Tetrahedron Lett.* **1998**, 39, 4559.

¹²³⁹ Qian, C.; Zhu, D. *Synth. Commun.* **1994**, 24, 2203.

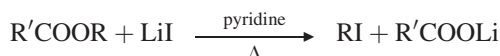
¹²⁴⁰ Kameyama, A.; Kiyota, M.; Nishikubo, T. *Tetrahedron Lett.* **1994**, 35, 4571.

¹²⁴¹ Kumar, M.; Pandey, S.K.; Gandhi, S.; Singh, V.K. *Tetrahedron Lett.* **2009**, 50, 363.

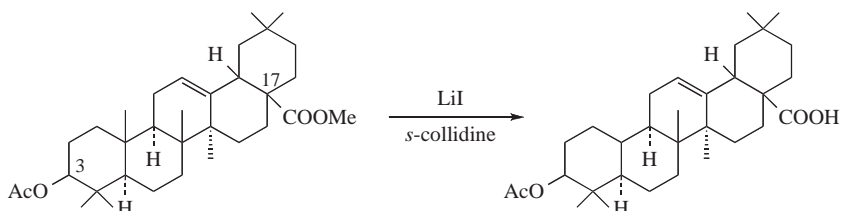
¹²⁴² Righi, G.; D'Achille, R.; Bonini, C. *Tetrahedron Lett.* **1996**, 37, 6893.

¹²⁴³ Fan, R.-H.; Zhou, Y.-G.; Zhang, W.-X.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2004**, 69, 335.

¹²⁴⁴ D'hooghe, M.; Speybroeck, V.V.; Waroquier, M.; De Kimpe, N. *Chem. Commun.* **2006**, 1554.

10-51 Cleavage of Carboxylic Esters with Lithium Iodide**Iodo-de-acyloxy-substitution**

Carboxylic esters, where R is methyl or ethyl, can be cleaved by heating with lithium iodide in refluxing pyridine or a higher-boiling amine.¹²⁴⁵ The reaction is useful where a molecule is sensitive to acid and base (so that Reaction 16-59 cannot be used) or where it is desired to cleave selectively only one ester group in a molecule containing two or more. For example, refluxing *O*-acetyloleanolic acid methyl ester with LiI in *s*-collidine



cleaved only the 17-carbomethoxy group, not the 3-acetyl group.¹²⁴⁶ Esters ($\text{RCO}_2\text{R}'$) and lactones can also be cleaved with a mixture of Me_3SiCl and NaI to give $\text{R}'\text{I}$ and RCO_2H .¹²⁴⁷ The reaction of acetyl chloride and an allylic acetate leads to the allylic chloride.¹²⁴⁸

10-52 Conversion of Diazo Ketones to α -halo Ketones**Hydro, halo-de-diazo bisubstitution**

When diazo ketones are treated with HBr or HCl , they give the respective α -halo ketones. Hydrogeniodide does not give the reaction, since it reduces the product to a methyl ketone (Reaction 19-67). α -Fluoro ketones can be prepared by addition of the diazo ketone to polyhydrogen fluoride–pyridine.¹²⁴⁹ This method is also successful for diazoalkanes.

Diazotization of α -amino acids in the above solvent at room temperature gives α -fluoro carboxylic acids.¹²⁵⁰ If this reaction is run in the presence of excess KCl or KBr , the corresponding α -chloro or α -bromo acid is obtained instead.¹²⁵¹

OS III, 119.

¹²⁴⁵ See McMurry, J. *Org. React.* **1976**, 24, 187–224.

¹²⁴⁶ Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1960**, 43, 113.

¹²⁴⁷ Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R.J. *Org. Chem.* **1979**, 44, 1247. See also, Kolb, M.; Barth, J. *Synth. Commun.* **1981**, 11, 763.

¹²⁴⁸ Yadav, V.K.; Babu, K.G. *Tetrahedron* **2003**, 59, 9111.

¹²⁴⁹ Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* **1979**, 44, 3872.

¹²⁵⁰ Olah, G.A.; Prakash, G.K.S.; Chao, Y.L. *Helv. Chim. Acta* **1981**, 64, 2528; Barber, J.; Keck, R.; Rétey, J. *Tetrahedron Lett.* **1982**, 23, 1549.

¹²⁵¹ Olah, G.A.; Shih, J.; Prakash, G.K.S. *Helv. Chim. Acta* **1983**, 66, 1028.

10-53 Conversion of Amines to Halides

Halo-de-amination



Primary alkyl amines (RNH_2) can be converted¹²⁵² to alkyl halides by (1) conversion to RNTs_2 (Sec. 10.G.ii) and treatment of this with I^- or Br^- in DMF,⁴¹⁵ or to $\text{N}(\text{Ts})-\text{NH}_2$ derivatives followed by treatment with NBS under photolysis conditions,¹²⁵³ (2) diazotization with *tert*-butylnitrite and a metal halide (e.g., TiCl_4 in DMF),¹²⁵⁴ or (3) the *Katritzky pyrylium-pyridinium method* (Sec. 10.G.ii).¹²⁵⁵ Alkyl groups can be cleaved from secondary and tertiary aromatic amines by concentrated HBr in a reaction similar to Reaction 10-49, for example,¹²⁵⁶



Tertiary aliphatic amines are also cleaved by HI , but useful products are seldom obtained. Tertiary amines can be cleaved by reaction with phenyl chloroformate¹²⁵⁷: $\text{R}_3\text{N} + \text{ClCOOPh} \rightarrow \text{RCI} + \text{R}_2\text{NCOOPh}$. α -Chloroethyl chloroformate behaves similarly.¹²⁵⁸ Alkyl halides may be formed when quaternary ammonium salts are heated: $\text{R}_4\text{N}^+ \text{X}^- \rightarrow \text{R}_3\text{N} + \text{RX}$.¹²⁵⁹

OS VIII, 119. See also, OS I, 428.

10-54 Conversion of Tertiary Amines to Cyanamides: The von Braun Reaction

Bromo-de-dialkylamino substitution



The *von Braun reaction* involves the cleavage of tertiary amines by cyanogen bromide to give an alkyl bromide and a disubstituted cyanamide, and can be applied to many tertiary amines.¹²⁶⁰ Usually, the R group that cleaves is the one that gives the most reactive halide (e.g., benzyl or allyl). For simple alkyl groups, the smallest are the most readily cleaved. One or two of the groups on the amine may be aryl, but they do not cleave. Cyclic amines have been frequently cleaved by this reaction. Secondary amines also give the reaction, but the results are usually poor.¹²⁶¹

¹²⁵² For another method, see Lorenzo, A.; Molina, P.; Vilaplana, M.J. *Synthesis* **1980**, 853.

¹²⁵³ Collazo, L.R.; Guziec Jr., F.S.; Hu, W.-X.; Pankayatselvan, R. *Tetrahedron Lett.* **1994**, 35, 7911.

¹²⁵⁴ Doyle, M.P.; Bosch, R.J.; Seites, P.G. *J. Org. Chem.* **1978**, 43, 4120.

¹²⁵⁵ Katritzky, A.R.; Chermprapai, A.; Patel, R.C. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2901.

¹²⁵⁶ Chambers, R.A.; Pearson, D.E. *J. Org. Chem.* **1963**, 28, 3144.

¹²⁵⁷ See Cooley, J.H.; Evain, E.J. *Synthesis* **1989**, 1.

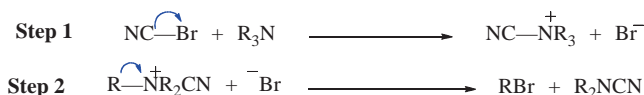
¹²⁵⁸ Olofson, R.A.; Martz, J.T.; Senet, J.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, 49, 2081; Olofson, R.A.; Abbott, D.E. *J. Org. Chem.* **1984**, 49, 2795. See also, Campbell, A.L.; Pilipauskas, D.R.; Khanna, I.K.; Rhodes, R. A. *Tetrahedron Lett.* **1987**, 28, 2331.

¹²⁵⁹ See Ko, E.C.F.; Leffek, K.T. **1971**, 49, 129; Deady, L.W.; Korytsky, O.L. *Tetrahedron Lett.* **1979**, 451.

¹²⁶⁰ See Cooley, J.H.; Evain, E.J. *Synthesis* **1989**, 1. See Vaccari, D.; Davoli, P.; Spaggiari, A.; Prati, F. *Synlett* **2008**, 1317.

¹²⁶¹ See Hageman, H.A. *Org. React.* **1953**, 205.

The mechanism consists of two successive nucleophilic substitutions, with the tertiary amine as the first nucleophile and the liberated bromide ion as the second:



The intermediate *N*-cyanoammonium bromide has been trapped, and its structure confirmed by chemical, analytical, and spectral data.¹²⁶² The BrCN in this reaction has been called a *counterattack reagent*; that is, a reagent that accomplishes, in one flask, two transformations designed to give the product.¹²⁶³

OS III, 608.

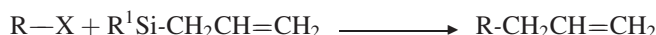
10.H.vi. Carbon Nucleophiles

In any heterolytic reaction in which a new carbon–carbon bond is formed,¹²⁶⁴ one carbon atom attacks as a nucleophile and the other as an electrophile. The classification of a given reaction as nucleophilic or electrophilic is a matter of convention and is usually based on analogy. Although not discussed in this chapter, Reactions **11-8–11-25** and **12-16–12-21** are nucleophilic substitutions with respect to one reactant, but following convention, we classify them with respect to the other. Similarly, all the reactions in this section would be called electrophilic substitution (aromatic or aliphatic) if we were to consider the reagent as the substrate.

In Reactions **10-56–10-65**, the nucleophile is a “carbanion” part of an organometallic compound, often a *Grignard reagent*. There is much that is still not known about the mechanisms of these reactions and many of them are not nucleophilic substitutions at all. In those reactions that are nucleophilic substitutions, the attacking carbon brings a pair of electrons with it to the new C—C bond, whether or not free carbanions are actually involved. The connection of two alkyl or aryl groups is called *coupling*. Reactions **10-56–10-65** include both symmetrical and unsymmetrical coupling reactions. The latter are also called *cross-coupling reactions*. Other coupling reactions are considered in later chapters.

10-55 Coupling with Silanes

De-silylalkyl-coupling



Organosilanes (RSiMe₃ or RSiMe₂F, where R can be vinylic, allylic, or alkynyl) couple with vinylic, allylic, and aryl bromides and iodides (R'X), in the presence of certain catalysts, to give RR' in good yields.¹²⁶⁵ Allylsilanes react with allylic acetates in the presence of iodine.¹²⁶⁶ The transition metal catalyzed coupling of silanes, particularly allyl

¹²⁶² Fodor, G.; Abidi, S.; Carpenter, T.C. *J. Org. Chem.* **1974**, *39*, 1507. See also, Paukstelis, J.V.; Kim, M. *J. Org. Chem.* **1974**, *39*, 1494.

¹²⁶³ See Hwu, J.R.; Gilbert, B.A. *Tetrahedron* **1989**, *45*, 1233.

¹²⁶⁴ See Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, **1979**; Noyori, R. in Alper, H. *Transition Metal Organometallics in Organic Synthesis* Vol. 1, Academic Press, NY, **1976**, pp. 83–187.

¹²⁶⁵ Cho, Y.S.; Kang, S.-H.; Han, J.-S.; Yoo, B.R.; Jung, I.N. *J. Am. Chem. Soc.* **2001**, *123*, 5584.

¹²⁶⁶ Yadav, J.S.; Reddy, B.V.S.; Rao, K.V.; Raj, K.S.; Rao, P.P.; Prasad, A.R.; Gunasekar, D. *Tetrahedron Lett.* **2004**, *45*, 6505.

silanes, is a mild method for incorporating alkyl fragments into a molecule.¹²⁶⁷ Here PhSiMe_2Cl couples to give biphenyl in the presence of CuI and Bu_4NF ,¹²⁶⁸ and vinyl silanes react with allylic carbonates and a palladium catalyst to give dienes.¹²⁶⁹ Allylsilanes have been coupled to substrates containing a benzotriazole unit, in the presence of $\text{BF}_3 \cdot \text{etherate}$.¹²⁷⁰ One variation used a silylmethyltin derivative in a palladium-catalyzed coupling with aryl iodides.¹²⁷¹ Homoallyl silanes coupled to Ph_3BiF_2 in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give the phenyl coupling product.¹²⁷²

α -Silyloxy methoxy derivatives $[\text{RCH}(\text{OMe})\text{OSiR}^1_3]$, react with allyltrimethylsilane ($\text{Me}_3\text{SiCH}_2\text{CH}=\text{CH}_2$) in the presence of TiX_4 derivatives to give displacement of the OMe group and $\text{RCH}(\text{OSiR}^1_3)\text{CH}_2\text{CH}=\text{CH}_2$.¹²⁷³ A tertiary silyloxy group was displaced by allyl in the presence of ZnCl_2 .¹²⁷⁴ Allylic acetates react with $\text{Me}_3\text{SiSiMe}_3$ and LiCl with a Pd catalyst to give the allyl silane.¹²⁷⁵ The RSiF_3 reagents can also be used in coupling reaction with aryl halides.¹²⁷⁶ Allyl silanes react with epoxides, in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give 2-allyl alcohols.¹²⁷⁷ The reaction of α -bromo lactones and $\text{CH}_2=\text{CHCH}_2\text{Si}(\text{SiMe}_3)_3$ and azoisobutyronitrile (AIBN) leads to the α -allyl lactone.¹²⁷⁸

Silyl epoxides have been prepared from epoxides via reaction with *sec*-butyllithium and chlorotrimethylsilane.¹²⁷⁹ α -Silyl-*N*-Boc-amines were prepared in a similar manner from the *N*-Boc-amine.¹²⁸⁰ Benzyl silanes coupled with allyl silanes to give $\text{ArCH}_2\text{—R}$ derivatives in the presence of $\text{VO}(\text{OEt})\text{Cl}_2$.¹²⁸¹ and allyltin compounds couple with allyl silanes in the presence of SnCl_4 .¹²⁸² Allyl silanes couple to the α -carbon of amines under photolysis conditions.¹²⁸³

Arylsilanes were prepared by reaction of an aryllithium intermediate with $\text{TfOSi}(\text{OEt})_3$.¹²⁸⁴ In the presence of $\text{BF}_3 \cdot \text{etherate}$, allyl silane and α -methoxy *N*-carbobenzoxy (*N*-Cbz) amines were coupled.¹²⁸⁵ Aryl cyanides have been converted to arylsilanes using a Rh catalyst and $\text{Me}_3\text{SiSiMe}_3$.¹²⁸⁶

¹²⁶⁷ See Kakiuchi, F.; Tsuchiya, K.; Matsumoto, M.; Mizushima, E.; Chatani, N. *J. Am. Chem. Soc.* **2004**, *126*, 12792; Nii, S.; Terao, J.; Kambe, N. *Tetrahedron Lett.* **2004**, *45*, 1699.

¹²⁶⁸ Kang, S.-K.; Kim, T.H.; Pyun, S.-J. *J. Chem. Soc. Perkin Trans. 1* **1997**, 797.

¹²⁶⁹ Matsushashi, H.; Asai, S.; Hirabayashi, K.; Hatanaka, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1943.

¹²⁷⁰ Katritzky, A.R.; Mehta, S.; He, H.-Y.; Cui, X. *J. Org. Chem.* **2000**, *65*, 4364.

¹²⁷¹ Itami, K.; Kamei, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2001**, *123*, 8773.

¹²⁷² Matano, Y.; Yoshimune, M.; Suzuki, H. *Tetrahedron Lett.* **1995**, *36*, 7475.

¹²⁷³ Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 6429.

¹²⁷⁴ Yokozawa, T.; Furuhashi, K.; Natsume, H. *Tetrahedron Lett.* **1995**, *36*, 5243.

¹²⁷⁵ Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* **1996**, *61*, 5779.

¹²⁷⁶ Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6511; Matsushashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6507.

¹²⁷⁷ Prestat, G.; Baylon, C.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3829.

¹²⁷⁸ Chatgililoglu, C.; Ferreri, C.; Ballestri, M.; Curran, D.P. *Tetrahedron Lett.* **1996**, *37*, 6387; Chatgililoglu, C.; Alberti, A.; Ballestri, M.; Macciantelli, D.; Curran, D.P. *Tetrahedron Lett.* **1996**, *37*, 6391.

¹²⁷⁹ Hodgson, D.M.; Norsikian, S.L.M. *Org. Lett.* **2001**, *3*, 461.

¹²⁸⁰ Harrison, J.R.; O'Brien, P.; Porter, D.W.; Smith, N.W. *Chem. Commun.* **2001**, 1202.

¹²⁸¹ Hirao, T.; Fujii, T.; Ohshiro, Y. *Tetrahedron Lett.* **1994**, *35*, 8005.

¹²⁸² Takeda, T.; Takagi, Y.; Takano, H.; Fujiwara, T. *Tetrahedron Lett.* **1992**, *33*, 5381.

¹²⁸³ Pandey, G.; Rani, K.S.; Lakshmaiah, G. *Tetrahedron Lett.* **1992**, *33*, 5107. See Gelas-Mialhe, Y.; Gramain, J.-C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* **1992**, *33*, 73.

¹²⁸⁴ Seganish, W.M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 6790.

¹²⁸⁵ Matos, M.R.P.N.; Afonso, C.A.M.; Batey, R.A. *Tetrahedron Lett.* **2001**, *42*, 7007.

¹²⁸⁶ Tobisu, M.; Kita, Y.; Ano, Y.; Chatani, N. *J. Am. Chem. Soc.* **2008**, *130*, 15982.

The reaction of a vinyl iodide with $(\text{EtO})_3\text{SiH}$ and a Pd catalyst generated a good yield of the corresponding vinylsilane.¹²⁸⁷

OSCV 10, 531.

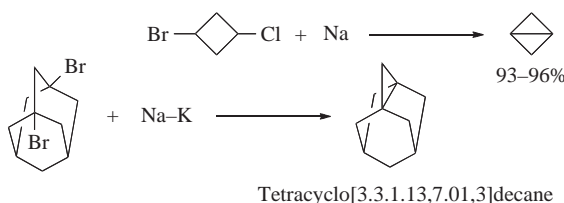
10-56 Coupling of Alkyl Halides: The Wurtz Reaction

De-halogen-coupling



The coupling of alkyl halides by treatment with sodium to give a symmetrical product is called the *Wurtz reaction*. Side reactions (elimination and rearrangement) are so common that the reaction is seldom used. Mixed Wurtz reactions of two alkyl halides are even less feasible because of the number of products obtained. A somewhat more useful reaction (but still not very good) takes place when a mixture of an alkyl and an aryl halide is treated with sodium to give an alkylated aromatic compound (the *Wurtz–Fittig reaction*).¹²⁸⁸ However, the coupling of two aryl halides with sodium is impractical (but see Reaction 13-11). Other metals have also been used to effect *Wurtz reactions*,¹²⁸⁹ notably Ag, Zn,¹²⁹⁰ Fe,¹²⁹¹ activated Cu,¹²⁹² In,¹²⁹³ La,¹²⁹⁴ and Mn compounds.¹²⁹⁵ Lithium, under the influence of ultrasound, has been used to couple alkyl, aryl, and benzylic halides.¹²⁹⁶

In a related reaction, *Grignard reagents* (Reaction 12-38) have been coupled in the presence of trifluorosulfonic anhydride.¹²⁹⁷ Tosylates and other sulfonates and sulfates couple with *Grignard reagents*,¹²⁹⁸ most often those prepared from aryl or benzylic halides.¹²⁹⁹ Alkyl sulfates and sulfonates generally make better substrates in reactions with *Grignard reagents* than the corresponding halides (Reaction 10-57). The method is useful for primary and secondary R.



¹²⁸⁷ Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **1999**, 40, 9255.

¹²⁸⁸ For an example, see Kwa, T.L.; Boelhouwer, C. *Tetrahedron* **1970**, 25, 5771.

¹²⁸⁹ For a list of reagents, including metals and other reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 83–84.

¹²⁹⁰ See, for example, Nosek, J. *Collect. Czech. Chem. Commun.* **1964**, 29, 597.

¹²⁹¹ Onsager, O. *Acta Chem. Scand. Ser. B*, **1978**, 32, 15.

¹²⁹² Ginah, F.O.; Donovan, T.A.; Suchan, S.D.; Pfennig, D.R.; Ebert, G.W. *J. Org. Chem.* **1990**, 55, 584.

¹²⁹³ Ranu, B.C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett.* **1998**, 39, 9557.

¹²⁹⁴ Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* **2002**, 67, 966.

¹²⁹⁵ See Ma, J.; Chan, T.-H. *Tetrahedron Lett.* **1998**, 39, 2499; Gilbert, B.C.; Lindsay, C.I.; McGrail, P.T.; Parsons, A.F.; Whittaker, D.T.E. *Synth. Commun.* **1999**, 29, 2711.

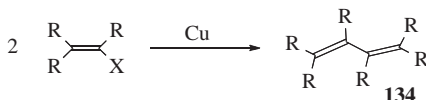
¹²⁹⁶ Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* **1981**, 22, 2757.

¹²⁹⁷ Nishiyama, T.; Seshita, T.; Shodai, H.; Aoki, K.; Kameyama, H.; Komura, K. *Chem. Lett.* **1996**, 549.

¹²⁹⁸ See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 1277–1286.

¹²⁹⁹ See Danheiser, R.L.; Tsai, Y.; Fink, D.M. *Org. Synth.* **66**, 1.

One type of *Wurtz reaction* that is quite useful is the closing of small rings, especially three-membered rings.¹³⁰⁰ For example, 1,3-dibromopropane can be converted to cyclopropane by Zn and NaI.¹³⁰¹ Two highly strained molecules prepared this way are bicyclobutane¹³⁰² and tetracyclo[3.3.1.1^{3,7}.0^{1,3}]decane.¹³⁰³ Three- and four-membered rings can also be closed in this manner with certain other reagents,¹³⁰⁴ including benzoyl peroxide,¹³⁰⁵ *t*-BuLi,¹³⁰⁶ and lithium amalgam,¹³⁰⁷ as well as electrochemically.¹³⁰⁸ The Pd or Ni catalyzed cross-coupling reaction of a *Grignard reagent* and an alkyl halide, is often called *Kumada coupling*.¹³⁰⁹



Vinyl halides can be coupled to give 1,3-butadienes (**134**) by treatment with activated Cu powder in a reaction analogous to the *Ullmann Reaction* (**13-11**).¹³¹⁰ This reaction is stereospecific, with retention of configuration at both carbons. Vinyl halides can also be coupled¹³¹¹ with Zn—NiCl₂,¹³¹² and with *n*-BuLi in ether in the presence of MnCl₂.¹³¹³ The coupling reaction with vinyltin reagents and vinyl halides occurs with a Pd catalyst.¹³¹⁴

It seems likely that the mechanism of the *Wurtz reaction* consists of two basic steps. The first is halogen-metal exchange to give an organometallic compound (RX + M → RM), which in many cases can be isolated (Reaction **12-38**). Following this, the organometallic compound reacts with a second molecule of alkyl halide (RX + RM → RR). This reaction and its mechanism are considered in Section (Reaction **10-57**).

OS **III**, 157; **V**, 328, 1058; **VI**, 133, 153.

¹³⁰⁰ See Freidlina, R.Kh.; Kamysheva, A.A.; Chukovskaya, E.Ts. *Russ. Chem. Rev.* **1982**, *51*, 368; in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, **1987**, the reviews by Tsuji, T.; Nishida, S. pp. 307–373, and Verhé, R.; De Kimpe, N. pp. 445–564.

¹³⁰¹ For a discussion of the mechanism, see Applequist, D.E.; Pfohl, W.F. *J. Org. Chem.* **1978**, *43*, 867.

¹³⁰² Wiberg, K.B.; Lampman, G.M. *Tetrahedron Lett.* **1963**, 2173; Lampman, G.M.; Aumiller, J.C. *Org. Synth.* **VI**, 133.

¹³⁰³ Pincock, R.E.; Schmidt, J.; Scott, W.B.; Torupka, E.J. *Can. J. Chem.* **1972**, *50*, 3958.

¹³⁰⁴ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 175–184.

¹³⁰⁵ Kaplan, L. *J. Am. Chem. Soc.* **1967**, *89*, 1753; *J. Org. Chem.* **1967**, *32*, 4059.

¹³⁰⁶ Bailey, W.F.; Gagnier, R.P. *Tetrahedron Lett.* **1982**, *23*, 5123.

¹³⁰⁷ Connor, D.S.; Wilson, E.R. *Tetrahedron Lett.* **1967**, 4925.

¹³⁰⁸ Rifi, M.R. *J. Am. Chem. Soc.* **1967**, *89*, 4442; *Org. Synth.* **VI**, 153.

¹³⁰⁹ Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374; Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545; Lopez-Perez, A.; Adrio, J.; Carretero, J.C. *Org. Lett.* **2009**, *11*, 5514; Frisch, A.C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem.*, **2002**, *114*, 4218. See Chen, X.; Wang, L.; Liu, J. *Synthesis* **2009**, 2408; Limmert, M.E.; Roy, A.H.; Hartwig, J.F. *J. Org. Chem.* **2005**, *70*, 9364; Tsai, F.-Y.; Lin, B.-N.; Chen, M.-J.; Mou, C.-Y.; Liu, S.T. *Tetrahedron* **2007**, *63*, 4304; Organ, M.G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C.J.; Valente, C. *Chemistry: European J.* **2007**, *13*, 150; Gauthier, D.; Beckendorf, S.; Gøgsig, T.M.; Lindhardt, A.T.; Skrydstrup, T. *J. Org. Chem.* **2009**, *74*, 3536. For a coupling reaction of aryl iodides with heterocyclic *Grignard reagents*, see Ruben Martin, R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2007**, *129*, 3844.

¹³¹⁰ Cohen, T.; Poeth, T. *J. Am. Chem. Soc.* **1972**, *94*, 4363.

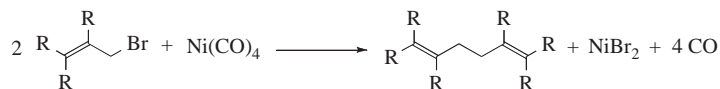
¹³¹¹ See Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1985**, 971; Vanderesse, R.; Fort, Y.; Becker, S.; Caubere, P. *Tetrahedron Lett.* **1986**, *27*, 3517.

¹³¹² Takagi, K.; Mimura, H.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3517.

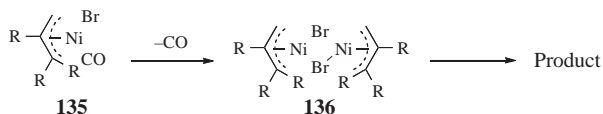
¹³¹³ Cahiez, G.; Bernard, D.; Normant, J.F. *J. Organomet. Chem.* **1976**, *113*, 99.

¹³¹⁴ Paley, R.S.; de Dios, A.; de la Pradilla, R.F. *Tetrahedron Lett.* **1993**, *34*, 2429.

A variation of the *Wurtz coupling* uses other metals to mediate or facilitate the coupling. In certain cases, such variations can be synthetically useful. Because of the presence of the 1,5-diene moiety in many naturally occurring compounds, methods that couple¹³¹⁵ allylic groups¹³¹⁶ are quite important. In one of these methods, allylic halides, tosylates, and acetates can be symmetrically coupled by treatment with nickel carbonyl¹³¹⁷ to give 1,5-dienes.¹³¹⁸ The order of halide reactivity is $I > Br > Cl$. With unsymmetrical allylic substrates, coupling nearly always takes place at the less-substituted end.



The reaction can be performed intramolecularly; large (11–20-membered) rings can be made in good yields (60–80%) by the use of high dilution.¹³¹⁹ The mechanism of coupling likely involves reaction of the allylic compound with Ni(CO)_4 to give one or more π -allyl complexes, one of which may be the η^3 -complex **135**. Loss of CO to give a π -allylnickel bromide (**136**) and ligand transfer leads to coupling and the final product. In some cases, the η^3 -complexes (**136**) can be isolated from the solution and crystallized as stable solids.



Unsymmetrical coupling can be achieved by treating an alkyl halide directly with **136**, in a polar aprotic solvent,¹³²⁰ and coupling occurs at the less substituted end. There is evidence that free radicals are involved in such couplings.¹³²¹ Hydroxy or carbonyl groups in the alkyl halide do not interfere. When **136** reacts with an allylic halide, a mixture of three products is obtained because of halogen–metal interchange. For example, allyl bromide treated with **136** prepared from methallyl bromide gave an approximately statistical mixture of 1,5-hexadiene, 2-methyl-1,5-hexadiene, and 2,5-dimethyl-1,5-hexadiene.¹³²² A symmetrical coupling of allylic tosylates used Ni(CO)_4 .



¹³¹⁵ See Magid, R.M. *Tetrahedron* **1980**, *36*, 1901, see pp. 1910–1924.

¹³¹⁶ In this section, methods are discussed in which one molecule is a halide. For other allylic coupling reactions, see **10-57**, **10-63**, and **10-60**.

¹³¹⁷ See Tamao, K.; Kumada, M. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond* Vol. 4, Wiley, NY, **1987**, pp. 819–887.

¹³¹⁸ Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, **1987**, pp. 739–748; Billington, D.C. *Chem. Soc. Rev.* **1985**, *14*, 93; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, **1978**, pp. 398–408; Semmelhack, M.F. *Org. React.* **1972**, *19*, 115, see pp. 162–170; Baker, R. *Chem. Rev.* **1973**, *73*, 487, see pp. 512–517.

¹³¹⁹ Corey, E.J.; Wat, E.K.W. *J. Am. Chem. Soc.* **1967**, *89*, 2757. See also, Reijnders, P.J.M.; Blankert, J.F.; Buck, H.M. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 30.

¹³²⁰ See Semmelhack, M.F. *Org. React.* **1972**, *19*, 115, see pp. 147–162; Semmelhack, M.F. *Org. React.* **1972**, *19*, 115, see pp. 144–146.

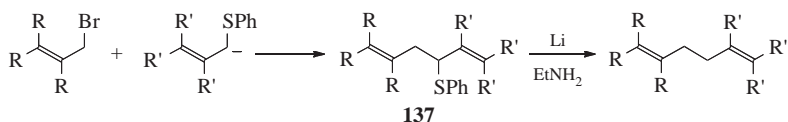
¹³²¹ Hegedus, L.S.; Thompson, D.H.P. *J. Am. Chem. Soc.* **1985**, *107*, 5663.

¹³²² Corey, E.J.; Semmelhack, M.F.; Hegedus, L.S. *J. Am. Chem. Soc.* **1968**, *90*, 2416.

Symmetrical coupling of allylic halides occurs by heating with magnesium in ether.¹³²³ The coupling of two different allylic groups has been achieved by treatment of an allylic bromide with an allylic *Grignard reagent* in THF containing HMPA,¹³²⁴ or with an allylic tin reagent.¹³²⁵ This type of coupling can be achieved with almost no allylic rearrangement in the substrate (and almost complete allylic rearrangement in the reagent) by treatment of allylic halides with lithium allylic boron ate complexes ($\text{RCH}=\text{CHCH}_2\text{B}-\text{R}'_2\text{Li}^+$).¹³²⁶ The reaction between primary and secondary halides and allyltributylstannane provides another method for unsymmetrical coupling $\text{RX} + \text{CH}_2=\text{CHCH}_2\text{SnBu}_3 \rightarrow \text{RCH}_2\text{CH}=\text{CH}_2$.¹³²⁷

In another method for the coupling of two different allylic groups,¹³²⁸ a carbanion derived from a β,γ -unsaturated thioether couples with an allylic halide to give **137**.¹³²⁹ The product (**137**) contains an SPh group that must be removed (with Li in ethylamine) to give the 1,5-diene. Unlike most of the methods previously discussed, this method has the advantage that the coupling preserves the original positions and configurations of the two double bonds; no allylic rearrangements take place.

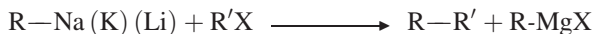
Treatment of conjugated ketones with SmI_2 in HMPA gave the coupled diketone via *Wurtz-type coupling*.¹³³⁰



OS **III**, 121; **IV**, 748; **VI**, 722.

10-57 The Reaction of Alkyl Halides and Sulfonate Esters with Group 1 and 2 Organometallic Reagents¹³³¹

Alkyl-de-halogenation



A variety of Group 1 and 2 organometallic compounds¹³³² couple with alkyl halides.¹³³³ Organosodium and organopotassium compounds are more reactive than *Grignard reagents*, and couple even with less reactive halides (see below). Coupling of

¹³²³ Turk, A.; Chanan, H. *Org. Synth.* **III**, 121.

¹³²⁴ Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* **1969**, 1393; Grieco, P.A. *J. Am. Chem. Soc.* **1969**, 91, 5660.

¹³²⁵ Hosomi, A.; Imai, T.; Endo, M.; Sakurai, H. *J. Organomet. Chem.* **1985**, 285, 95. See also, Yanagisawa, A.; Norikate, Y.; Yamamoto, H. *Chem. Lett.* **1988**, 1899.

¹³²⁶ Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, 103, 1969.

¹³²⁷ See Keck, G.E.; Yates, J.B. *J. Am. Chem. Soc.* **1982**, 104, 5829; Migita, T.; Nagai, K.; Kosugi, M. *Bull. Chem. Soc. Jpn* **1983**, 56, 2480.

¹³²⁸ See Axelrod, E.H.; Milne, G.M.; van Tamelen, E.E. *J. Am. Chem. Soc.* **1970**, 92, 2139; Morizawa, Y.; Kanemoto, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, 23, 2953.

¹³²⁹ Biellmann, J.F.; Ducep, J.B. *Tetrahedron Lett.* **1969**, 3707.

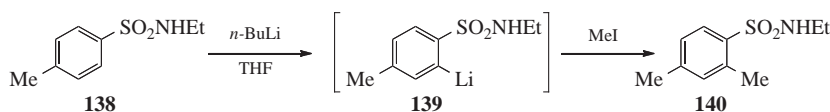
¹³³⁰ Cabrera, A.; Rosas, N.; Sharma, P.; LeLagadec, R.; Velasco, L.; Salmón, M. *Synth. Commun.* **1998**, 28, 1103.

¹³³¹ See Naso, F.; Marchese, G. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, **1983**, pp. 1353–1449.

¹³³² For lists of reagents and substrates, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 101–127.

¹³³³ See Beletskaya, I.P. *J. Organomet. Chem.* **1983**, 250, 551; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, **1985**, pp. 249–262.

organolithium compounds with alkyl halides¹³³⁴ or aryl halides¹³³⁵ is possible.¹³³⁶ Unactivated aryl halides couple with alkylolithium reagents in THF.¹³³⁷ The reaction of *n*-butyllithium/TMEDA with a homoallylic alcohol [CH₂=C(Me)CH₂CH₂OH] leads to the allyllithium reagent, and subsequent reaction with an alkyl halide gives the substituted homoallylic alcohol [CH₂=C(CH₂R)CH₂CH₂OH].¹³³⁸ Organolithium reagents exhibit an important side reaction: They react with ether solvents, and their half-life in such solvents is known.¹³³⁹ With highly reactive organolithium reagents, preparing and keeping them long enough for the alkyl halide to be added is sometimes a problem (but usually not with simple primary organolithium reagents). Alkenes can be prepared by the coupling of vinylic lithium compounds with primary halides¹³⁴⁰ or of vinylic halides with alkylolithium reagents in the presence of a Pd or Ru catalyst.¹³⁴¹ α -Lithioepoxides can also be formed, and reaction with an alkyl halide gives the substituted epoxide.¹³⁴² Arylsilanes (e.g., 2-trimethylsilylpyridine) undergo a deprotonation reaction of a silyl methyl group when treated with *tert*-butyllithium to give the corresponding ArMe₂SiCH₂Li reagent.¹³⁴³ Subsequent reaction with an alkyl halide leads to the substituted silane. Organolithium reagents formed by Li–H exchange in the presence of (–)-sparteine couple with alkyl halides with high asymmetric induction.¹³⁴⁴ Exchange of organotin compounds with organolithium reagents generates a new organolithium, and in one case intramolecular coupling in the presence of (–)-sparteine led to chiral pyrrolidine derivatives.¹³⁴⁵ Propargyl lithium reagents formed in the presence of mercuric salts couple with halides.¹³⁴⁶ Note that 1-lithioalkynes were coupled to alkyl halides in the presence of a palladium catalyst.¹³⁴⁷



Aryllithium reagents are formed by metal–halogen exchange with aryl halides or H–metal exchange with various aromatic compounds, and they react with alkyl halides. The reaction of **138** with *n*-butyllithium, for example, generated the aryllithium (**139**), which reacted with iodomethane to give **140**.¹³⁴⁸ When an aromatic ring has an attached heteroatom or an heteroatom-containing substituent, reaction with a strong base (e.g., an

¹³³⁴ Snieckus, V.; Rogers-Evans, M.; Beak, P.; Lee, W.K.; Yum, E.K.; Freskos, J. *Tetrahedron Lett.* **1994**, 35, 4067.

¹³³⁵ Dieter, R.K.; Li, S.J. *J. Org. Chem.* **1997**, 62, 7726. Also see Beak, P.; Wu, S.; Yum, E.K.; Jun, Y.M. *J. Org. Chem.* **1994**, 59, 276.

¹³³⁶ For example, see Brimble, M.A.; Gorsuch, S. *Aust. J. Chem.* **1999**, 52, 965.

¹³³⁷ Merrill, R.E.; Negishi, E. *J. Org. Chem.*, **1974**, 39, 3452. For another method, see Hallberg, A.; Westerlund, C. *Chem. Lett.*, **1982**, 1993.

¹³³⁸ Yong, K.H.; Lotoski, J.A.; Chong, J.M. *J. Org. Chem.* **2001**, 66, 8248.

¹³³⁹ Stanetty, P.; Mihovilovic, M.D. *J. Org. Chem.* **1997**, 62, 1514.

¹³⁴⁰ Duhamel, L.; Poirier, J. *J. Am. Chem. Soc.* **1977**, 99, 8356.

¹³⁴¹ Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, 44, 2408.

¹³⁴² Marié, J.-C.; Curillon, C.; Malacria, M. *Synlett* **2002**, 553.

¹³⁴³ Itami, K.; Kamei, T.; Mitsudo, K.; Nokami, T.; Yoshida, J.-i. *J. Org. Chem.* **2001**, 66, 3970.

¹³⁴⁴ Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, 118, 1575; Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, 118, 715; Dieter, R.K.; Sharma, R.R. *Tetrahedron Lett.* **1997**, 38, 5937.

¹³⁴⁵ Serino, C.; Stehle, N.; Park, Y.S.; Florio, S.; Beak, P. *J. Org. Chem.* **1999**, 64, 1160.

¹³⁴⁶ Ma, S.; Wang, L. *J. Org. Chem.* **1998**, 63, 3497.

¹³⁴⁷ Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, 6, 1461.

¹³⁴⁸ MacNeil, S.L.; Familoni, O.B.; Snieckus, V. *J. Org. Chem.* **2001**, 66, 3662.

organolithium reagent) usually leads to an *ortho* lithiated species.¹³⁴⁹ Subsequent reaction with an electrophilic species gives the *ortho* substituted product. This phenomenon is known as *directed ortho metalation* (See **13-17**). This selectivity was discovered independently by Gilman and by Wittig in 1939–1940, when anisole was found to give *ortho* deprotonation in the presence of butyllithium.¹³⁵⁰ Alkylation *ortho* to a carbonyl is possible, and treatment of the acyl hydrazide [PhC(=O)NHNMe₂] with *sec*-butyllithium and then iodoethane gave the *ortho* ethyl derivative.¹³⁵¹ Note that aminonaphthalene derivatives were reacted with *tert*-butyllithium and aryllithium formation occurred on the ring distal to the amino group, and subsequent reaction with iodomethane gave methylation on that ring.¹³⁵²

In a method for propargylating an alkyl halide without allylic rearrangement, the halide is treated with lithio-1-trimethylsilylpropyne (**141**), which is a lithium compound protected by an SiMe₃ group.¹³⁵³ Reaction at its 1 position (which gives an allene) takes place only to a small extent, because of steric blockage by the large SiMe₃ group. The SiMe₃ group is easily removed by treatment with Ag⁺ followed by CN[−]. Propargyl derivative **141** is prepared by treating propynyllithium with Me₃SiCl to give MeC≡CSiMe₃ from which a proton is removed with BuLi. The R group may be primary or allylic.¹³⁵⁴ On the other hand, propargylic halides can be alkylated with essentially complete allylic rearrangement, to give allenes, by treatment with *Grignard reagents* and metallic salts,¹³⁵⁵ or with dialkylcuprates (R₂Cu).¹³⁵⁶



Grignard reagents are generally unreactive with alkyl halides unless allylic and benzylic reagents and substrates are used.¹³⁵⁷ *Grignard reagents* have the advantage that they are usually simpler to prepare than the corresponding R'₂CuLi (see Reaction **10-58**), but the reaction is much narrower in scope. *Grignard reagents* couple only with active halides: allylic (though allylic rearrangements are common) and benzylic. They also couple with tertiary alkyl halides, but generally in low or moderate yields.¹³⁵⁸

Allylic halides are more reactive than aliphatic alkyl halides, but Cu salts have been used to facilitate coupling with alkylmagnesium halides.¹³⁵⁹ Indeed, *Grignard reagents*

¹³⁴⁹ See Snieckus, V. *Chem. Rev.* **1990**, 90, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* **1979**, 26, 1. See also, Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* **1999**, 36, 1453.

¹³⁵⁰ Gilman, H.; Bebb, R.L. *J. Am. Chem. Soc.* **1939**, 61, 109; Wittig, G.; Fuhrman, G. *Chem. Ber.* **1940**, 73, 1197.

¹³⁵¹ McCombie, S.W.; Lin, S.-I.; Vice, S.F. *Tetrahedron Lett.* **1999**, 40, 8767.

¹³⁵² Kraus, G.A.; Kim, J. *J. Org. Chem.* **2002**, 67, 2358.

¹³⁵³ Corey, E.J.; Kirst, H.A.; Katzenellenbogen, J.A. *J. Am. Chem. Soc.* **1970**, 92, 6314.

¹³⁵⁴ See Ireland, R.E.; Dawson, M.I.; Lipinski, C.A. *Tetrahedron Lett.* **1970**, 2247.

¹³⁵⁵ Pasto, D.J.; Chou, S.; Waterhouse, A.; Shults, R.H.; Hennion, G.F. *J. Org. Chem.* **1978**, 43, 1385; Jeffery-Luong, T.; Linstumelle, G. *Tetrahedron Lett.* **1980**, 21, 5019.

¹³⁵⁶ Pasto, D.J.; Chou, S.; Fritzen, E.; Shults, R.H.; Waterhouse, A.; Hennion, G.F. *J. Org. Chem.* **1978**, 43, 1389.

See also, Tanigawa, Y.; Murahashi, S. *J. Org. Chem.* **1980**, 45, 4536.

¹³⁵⁷ See Raston, C.L.; Salem, G. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 161–306, 269–283; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 1046–1165.

¹³⁵⁸ See Ohno, M.; Shimizu, K.; Ishizaki, K.; Sasaki, T.; Eguchi, S. *J. Org. Chem.* **1988**, 53, 729.

¹³⁵⁹ Tissot-Croset, K.; Alexakis, A. *Tetrahedron Lett.* **2004**, 45, 7375; Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, 43, 2426.

may react with alkyl halides in the presence of certain metal catalysts,¹³⁶⁰ and stereocontrol is possible in these reactions.¹³⁶¹ These catalysts include Cu(I) compounds (see Reaction 10-58),¹³⁶² Ag compounds,¹³⁶³ Pd¹³⁶⁴ complexes, Co compounds,¹³⁶⁵ Fe compounds,¹³⁶⁶ and an Fe–amine complex was shown to catalyze Grignard coupling reactions.¹³⁶⁷ Iron nanoparticles have also been employed to facilitate this type of coupling.¹³⁶⁸ Alkyl triflates have been used rather than alkyl halides.¹³⁶⁹ Chiral Cu complexes have been used with allylic halides to give rearranged alkylated products, with high enantioselectivity.¹³⁷⁰ A similar reaction was reported using a *Grignard reagent* and a chiral imidazolium carbene complex.¹³⁷¹ As noted above, *Grignard reagents* react with allylic substrates, but if there is steric hindrance at the carbon bearing the leaving group, the reaction may proceed by an S_N2' pathway (Sec. 10.E).¹³⁷²

Aryl halides, even when activated, generally do not couple with *Grignard reagents*, although certain transition metal catalysts do effect this reaction in variable yields,¹³⁷³ including V compounds.¹³⁷⁴ The reaction with *Grignard reagents* proceeds better when OR can be the leaving group, providing that activating groups are present in the ring. Aryl triflates couple with arylmagnesium halides in the presence of a Pd catalyst,¹³⁷⁵ as do vinyl halides with RMgX with a Pd¹³⁷⁶ or Ni catalyst.¹³⁷⁷ Alkyl halides are coupled to arylmagnesium bromides in the presence of a Co catalyst.¹³⁷⁸ It is also possible to couple alkynylmagnesium halides with aryl iodides in the presence of Pd catalysts.¹³⁷⁹ A silica-supported phosphine–Pd complex was used to couple arylmagnesium halides with aryl iodides.¹³⁸⁰ Aryl *Grignard reagents* couple with alkyl halides, including neopentyl iodide, in the presence of ZnCl₂ and a Ni catalyst.¹³⁸¹

¹³⁶⁰ See Erdik, E. *Tetrahedron* **1984**, 40, 641; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, **1978**, pp. 374–398.

¹³⁶¹ Bäckvall, J.-E.; Persson, E.S.M.; Bombrun, A. *J. Org. Chem.* **1994**, 59, 4126.

¹³⁶² Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, 125, 5646. See also, Hintermann, L.; Xiao, L.; Labonne, A. *Angew. Chem. Int. Ed.* **2008**, 47, 8246; Cahiez, G.; Gager, O.; Buendia, J. *Synlett* **2010**, 299.

¹³⁶³ Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, 10, 969.

¹³⁶⁴ López-Pérez, A.; Adrio, J.; Carretero, J.C. *Org. Lett.* **2009**, 11, 5514. For other references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 386–392.

¹³⁶⁵ Hamaguchi, H.; Uemura, M.; Yasui, H.; Yorimitsu, H.; Koichiro Oshima, K. *Chem. Lett.* **2008**, 37, 1178.

¹³⁶⁶ Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem. Int. Ed.* **2007**, 46, 4364; Molander, G.A.; Rahn, B.J.; Shubert, D.C.; Bonde, S.E. *Tetrahedron Lett.* **1983**, 24, 5449. See Bedford, R.B.; Bruce, D.W.; Frost, R.M.; Goodby, J.W.; Hird, M. *Chem. Commun.* **2004**, 2822.

¹³⁶⁷ Bedford, R.B.; Bruce, D.W.; Frost, R.M.; Hird, M. *Chem. Commun.* **2005**, 4161.

¹³⁶⁸ Bedford, R.B.; Betham, M.; Bruce, D.W.; Davis, S.A.; Frost, R.M.; Hird, M. *Chem. Commun.* **2006**, 1398.

¹³⁶⁹ Wang, S.; Zhang, A. *Org. Prep. Proceed. Int.* **2008**, 40, 293.

¹³⁷⁰ Geurts, K.; Fletcher, S.P.; Feringa, B.L. *J. Am. Chem. Soc.* **2006**, 128, 15572.

¹³⁷¹ Lee, Y.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2006**, 128, 15604.

¹³⁷² Kar, A.; Argade, N.P. *Synthesis* **2005**, 2995. For an example, see Sen, S.; Singh, S.; Sieburth, S.McN. *J. Org. Chem.* **2009**, 74, 2884.

¹³⁷³ See Bell, T.W.; Hu, L.; Patel, S.V. *J. Org. Chem.*, **1987**, 52, 3847; Ozawa, F.; Kurihara, K.; Fujimori, M.; Hidaka, T.; Toyoshima, T.; Yamamoto, A. *Organometallics* **1989**, 8, 180.

¹³⁷⁴ Yasuda, S.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, 81, 287.

¹³⁷⁵ Kamikawa, T.; Hayashi, T. *Synlett*, **1997**, 163.

¹³⁷⁶ Hoffmann, R.W.; Gieson, V.; Fuest, M. *Liebigs Ann. Chem.* **1993**, 629.

¹³⁷⁷ Babudri, F.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron Lett.* **1994**, 35, 8847.

¹³⁷⁸ Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, 128, 1886.

¹³⁷⁹ Negishi, E.; Kotori, M.; Xu, C. *J. Org. Chem.* **1997**, 62, 8957.

¹³⁸⁰ Cai, M.-Z.; Song, C.-S.; Huang, X. *J. Chem. Res. (S)* **1998**, 264.

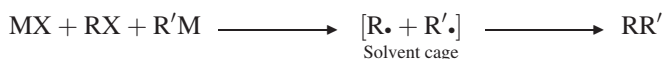
¹³⁸¹ Kondo, S.; Ohira, M.; Kawasoe, S.; Kunisada, H.; Yuki, Y. *J. Org. Chem.* **1993**, 58, 5003.

Vinyl¹³⁸² and aryl halides¹³⁸³ also couple with alkyl *Grignard reagents* in the presence of a catalytic amount of an Fe catalyst,¹³⁸⁴ as do vinyl triflates with CuI¹³⁸⁵ or vinyl halides with a Co catalyst.¹³⁸⁶ *Grignard reagents* prepared from primary or secondary¹³⁸⁷ alkyl or aryl halides can be coupled with vinylic or aryl halides (see Reaction 13-9) in high yields in the presence of a Ni(II) catalyst.¹³⁸⁸ When a chiral Ni(II) catalyst is used, optically active hydrocarbons can be prepared from achiral reagents.¹³⁸⁹ The Pd catalyzed coupling of arylmagnesium halides and vinyl bromides has also been reported.¹³⁹⁰

Because *Grignard reagents* react with the C=O group (Reaction 16-24 and 16-82), they cannot be used to couple with halides containing ketone, CO₂R, or amide functions. Although the coupling of *Grignard reagents* with ordinary alkyl halides is usually not useful for synthetic purposes, small amounts of symmetrical coupling product are commonly formed while *Grignard reagents* are being prepared.

For symmetrical coupling of organometallic reagents (2RM → RR), see Reaction 14-24 and 14-25.

Much study has been devoted to the mechanisms of these reactions,¹³⁹¹ but firm conclusions are still lacking, in part because the mechanisms vary depending on the metal, the R group, the catalyst, if any, and the reaction conditions. Two basic pathways can be envisioned: a nucleophilic substitution process (which might be S_N1 or S_N2) and a free radical mechanism. This could be an SET pathway, or some other route that provides radicals. In either case, the two radicals R• and R'• would be in a solvent cage:



It is necessary to postulate the solvent cage because, if the radicals were completely free, the products would be ~ 50% RR', 25% RR, and 25% R'R'. This is generally not the case; in most of these reactions RR' is the predominant or exclusive product.¹³⁹² An example where an S_N2 mechanism has been demonstrated (by the finding of inversion of configuration at R) is the reaction between allylic or benzylic lithium reagents with secondary halides.¹³⁹³ The fact that in some of these cases the reaction can be successfully applied to aryl and vinylic substrates indicates that a simple S_N process cannot be the only

¹³⁸² Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, 6, 1297; Terao, J.; Watabe, H.; Kambe, N. *J. Am. Chem. Soc.* **2005**, 127, 3656.

¹³⁸³ Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, 43, 3955.

¹³⁸⁴ Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901. See Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, 69, 3943.

¹³⁸⁵ Karlström, A.S.E.; Rönn, M.; Thorarensen, A.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, 63, 2517.

¹³⁸⁶ Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* **1998**, 39, 6159.

¹³⁸⁷ Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, 106, 158.

¹³⁸⁸ Böhm, V.P.W.; Gstöttmayr, C.W.K.; Weskamp, T.; Hermann, W.A. *Angew. Chem. Int. Ed.* **2001**, 40, 3387; Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, 124, 4222. See Kumada, M. *Pure Appl. Chem.* **1980**, 52, 669.

¹³⁸⁹ See Hayashi, T.; Kumada, M. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, **1985**, pp. 147–169. See also, Iida, A.; Yamashita, M. *Bull. Chem. Soc. Jpn.* **1988**, 61, 2365.

¹³⁹⁰ Rathore, R.; Deselnicu, M.I.; Burns, C.L. *J. Am. Chem. Soc.* **2002**, 124, 14832.

¹³⁹¹ See Beletskaya, I.P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* **1976**, 45, 330.

¹³⁹² When a symmetrical distribution of products is found, this is evidence for a free-radical mechanism: the solvent cage is not efficient and breaks down.

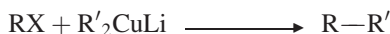
¹³⁹³ Sommer, L.H.; Korte, W.D. *J. Org. Chem.* **1970**, 35, 22; Korte, W.D.; Kinner, L.; Kaska, W.C. *Tetrahedron Lett.* **1970**, 603. See also, Schlosser, M.; Fouquet, G. *Chem. Ber.* **1974**, 107, 1162, 1171.

mechanism. One possibility is that the reagents first undergo an exchange reaction: $\text{ArX} + \text{RM} \rightarrow \text{RX} + \text{ArM}$, and then a nucleophilic substitution takes place. On the other hand, there is much evidence that many coupling reactions involving organometallic reagents with simple alkyl groups occur by free radical mechanisms. Among the evidence¹³⁹⁴ is the observation of CIDNP in reactions of alkyl halides with simple organolithium reagents¹³⁹⁵ (see Sec. 5.C.i), the detection of free radicals by ESR spectroscopy¹³⁹⁶ (Sec. 5.C.i), and the formation of 2,3-dimethyl-2,3-diphenylbutane when the reaction was carried out in the presence of cumene¹³⁹⁷ (this product is formed when a free radical abstracts a hydrogen from cumene to give PhCMe_2 , which dimerizes). Evidence for free radical mechanisms has also been found for the coupling of alkyl halides with simple organosodium compounds (Wurtz),¹³⁹⁸ with *Grignard reagents*,¹³⁹⁹ and with lithium dialkylcopper reagents (see Reaction 10-58).¹⁴⁰⁰ Free radicals have also been implicated in the metal-ion catalyzed coupling of alkyl and aryl halides with *Grignard reagents*.¹⁴⁰¹

OS I, 186; III, 121; IV, 748; VI, 407; VII, 77, 172, 326, 485; VIII, 226, 396; IX, 530; X, 332, 396.

10-58 Reaction of Alkyl Halides and Sulfonate Esters with Organocuprates

Alkyl-de-halogenation



The reagents lithium dialkylcopper¹⁴⁰² (known as lithium dialkyl cuprates, also called *Gilman reagents*)¹⁴⁰³ react with alkyl bromides, chlorides, and iodides in ether or THF to give good yields of the cross-coupling products.¹⁴⁰⁴ They are prepared (see Reaction 12-36) by the reaction of an organolithium compound with CuI or CuBr, but other Cu(I) compounds can be used.¹⁴⁰⁵ They are usually generated at temperatures $<0^\circ\text{C}$ due

¹³⁹⁴ See Muraoka, K.; Nojima, M.; Kusabayashi, S.; Nagase, S. *J. Chem. Soc. Perkin Trans. 2* **1986**, 761.

¹³⁹⁵ Podoplelov, A.V.; Leshina, T.V.; Sagdeev, R.Z.; Kamkha, M.A.; Shein, S.M. *J. Org. Chem. USSR* **1976**, 12, 488; Ward, H.R.; Lawler, R.G.; Cooper, R.A. in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, **1973**, pp. 281–322.

¹³⁹⁶ Russell, G.A.; Lamson, D.W. *J. Am. Chem. Soc.* **1969**, 91, 3967.

¹³⁹⁷ Bryce-Smith, D. *Bull. Soc. Chim. Fr.* **1963**, 1418.

¹³⁹⁸ Garst, J.F.; Hart, P.W. *J. Chem. Soc. Chem. Commun.* **1975**, 215.

¹³⁹⁹ Kasukhin, L.F.; Ponomarchuk, M.P.; Buteiko, Zh.F. *J. Org. Chem. USSR* **1972**, 8, 673; Singh, P.R.; Tayal, S.R.; Nigam, A. *J. Organomet. Chem.* **1972**, 42, C9.

¹⁴⁰⁰ Bertz, S.H.; Dabbagh, G.; Muijsce, A.M. *J. Am. Chem. Soc.* **1991**, 113, 631.

¹⁴⁰¹ Tamura, M.; Kochi, J.K. *J. Am. Chem. Soc.* **1971**, 93, 1483, 1485, 1487; *J. Organomet. Chem.* **1971**, 31, 289; **1972**, 42, 205; Lehr, G.F.; Lawler, R.G. *J. Am. Chem. Soc.* **1986**, 106, 4048.

¹⁴⁰² See Pearson, R.G.; Gregory, C.D. *J. Am. Chem. Soc.* **1976**, 98, 4098. See also, Lipshutz, B.H.; Kozlowski, J. A.; Breneman, C.M. *Tetrahedron Lett.* **1985**, 26, 5911; Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, **1987**, pp. 682–698.

¹⁴⁰³ See Stemmler, T.L.; Barnhart, T.M.; Penner-Hahn, J.E.; Tucker, C.E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* **1995**, 117, 12489. Solution compositions of Gilman reagents have also been studied. See Lipshutz, B.H.; Kayser, F.; Siegmann, K. *Tetrahedron Lett.* **1993**, 34, 6693.

¹⁴⁰⁴ Bergbreiter, D.E.; Whitesides, G.M. *J. Org. Chem.* **1975**, 40, 779. See Bertz, S.H.; Eriksson, M.; Miao, G.; Snyder, J.P. *J. Am. Chem. Soc.* **1998**, 118, 10906 for the reactivity of β -silyl organocuprates.

¹⁴⁰⁵ For an example using a Cu(II) salt, see Nguyen, T.T.; Chevallier, F.; Jouikov, V.; Mongin, F. *Tetrahedron Lett.* **2009**, 50, 6787.

to the thermal instability of any dialkyl cuprate that has a hydrogen atom on a carbon that is β - to the Cu.

The reaction with alkyl halides is of wide scope¹⁴⁰⁶ and R in R_2CuLi may be primary alkyl, allylic, benzylic, aryl, vinylic, or allenic, and may contain keto, CO_2H , CO_2R , or $CONR_2$ groups.¹⁴⁰⁷ The mechanism of these reactions probably involves formation of a Cu(II) intermediate.¹⁴⁰⁸ Reaction with allylic substrates usually proceeds with high selectivity for the γ -position,¹⁴⁰⁹ in S_N2' -type reactions.¹⁴¹⁰

Inversion of configuration has been shown in the reaction of 2-bromobutane with Ph_2CuLi ,¹⁴¹¹ but the same reaction with 2-iodobutane was reported to proceed with racemization.¹⁴¹² The reaction at a vinylic substrate occurs stereospecifically, with retention of configuration.¹⁴¹³ Many *gem*-dihalides do not react, but when the two halogens are on a carbon α to an aromatic ring¹⁴¹⁴ or on a cyclopropane ring,¹⁴¹⁵ both halogens can be replaced by R (e.g., $PhCHCl_2 \rightarrow PhCHMe_2$). However, 1,2-dibromides give exclusive elimination (Reaction 17-22).¹⁴¹⁶ Vinylmagnesium halides, upon addition of a catalytic amount of Li_2CuCl_4 , couple to alkyl halide.¹⁴¹⁶

Lithium dialkylcopper reagents couple with alkyl tosylates.¹⁴¹⁷ High yields are obtained with primary tosylates; secondary tosylates give lower yields,¹⁴¹⁸ but aryl tosylates do not react. Vinylic triflates¹⁴¹⁹ couple very well to give alkenes¹⁴²⁰ and they also couple with allylic cuprates, to give 1,4-dienes.¹⁴²¹ Propargylic tosylates couple with vinylic cuprates to give vinylic allenes.¹⁴²²

The R' in R'_2CuLi may be primary alkyl, vinylic, allylic, or aryl. Thus, in the reaction so far described, the alkyl groups on the organocuprate or the alkyl halide may *not* be secondary or tertiary alkyl. However, secondary and tertiary alkyl coupling can be achieved

¹⁴⁰⁶ See Posner, G.H. *Org. React.* **1975**, 22, 253; Lipshutz, B.H. *Accts. Chem. Res.* **1997**, 30, 277; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, **1980**. For lists of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 392–399, 599–604, 1564.

¹⁴⁰⁷ See Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, 122, 7294.

¹⁴⁰⁸ For an extensive discussion of the mechanism of reaction between organocuprates and alkyl halides or epoxides, see Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, 122, 7294; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, **1980**. See Bertz, S.H.; Cope, S.; Dorton, D.; Murphy, M.; Ogle, C.A. *Angew. Chem. Int. Ed.* **2007**, 46, 7082.

¹⁴⁰⁹ Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, 130, 12862.

¹⁴¹⁰ Some intermediates in this reaction have been prepared, see Bartholomew, E.R.; Bertz, S.H.; Cope, S.; Murphy, M.; Ogle, C.A. *J. Am. Chem. Soc.* **2008**, 130, 11244. For a review, see Falcioni, C.A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765.

¹⁴¹¹ Posner, G.H.; Ting, J. *Synth. Commun.* **1973**, 3, 281.

¹⁴¹² Lipshutz, B.H.; Wilhelm, R.S.; Nugent, S.T.; Little, R.D.; Baizer, M.M. *J. Org. Chem.* **1983**, 48, 3306.

¹⁴¹³ Klein, J.; Levene, R. *J. Am. Chem. Soc.* **1972**, 94, 2520. For a discussion of the mechanism, see Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, 126, 12264.

¹⁴¹⁴ Posner, G.H.; Brunelle, D.J. *Tetrahedron Lett.* **1972**, 293.

¹⁴¹⁵ See Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, 50, 1600.

¹⁴¹⁶ Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, 56, 2733.

¹⁴¹⁷ Johnson, C.R.; Dutra, G.A. *J. Am. Chem. Soc.* **1973**, 95, 7777, 7783. See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, **1980**, pp. 85–90.

¹⁴¹⁸ Secondary tosylates give higher yields when they contain an O or S atom: Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* **1989**, 54, 5831.

¹⁴¹⁹ See Scott, W.J.; McMurtry, J.E. *Acc. Chem. Res.* **1988**, 21, 47.

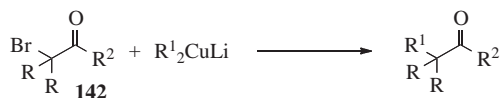
¹⁴²⁰ Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313.

¹⁴²¹ Lipshutz, B.H.; Elworthy, T.R. *J. Org. Chem.* **1990**, 55, 1695.

¹⁴²² Baudouy, R.; Goré, J. *J. Chem. Res. (S)* **1981**, 278. See also, Elsevier, C.J.; Vermeer, P. *J. Org. Chem.* **1989**, 54, 3726.

(on primary RX) by the use of $R'_2CuLi \bullet P Bu_2$ ¹⁴²³ (but this procedure introduces problems in the workup) or by the use of $PhS(R')CuLi$,¹⁴²⁴ which selectively couples a secondary or tertiary R' with a primary iodide (RI) to give RR' .¹⁴²⁵ It is possible to prepare mixed cuprates, where one ligand is tightly bound to the copper, allowing the other ligand to be transferred in a coupling reaction. A common example is adds a 2-thienyl group to the cuprate to give $R(Th)CuLi$, where the R group is transferred in lieu of the thienyl unit.¹⁴²⁶ A lithium neopentyl aryl cuprate selectively transferred from an aryl group to an allylic halide.¹⁴²⁷

Coupling to a secondary alkyl halide (R in RX above = secondary) can be achieved in high yield with the reagents $R'_2Cu(CN)Li_2$,¹⁴²⁸ where R' is primary alkyl or vinylic (but not aryl).¹⁴²⁹ This modified reagent is commonly known as a *higher order mixed cuprate*. The reagents $RCu(PPh_2)Li$, $RCu(NR'_2)Li$, and $RCu(PR'_2)Li$ (R' = cyclohexyl) are more stable than R_2CuLi and can be used at higher temperatures.¹⁴³⁰ These reagents are rather reactive. Unactivated aryl triflates¹⁴³¹ ($ArOSO_2CF_3$) react to give ArR in good yields when treated with $R_2Cu(CN)Li_2$,¹⁴³² with R_3Al ,¹⁴³³ or with R_3SnR and a Pd complex catalyst.¹⁴³⁴ See Reaction 10-59 for other examples involving Al, Sn, and Pd coupling reactions. Both OTf units in $RCH(OTf)_2$ can be replaced with $Me_2(CN)CuLi_2$.¹⁴³⁵ With an allenic substrate, reaction with $R(CN)CuLi$ can give ordinary displacement (with retention of configuration)¹⁴³⁶ or an S_N2' reaction to produce an alkyne.¹⁴³⁷ In the latter case, a chiral allene (see Sec. 4.C, category 5) gave a chiral alkyne. The structures of these “higher order mixed” cuprates has been called into question¹⁴³⁸ by Bertz,¹⁴³⁹ who suggested the reagent actually existed as $R_2CuLi \bullet LiCN$ in THF. This was contradicted by Lipshutz and James.¹⁴⁴⁰



¹⁴²³ Whitesides, G.M.; Fischer, Jr., W.F.; San Filippo, Jr., J.; Bashe, R.W.; House, H.O., *J. Am. Chem. Soc.* **1969**, 91, 4871.

¹⁴²⁴ Prepared as in Ref. 1444 or treatment of $PhSCu$ with RLi : Posner, G.H.; Brunelle, D.J.; Sinoway, L. *Synthesis* **1974**, 662.

¹⁴²⁵ Posner, G.H.; Whitten, C.E.; Sterling, J.J. *J. Am. Chem. Soc.* **1973**, 95, 7788.

¹⁴²⁶ See Malmberg, H.; Nilsson, M.; Ullenius, C. *Tetrahedron Lett.* **1982**, 23, 3823; Lipshutz, B.H.; Kozlowski, J.A.; Parker, D.A.; Nguyen, S.L.; McCarthy, K.E. *J. Organomet. Chem.* **1985**, 285, 437.

¹⁴²⁷ Piazza, C.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, 41, 3263.

¹⁴²⁸ See Lipshutz, B.H. *Synthesis* **1987**, 325; *Synlett* **1990**, 119. See also, Bertz, S.H. *J. Am. Chem. Soc.* **1990**, 112, 4031; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* **1990**, 112, 4032.

¹⁴²⁹ Lipshutz, B.H.; Wilhelm, R.S.; Floyd, D.M. *J. Am. Chem. Soc.* **1981**, 103, 7672.

¹⁴³⁰ Bertz, S.H.; Dabbagh, G. *J. Org. Chem.* **1984**, 49, 1119.

¹⁴³¹ See Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.*, **1988**, 110, 3296.

¹⁴³² McMurry, J.E.; Mohanraj, S. *Tetrahedron Lett.*, **1983**, 24, 2723.

¹⁴³³ Hirota, K.; Isobe, Y.; Maki, Y. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 2513.

¹⁴³⁴ Echevarren, E.M.; Stille, J.K. *J. Am. Chem. Soc.*, **1987**, 109, 5478. For a similar reaction with aryl fluorosulfonates, see Roth, G.P.; Fuller, C.E. *J. Org. Chem.*, **1991**, 56, 3493.

¹⁴³⁵ Martínez, A.G.; Barcina, J.O.; Díez, B.R.; Subramanian, L.R. *Tetrahedron* **1994**, 50, 13231.

¹⁴³⁶ Mooiweer, H.H.; Elsevier, C.J.; Wijkens, P.; Vermeer, P. *Tetrahedron Lett.* **1985**, 26, 65.

¹⁴³⁷ Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1984**, 25, 3059, 3063. For the reaction of these reagents with haloalkynes, see Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* **1989**, 30, 4799.

¹⁴³⁸ Bertz, S.H.; Miao, G.; Eriksson, M. *Chem. Commun.* **1996**, 815; Snyder, J.P.; Bertz, S.H. *J. Org. Chem.* **1995**, 60, 4312. Also see, Snyder, J.P.; Tipsword, G.E.; Spangler, D.P. *J. Am. Chem. Soc.* **1992**, 114, 1507.

¹⁴³⁹ Bertz, S.H. *J. Am. Chem. Soc.* **1990**, 112, 4031.

¹⁴⁴⁰ Lipshutz, B.H.; James, B. *J. Org. Chem.* **1994**, 59, 7585 and references cited therein.

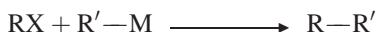
The fact that R'_2CuLi do not react with ketones provides a method for the alkylation of ketones via the organocuprate coupling with α -haloketones (e.g., **142**¹⁴⁴¹; see also, Reactions **10-68** and **10-73**). Note that halogen-metal exchange (Reaction **12-39**) is a side reaction and can become the main reaction.¹⁴⁴² When α,α' -dibromo ketones are treated with Me_2CuLi in ether at $-78^\circ C$ and the mixture quenched with methanol, monomethylation takes place¹⁴⁴³ (no dimethylation is observed). It has been suggested that the reaction involves cyclization (**10-56**) to a cyclopropanone followed by nucleophilic attack to give the enolate anion, which is protonated by the methanol. If iodomethane is added instead of methanol, an α,α' -dimethyl ketone is obtained, presumably from S_N2 attack (Reaction **10-68**). Primary, secondary, and tertiary monoalkylation can be achieved with a lithium *tert*-butoxy(alkyl)copper reagent¹⁴⁴⁴ instead of Me_2CuLi , one of the few methods for introducing a tertiary alkyl group to a carbonyl group.

When dialkylcopperzinc reagents ($R_2CuZnCl$) couple with allylic halides, allylic rearrangement occurs (S_N2') almost completely, and the reaction is diastereoselective if the allylic halide contains a δ alkoxy group.¹⁴⁴⁵ Another type of copper reagent was prepared from $RZnI/CuCN$, and was shown to couple with alkenyl halides.¹⁴⁴⁶ Diethylzinc in the presence of a catalytic amount of $CuBr$ coupled to allylic chlorides.¹⁴⁴⁷ When treated with organocopper compounds and Lewis acids (e.g., $n-BuCu \bullet BF_3$), allylic halides give substitution with almost complete allylic rearrangement, independently of the degree of substitution at the two ends of the allylic system.¹⁴⁴⁸

OS IX, 502.

10-59 Reaction of Alkyl Halides and Sulfonate Esters with Other Organometallic Reagents

Alkyl-de-halogenation



In addition of Mg, Li, and Cu, other metals and metal complexes can be used to catalyze or mediate coupling reactions. Organoaluminum compounds couple very well with tertiary (to give products containing a quaternary carbon) and benzylic halides at $-78^\circ C$.¹⁴⁴⁹ This reaction can also be applied to allylic, secondary, and some primary halides, but several days standing at room temperature is required (see also, Reaction **10-63**). Vinylic aluminum compounds (in the presence of a suitable transition metal catalyst) couple

¹⁴⁴¹ Dubois, J.E.; Fournier, P.; Lion, C. *Bull. Soc. Chim. Fr.* **1976**, 1871.

¹⁴⁴² See Corey, E.J.; Posner, G.H. *J. Am. Chem. Soc.* **1967**, 89, 3911; Wakselman, C.; Mondon, M. *Tetrahedron Lett.* **1973**, 4285.

¹⁴⁴³ Posner, G.H.; Sterling, J.J. *J. Am. Chem. Soc.* **1973**, 95, 3076. See also, Posner, G.H.; Sterling, J.J.; Whitten, C.E.; Lentz, C.M.; Brunelle, D.J. *J. Am. Chem. Soc.* **1975**, 97, 107; Lion, C.; Dubois, J.E. *Tetrahedron* **1975**, 31, 1223. See Lei, X.; Doubleday, Jr., C.; Turro, N.J. *Tetrahedron Lett.* **1986**, 27, 4671.

¹⁴⁴⁴ Prepared by treating CuI with *t*-BuOLi in THF at $0^\circ C$ and adding RLi to this solution.

¹⁴⁴⁵ Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, 111, 3091.

¹⁴⁴⁶ Marquais, S.; Cahiez, G.; Knochel, P. *Synlett*, **1994**, 849.

¹⁴⁴⁷ Malda, H.; van Zijl, A.W.; Arnold, L.A.; Feringa, B.L. *Org. Lett.* **2001**, 3, 1169.

¹⁴⁴⁸ Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, 102, 2318. See also, Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H. *J. Am. Chem. Soc.* **1990**, 112, 5869.

¹⁴⁴⁹ Kennedy, J.P. *J. Org. Chem.* **1970**, 35, 532. See also, Sato, F.; Kodama, H.; Sato, M. *J. Organomet. Chem.* **1978**, 157, C30.

with allylic halides, acetates, and alcohol derivatives to give 1,4-dienes,¹⁴⁵⁰ and with vinylic and benzylic halides to give 1,3-dienes and allylic arenes, respectively.¹⁴⁵¹ Note that alkylboronic acids are coupled in the presence of Ag₂O and a catalytic amount of CrCl₂ to give the symmetrical alkyl derivative.¹⁴⁵²

Products containing a quaternary carbon can also be obtained by treatment of tertiary halides with dialkyl or diaryl zinc reagents in CH₂Cl₂,¹⁴⁵³ with Me₃Si and AlCl₃,¹⁴⁵⁴ or with alkyltitanium reagents (RTiCl₃ and R₂TiCl₂).¹⁴⁵⁵ Alkyl or aryl triflates (halides) couple with alkyl or ArZn(halide) reagents in the presence of a Pd catalyst.¹⁴⁵⁶ This organozinc coupling reaction has been done in ionic liquids.¹⁴⁵⁷ Vinyl halides can be coupled with vinyltin reagents in the presence of CuI,¹⁴⁵⁸ and aryl tin compounds couple with vinyl halides¹⁴⁵⁹ or vinyl triflates when a Pd catalyst is present.¹⁴⁶⁰ When the vinyltin reagent is coupled with a vinyl triflate in the presence of a Pd catalyst, the reaction is known as the *Stille reaction* (Reaction 12-15). In the *Stille reaction*, vinylic triflates, in the presence of a Pd catalyst and LiCl, couple with organotin compounds (R'SnMe₃), where R' can be alkyl, allylic, vinylic, or alkynyl.¹⁴⁶¹ The reaction has been performed intramolecularly, to prepare large-ring lactones.¹⁴⁶²

The coupling of alkyl or alkenyl halides and an organozinc compound with a Ni complex has come to be known as *Negishi coupling*.¹⁴⁶³ Several variations have been reported over the years. Arylzinc compounds¹⁴⁶⁴ have been used, and also arylvinyl iodides.¹⁴⁶⁵ The structure of bis(iodozincio)methane in THF solution has been reported.¹⁴⁶⁶ Pyridylzinc compounds have been used in *Negishi coupling*.¹⁴⁶⁷

¹⁴⁵⁰ See Lee, Y.; Akiyama, K.; Gillingham, D.G.; Brown, M.K.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2008**, *130*, 446.

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¹⁴⁶² Stille, J.K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785.

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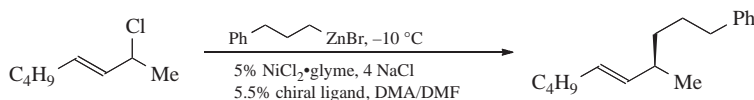
¹⁴⁶⁴ Mutule, I.; Suna, E. *Tetrahedron* **2005**, *61*, 11168.

¹⁴⁶⁵ Kabir, M.S.; Monte, A.; Cook, J.M. *Tetrahedron Lett.* **2007**, *48*, 7269.

¹⁴⁶⁶ Matsubara, S.; Oshima, K.; Matsuoka, H.; Matsumoto, K.; Ishikawa, K.; Matsubara, E. *Chem. Lett.* **2005**, *34*, 952.

¹⁴⁶⁷ Coleridge, B.M.; Bello, C.S.; Ellenberger, D.H.; Leitner, A. *Tetrahedron Lett.* **2010**, *51*, 357.

Carbonylative cross coupling reactions have been reported.¹⁴⁶⁸ Palladium-catalyzed variations are also known for alkyl or vinyl halides with organozinc compounds.¹⁴⁶⁹ Dialkylzinc compounds can be coupled to alkyl halides in the presence of a nickel catalyst,¹⁴⁷⁰ but with geminal diiodo compounds without a catalyst.¹⁴⁷¹ Asymmetric variations are known using various chiral additives or chiral catalysts,¹⁴⁷² including the example shown for an allylic chloride (DMA = dimethylacetamide).¹⁴⁷³ Coupling with propargylic substrates has also been reported.¹⁴⁷⁴



Copper compounds can also be used as catalysts with dialkylzinc reagents.¹⁴⁷⁵ The reaction of aryl halides with Me_4ZnLi_2 and then $\text{VO}(\text{OEt})\text{Cl}_2$ leads to the methylated aryl.¹⁴⁷⁶ Isopropylzinc ($i\text{PrZn}$) displaces the iodide in γ -iodo ketones to give the alkyl substitution product, without reaction at the carbonyl.¹⁴⁷⁷ Reactions of organozinc reagents with a carbonyl compound via acyl addition is presented in **16-31** (the *Reformatsky reaction*). Tertiary halides have also been coupled to allyltin reagents in the presence of AIBN.¹⁴⁷⁸ Alkyl halides can be treated with SmI_2 and then CuBr to give a reactive species that couples with other alkyl halides.¹⁴⁷⁹ Trialkylindium compounds couple to allylic bromides in the presence of $\text{Cu}(\text{OTf})_2 \cdot \text{P}(\text{OEt})_3$ ¹⁴⁸⁰ and vinyl indium compounds are coupled to α -halo esters with a BEt_3 catalyst.¹⁴⁸¹ Arylsulfonyl chlorides couple with allyl halides in the presence of bismuth to give allyl-aryls.¹⁴⁸² Vinyl iodides couple with RMnCl with an iron catalyst¹⁴⁸³ and Bu_3MnMgBr reacted with a geminal dibromocyclopropane to give a dialkylated cyclopropane.¹⁴⁸⁴ α -Haloketones are coupled with aryl halides using a

¹⁴⁶⁸ Wang, Q.; Chen, C. *Tetrahedron Lett.* **2008**, 49, 2916.

¹⁴⁶⁹ See Hadei, N.; Kantchev, E.A.B.; O'Brien, C.J.; Organ, M.G. *J. Org. Chem.* **2005**, 70, 8503; Andrei, D.; Wnuk, S.F. *J. Org. Chem.* **2006**, 71, 405. For a variation using Pd-nanoparticles, see Liu, J.; Deng, Y.; Wang, H.; Zhang, H.; Yu, G.; Wu, B.; Zhang, H.; Li, Q.; Marder, T.B.; Yang, Z.; Lei, A. *Org. Lett.* **2008**, 10, 2661.

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¹⁴⁷¹ Shibli, A.; Varghese, J.P.; Knochel, P.; Marek, I. *Synlett* **2001**, 818.

¹⁴⁷² See Fischer, C.; Fu, G.C. *J. Am. Chem. Soc.* **2005**, 127, 4594; Arp, F.O.; Fu, G.C. *J. Am. Chem. Soc.* **2005**, 127, 10482.

¹⁴⁷³ Son, S.; Fu, G.C. *J. Am. Chem. Soc.* **2008**, 130, 2756.

¹⁴⁷⁴ Smith, S.W.; Fu, G.C. *Angew. Chem. Int. Ed.* **2008**, 47, 9334.

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¹⁴⁷⁶ Hu, J.-b.; Zhao, G.; Yang, G.-s.; Ding, Z.-d. *J. Org. Chem.* **2001**, 66, 303.

¹⁴⁷⁷ Jensen, A.E.; Knochel, P. *J. Org. Chem.* **2002**, 67, 79.

¹⁴⁷⁸ Kraus, G.A.; Anshers, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, 34, 1741.

¹⁴⁷⁹ Berkowitz, W.F.; Wu, Y. *Tetrahedron Lett.* **1997**, 38, 3171.

¹⁴⁸⁰ Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* **2003**, 68, 2518.

¹⁴⁸¹ Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, 6, 4555.

¹⁴⁸² Baruah, M.; Boruah, A.; Prajapati, D.; Sandu, J.S. *Synlett*, **1998**, 1083.

¹⁴⁸³ Cahiez, G.; Marquais, S. *Tetrahedron Lett.* **1996**, 37, 1773.

¹⁴⁸⁴ Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2000**, 56, 2131.

Ni catalyst.¹⁴⁸⁵ Allylgallium reagents have been coupled to α -bromo esters in the presence of BEt_3/O_2 .¹⁴⁸⁶

Arylpalladium salts (ArPdX) prepared from arylmercury compounds and lithium palladium chloride couple with allylic chlorides in moderate yields, although allylic rearrangements can occur.¹⁴⁸⁷ In most cases, better yields are obtained by addition of a Pd complex to the substrate, sometimes in conjunction with another metal, to facilitate coupling. Under these conditions, any arylpalladium species is generated *in situ*. Allylic, benzylic, vinylic, and aryl halides or triflates (trifluoromethylsulfonates) couple with organotin reagents in a reaction catalyzed by Pd complexes.¹⁴⁸⁸ The advantage of this procedure is that the aryl group may contain nitro, ester, or aldehyde groups, and so on, which cannot be present in a *Grignard reagent*. Such functional groups as CO_2R , CN , OH , and CHO may be present in either reagent, but the substrate may not bear a β hydrogen on an sp^3 carbon, because that results in elimination. Indium metal has been used to mediate the coupling of an allylic halide and an arylpalladium complex.¹⁴⁸⁹ Organoindium compounds were coupled to 1-iodonaphthalene with a Pd catalyst.¹⁴⁹⁰ Aryl halides were also coupled to allylic silanes in the presence of a Pd catalyst.¹⁴⁹¹

Dimethylzinc was coupled to aryl halides with a Pd catalyst,¹⁴⁹² and *Reformatsky-type* zinc derivatives (see Reaction **16-28**) have been coupled to aryl halides using a Pd catalyst and microwave irradiation.¹⁴⁹³ Alkyl halides couple with ArMnCl or RMnCl in the presence of a Pd catalyst.¹⁴⁹⁴ Cobalt-catalyzed coupling reactions are known.¹⁴⁹⁵

In many cases, the organometallic reagent is prepared from the corresponding organolithium reagent (Reaction **10-57**), as in the conversion of an aryllithium to an arylzirconium reagent, which was subsequently coupled to an aryl halide in the presence of a Pd catalyst.¹⁴⁹⁶ Vinylzirconium reagents can be coupled to allylic halides in the presence of Cu(I) compounds.¹⁴⁹⁷

Alkylboranes are coupled to alkyl halides in the presence of a Ni catalyst.¹⁴⁹⁸
OS VII, 245; VIII, 295; X, 391.

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¹⁴⁸⁸ See Stille, J.K. *Angew. Chem. Int. Ed.* **1986**, 25, 508; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* **1990**, 59, 1174. See Martínez, A.G.; Barcina, J.O.; Heras, Md.R.C.; Cerezo, A.d.F. *Org. Lett.* **2000**, 2, 1377.

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¹⁴⁹⁰ Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* **2004**, 69, 8136.

¹⁴⁹¹ Denmark, S.E.; Werner, N.S. *J. Am. Chem. Soc.* **2008**, 130, 16382.

¹⁴⁹² Herbert, J.M. *Tetrahedron Lett.* **2004**, 45, 817.

¹⁴⁹³ Bentz, E.; Moloney, M.G.; Westaway, S.M. *Tetrahedron Lett.* **2004**, 45, 7395.

¹⁴⁹⁴ Riquet, E.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* **1997**, 38, 4397.

¹⁴⁹⁵ Czaplik, W.M.; Mayer, M.; Jacobi von Wangelin, A. *Synlett* **2009**, 2931.

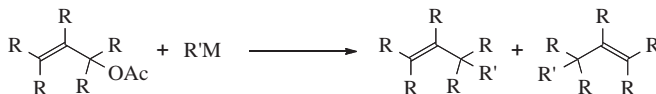
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10-60 Coupling of Organometallic Reagents with Carboxylic Esters

Alkyl-de-acyloxy-substitution



Several organometallic reagents react with allylic esters and carbonates to give the coupling product. Lithium dialkylcopper reagents couple with allylic acetates to give normal coupling products or those resulting from allylic rearrangement, depending on the substrate.¹⁴⁹⁹ A mechanism involving a σ -allylic copper(III) complex has been suggested.¹⁵⁰⁰ Silyl cuprates have also been used, with benzoate esters, to give allyl silanes.¹⁵⁰¹ Interestingly, allylic silanes have been coupled to acetates using $\text{B}(\text{C}_6\text{F}_5)_3$ ¹⁵⁰² or BF_3 .¹⁵⁰³



Allenes are obtained when propargyl acetates are treated with methylmagnesium iodide.¹⁵⁰⁴ Lithium dialkylcopper reagents give normal coupling products with enol acetates of β -dicarbonyl compounds.¹⁵⁰⁵ It is also possible to carry out the coupling of allylic acetates with *Grignard reagents*, if catalytic amounts of cuprous salts are present.¹⁵⁰⁶ Yields are better with this method, and regioselectivity can be controlled by the choice of cuprous salts.

Several metal-catalyzed coupling reactions are known. Allylic, benzylic, and cyclopropylmethyl acetates couple with trialkylaluminums,¹⁵⁰⁷ and allylic acetates couple with aryl and vinylic tin reagents, in the presence of a Pd catalyst¹⁵⁰⁸ (see below). Allylic acetates can be symmetrically coupled by treatment with $\text{Ni}(\text{CO})_4$ (Reaction 10-56) or with Zn and a Pd—complex catalyst,¹⁵⁰⁹ or converted to unsymmetrical 1,5-dienes by treatment with an allylic stannane ($\text{R}_2\text{C}=\text{CHCH}_2\text{SnR}_3$) in the presence of a Pd complex.¹⁵¹⁰ Other Ni(0) coupling reactions are known.¹⁵¹¹ Titanium-mediated¹⁵¹² coupling, Ir catalyzed,¹⁵¹³

¹⁴⁹⁹ Purpura, M.; Krause, N. *Eur. J. Org. Chem.* **1999**, 267.

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¹⁵⁰² Rubin, M.; Gevorgyan, V. *Org. Lett.* **2001**, 3, 2705. See Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* **2004**, 6, 1999.

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¹⁵⁰⁶ Karlström, A.S.E.; Huerta, F.F.; Muezelaar, G.J.; Bäckvall, J.-E. *Synlett* **2001**, 923; Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournieux, X. *Synlett* **2001**, 927.

¹⁵⁰⁷ van Klaveren, M.; Persson, E.S.M.; del Villar, A.; Grove, D.M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* **1995**, 36, 3059.

¹⁵⁰⁸ Del Valle, L.; Stille, J.K.; Hegedus, L.S. *J. Org. Chem.* **1990**, 55, 3019. For another method, see Legros, J.; Fiaud, J. *Tetrahedron Lett.* **1990**, 31, 7453.

¹⁵⁰⁹ Sasaoka, S.; Yamamoto, T.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1985**, 315.

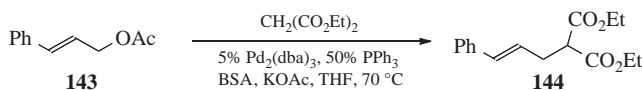
¹⁵¹⁰ Trost, B.M.; Keinan, E. *Tetrahedron Lett.* **1980**, 21, 2595.

¹⁵¹¹ Yatsumonji, Y.; Ishida, Y.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2007**, 9, 4603.

¹⁵¹² Mandal, S.K.; Paira, M.; Roy, S.C. *J. Org. Chem.* **2008**, 73, 3823.

¹⁵¹³ Spiess, S.; Welter, C.; Franck, G.; Taquet, J.-P.; Helmchen, G. *Angew. Chem. Int. Ed.* **2008**, 47, 7652.

and Fe catalyzed¹⁵¹⁴ reactions are also known. Aryl halides can be coupled to allylic acetates with $\text{CoBr}_2/\text{Mn}/\text{FeBr}_2$.¹⁵¹⁵ Allylic phosphonates have been used as substrates for displacement by higher order cuprates¹⁵¹⁶ (see Reaction **10-58**) or dialkylzinc reagents.¹⁵¹⁷



A common method is the reaction of η^3 - π -allyl palladium complexes¹⁵¹⁸ (see Sec 3.C.i) with various nucleophiles,¹⁵¹⁹ where the complex is obtained from allylic esters (acetate is the most common) or allylic carbonates (also see Reaction **10-31**). This coupling reaction is often called the *Tsuji-Trost* reaction.¹⁵²⁰ The mechanism of such π -allyl palladium reactions has been discussed.¹⁵²¹ The structure and nature of the ligands associated with the metal are important to the reaction, particularly with respect to stereoselectivity of a given reaction.¹⁵²² A typical transformation is shown for the reaction of **143** with diethyl malonate, BSA (N,O-bis(trimethylsilyl)acetamide), and potassium acetate, which gives coupling product **144** in the presence of the Pd catalyst.¹⁵²³ This reaction is a variation of the basic transformation reported several years ago by Trost et al.¹⁵²⁴ Enolate anions of active methylene compounds¹⁵²⁵ and also sulfone anions¹⁵²⁶ have been used as nucleophiles most of the time. In most reported cases, the $\text{R}'\text{M}$ species is the anion of an active methylene compound (e.g., sodium, potassium, or lithium dimethylmalonate) or *Knoevenagel-type* carbanions (see Reaction **16-38**) or amino acid surrogates.¹⁵²⁷ Enolate

¹⁵¹⁴ Plietker, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 6053.

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¹⁵²² For example, see Liu, D.; Xie, F.; Zhang, W. *Tetrahedron Lett.* **2007**, *48*, 585; Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron Asymmetry* **2005**, *16*, 959; Mikhael, I.; Goux-Henry, C.; Sinou, D. *Tetrahedron Asymmetry* **2006**, *17*, 1853; Ruzziconi, R.; Santi, C.; Spizzichino, S. *Tetrahedron Asymmetry* **2007**, *18*, 1742; Wang, Q.-F.; He, W.; Liu, X.-Y.; Chen, H.; Qin, X.-Y.; Zhang, S.-Y. *Tetrahedron Asymmetry* **2008**, *19*, 2447; Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrach, K. *Chem. Eur. J.* **2006**, *12*, 3596. Also see Mino, T.; Sato, Y.; Saito, A.; Tanaka, Y.; Saotome, H.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 7979.

¹⁵²³ Poli, G.; Giambastiani, G.; Mordini, A. *J. Org. Chem.* **1999**, *64*, 2962.

¹⁵²⁴ Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* **1978**, *100*, 3416, 3426. These papers include a discussion of the mechanism of this reaction.

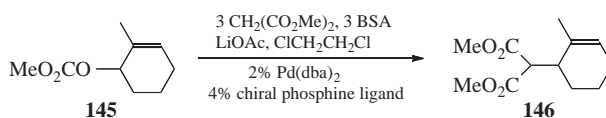
¹⁵²⁵ Braun, M.; Meier, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6952.

¹⁵²⁶ Manchand, P.S.; Wong, H.S.; Blount, J.F. *J. Org. Chem.* **1978**, *43*, 4769.

¹⁵²⁷ Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329.

anions (see Reaction 10-68) have also been used.¹⁵²⁸ Other nucleophiles can be used to displace allylic acetates.¹⁵²⁹ The Pd catalyst used, the reaction conditions, and the nature of the organometallic compounds varies widely. Although two allylic coupling products are possible via the π -allyl intermediate, attack at the less substituted position is generally favored. This transformation has been done in ionic liquids¹⁵³⁰ and ionic liquids have been used as additives in catalytic amounts in other solvents.¹⁵³¹ Palladium nanoparticles have been used to catalyze the reaction.¹⁵³² The S_N2' reactions with allylic substrates have been reported.¹⁵³³ Benzoate esters have been used successfully in lieu of the acetate.¹⁵³⁴ Catalyst metals other than Pd have been used for this reaction with allylic acetates.¹⁵³⁵

The use of chiral ligands¹⁵³⁶ or chiral additives that may act as ligands¹⁵³⁷ lead to asymmetric induction in the coupling product.¹⁵³⁸



As mentioned above, a common variation is to replace the acetate leaving group with a carbonate ($-\text{OCO}_2\text{R}$), where methyl carbonate ($-\text{OCO}_2\text{Me}$) is most common.¹⁵³⁹ A representative reaction is the transformation of **145** to **146**,¹⁵⁴⁰ where the use of a chiral ligand led to modest asymmetric induction. Indeed, as with allylic acetates, chiral ligands and chiral additives lead to asymmetric induction.¹⁵⁴¹ A variety of active

¹⁵²⁸ Braun, M.; Laicher, F.; Meier, T. *Angew. Chem. Int. Ed.* **2000**, 39, 3494.

¹⁵²⁹ $\text{NaN}(\text{CHO})_2$: Wang, Y.; Ding, K. *J. Org. Chem.* **2001**, 66, 3238. **Indene**: Hayashi, T.; Suzuka, T.; Okada, A.; Kawatsura, M. *Tetrahedron Asymmetry* **2004**, 15, 545.

¹⁵³⁰ See Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun.* **1999**, 1247.

¹⁵³¹ Sato, Y.; Yoshino, T.; Mori, M. *Org. Lett.* **2003**, 5, 31.

¹⁵³² Jansat, S.; Gómez, M.; Philippot, K.; Muller, G.; Guiu, E.; Claver, C.; Castillón, S.; Chaudret, B. *J. Am. Chem. Soc.*, **2004**, 126, 1592.

¹⁵³³ Falciola, C.A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem. Int. Ed.* **2006**, 45, 5995.

¹⁵³⁴ Krafft, M.E.; Sugiura, M.; Abboud, K.A. *J. Am. Chem. Soc.* **2001**, 123, 9174.

¹⁵³⁵ **Ir**: Kinoshita, N.; Marx, K.H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. *J. Org. Chem.* **2004**, 69, 7960. **Pt**: Blacker, A.J.; Clarke, M.L.; Loft, M.S.; Mahon, M.F.; Humphries, M.E.; Williams, J.M.J. *Chem. Eur. J.* **2000**, 6, 353. **Ru**: Renaud, J.-L.; Bruneau, C.; Demerseman, B. *Synlett* **2003**, 408.

¹⁵³⁶ See Boaz, N.W.; Ponaskik Jr., J.A.; Large, S.E.; Debenham, S.D. *Tetrahedron Asymmetry* **2004**, 15, 2151.

¹⁵³⁷ Molander, G.A.; Burke, J.P.; Carroll, P.J. *J. Org. Chem.* **2004**, 69, 8062; Kloetzing, R.J.; Lotz, M.; Knochel, P. *Tetrahedron Asymmetry* **2003**, 14, 255; Nakano, H.; Yokayama, J.-i.; Koizumi, Y.; Fjita, R.; Hongo, H. *Tetrahedron Asymmetry* **2003**, 14, 2361; Mercier, F.; Brebion, F.; Dupont, R.; Mathey, F. *Tetrahedron Asymmetry* **2003**, 14, 3137.

¹⁵³⁸ See Consiglio, G.; Waymouth, R.M. *Chem. Rev.* **1989**, 89, 257.

¹⁵³⁹ See Ito, K.; Kashiwagi, R.; Hayashi, S.; Uchida, T.; Katsuki, T. *Synlett* **2001**, 284.

¹⁵⁴⁰ Hamada, Y.; Sakaguchi, K.-e.; Hatano, K.; Hara, O. *Tetrahedron Lett.* **2001**, 42, 1297.

¹⁵⁴¹ Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, 125, 12104; Faller, J.W.; Wilt, J.C. *Tetrahedron Lett.* **2004**, 45, 7613.

methylene compounds can be used as nucleophiles,¹⁵⁴² including enolate anions.¹⁵⁴³ Other nucleophiles can be used to displace allylic carbonates,¹⁵⁴⁴ often in conjunction with chiral ligands to give the product with enantioselectivity. Polymer-supported phosphine ligands have been used successfully,¹⁵⁴⁵ and catalyst systems other than Pd have been used for this reaction with allylic carbonates.¹⁵⁴⁶ Potassium vinyltrifluoroborates (Reaction **10-73**) have also been used in Pd catalyzed coupling reactions with allylic acetates.¹⁵⁴⁷

Intramolecular cyclization is possible when the active methylene compound and an allylic acetate or carbonate is incorporated into the same molecule.¹⁵⁴⁸ Propargylic esters have been used in Pd catalyzed coupling reactions, including a reaction with trialkylindium reagents.¹⁵⁴⁹

10-61 Coupling of Organometallic Reagents with Sulfate Esters, Sulfoxides, Sulfones, Nitro, and Acetals

Alkyl-de-sulfonyl and de-sulfonyloxy-substitution, and so on; **Alkyl-de-alkoxy-substitution**, and so on; **Alkyl-de-nitration**, and so on



Leaving groups other than halide, esters or carbonate, or sulfonate esters are sometimes used. Sulfates, sulfonates, and epoxides give the expected products. The reactions of sodium sulfonates and alkyl halides in ionic liquids have been reported.¹⁵⁵⁰ The SO₂Ph group of allylic sulfones can be a leaving group if a Pd complex is present.¹⁵⁵¹ The NR₂ group from *Mannich bases* (e.g., RCOCH₂CH₂NR₂), can also act as a leaving group

¹⁵⁴² **Amide esters:** Kazmaieer, U.; Zumpe, F.L. *Angew. Chem. Int. Ed.* **1999**, 38, 1468.

¹⁵⁴³ Evans, P.A.; Lawler, M.J. *J. Am. Chem. Soc.* **2004**, 126, 8642. For a reaction is a silyl enol ether see Muraoka, T.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* **2000**, 41, 8807.

¹⁵⁴⁴ **Aryllithium reagents:** Evans, P.A.; Uraguchi, D. *J. Am. Chem. Soc.* **2003**, 125, 7158. **Alkoxides:** Evans, P.A.; Leahy, D.K.; Sliker, L.M. *Tetrahedron Asymmetry* **2003**, 14, 3613. **Phenoxide anions:** Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* **2000**, 122, 5012; López, F.; Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* **2003**, 125, 3426. **Secondary amines:** Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.-a.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, 123, 10405. **Primary amines:** Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* **2002**, 124, 15164. **N-Lithio-sulfonamides:** Evans, P.A.; Robinson, J.E.; Baum, E.W.; Fazal, A.N. *J. Am. Chem. Soc.* **2002**, 124, 8782. **C-Alkylation with an indole:** Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, 6, 3199. **Michael addition of conjugated esters:** Muraoka, T.; Matsuda, I.; Itoh, K. *J. Am. Chem. Soc.* **2000**, 122, 9552.

¹⁵⁴⁵ Uozumi, Y.; Shibamoto, K. *J. Am. Chem. Soc.* **2001**, 123, 2919.

¹⁵⁴⁶ **Ru:** Trost, B.M.; Fraise, P.L.; Ball, Z.T. *Angew. Chem. Int. Ed.* **2002**, 41, 1059. **Mo:** Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, 1, 141; Malkov, A.V.; Spoor, P.; Vinader, V.; Kocovsky, P. *Tetrahedron Lett.* **2001**, 42, 509. **Ir:** Alexakis, A.; Polet, D. *Org. Lett.* **2004**, 6, 3529; Lee, P.H.; Sung, S.-y.; Lee, K.; Chang, S. *Synlett* **2002**, 146.

¹⁵⁴⁷ Kabalka, G.W.; Al-Masum, M. *Org. Lett.* **2006**, 8, 11.

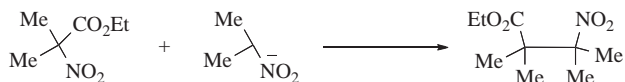
¹⁵⁴⁸ Castaño, A.M.; Méndez, M.; Ruano, M.; Echavarren, A.M. *J. Org. Chem.* **2001**, 66, 589. See also, Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* **2001**, 66, 7676.

¹⁵⁴⁹ Riveiros, R.; Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *Org. Lett.* **2006**, 8, 1403.

¹⁵⁵⁰ Hu, Y.; Chen, Z.-C.; Le, Z.-G.; Zheng, Q.G. *Synth. Commun.* **2004**, 34, 4031.

¹⁵⁵¹ Trost, B.M.; Schmuff, N.R.; Miller, M.J. *J. Am. Chem. Soc.* **1980**, 102, 5979.

in this reaction (elimination–addition mechanism, Sec. 10.F). A nitro group can be displaced¹⁵⁵² from α -nitro esters, ketones, nitriles, and α,α -dinitro compounds,¹⁵⁵³ and even from simple tertiary nitro compounds of the form R_3CNO_2 ¹⁵⁵⁴ or ArR_2CNO_2 ¹⁵⁵⁵ by salts of nitroalkanes, for example,



These reactions take place by SET mechanisms.¹⁵⁵⁶ However, with α -nitro sulfones it is the sulfone group that is displaced, rather than the nitro group.¹⁵⁵⁷ The SO_2R group of allylic sulfones can be replaced by CHZZ' ($\text{C}=\text{CCH}_2\text{---SO}_2\text{R} \rightarrow \text{C}=\text{CCH}_2\text{---CHZZ'}$) if a $\text{Mo}(\text{CO})_6$ catalyst is used.¹⁵⁵⁸

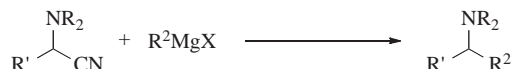
tert-Butylsulfones react with organolithium reagents, in the presence of a catalytic amount of an iron complex, to give coupling.¹⁵⁵⁹ In this case the *t*-BuSO₂ unit becomes a “leaving group”. A sulfoxide was a “leaving group” in the cyclization of a carboxylic acid that contains a sulfoxide unit at C-4. Treatment with phenyliodonium bis(trifluoroacetate) gave the five-membered ring lactone.¹⁵⁶⁰ Similar displacement of ToISO_2 was observed with tolylsulfones and diethylzinc.¹⁵⁶¹

Phosphonic esters, $\text{ROPO}(\text{OR})_2$, react with allylic *Grignard reagents* to give the coupling product.¹⁵⁶²

OS I, 471; II, 47, 360; VII, 351; VIII, 97, 471.

10-62 The Bruylants Reaction

Alkyl-de-cyanation



The *Bruylants reaction* is the reaction of an aminonitrile with a *Grignard reagent* to give a substituted amine.¹⁵⁶³ This reaction is most often used for the preparation of aliphatic amines via aliphatic *Grignard reagents*. In a few cases, vinylic *Grignard reagents* can be used to prepare allylic amines.¹⁵⁶⁴ The use of AgBF_4 to convert amino nitriles to the

¹⁵⁵² See Kornblum, N. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, **1982**, pp. 361–393; Kornblum, N. *Angew. Chem. Int. Ed.* **1975**, *14*, 734; Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423; Kornblum, N. in Feuer, H.; Nielsen, A.T. *Nitro Compounds: Recent Advances in Synthesis and Chemistry*, VCH, NY, **1990**, pp. 46–85.

¹⁵⁵³ Kornblum, N.; Kelly, W.J.; Kestner, M.M. *J. Org. Chem.* **1985**, *50*, 4720.

¹⁵⁵⁴ Kornblum, N.; Erickson, A.S. *J. Org. Chem.* **1981**, *46*, 1037.

¹⁵⁵⁵ Kornblum, N.; Carlson, S.C.; Widmer, J.; Fifolt, M.J.; Newton, B.N.; Smith, R.G. *J. Org. Chem.* **1978**, *43*, 1394.

¹⁵⁵⁶ For a review of the mechanism, see Beletskaya, I.P.; Drozd, V.N. *Russ. Chem. Rev.* **1979**, *48*, 431. See also, Kornblum, N.; Wade, P.A. *J. Org. Chem.* **1987**, *52*, 5301; Bowman, W.R. *Chem. Soc. Rev.* **1988**, *17*, 283; Ref. 1479.

¹⁵⁵⁷ Kornblum, N.; Boyd, S.D.; Ono, N. *J. Am. Chem. Soc.* **1974**, *96*, 2580.

¹⁵⁵⁸ Trost, B.M.; Merlic, C.A. *J. Org. Chem.* **1990**, *55*, 1127.

¹⁵⁵⁹ Jin, L.; Julia, M.; Verpeaux, J.N. *Synlett* **1994**, 215.

¹⁵⁶⁰ Casey, M.; Manage, A.C.; Murphy, P.J. *Tetrahedron Lett.* **1992**, *33*, 965.

¹⁵⁶¹ Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940.

¹⁵⁶² Yanagisawa, A.; Hibino, H.; Nomura, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 5879.

¹⁵⁶³ Bruylants, P. *Bull. Soc. Chem. Belg.* **1924**, *33*, 467.

¹⁵⁶⁴ Trost, B.M.; Spagnol, M.D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2083.

corresponding iminium ion facilitates the *Bruylants reaction* with vinylic *Grignard reagents*.¹⁵⁶⁵ Replacement of the cyano group in a tertiary nitrile is also possible.¹⁵⁶⁶

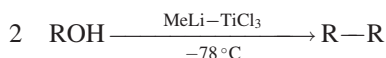
Displacement of a cyano group in α -cyanoketones is possible. Treatment of the α -cyanoketone with SmI_2 followed by addition of an excess of allyl bromide gave the α -allyl ketone derivative.¹⁵⁶⁷ α -Cyano amines react with allyl bromide and then zinc metal to give homoallylic amines after treatment with dilute acetic acid in THF.¹⁵⁶⁸

10-63 Coupling Involving Alcohols

De-hydroxyl-coupling



In some cases, it is possible to couple an alcohol in the presence of an organometallic compound.¹⁵⁶⁹ Allylic alcohols are coupled with alkylmagnesium bromides in the presence of $\text{Ti}(\text{O}i\text{Pr})_4$, for example.¹⁵⁷⁰ Allylic alcohols can be coupled with arylboronic acids in an ionic liquid solvent and a Rh catalyst.¹⁵⁷¹ The Pd catalyzed reaction of active methylene compounds with allylic alcohols¹⁵⁷² or benzylic alcohols¹⁵⁷³ is also known. The coupling of an alcohol to the α carbon of a ketone ($\text{RCOMe} + \text{R}'\text{OH}$) to give a β -substituted alcohol [$\text{RCH}(\text{OH})\text{CH}_2\text{R}'$] is possible in the presence of a Ru catalyst.¹⁵⁷⁴ Alcohols are coupled to allenes in the presence of an Ir catalyst.¹⁵⁷⁵ Allylic carbonates are coupled to allylic alcohols with a Ni catalyst.¹⁵⁷⁶



Allylic or benzylic alcohols can be symmetrically coupled¹⁵⁷⁷ by treatment with methyllithium and titanium trichloride at -78°C ¹⁵⁷⁸ or by refluxing with TiCl_3 and LiAlH_4 (as shown).¹⁵⁷⁹ When the substrate is an allylic alcohol, the reaction is not regiospecific, but a mixture of normal coupling and allylic-rearranged products is found. A free radical mechanism is involved.¹⁵⁸⁰ The TiCl_3 — LiAlH_4 reagent can also convert 1,3-diols to cyclopropanes, provided that at least one phenyl group is present.¹⁵⁸¹

¹⁵⁶⁵ Agami, C.; Couty, F.; Evano, G. *Org. Lett.* **2000**, 2, 2085.

¹⁵⁶⁶ Katritzky, A.R.; Yang, H.; Singh, S.K. *J. Org. Chem.* **2005**, 70, 286.

¹⁵⁶⁷ Zhu, J.-L.; Shia, K.-S.; Liu, H.-J. *Tetrahedron Lett.* **1999**, 40, 7055.

¹⁵⁶⁸ Bernardi, L.; Bonini, B.F.; Capitò, E.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Ricci, A. *Synlett* **2003**, 1778.

¹⁵⁶⁹ For a review of Pd catalyzed reactions, see Muzart, J. *Tetrahedron* **2005**, 61, 4179.

¹⁵⁷⁰ Kulinkovich, O.G.; Epstein, O.L.; Isakov, V.E.; Khmel'nitskaya, E.A. *Synlett* **2001**, 49.

¹⁵⁷¹ Kabalka, G.W.; Dong, G.; Venkataiah, B. *Org. Lett.* **2003**, 5, 893.

¹⁵⁷² Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, 6, 4085.

¹⁵⁷³ Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823.

¹⁵⁷⁴ Cho, C.S.; Kim, B.T.; Kim, T.-J.; Shim, S.C. *J. Org. Chem.* **2001**, 66, 9020. See also, Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2007**, 2850.

¹⁵⁷⁵ Bower, J.F.; Skucas, E.; Patman, R.L.; Krische, M.J. *J. Am. Chem. Soc.* **2007**, 129, 15134.

¹⁵⁷⁶ Sumida, Y.; Hayashi, S.; Hirano, K.; Hideki, H.; Oshima, K. *Org. Lett.* **2008**, 10, 1629.

¹⁵⁷⁷ See Lai, Y. *Org. Prep. Proceed. Int.* **1980**, 12, 363, pp. 377–388.

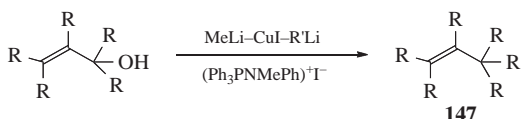
¹⁵⁷⁸ Sharpless, K.B.; Hanzlik, R.P.; van Tamelen, E.E. *J. Am. Chem. Soc.* **1968**, 90, 209.

¹⁵⁷⁹ McMurtry, J.E.; Silvestri, M.G.; Fleming, M.P.; Hoz, T.; Grayston, M.W. *J. Org. Chem.* **1978**, 43, 3249. For another method, see Nakanishi, S.; Shundo, T.; Nishibuchi, T.; Otsuji, Y. *Chem. Lett.* **1979**, 955.

¹⁵⁸⁰ van Tamelen, E.E.; Åkermark, B.; Sharpless, K.B. *J. Am. Chem. Soc.* **1969**, 91, 1552.

¹⁵⁸¹ Walborsky, H.M.; Murati, M.P. *J. Am. Chem. Soc.* **1980**, 102, 426.

Tertiary alcohols (R_3C-OH) react with trimethylaluminum at 80–200 °C to give methylation (R_3C-Me).¹⁵⁸² The presence of side products from elimination and rearrangement, as well as the lack of stereospecificity,¹⁵⁸³ indicate an S_N1 mechanism. The reaction can also be applied to primary and secondary alcohols if these contain an aryl group in the α position. Higher trialkylaluminums are far less suitable, because reduction competes with alkylation [see also, reactions of Me_3Al with ketones (**16-24**) and with carboxylic acids (**16-82**)]. The Me_2TiCl_2 compound reacts with tertiary alcohols in the same way.¹⁵⁸⁴ β -Alkylation of secondary alcohols has been reported using alcohol substrates in the presence of an Ir complex.¹⁵⁸⁵



Allylic alcohols couple with a reagent prepared from $MeLi$, CuI , or $R'Li$ in the presence of $(Ph_3PNMePh)^+ I^-$ to give alkenes (e.g., **147**) that are products of allylic rearrangement.¹⁵⁸⁶

The reaction gives good yields with primary, secondary, and tertiary alcohols, and with alkyl and aryllithium reagents.¹⁵⁸⁷ Allylic alcohols also couple with certain *Grignard reagents*¹⁵⁸⁸ in the presence of a nickel complex to give both normal products and the products of allylic rearrangement.

Allenic alcohols couple with allyl indium reagents at 140 °C to give allylic alcohol products.¹⁵⁸⁹ Similarly, ω -hydroxy lactones couple with organoindium reagents.¹⁵⁹⁰ Phenols react with vinyl boronates and a copper catalyst to give aryl vinyl ethers.¹⁵⁹¹

Alcohols react with allylsilanes, in the presence of an $InCl_3$ ¹⁵⁹² or $InBr_3$ ¹⁵⁹³ catalyst to give the corresponding coupling product ($R_2CHOH \rightarrow R_2CH-CH_2CH=CH_2$). Silyl ethers are also coupled to allylsilanes in the presence of $InCl_3$.¹⁵⁹⁴ Propargylic alcohols have been coupled to allylic silanes using an Au catalyst¹⁵⁹⁵ or a Rh catalyst.¹⁵⁹⁶

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¹⁵⁸³ Salomon, R.G.; Kochi, J.K. *J. Org. Chem.* **1973**, 38, 3715.

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¹⁵⁸⁷ See Cella, J.A. *J. Org. Chem.* **1982**, 47, 2125.

¹⁵⁸⁸ Consiglio, G.; Morandini, F.; Piccolo, O. *J. Am. Chem. Soc.* **1981**, 103, 1846, and references cited therein. See Felkin, H.; Swierczewski, G. *Tetrahedron* **1975**, 31, 2735; Fujisawa, T.; Iida, S.; Yukizaki, H.; Sato, T. *Tetrahedron Lett.* **1983**, 24, 5745.

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¹⁵⁹⁰ Bernardelli, P.; Paquette, L.A. *J. Org. Chem.* **1997**, 62, 8284.

¹⁵⁹¹ McKinley, N.F.; O'Shea, D.F. *J. Org. Chem.* **2004**, 69, 5087.

¹⁵⁹² Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, 71, 8516; Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem. Int. Ed.* **2006**, 45, 793.

¹⁵⁹³ Kim, S.H.; Shin, C.; Pae, A.N.; Koh, H.Y.; Chang, M.H.; Chung, B.Y.; Cho, Y.S. *Synthesis* **2004**, 1581.

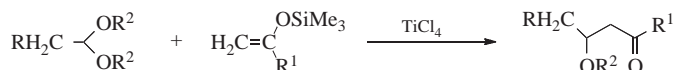
¹⁵⁹⁴ Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2007**, 72, 8588.

¹⁵⁹⁵ Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, 127, 14180.

¹⁵⁹⁶ Funayama, A.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2005**, 127, 15354.

10-64 Coupling of Organometallic Reagents with Compounds Containing the Ether Linkage¹⁵⁹⁷**Alkyl-de-alkoxy-substitution**

Acetals,¹⁵⁹⁸ ketals, and ortho esters¹⁵⁹⁹ react with *Grignard reagents* to give, respectively, ethers and acetals (or ketals). The latter can be hydrolyzed to aldehydes or ketones (Reaction **10-6**). This procedure is a way of converting a halide ($\text{R}''\text{X}$, which may be alkyl, aryl, vinylic, or alkynyl) to an aldehyde ($\text{R}''\text{CHO}$), increasing the length of the carbon chain by one carbon (see also, Reaction **10-76**). The ketone synthesis generally gives lower yields. Acetals, including allylic acetals, also give this reaction with organocopper compounds and BF_3 .¹⁶⁰⁰ Dihydropyrans react with *Grignard reagents* in the presence of a Ni catalyst.¹⁶⁰¹ Acetals also undergo substitution when treated with silyl enol ethers or allylic silanes, with a Lewis acid catalyst,¹⁶⁰² for example,



ω -Ethoxy lactams react with *Grignard reagents* to give ω -substituted lactams.¹⁶⁰³ Tertiary amines can be prepared by the reaction of amino ethers with *Grignard reagents*,¹⁶⁰⁴ ($\text{R}_2\text{NCH}_2\text{—OR}' + \text{R}^2\text{MgX} \rightarrow \text{R}_2\text{NCH}_2\text{—R}^2$) or with lithium dialkylcopper reagents.¹⁶⁰⁵

Ordinary ethers are not cleaved by *Grignard reagents* (in fact, diethyl ether and THF are the most common solvents for *Grignard reagents*), although more active organometallic compounds often do cleave them.¹⁶⁰⁶ However, methyl ethers have been replaced with a methyl group ($\text{MeMgX} + \text{ROMe} \rightarrow \text{R—Me}$) via a Ni catalyzed coupling reaction with MeMgBr .¹⁶⁰⁷ Oxetanes have been opened with organolithium reagents and $\text{BF}_3 \bullet \text{OEt}_2$ ¹⁶⁰⁸ and also with excess Li metal with a biphenyl catalyst.¹⁶⁰⁹ Allylic ethers can be cleaved by

¹⁵⁹⁷ See Trofimov, B.A.; Korostova, S.E. *Russ. Chem. Rev.* **1975**, *44*, 41.

¹⁵⁹⁸ See Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043; Abell, A.D.; Massy-Westropp, R.A. *Aust. J. Chem.* **1985**, *38*, 1031. For a list of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 934–942.

¹⁵⁹⁹ See DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, **1970**, pp. 44–45, 224–230.

¹⁶⁰⁰ Normant, J.F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* **1989**, *45*, 507; Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J.F. *Pure Appl. Chem.* **1988**, *60*, 49.

¹⁶⁰¹ Ducoux, J.-P.; LeMénez, P.; Kunesch, N.; Wenkert, E. *J. Org. Chem.* **1993**, *58*, 1290.

¹⁶⁰² See Mori, I.; Ishihara, K.; Flippin, L.A.; Nozaki, K.; Yamamoto, H.; Bartlett, P.A.; Heathcock, C.H. *J. Org. Chem.* **1990**, *55*, 6107, and references cited therein.

¹⁶⁰³ Wei, Z.Y.; Knaus, E.E. *Org. Prep. Proceed. Int.* **1993**, *25*, 255.

¹⁶⁰⁴ See Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* **1989**, *373*, 1. See also, Bourhis, M.; Bosc, J.; Golse, R. *J. Organomet. Chem.* **1983**, *256*, 193.

¹⁶⁰⁵ Germon, C.; Alexakis, A.; Normant, J.F. *Bull. Soc. Chim. Fr.* **1984**, II-377.

¹⁶⁰⁶ See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 1013–1045.

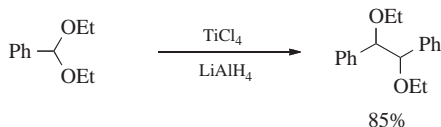
¹⁶⁰⁷ Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268.

¹⁶⁰⁸ Bach, T.; Eilers, F. *Eur. J. Org. Chem.* **1998**, 2161.

¹⁶⁰⁹ Rama, K.; Pasha, M.A. *Tetrahedron Lett.* **2000**, *41*, 1073.

Grignard reagents in THF if CuBr is present.¹⁶¹⁰ The reaction can take place either with or without allylic rearrangement.¹⁶¹¹ Propargylic ethers give allenes.¹⁶¹² Vinylic ethers can also be cleaved by *Grignard reagents* in the presence of a catalyst, in this case, a Ni complex.¹⁶¹³ Silyl enol ethers $R_2C=CROSiMe_3$ behave similarly.¹⁶¹⁴ Bicyclic benzo-furans can be opened by dialkylzinc reagents in the presence of a Pd catalyst.¹⁶¹⁵

Certain acetals and ketals can be dimerized in a reaction similar to Reaction 10-56 by treatment with $TiCl_4-LiAlH_4$, for example,¹⁶¹⁶

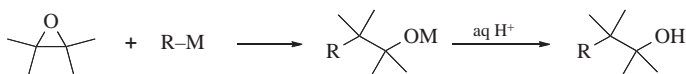


Also see, Reaction 10-65.

OS II, 323; III, 701. Also see, OS V, 431.

10-65 The Reaction of Organometallic Reagents with Epoxides

3(OC)-seco-Alkyl-de-alkoxy-substitution



The reaction between *Grignard reagents* or organolithium reagents and epoxides is very valuable and is often used to increase the length of a carbon chain by two carbons.¹⁶¹⁷ The *Grignard reagent* may be aromatic or aliphatic, although tertiary *Grignard reagents* give low yields. As expected for an S_N2 process, attack is at the less substituted carbon. With allylic *Grignard reagents*, the addition of a catalytic amount of $Yb(OTf)_3$ facilitated alkylation.¹⁶¹⁸ Organolithium reagents,¹⁶¹⁹ in the presence of chiral additives, lead to the 2-substituted alcohol with good enantioselectivity. Similar reaction with a chiral *Schiff base* gave the same type of product, with excellent enantioselectivity.¹⁶²⁰

¹⁶¹⁰ Commercon, A.; Bourgain, M.; Delaumeny, M.; Normant, J.F.; Villieras, J. *Tetrahedron Lett.* **1975**, 3837; Claesson, A.; Olsson, L. *J. Chem. Soc., Chem. Commun.* **1987**, 621.

¹⁶¹¹ Calo, V.; Lopez, L.; Pesce, G. *J. Chem. Soc. Perkin Trans. 1* **1988**, 1301. See also, Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A.M. *J. Org. Chem.* **1990**, 55, 2294.

¹⁶¹² Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *J. Am. Chem. Soc.* **1990**, 112, 8042.

¹⁶¹³ Kocienski, P.; Dixon, N.J.; Wadman, S. *Tetrahedron Lett.* **1988**, 29, 2353.

¹⁶¹⁴ Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* **1980**, 21, 3915.

¹⁶¹⁵ Lauens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **200**, 122, 1804.

¹⁶¹⁶ Ishikawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, 51, 2059.

¹⁶¹⁷ See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 961–1012; Schaap, A.; Arens, J.F. *Recl. Trav. Chim. Pays-Bas* **1968**, 87, 1249. Also see Schrupf, G.; Grätz, W.; Meinecke, A.; Fellenberger, K. *J. Chem. Res. (S)* **1982**, 162.

¹⁶¹⁸ Likhar, P.R.; Kumar, M.P.; Bandyopadhyay, A.K. *Tetrahedron Lett.* **2002**, 43, 3333.

¹⁶¹⁹ Hodgson, D.M.; Stent, M.A.H.; Stefane, B.; Wilson, F.X. *Org. Biomol. Chem.* **2003**, 1, 1139; Hodgson, D.M.; Maxwell, C.R.; Miles, T.J.; Paruch, E.; Stent, M.A.H.; Matthews, I.R.; Wilson, F.X.; Witherington, J. *Angew. Chem. Int. Ed.* **2002**, 41, 4313.

¹⁶²⁰ Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, 39, 9023.

Lithium dialkylcopper reagents also give the reaction,¹⁶²¹ as do higher order cuprates,¹⁶²² often producing higher yields. They have the additional advantage that they do not react with ester, ketone, or carboxyl groups so that the epoxide ring of epoxy esters, ketones, and carboxylic acids can be selectively attacked, often in a regioselective manner.¹⁶²³ The use of BF_3 increases the reactivity of R_2CuLi , enabling it to be used with thermally unstable epoxides.¹⁶²⁴ Lithium diaminocyno cuprates have also been used.¹⁶²⁵

The reaction has also been performed with other organometallic compounds.¹⁶²⁶ Trialkylaluminum reagents open epoxides with delivery of the alkyl group to carbon.¹⁶²⁷ In the presence of a Lewis acid catalyst (e.g., BF_3), alkylation can occur at the more substituted carbon.¹⁶²⁸ *Friedel–Crafts type alkylation* (see Reaction 11-11) is possible when an aromatic compound reacts with an epoxide and AlCl_3 .¹⁶²⁹ Epoxides react with allyl bromide in the presence of In metal, with the expected delivery of allyl to the less substituted carbon.¹⁶³⁰ When a substituted epoxide was treated with CO , $\text{BF}_3 \cdot \text{OEt}_2$, and a Co catalyst, carbonylation occurred and the final product was a β -lactone.¹⁶³¹ Similar β -lactone forming reactions were reported using substituted epoxides, CO , and a metal compound– BF_3 complex.¹⁶³² A double carbonylation reaction was reported in the presence of an Al complex, generating an anhydride.¹⁶³³ Five-membered ring lactams were formed from substituted epoxides using $\text{BF}_3 \cdot \text{OEt}_2$ followed by treatment with KHF_2 .¹⁶³⁴ Ring opening of epoxides with Ti compounds has been shown to be selective for the more substituted carbon.¹⁶³⁵ Epoxides react with Ag salts of alkynes, in the

¹⁶²¹ See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, **1980**, pp. 103–113. See also, Lipshutz, B.H.; Kozlowski, J.; Wilhelm, R.S. *J. Am. Chem. Soc.* **1982**, *104*, 2305; Blanchot-Courtois, V.; Hanna, I. *Tetrahedron Lett.* **1992**, *33*, 8087.

¹⁶²² Chauret, D.C.; Chong, J.M. *Tetrahedron Lett.* **1993**, *34*, 3695.

¹⁶²³ Chong, J.M.; Cyr, D.R.; Mar, E.K. *Tetrahedron Lett.* **1987**, *28*, 5009; Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993.

¹⁶²⁴ See Alexakis, A.; Jachiet, D.; Normant, J.F. *Tetrahedron* **1986**, *42*, 5607.

¹⁶²⁵ Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J.G.; Nakamura, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1201.

¹⁶²⁶ See Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, **1985**, pp. 307–310; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1045–1063. **Ba**: Yasue, K.; Yanagisawa, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 493. **Mn**: Tang, J.; Yorimitsu, H.; Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1997**, *38*, 9019. **Sn**: Yadav, J.S.; Reddy, B.V.S.; Sathesh, G. *Tetrahedron Lett.* **2003**, *44*, 6501. **Zn**: Equey, O.; Vrancken, E.; Alexakis, A. *Eur. J. Org. Chem.* **2004**, 2151.

¹⁶²⁷ Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* **2001**, 4445; Sasaki, M.; Tanino, K.; Miyashita, M. *J. Org. Chem.* **2001**, *66*, 5388; Sasaki, M.; Tanino, K.; Miyashita, M. *Org. Lett.* **2001**, *3*, 1765; Shanmugam, P.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3265 (formation of *O*-silyl ether product). For the reaction in an ionic liquid see Zhou, H.; Campbell, E.J.; Nguyen, S.T. *Org. Lett.* **2001**, *3*, 2229.

¹⁶²⁸ See Zhao, H.; Pagenkopf, B.L. *Chem. Commun.* **2003**, 2592.

¹⁶²⁹ Lin, J.; Kanazaki, S.; Kashino, S.; Tsuboi, S. *Synlett* **2002**, 899.

¹⁶³⁰ Hirashita, T.; Mitsui, K.; Hayashi, Y.; Araki, S. *Tetrahedron Lett.* **2004**, *45*, 9189. For a reaction using Pd nanoparticles, see Jiang, N.; Hu, Q.; Reid, C.S.; Ou, Y.; Li, C.J. *Chem. Commun.* **2003**, 2318.

¹⁶³¹ Lee, J.T.; Thomas, P.J.; Apler, H. *J. Org. Chem.* **2001**, *66*, 5424.

¹⁶³² Schmidt, J.A.R.; Mahadevan, V.; Getzler, Y.D.Y.L.; Coates, G.W. *Org. Lett.* **2004**, *6*, 373.

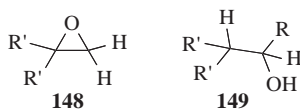
¹⁶³³ Rowley, J.M.; Lobkovsky, E.B.; Coates, G.W. *J. Am. Chem. Soc.* **2007**, *129*, 4948.

¹⁶³⁴ Movassaghi, M.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2002**, *124*, 2456.

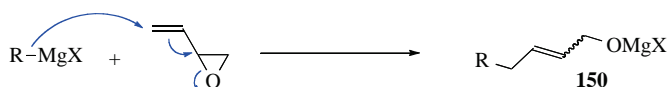
¹⁶³⁵ Tanaka, T.; Hiramatsu, K.; Kobayashi, Y.; Ohno, H. *Tetrahedron* **2005**, *61*, 6726.

presence of Zr compounds, to give the rearrangement product, a propargylic alcohol.¹⁶³⁶ A Ga/Sm induced ring opening with alkyl halides has been reported.¹⁶³⁷

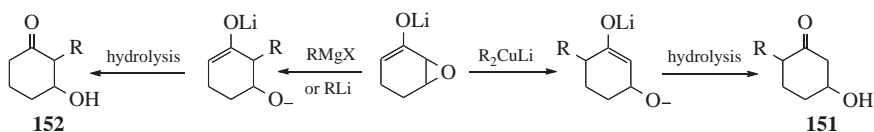
In the presence of a Sc catalyst, chiral allylic boranes open epoxides at the less substituted position to generate chiral, homoallylic alcohols.¹⁶³⁸



When *gem*-disubstituted epoxides (**148**), and sometimes other epoxides, are treated with *Grignard reagents*, the product may be **149**, that is, the new alkyl group may appear on the same carbon as the OH. In such cases, the epoxide is isomerized to an aldehyde or a ketone before reacting with the *Grignard reagent*. Halohydrins are often side products.



When the substrate is a vinylic epoxide,¹⁶³⁹ *Grignard reagents* generally give a mixture of the normal product and the product of allylic rearrangement (**150**).¹⁶⁴⁰ Butyllithium reacted with a *gem*-difluoroalkylidene epoxide ($\text{F}_2\text{C}=\text{CR}$ -epoxide) and $\text{S}_{\text{N}}2'$ displacement gave alkylation at the difluoro carbon and opened the epoxide.¹⁶⁴¹ The latter often predominates. In the case of R_2CuLi ,¹⁶⁴² acyclic substrates give mostly allylic rearrangement ($\text{S}_{\text{N}}2'$).¹⁶³⁹ The double bond of the “vinylic” epoxide can be part of an enolate anion. In this case, R_2CuLi give exclusive allylic rearrangement ($\text{S}_{\text{N}}2'$) to **151** after hydrolysis, while *Grignard* and organolithium reagents opened the epoxide directly ($\text{S}_{\text{N}}2$) to give **152** after hydrolysis.¹⁶⁴³



An organometallic equivalent that opens epoxides is a hydrosilane, for example, Me_3SiH , and CO, catalyzed by dicobalt octacarbonyl:¹⁶⁴⁴ See Reaction 10-55 for other coupling reactions with organosilanes. Silyl enol ethers react with epoxides in a related reaction, but a Lewis acid (e.g., TiCl_4) is required.¹⁶⁴⁵

OS I, 306; VII, 501; VIII, 33, 516; X, 297.

¹⁶³⁶ Albert, B.J.; Koide, K. *J. Org. Chem.* **2008**, 73, 1093.

¹⁶³⁷ Gohain, M.; Prajapati, D. *Chem. Lett.* **2005**, 34, 90.

¹⁶³⁸ Lautens, M.; Maddess, M.L.; Sauer, E.L.O.; Oullet, S.G. *Org. Lett.* **2002**, 4, 83.

¹⁶³⁹ For a list of organometallic reagents that react with vinylic epoxides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 244–250.

¹⁶⁴⁰ Marshall, J.A.; Trometer, J.D.; Cleary, D.G. *Tetrahedron* **1989**, 45, 391.

¹⁶⁴¹ Ueki, H.; Chiba, T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2004**, 69, 7616.

¹⁶⁴² See Marshall, J.A. *Chem. Rev.* **1989**, 89, 1503.

¹⁶⁴³ Wender, P.A.; Erhardt, J.M.; Letendre, L.J. *J. Am. Chem. Soc.* **1981**, 103, 2114.

¹⁶⁴⁴ Murai, T.; Kato, S.; Murai, T.; Toki, T.; Suzuki, S.; Sonoda, N. *J. Am. Chem. Soc.* **1984**, 106, 6093.

¹⁶⁴⁵ Lalic, G.; Petrovski, Z.; Galonic, D.; Matovic, R.; Saicic, R.N. *Tetrahedron* **2001**, 57, 583.

10-66 Reaction of Organometallics with Aziridines



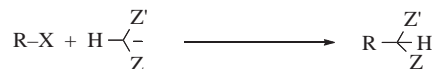
Aziridines have been opened by organometallic reagents to give amines.¹⁶⁴⁶ It is also possible to open aziridines, although they are less reactive than epoxides,¹⁶⁴⁷ with organometallic reagents particularly when there is an *N*-sulfonyl group (e.g., tosyl, formally making it a sulfonamide). *Grignard reagents* react with *N*-tosyl 2-phenylaziridine to give the corresponding *N*-tosylamine.¹⁶⁴⁸ Organocuprates (**10-58**) reaction with *N*-allylaziridines to give the corresponding amine.¹⁶⁴⁹ In a *Friedel–Crafts type reaction* (**11-11**), aziridines react with benzene, in the presence of $\text{In}(\text{OTf})_3$, to give the β -aryl amine.¹⁶⁵⁰

N-Tosyl aziridines have also been opened with enolate anions, which led to a pyrroline derivative,¹⁶⁵¹ and with $\text{Me}_2\text{S}=\text{CHCO}_2\text{Et}$ (see Reaction **16-46**) to generate a *N*-tosyl azetidine.¹⁶⁵² Allylic alcohols open *N*-tosylaziridines with KSF–Montmorillonite clay.¹⁶⁵³ *C*-Arylation is possible with a $\text{Ag}(\text{I})$ catalyst.¹⁶⁵⁴ *N*-Sulfonyl aziridines react with the enolate anions of β -keto esters under phase-transfer conditions.¹⁶⁵⁵ *N*-Tosylaziridines react with InCl_3 to give the chloro *N*-tosylamine.¹⁶⁵⁶

Aziridines react with nucleophiles other than carbon nucleophiles. In the presence of tetrabutylammonium fluoride (TBAF), trimethylsilyl azide reacts with *N*-tosylaziridines to give the azido *N*-tosylamine.¹⁶⁵⁷ *N*-Benzylic aziridines are opened by trimethylsilyl azide in the presence of a Cr catalyst.¹⁶⁵⁸ Acetic anhydride reacts with *N*-tosylaziridines, in the presence of PBu_3 , to give the *N*-tosylamino acetate.¹⁶⁵⁹ Mediated by Lewis bases, aziridines react with silylated nucleophiles.¹⁶⁶⁰

10-67 Alkylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on



The metal-catalyzed displacement of allylic acetates and carbonates (Reaction **10-60**) clearly falls into this category. However, this section will focus on the more general reaction of active methylene compounds with substrates bearing a leaving group, not

¹⁶⁴⁶ See Onistschenko, A.; Buchholz, B.; Stamm, H. *Tetrahedron* **1987**, *43*, 565.

¹⁶⁴⁷ Crotti, P.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1995**, *60*, 2514.

¹⁶⁴⁸ Müller, P.; Nury, P. *Org. Lett.* **1999**, *1*, 439; Müller, P.; Nury, P. *Helv. Chim. Acta* **2001**, *84*, 662.

¹⁶⁴⁹ Penkett, C.S.; Simpson, I.D. *Tetrahedron Lett.* **2001**, *42*, 1179.

¹⁶⁵⁰ Saidi, M.R.; Azizi, N.; Naimi-Jamal, M.R. *Tetrahedron Lett.* **2001**, *42*, 8111.

¹⁶⁵¹ Lygo, B. *Synlett* **1993**, 764.

¹⁶⁵² Nadir, U.K.; Arora, A. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2605.

¹⁶⁵³ Yadav, J.S.; Reddy, B.V.S.; Balanarsaiah, E.; Raghavendra, S. *Tetrahedron Lett.* **2002**, *43*, 5105.

¹⁶⁵⁴ Bera, M.; Roy, S. *Tetrahedron Lett.* **2007**, *48*, 7144.

¹⁶⁵⁵ Moss, T.A.; Fenwick, D.R.; Dixon, D.J. *J. Am. Chem. Soc.* **2008**, *130*, 10076.

¹⁶⁵⁶ Yadav, J.S.; Subba Reddy, B.V.; Kumar, G.M. *Synlett* **2001**, 1417.

¹⁶⁵⁷ Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2000**, *65*, 1344.

¹⁶⁵⁸ Li, Z.; Fernández, M.; Jacobsen, E.N. *Org. Lett.* **1999**, *1*, 1611.

¹⁶⁵⁹ Fan, R.-H.; Hou, X.-L. *Tetrahedron Lett.* **2003**, *44*, 4411.

¹⁶⁶⁰ Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2005**, *7*, 3509. See also Matsukawa, S.; Tsukamoto, K. *Org. Biomol. Chem.* **2009**, *7*, 3792.

necessarily allylic substrates or metal catalyzed. When compounds contain two or three strong electron-withdrawing groups on a carbon atom bearing a proton (the so-called α -proton), that proton is more acidic than compounds without such groups (Sec. 5.B.i, category 1). Treatment with a suitable base (a base that has a conjugate acid with a pK_a greater than the α -proton) removes the α -proton and generates the corresponding enolate anion (Reaction 10-68). These enolate anions react as carbon nucleophiles and attack alkyl halides, resulting in their alkylation.¹⁶⁶¹ Both Z and Z' may be COOR', CHO, COR',¹⁶⁶² CONR'₂, COO⁻, CN,¹⁶⁶³ NO₂, SOR', SO₂R',¹⁶⁶⁴ SO₂OR', SO₂NR'₂ or similar groups.¹⁶⁶⁵ Some commonly used bases are sodium ethoxide and potassium *tert*-butoxide, each in its respective alcohol as solvent. With particularly acidic compounds (e.g., β -diketones—Z, Z' = COR'), sodium hydroxide in water or aq alcohol or acetone, or even sodium carbonate,¹⁶⁶⁶ is a strong enough base for the reaction. If at least one Z group is COOR', saponification is a possible side reaction. In addition to the groups listed above, Z may also be phenyl, but if two phenyl groups are on the same carbon, the acidity is less than in the other cases and a stronger base must be used. However, the reaction can be successfully carried out with diphenylmethane with NaNH₂ as the base.¹⁶⁶⁷ If the solvent used in the reaction is acidic enough to protonate either the enolate anion or the base, an equilibrium will be established leading to only small amounts of the enolate anion (thermodynamic conditions). Such protic solvents include water, alcohols, or amines. To avoid this reaction, solvents that do not contain an acidic proton (aprotic solvents) are used, but protic solvents can be used in some cases. The use of polar aprotic solvents (e.g., DMF or DMSO), markedly increases the rate of alkylation¹⁶⁶⁸ but also increases the extent of alkylation at the oxygen rather than the carbon with highly reactive species (e.g., iodomethane, Sec. 10. G.viii). In general, enolate anions, such as those described here, react with alkyl halides via C-alkylation, although trialkylsilyl halides and anhydrides tend to react via O-alkylation. Phase-transfer catalysis has also been used,¹⁶⁶⁹ and the use of chiral phase-transfer catalysts led to enantioselectivity in the alkylated product.¹⁶⁷⁰ The reaction is successful for primary and secondary alkyl, allylic (with allylic rearrangement possible), and benzylic RX, but fails for tertiary halides, since these undergo elimination under the reaction conditions (see, however, Reaction 10-67). Various functional groups may be present in RX as long as they are not sensitive to base. Side reactions that may cause problems are the above-mentioned competing O-alkylation, elimination (if the enolate anion is a strong enough base), and dialkylation.

With substrates (e.g., ZCH₂Z') it is possible to alkylate twice. Initial removal of the proton with a base followed by alkylation of the resulting enolate anion with RX, can be

¹⁶⁶¹ For discussions of Reactions 10-67 and 10-68, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, NY, 1972, pp. 492–570, 586–595; Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed., Cambridge University Press, Cambridge, 1986, pp. 1–26.

¹⁶⁶² See Christoffers, J. *Synth. Commun.* 1999, 29, 117.

¹⁶⁶³ See Fatiadi, A.J. *Synthesis* 1978, 165, 241; Freeman, F. *Chem. Rev.* 1969, 69, 591.

¹⁶⁶⁴ See Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *Russ. Chem. Rev.* 1986, 55, 883.

¹⁶⁶⁵ For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, 1999, pp. 1522–1527 ff, 1765–1769.

¹⁶⁶⁶ See Fedorynski, M.; Wojciechowski, K.; Matacz, Z.; Makosza, M. *J. Org. Chem.* 1978, 43, 4682.

¹⁶⁶⁷ Murphy, W.S.; Hamrick, Jr., P.J.; Hauser, C.R. *Org. Synth.* V. 523.

¹⁶⁶⁸ Zaug, H.E.; Dunnigan, D.A.; Michaels, R.J.; Swett, L.R.; Wang, T.S.; Sommers, A.H.; DeNet, R.W. *J. Org. Chem.* 1961, 26, 644; Johnstone, R.A.W.; Tuli, D.; Rose, M.E. *J. Chem. Res. (S)* 1980, 283.

¹⁶⁶⁹ See Tundo, P.; Venturello, P.; Angeletti, E. *J. Chem. Soc. Perkin Trans. 1* 1987, 2159.

¹⁶⁷⁰ Park, E.J.; Kim, M.H.; Kim, D.Y. *J. Org. Chem.* 2004, 69, 6897.

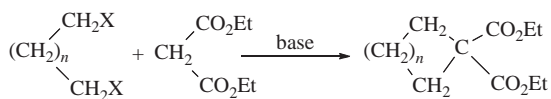
β -Keto sulfoxides [e.g., **156** or sulfones ($-\text{SO}_2-$)] are easily prepared (Reaction **16-86**). When one group attached to the sulfur atom is chiral, the alkylation proceeds with reasonable enantioselectivity.¹⁶⁷⁸

Other examples of the reaction are the *cyanoacetic ester synthesis*, in which Z is CO_2Et and Z' is CN (as in the malonic ester synthesis, the product here can be hydrolyzed and decarboxylated), and the *Sorensen* method of amino acid synthesis, using *N*-acetylamino malonic esters, $(\text{EtO}_2\text{C})_2\text{CHNHCOCH}_3$. Hydrolysis and decarboxylation of the product in this case gives an α -amino acid. The amino group is also frequently protected by conversion to a phthalimido group.

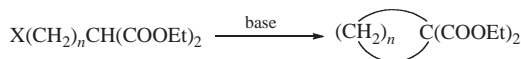
The reaction is not limited to $\text{Z}-\text{CH}_2-\text{Z}'$ compounds. Other compounds have acidic CH hydrogens. Some examples are the methyl hydrogens of α -aminopyridines, the methyl hydrogens of ynamines of the form $\text{CH}_3\text{C}\equiv\text{CNR}_2$ ¹⁶⁷⁹ (the product in this case can be hydrolyzed to an amide $\text{RCH}_2\text{CH}_2\text{CONR}_2$), the CH_2 hydrogens of cyclopentadiene and its derivatives (Sec. 2.I.ii), hydrogens connected to a triple-bond carbon (Reaction **10-74**), and the hydrogen of HCN (Reaction **10-75**) can also be removed with a base and the resulting ion alkylated (see also, Reactions **10-68–10-72**). α -Imino esters have been used since treatment with a strong base with a titanium catalyst followed by an aldehyde leads to hydroxy amino esters.¹⁶⁸⁰

Alkylation takes place at the most acidic position of a reagent molecule; for example, acetoacetic ester ($\text{CH}_3\text{COCH}_2\text{COOEt}$) is alkylated at the methylene and not at the methyl group, because the former is more acidic than the latter, and hence gives up its proton to the base. However, if 2 molar equivalents of base are used, then not only is the most acidic proton removed but also the second most acidic. Alkylation of this doubly charged anion (a dianion) occurs at the less acidic position, in this case the second most acidic position¹⁶⁸¹ (see Sec. 10.G.vii). The first and second ion pair acidities of β -diketones has been studied.¹⁶⁸²

When ω,ω' -dihalides are used, ring closures can be effected.¹⁶⁸³



This method has been used to close rings of three ($n=0$) to seven members, although five-membered ring closures proceed in highest yields. Another ring-closing method involves internal alkylation.¹⁶⁸⁴



¹⁶⁷⁸ Enders, D.; Harnying, W.; Vignola, N. *Eur. J. Org. Chem.* **2003**, 3939.

¹⁶⁷⁹ Corey, E.J.; Cane, D.E. *J. Org. Chem.* **1970**, 35, 3405.

¹⁶⁸⁰ Kanemasa, S.; Mori, T.; Wada, E.; Tatsukawa, A. *Tetrahedron Lett.* **1993**, 34, 677. See Kotha, S.; Kuki, A. *Tetrahedron Lett.* **1992**, 33, 1565 for a related reaction.

¹⁶⁸¹ For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1540–1541. Also see, Lu, Y.-Q.; Li, C.-J. *Tetrahedron Lett.* **1996**, 37, 471.

¹⁶⁸² Facchetti, A.; Streitwieser, A. *J. Org. Chem.* **2004**, 69, 8345.

¹⁶⁸³ Zefirov, N.S.; Kuznetsova, T.S.; Kozhushkov, S.I.; Surmina, L.S.; Rashchupkina, Z.A. *J. Org. Chem. USSR* **1983**, 19, 474.

¹⁶⁸⁴ See Walborsky, H.M.; Murari, M.P. *Can. J. Chem.* **1984**, 62, 2464; Bose, A.K.; Manhas, M.S.; Chatterjee, B.G.; Abdulla, R.F. *Synth. Commun.* **1971**, 1, 51. For a list of examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 156–157, 165–166.

This method has been shown to be applicable to medium rings (10–14 members) without the use of high-dilution techniques.¹⁶⁸⁵

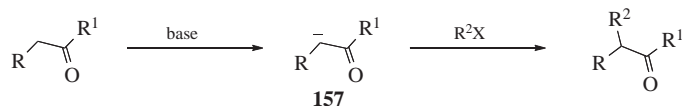
The mechanism of these reactions is usually S_N2 with inversion taking place at a chiral RX, although an SET¹⁶⁸⁶ mechanism may be involved in certain cases,¹⁶⁸⁷ especially where the nucleophile is an α -nitro carbanion¹⁶⁸⁸ and/or the substrate contains a nitro or cyano¹⁶⁸⁹ group. Tertiary alkyl groups can be introduced by an S_N1 mechanism if the ZCH_2Z' compound (not the enolate anion) is treated with a tertiary carbocation generated *in situ* from an alcohol or alkyl halide and BF_3 or $AlCl_3$,¹⁶⁹⁰ or with a tertiary alkyl perchlorate.¹⁶⁹¹

Alkylation α to a nitro group can be achieved with the *Katritzky pyrylium–pyridinium reagents*.¹⁶⁹² This reaction probably has a free radical mechanism.¹⁶⁹³

OS **I**, 248, 250; **II**, 262, 279, 384, 474; **III**, 213, 219, 397, 405, 495, 705; **IV**, 10, 55, 288, 291, 623, 641, 962; **V**, 76, 187, 514, 523, 559, 743, 767, 785, 848, 1013; **VI**, 223, 320, 361, 482, 503, 587, 781, 991; **VII**, 339, 411; **VIII**, 5, 312, 381. See also, OS **VIII**, 235.

10-68 Alkylation of Ketones, Aldehydes, Nitriles, and Carboxylic Esters

α -Acylalkyl-de-halogenation, and so on



Ketones,¹⁶⁹⁴ nitriles,¹⁶⁹⁵ and carboxylic esters¹⁶⁹⁶ can be alkylated in the α position in a reaction similar to **10-67**.¹⁶⁵² The pK_a of the proton α to the carbonyl or CN is in the range of 19–25 depending on the number of substituents (see Table 8.1), and a base that has a conjugate acid with a pK_a greater than that proton must be employed. Note that since only one activating group is present, compared with two activating groups for the substrates in Reaction **10-67**, the pK_a of the α -proton is higher (a weaker acid) and a stronger base is required. Reaction of the α -proton with the base generates the key nucleophilic

¹⁶⁸⁵ Deslongchamps, P.; Lamothe, S.; Lin, H. *Can. J. Chem.* **1987**, 65, 1298; Brillon, D.; Deslongchamps, P. *Can. J. Chem.* **1987**, 65, 43, 56.

¹⁶⁸⁶ These SET mechanisms are often called $S_{RN}1$ mechanisms. See also, Ref. 107.

¹⁶⁸⁷ Bordwell, F.G.; Harrelson, Jr., J.A. *J. Am. Chem. Soc.* **1989**, 111, 1052.

¹⁶⁸⁸ For a review of mechanisms with these nucleophiles, see Bowman, W.R. *Chem. Soc. Rev.* **1988**, 17, 283.

¹⁶⁸⁹ Kornblum, N.; Fifolt, M. *Tetrahedron* **1989**, 45, 1311.

¹⁶⁹⁰ See Crimmins, T.F.; Hauser, C.R. *J. Org. Chem.* **1967**, 32, 2615; Boldt, P.; Militzer, H.; Thielecke, W.; Schulz, L. *Liebigs Ann. Chem.* **1968**, 718, 101.

¹⁶⁹¹ Boldt, P.; Ludwig, A.; Militzer, H. *Chem. Ber.* **1970**, 103, 1312.

¹⁶⁹² Katritzky, A.R.; Kashmiri, M.A.; Wittmann, D.K. *Tetrahedron* **1984**, 40, 1501.

¹⁶⁹³ Katritzky, A.R.; Chen, J.; Marson, C.M.; Maia, A.; Kashmiri, M.A. *Tetrahedron* **1986**, 42, 101.

¹⁶⁹⁴ See Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1; Marcel Dekker, NY, **1979**, pp. 85–352.

¹⁶⁹⁵ See Arseniyadis, S.; Kyler, K.S.; Watt, D.S. *Org. React.* **1984**, 31, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1801–1808. See Taber, D.F.; Kong, S. *J. Org. Chem.* **1997**, 62, 8575; Rojas, G.; Baughman, T.W.; Wagener, K.B. *Synth. Commun.* **2007**, 37, 3923.

¹⁶⁹⁶ See Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1724–1758ff.

intermediate, an enolate anion (**157**). The most common bases¹⁶⁹⁷ are lithium diethylamide (Et_2NLi), lithium diisopropylamide [$(\text{Me}_2\text{CH})_2\text{NLi}$, LDA],¹⁶⁹⁸ lithium hexamethyldisilazide [$\text{LiN}(\text{SiMe}_3)_2$], $t\text{-BuOK}$, NaNH_2 , and KH . The base lithium N -isopropyl- N -cyclohexylamide (LICA) is particularly successful for carboxylic esters¹⁶⁹⁹ and nitriles.¹⁷⁰⁰ Enolate anion formation with lithium amides can also be regioselective (see Reaction **12-22**).¹⁷⁰¹ Lithium enolate anions exist as aggregates in solution.¹⁷⁰² The mechanism for this deprotonation reaction has been studied,¹⁷⁰³ as has the rate of deprotonation.¹⁷⁰⁴

Solid KOH in Me_2SO has been used to methylate ketones, in high yields.¹⁷⁰⁵ Some of these bases are strong enough to convert the ketone, nitrile, or ester completely to its enolate anion conjugate base; others (especially $t\text{-BuOK}$) convert a significant fraction of the molecules. In the latter case, the *aldol reaction* (**16-34**) or *Claisen condensation* (**16-85**) may be side reactions, since under the thermodynamic conditions associated with this base both the free molecule and its conjugate base are present at the same time. Both lactones¹⁷⁰⁶ and lactams are similarly alkylated.¹⁷⁰⁷ Protic solvents are generally not suitable because they protonate the base (though of course this is not a problem with a conjugate pair, e.g., $t\text{-BuOK}$ in $t\text{-BuOH}$). Some common solvents are DME, THF, DMF, and liquid NH_3 . Phase-transfer catalysis has been used to alkylate many nitriles, as well as some esters and ketones.¹⁷⁰⁸ Amino acid surrogates (**158**, $\text{R}=\text{N}$ derivative) can be alkylated, often under phase-transfer conditions.¹⁷⁰⁹

Direct alkylation of aldehydes is difficult when bases (e.g., KOH and NaOMe) are used, due to rapid aldol reaction (**16-34**), but aldehydes bearing only one α hydrogen have been alkylated with allylic and benzylic halides in good yields using the base KH to prepare the potassium enolate,¹⁷¹⁰ or in moderate yields, by the use of a phase-transfer catalyst.¹⁷¹¹

¹⁶⁹⁷ For a list of some bases, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1476–1479.

¹⁶⁹⁸ See Klusener, P.A.A.; Brandsma, L.; Verkruijsse, H.D.; Schleyer, P.v.R.; Friedl, T.; Pi, R. *Angew. Chem. Int. Ed.* **1986**, 25, 465.

¹⁶⁹⁹ Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, 93, 2319; Bos, W.; Pabon, H.J.J. *Recl. Trav. Chim. Pays-Bas* **1980**, 99, 141. See also, Cregge, R.J.; Herrmann, J.L.; Lee, C.S.; Richman, J.E.; Schlessinger, R.H. *Tetrahedron Lett.* **1973**, 2425.

¹⁷⁰⁰ Watt, D.S. *Tetrahedron Lett.* **1974**, 707.

¹⁷⁰¹ See Comins, D.L.; Killpack, M.O. *J. Org. Chem.* **1987**, 52, 104. See Xie, L.; Isenberger, K.M.; Held, G.; Dahl, M. *J. Org. Chem.* **1997**, 62, 7516 for steric versus electronic effects in kinetic enolate formation.

¹⁷⁰² Liou, L.R.; McNeil, A.J.; Toombes, G.E.S.; Collum, D.B. *J. Am. Chem. Soc.* **2008**, 130, 17334; Khartabil, H.K.; Gros, P.C.; Fort, Y.; Ruiz-López, M.F. *J. Org. Chem.* **2008**, 73, 9393; Pratt, L.M.; Mu, R.; Carter, C.; Woodford, B. *Tetrahedron* **2007**, 63, 1331. See also Pratt, L.M.; Nguyen, S.C.; Thanh, B.T. *J. Org. Chem.* **2008**, 73, 6086.

¹⁷⁰³ Sun, X.; Kenkre, S.L.; Remenar, J.F.; Gilchrist, J.H. *J. Am. Chem. Soc.* **1997**, 119, 4765.

¹⁷⁰⁴ Majewski, M.; Nowak, P. *Tetrahedron Lett.* **1998**, 39, 1661.

¹⁷⁰⁵ Langhals, E.; Langhals, H. *Tetrahedron Lett.* **1990**, 31, 859.

¹⁷⁰⁶ See Ibrahim-Ouali, M.; Parrain, J.-L.; Santelli, M. *Org. Prep. Proceed. Int.* **1999**, 31, 467. Enolate anions of β -lactones are subject to ring opening: see Mori, S.; Shindo, M. *Org. Lett.* **2004**, 6, 3945.

¹⁷⁰⁷ Matsuo, J.-i.; Kobayashi, S.; Koga, K. *Tetrahedron Lett.* **1998**, 39, 9723.

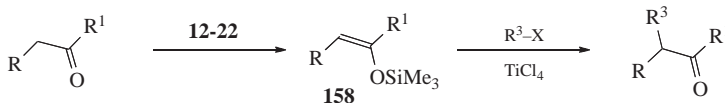
¹⁷⁰⁸ See Makosza, M. *Russ. Chem. Rev.* **1977**, 46, 1151; *Pure Appl. Chem.* **1975**, 43, 439; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, **1978**, pp. 170–217; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, **1977**, pp. 136–204.

¹⁷⁰⁹ Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, 127, 5073.

¹⁷¹⁰ Artaud, I.; Torossian, G.; Viout, P. *Tetrahedron* **1985**, 41, 5031.

¹⁷¹¹ Purohit, V.G.; Subramanian, R. *Chem. Ind. (London)* **1978**, 731; Buschmann, E.; Zeeh, B. *Liebigs Ann. Chem.* **1979**, 1585.

Even the use of amide bases (e.g., lithium diisopropylamide, LDA), lithium hexamethyl disilazide (LHMDS), or lithium tetramethylpiperidide (LTMP) to generate the enolate anion in an aprotic solvent (e.g., ether or THF) cannot completely suppress rapid aldol side reactions.



As in Reaction **10-67**, the alkyl halide that reacts with the enolate anion may be primary or secondary. Tertiary halides give elimination. Even primary and secondary halides may give predominant elimination if the enolate anion is a strong enough base (e.g., the enolate anion from Me_3CCOMe).¹⁷¹² Tertiary alkyl groups, as well as other groups that normally give $\text{S}_{\text{N}}1$ reactions, can be introduced if the reaction is performed on a silyl enol ether¹⁷¹³ of a ketone, aldehyde, or ester (see **158**) with a Lewis acid catalyst.¹⁷¹⁴ Tertiary alkyl fluorides were coupled to silyl enol ethers with $\text{BF}_3 \cdot \text{etherate}$.¹⁷¹⁵ Note that tin enolates ($\text{C}=\text{C}-\text{OSnR}_3$) react with halides in the presence of a Zn catalyst.¹⁷¹⁶ A chiral variation of this latter reaction was reported involving generation of the enolate anion in the presence of Me_3SnCl , a Pd catalyst, and a chiral ligand.¹⁷¹⁷

Metal-catalyzed alkylations that are related to this reaction are known. 1,3-Diketones are benzylated or allylated using Bi catalysts.¹⁷¹⁸ Monoalkylation is possible using Pd catalysts,¹⁷¹⁹ and Pd catalyzed asymmetric allylic alkylation is known.¹⁷²⁰ α -Alkylation of ketones with alcohols uses a Ru catalyst,¹⁷²¹ or Ni nanoparticles.¹⁷²² A recyclable Pd catalyst is available.¹⁷²³ Zinc enolate anions have been used in enantioselective Pd catalyzed alkylation reactions.¹⁷²⁴

Silyl enol ethers can be converted to the enolate anion, which can then be alkylated in the usual manner. The reaction of silyl enol ether (**159**) with KOEt followed by LiBr and a catalytic amount of *n*-butyllithium with allyl iodide gave **160**.¹⁷²⁵ Metal-catalyzed alkylation reactions are known with silyl enol ethers, including an In catalyzed¹⁷²⁶ reaction. An Ir catalyzed regioselective and enantioselective alkylation of silyl enol ethers using allylic carbonates as a substrate has been reported.¹⁷²⁷

¹⁷¹² Zook, H.D.; Kelly, W.L.; Posey, I.Y. *J. Org. Chem.* **1968**, *33*, 3477.

¹⁷¹³ For a list of alkylations of silyl enol ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1494–1505.

¹⁷¹⁴ Kang, S.-K.; Ryu, H.-C.; Hong, Y.-T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3350. For a review, see Reetz, M.T. *Angew. Chem. Int. Ed.* **1982**, *21*, 96.

¹⁷¹⁵ Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2004**, *45*, 2555.

¹⁷¹⁶ Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 7440.

¹⁷¹⁷ Trost, B.M.; Schroeder, G.M. *J. Am. Chem. Soc.* **1999**, *121*, 6759.

¹⁷¹⁸ Rueping, M.; Nachtsheim, B.J.; Kuenkel, A. *Org. Lett.* **2007**, *9*, 825.

¹⁷¹⁹ Ranu, B.C.; Chattopadhyay, K.; Adak, L. *Org. Lett.* **2007**, *9*, 4595. See Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718.

¹⁷²⁰ Trost, B.M.; Schroeder, G.M. *Chemistry: European J.* **2005**, *11*, 174.

¹⁷²¹ Martínez, R.; Ramón, D.J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988.

¹⁷²² Alonso, F.; Riente, P.; Yus, M. *Synlett* **2007**, 1872.

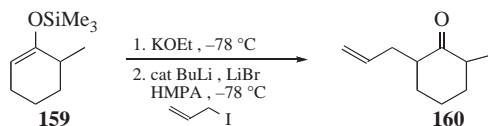
¹⁷²³ Kwon, M.S.; Kim, N.; Seo, S.H.; Park, I.S.; Cheedra, R.K.; Park, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6913.

¹⁷²⁴ Kinoshita, N.; Kawabata, T.; Tsubaki, K.; Bando, M.; Fuji, K. *Tetrahedron* **2006**, *62*, 1756.

¹⁷²⁵ Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, *42*, 369.

¹⁷²⁶ Nishimoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2009**, *65*, 5462.

¹⁷²⁷ Graening, T.; Hartwig, J.F. *J. Am. Chem. Soc.* **2005**, *127*, 17192.



The metal-catalyzed (usually Ni) coupling reaction of an alkyl halide or an electrophilic substrate with a silane¹⁷²⁸ is known as *Hiyama coupling*.¹⁷²⁹ A Ni catalyzed Hiyama cross-coupling with a chiral additive leads to a chiral alkylated ketone.¹⁷³⁰ The nature of the ligand has an important impact on the reaction.¹⁷³¹ There is a Pd catalyzed Hiyama cross-coupling.¹⁷³² Aryl siloxanes have been used in this reaction.¹⁷³³

Enol carbonates react with alkylating agents in the presence of a Pd catalyst. The decarboxylative alkylation of allyl enol carbonates to the corresponding allylcyclohexanone derivatives is known.¹⁷³⁴ An asymmetric version of this reaction has been reported.¹⁷³⁵ The same reaction can be done using enolate anion and allylic acetates with a Pd catalyst.¹⁷³⁶

Vinyllic and aryl halides can be used to vinylate or arylate carboxylic esters (but not ketones) by the use of NiBr₂ as a catalyst.¹⁷³⁷ Ketones have been vinylated by treating their enol acetates with vinyllic bromides in the presence of a Pd catalyst,¹⁷³⁸ but direct reaction of a ketone, a vinyl halide, sodium *tert*-butoxide and a Pd catalyst also give the α -vinyl ketone.¹⁷³⁹ Also as in Reaction 10-67, this reaction can be used to close rings.¹⁷⁴⁰ Rings have been closed by treating a dianion of a dialkyl succinate with a 1, ω -dihalide or ditosylate.¹⁷⁴¹ This was applied to the synthesis of three-, four-, five-, and six-membered rings. When the attached groups were chiral (e.g., menthyl) the product was formed with > 90% ee.¹⁷⁴⁰

¹⁷²⁸ For a reaction with a vinyl silane substrate, see Wang, Z.; Pitteloud, J.-P.; Montes, L.; Rapp, M.; Derane, D.; Wnuk, S.F. *Tetrahedron* **2008**, *64*, 5322.

¹⁷²⁹ Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61; Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*, de Meijere, A.; Diederich, F., Eds., Wiley-VCH, New York, **2004**; Chap. 4.

¹⁷³⁰ Dai, X.; Strotman, N.A.; Fu, G.C. *J. Am. Chem. Soc.* **2008**, *130*, 3302.

¹⁷³¹ Raders, S.M.; Kingston, J.V.; Verkade, J.G. *J. Org. Chem.* **2010**, *75*, 1744.

¹⁷³² Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250; Zhang, L.; Qing, J.; Yang, P.; Wu, J. *Org. Lett.* **2008**, *10*, 4971; Ranu, B.C.; Dey, R.; Chattopadhyay, K. *Tetrahedron Lett.* **2008**, *49*, 3430; Li, J.-H.; Deng, C.-L.; Liu, W.-J.; Xie, Y.-X. *Synthesis* **2005**, 3039; Li, J.-H.; Deng, C.-L.; Xie, Y.-X. *Synthesis* **2006**, 969.

¹⁷³³ Chen, S.-N.; Wu, W.-Y.; Tsai, F.-Y. *Tetrahedron* **2008**, *64*, 8164.

¹⁷³⁴ Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. See also, Nicolaou, K.C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2482.

¹⁷³⁵ Behenna, D.C.; Stoltz, B.M. *J. Am. Chem. Soc.* **2004**, *126*, 15044.

¹⁷³⁶ Trost, B.M.; Schroeder, G.M.; Kristensen, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3492.

¹⁷³⁷ Millard, A.A.; Rathke, M.W. *J. Am. Chem. Soc.* **1977**, *99*, 4833.

¹⁷³⁸ Kosugi, M.; Hagiwara, I.; Migita, T. *Chem. Lett.* **1983**, 839. For other methods, see Negishi, E.; Akiyoshi, K. *Chem. Lett.* **1987**, 1007; Chang, T.C.T.; Rosenblum, M.; Simms, N. *Org. Synth.* **66**, 95.

¹⁷³⁹ Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J.M.; Buchwald, S.L. *Org. Lett.* **2001**, *3*, 1897.

¹⁷⁴⁰ See Stork, G.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* **1973**, *95*, 2016; Stork, G.; Cohen, J.F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. In the last case, the substrate moiety is an epoxide function.

¹⁷⁴¹ Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 3343; Furuta, K.; Iwanaga, K.; Yamamoto, H. *Org. Synth.* **67**, 76.

Efficient enantioselective alkylations are known,¹⁷⁴² including the use of a chiral base to form the enolate anion.¹⁷⁴³ Alternatively, a chiral auxiliary can be attached. Many auxiliaries are based on the use of chiral amides¹⁷⁴⁴ or esters.¹⁷⁴⁵ Subsequent formation of the enolate anion allows alkylation to proceed with high enantioselectivity. A subsequent step is required to convert the chiral amide or ester to the corresponding carboxylic acid. Chiral additives can also be used,¹⁷⁴⁶ and the influence of chelating ligands and hydrocarbon cosolvents has been studied for $\text{LiN}(\text{TMS})_2$ mediated enolization reactions.¹⁷⁴⁷ The addition of triethylamine influences the (*E/Z*) selectivity of the enolate anion.¹⁷⁴⁸ Dynamic kinetic resolution has been used for the asymmetric alkylation of malonate derivatives using allenyl acetates.¹⁷⁴⁹

When the compound to be alkylated is an unsymmetrical ketone, the question arises as to which side will be alkylated (regioselectivity). If a phenyl or a vinylic group is present on one side, alkylation goes predominantly on that side. When only alkyl groups are present, the reaction is generally not regioselective; mixtures are obtained in which sometimes the more alkylated and sometimes the less alkylated side is predominantly alkylated. Which product is found in higher yield depends on the nature of the substrate, the base,¹⁷⁵⁰ the cation, and the solvent. In any case, di- and trisubstitution are frequent¹⁷⁵¹ and it is often difficult to stop with the introduction of just one alkyl group.¹⁷⁵²

Several methods have been developed for ensuring that alkylation takes place regioselectively on the *desired* side of a ketone.¹⁷⁵³ Among these are the following:

1. Block one side of the ketone by introducing a removable group. Alkylation takes place on the other side; the blocking group is then removed. A common reaction for this purpose is formylation with ethyl formate (Reaction **16-86**). This generally blocks the less hindered side. The formyl group is easily removed by alkaline hydrolysis (Reaction **12-43**).
2. Introduce an activating group on one side. Alkylation then takes place on that side (Reaction **10-67**). The activating group is then removed.

¹⁷⁴² See Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, **1986**, pp. 236–245; Evans, D.A. in Morrison, J.D. *Asymmetric Synthesis* Vol. 3, Academic Press, NY, **1984**, pp. 1–110.

¹⁷⁴³ See Murakata, M.; Nakajima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657. For a review, see Cox, P.J.; Simpkins, N.S. *Tetrahedron: Asymmetry* **1991**, 2, 1, pp. 6–13.

¹⁷⁴⁴ See Lafontaine, J.A.; Provencal, D.P.; Gardelli, C.; Leahy, J.W. *J. Org. Chem.* **2003**, 68, 4215. See Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* **1984**, 25, 4071; Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, 106, 4261; Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* **1985**, 68, 2100; Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem. Int. Ed.* **1981**, 20, 207.

¹⁷⁴⁵ Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, 68, 212.

¹⁷⁴⁶ Denmark, S.E.; Stavenger, R.A. *Acc. Chem. Res.* **2000**, 33, 432; Machajewski, T.D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, 39, 1352.

¹⁷⁴⁷ Godenschwager, P.F.; Collum, D.B. *J. Am. Chem. Soc.* **2007**, 129, 12023.

¹⁷⁴⁸ Godenschwager, P.F.; Collum, D.B. *J. Am. Chem. Soc.* **2008**, 130, 8726.

¹⁷⁴⁹ Trost, B.M.; Fandrick, D.R.; Dinh, D.C. *J. Am. Chem. Soc.* **2005**, 127, 14186.

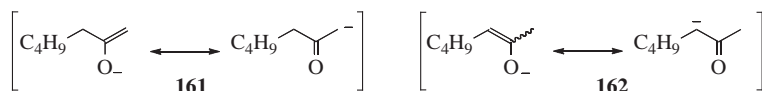
¹⁷⁵⁰ See, for example, Prieto, J.A.; Suarez, J.; Larson, G.L. *Synth. Commun.* **1988**, 18, 253; Gaudemar, M.; Bellassoued, M. *Tetrahedron Lett.* **1989**, 30, 2779.

¹⁷⁵¹ See Lissel, M.; Neumann, B.; Schmidt, S. *Liebigs Ann. Chem.* **1987**, 263.

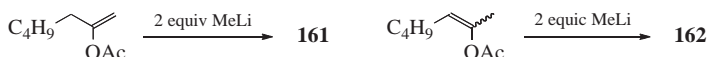
¹⁷⁵² See Morita, J.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, 54, 1785.

¹⁷⁵³ See House, H.O. *Rec. Chem. Prog.* **1968**, 28, 99; Podraza, K.F. *Org. Prep. Proced. Int.* **1991**, 23, 217.

3. Prepare the desired one of the two possible enolate anions.¹⁷⁵⁴ The two ions (e.g., **161** and **162**) for

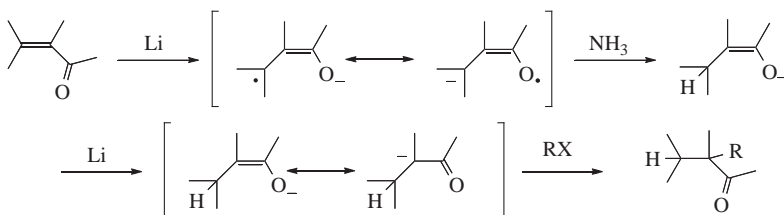


2-heptanone, interconvert rapidly only in the presence of the parent ketone or any stronger acid.¹⁷⁵⁵ In the absence of such acids, it is possible to prepare either **161** or **162** and thus achieve selective alkylation on either side of the ketone.¹⁷⁵⁶ The desired enolate anion can be obtained by treatment of the corresponding enol acetate with 2 equiv of methyllithium in 1,2-dimethoxyethane. Each enol acetate gives the corresponding enolate, for example,



The enol acetates, in turn, can be prepared by treatment of the parent ketone with an appropriate reagent.¹⁷⁴⁵ Such treatment generally gives a mixture of the two enol acetates in which one or the other predominates, depending on the reagent. The mixtures are easily separable.¹⁷⁵⁵ An alternate procedure involves conversion of a silyl enol ether¹⁷⁵⁷ (see Reaction 12-17) or a dialkylboron enol ether¹⁷⁵⁸ (an enol borinate, see Reaction 10-73) to the corresponding enolate anion. If the less hindered enolate anion is desired (e.g., **161**), it can be prepared directly from the ketone by treatment with LDA in THF or DME at -78°C .¹⁷⁵⁹

4. Begin not with the ketone itself, but with an α,β -unsaturated ketone in which the double bond is present on the side where alkylation is desired. Upon treatment with lithium in liquid NH_3 , such a ketone is reduced to an enolate anion. When the alkyl halide is added, it must react with the enolate anion on the side where the double bond was.¹⁷⁶⁰ Of course, this method is not actually an alkylation of the ketone, but of the α,β -unsaturated ketone, although the product is the same as if the saturated ketone had been alkylated on the desired side.



¹⁷⁵⁴ See d'Angelo, J. *Tetrahedron* **1976**, 32, 2979; Stork, G. *Pure Appl. Chem.* **1975**, 43, 553.

¹⁷⁵⁵ House, H.O.; Trost, B.M. *J. Org. Chem.* **1965**, 30, 1341.

¹⁷⁵⁶ House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* **1971**, 36, 2361. For an improved procedure, see Liotta, C.L.; Caruso, T.C. *Tetrahedron Lett.* **1985**, 26, 1599.

¹⁷⁵⁷ See Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, 18, 181; Rasmussen, J.K. *Synthesis* **1977**, 91. See Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, 129, 1034.

¹⁷⁵⁸ Pasto, D.J.; Wojtkowski, P.W. *J. Org. Chem.* **1971**, 36, 1790.

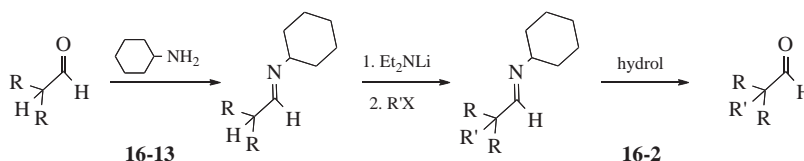
¹⁷⁵⁹ House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* **1971**, 36, 2361. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* **1984**, 25, 495.

¹⁷⁶⁰ See Caine, D. *Org. React.* **1976**, 23, 1. Also see Näf, F.; Decorzant, R. *Helv. Chim. Acta* **1974**, 57, 1317; Wender, P.A.; Eissenstat, M.A. *J. Am. Chem. Soc.* **1978**, 100, 292.

Both sides of acetone have been alkylated with different alkyl groups, in one operation, by treatment of the *N,N*-dimethylhydrazone of acetone with *n*-BuLi, followed by a primary alkyl, benzylic, or allylic bromide or iodide; then another mole of *n*-BuLi, a second halide, and finally hydrolysis of the hydrazone.¹⁷⁶¹ Alkylation of an unsymmetrical ketone at the more substituted position was reported using an alkyl bromide, NaOH, and a calix[*n*]arene catalyst (see Sec. 4.H. category 2 for calixarenes).¹⁷⁶²

Among other methods for the preparation of alkylated ketones are (1) Alkylation of silyl enol ethers using various reagents as noted above, (2) the *Stork enamine reaction* (Reaction 10-69), (3) the acetoacetic ester synthesis (Reaction 10-67), (4) alkylation of β -keto sulfones or sulfoxides (Reaction 10-67), (5) acylation of $\text{CH}_3\text{SOCH}_2^-$ followed by reductive cleavage (Reaction 16-86), (6) treatment of α -halo ketones with lithium dialkylcopper reagents (Reaction 10-57), and (7) treatment of α -halo ketones with trialkylboranes (Reaction 10-73).

Aldehydes can be indirectly alkylated via an imine derivative of the aldehyde.¹⁷⁶³ The derivative is easily prepared (Reaction 16-13) and the product easily hydrolyzed to the aldehyde (Reaction 16-2). Either or both R groups may be hydrogen, so that mono-, di-, and trisubstituted acetaldehydes can be prepared by this method. The R' group may be primary alkyl, allylic, or benzylic. Imine alkylation can also be applied to the preparation of substituted amine derivatives. An amino acid surrogate (e.g., $\text{Ph}_2\text{C}=\text{NCH}_2\text{CO}_2\text{R}$), when treated with KOH and an alkyl halide gives the C-alkylated product.¹⁷⁶⁴ When a chiral additive is used, good enantioselectivity was observed. This reaction has also been done in the ionic liquid Bmim tetrafluoroborate (see Sec. 9.D.iii).¹⁷⁶⁵ It is possible to alkylate α -amino amides directly.¹⁷⁶⁶



Hydrazones and other compounds with C=N bonds can be similarly alkylated.¹⁷⁴³ The use of chiral amines or hydrazines¹⁷⁶⁷ [followed by hydrolysis (Reaction 16-2) of the alkylated imine] can lead to chiral alkylated ketones in high optical yields¹⁷⁶⁸ (for an example, see Sec. 4.J). Lithiated imines are generated by the treatment of an imine with a

¹⁷⁶¹ Yamashita, M.; Matsuyama, K.; Tanabe, M.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* **1985**, 58, 407.

¹⁷⁶² Shimizu, S.; Suzuki, T.; Sasaki, Y.; Hirai, C. *Synlett* **2000**, 1664.

¹⁷⁶³ See Fraser, R.R. in Buncl, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, **1984**, pp. 65–105; Whitesell, J.K.; Whitesell, M.A. *Synthesis* **1983**, 517. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1513–1518. Also see Goering, H. L.; Tseng, C.C. *J. Org. Chem.* **1981**, 46, 5250.

¹⁷⁶⁴ Park, H.-g.; Jeong, B.-s.; Yoo, M.-s.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, 42, 4645; Jew, S.-s.; Jeong, B.-s.; Yoo, M.-s.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244.

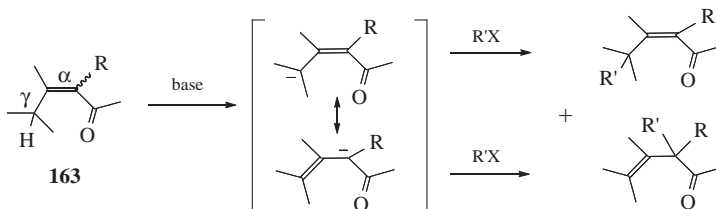
¹⁷⁶⁵ Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, 59, 701.

¹⁷⁶⁶ Myers, A.G.; Schnider, P.; Kwon, S.; Kung, D.W. *J. Org. Chem.* **1999**, 64, 3322.

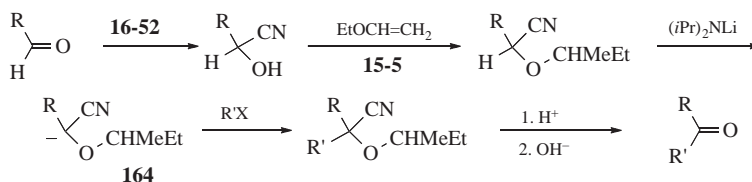
¹⁷⁶⁷ See Enders, D. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, **1984**, pp. 275–339.

¹⁷⁶⁸ Meyers, A.I.; Williams, D.R.; White, S.; Erickson, G.W. *J. Am. Chem. Soc.* **1981**, 103, 3088; Enders, D.; Bockstiegel, B. *Synthesis* **1989**, 493; Enders, D.; Kipphardt, H.; Fey, P. *Org. Synth.* 65, 183.

suitable base, and reaction with an alkyl halide gives the alkylated imine.¹⁷⁶⁹ α -Magnesio imines also react with alkyl halides.¹⁷⁷⁰



In α,β -unsaturated ketones, nitriles, and esters (e.g., **163**), the γ hydrogen assumes the acidity normally held by the position α to the carbonyl group, especially when R is not hydrogen and so cannot compete. This principle, called *vinylity* (see Sec. 6.B), operates because the resonance effect is transmitted through the double bond. However, because of the resonance, alkylation at the α position (with allylic rearrangement) competes with alkylation at the γ position and usually predominates.



α -Hydroxynitriles (cyanohydrins), protected by conversion to acetals with ethyl vinyl ether (Reaction **15-5**), can be easily alkylated with primary or secondary alkyl or allylic halides.¹⁷⁷¹ The R group can be aryl or a saturated or unsaturated alkyl. Since the cyanohydrins¹⁷⁷² are easily formed from aldehydes (Reaction **16-52**) and the product is easily hydrolyzed to a ketone, this is a method for converting an aldehyde (RCHO) to a ketone (RCOR')¹⁷⁷³ (for other methods, see Reactions **10-71**, **16-82**, and **18-9**).¹⁷⁷⁴ In this procedure, the normal mode of reaction of a carbonyl carbon is reversed. The C atom of an aldehyde molecule is normally electrophilic and is attacked by nucleophiles (Chapter 16), but by conversion to the protected cyanohydrin this carbon atom has been induced to perform as a nucleophile.¹⁷⁷⁵ The German word *Umpolung*¹⁷⁷⁶ is used to describe this kind of reversal (another example is found in Reaction **10-71**). Since the ion **164** serves as a substitute for the unavailable $\text{R}(\text{C}=\text{O})^-$ anion, it is often called a “masked” $\text{R}(\text{C}=\text{O})^-$ ion.

¹⁷⁶⁹ Zuend, S.J.; Ramirez, A.; Lobkovsky, E.; Collum, D.B. *J. Am. Chem. Soc.* **2006**, *128*, 5939.

¹⁷⁷⁰ Hatakeyama, T.; Ito, S.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 14192.

¹⁷⁷¹ Stork, G.; Depezay, J.C.; D'Angelo, J. *Tetrahedron Lett.* **1975**, 389. See also, Hünig, S.; Marschner, C.; Peters, K.; von Schnering, H.G. *Chem. Ber.* **1989**, *122*, 2131, and other papers in this series.

¹⁷⁷² For a review of **164**, see Albright, J.D. *Tetrahedron* **1983**, *39*, 3207.

¹⁷⁷³ Also see Stetter, H.; Schmitz, P.H.; Schreckenberger, M. *Chem. Ber.* **1977**, *110*, 1971; Hünig, S. *Chimia*, **1982**, *36*, 1.

¹⁷⁷⁴ See Martin, S.F. *Synthesis* **1979**, 633.

¹⁷⁷⁵ See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**, pp. 56–67; Gröbel, B.; Seebach, D. *Synthesis* **1977**, 357; Lever, Jr., O.W. *Tetrahedron* **1976**, *32*, 1943; Seebach, D. *Angew. Chem. Int. Ed.* **1969**, *8*, 639. Also see Hase, T.A.; Koskimies, J.K. *Aldrichimica Acta* **1981**, *14*, 73; Hase, T.A. *Unpoled Synthons*, Wiley, NY, **1987**, pp. xiii–xiv, 7–18, 219–317. For lists of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1435–1438.

¹⁷⁷⁶ See Hase, T.A. *Unpoled Synthons*, Wiley, NY, **1987**; Seebach, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 239.

This method fails for formaldehyde ($R = H$), but other masked formaldehydes have proved successful.¹⁷⁷⁷ In an interesting variation of nitrile alkylation, a quaternary bromide [$\text{PhC}(\text{Br})(\text{Me})\text{CN}$] reacted with allyl bromide, in the presence of a *Grignard reagent*, to give the alkylated product [$\text{PhC}(\text{CN})(\text{Me})\text{CH}_2\text{CH}=\text{CH}_2$].¹⁷⁷⁸

A coupling reaction of two ketones to form a 1,4-diketone has been reported, using $\text{ZnCl}_2/\text{Et}_2\text{NH}$.¹⁷⁷⁹ An interesting allylic substitution at a 3° center involves the reaction of 3° 2-bromonitriles with $i\text{PrMgBr}$ and allyl bromide to give the 2-allyl nitrile.¹⁷⁸⁰

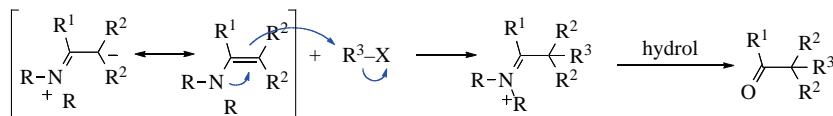
α -Alkylation of ketones with primary alcohols is possible using polymer-associated nanoparticulate Pd.¹⁷⁸¹

Protonation of enolate anions is discussed in Reaction 16-34, in connection with the aldol condensation.

OS **III**, 44, 219, 221, 223, 397; **IV**, 278, 597, 641, 962; **V**, 187, 514, 559, 848; **VI**, 51, 115, 121, 401, 818, 897, 958, 991; **VII**, 153, 208, 241, 424; **VIII**, 141, 173, 241, 403, 460, 479, 486; **X**, 59, 460; **80**, 31.

10-69 The Stork Enamine Reaction

α -Acylalkyl-de-halogenation¹⁷⁸²



When enamines are treated with alkyl halides, an alkylation occurs to give an iminium salt via electron transfer from the electron pair on nitrogen, through the $\text{C}=\text{C}$ to the electrophilic carbon of the alkyl halide.¹⁷⁸³ In effect, an enamine behaves as a “nitrogen enolate anion” and generally reacts as carbon nucleophiles.¹⁷⁸⁴ Hydrolysis of the iminium salt gives a ketone. Since the enamine is normally formed from a ketone (Reaction 16-13), the net result is alkylation of the ketone at the α position. The method, known as the *Stork enamine reaction*,¹⁷⁸⁵ is an alternative to the ketone alkylation considered in Reaction 10-68, generally giving monoalkylation of the ketone. Alkylation usually takes place on the less substituted side of the original ketone. The most commonly used amines are the cyclic amines piperidine, morpholine, and pyrrolidine. There are metal-catalyzed enamine alkylation reactions, including the use of Ir catalysts.¹⁷⁸⁶ There are reactions that are catalyzed by enamines, including asymmetric reactions.¹⁷⁸⁷

¹⁷⁷⁷ Stork, G.; Ozorio, A.A.; Leong, A.Y.W. *Tetrahedron Lett.* **1978**, 5175.

¹⁷⁷⁸ Fleming, F.F.; Zhang, Z.; Knochel, P. *Org. Lett.* **2004**, 6, 501.

¹⁷⁷⁹ Nevar, N.M.; Kel'in, A.V.; Kulinkovich, O.G. *Synthesis* **2000**, 1259.

¹⁷⁸⁰ Fleming, F.F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, 70, 2200.

¹⁷⁸¹ Yamada, Y.M.A.; Uozumi, Y. *Org. Lett.* **2006**, 8, 1375.

¹⁷⁸² This is the IUPAC name with respect to the halide as substrate.

¹⁷⁸³ See Adams, J.P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 125.

¹⁷⁸⁴ See Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* **2003**, 9, 2209.

¹⁷⁸⁵ See Hickmott, P.W. *Tetrahedron*, **1984**, 40, 2989; **1982**, 38, 1975, 3363; Granik, V.G. *Russ. Chem. Rev.*, **1984**, 53, 383. Also see in Cook, A.G. *Enamines*, 2nd ed.; Marcel Dekker, NY, **1988**, the articles by Alt, G.H.; Cook, A. G. pp. 181–246, and Gadamasetti, G.; Kuehne, M.E. pp. 531–689; Whitesell, J.K.; Whitesell, M.A. *Synthesis*, **1983**, 517; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 570–582, 766–772; Bláha, K.; Cervinka, O. *Adv. Heterocycl. Chem.*, **1966**, 6, 147, p. 186.

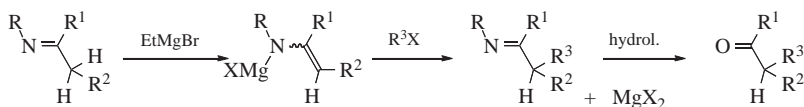
¹⁷⁸⁶ Weix, D.J.; Hartwig, J.F. *J. Am. Chem. Soc.* **2007**, 129, 7720.

¹⁷⁸⁷ Mukherjee, S.; Yang, J.W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, 107, 5471.

The method is quite useful for particularly active alkyl halides, (e.g., allylic, benzylic, and propargylic halides), and for α -halo ethers and esters. Other primary and secondary halides can show sluggish reactivity. The reaction of enamines with benzotriazole derivatives has been reported.¹⁷⁸⁸ Tertiary halides do not give the reaction at all since, with respect to the halide, this is nucleophilic substitution and elimination predominates. The reaction can also be applied to activated aryl halides (e.g., 2,4-dinitrochlorobenzene; see Chapter 13), to epoxides,¹⁷⁸⁹ and to activated alkenes (e.g., acrylonitrile). The latter is a *Michael-type reaction* (**15-24**) with respect to the alkene.

Acylation¹⁷⁹⁰ can be accomplished with acyl halides or with anhydrides. Hydrolysis of the resulting iminium salt leads to a 1,3-diketone. A COOEt group can be introduced by treatment of the enamine with ethyl chloroformate (ClCOOEt;¹⁷⁹¹ a CN group with cyanogen chloride¹⁷⁹² (not cyanogen bromide or iodide, which leads to halogenation of the enamine); a CHO group with the mixed anhydride of formic and acetic acids¹⁷⁹¹ or with DMF and phosgene,¹⁷⁹³ and a C(R)=NR' group with a nitrilium salt RC \equiv N⁺R'.¹⁷⁹⁴ The acylation of the enamine can take place by the same mechanism as alkylation, but another mechanism is also possible, if the acyl halide has an α hydrogen and if a tertiary amine is present, as it often is (it is added to neutralize the HX given off). In this mechanism, the acyl halide is dehydrohalogenated by the tertiary amine, producing a ketene (Reaction **17-14**), which adds to the enamine to give a cyclobutanone (Reaction **15-63**). This compound can be cleaved in the solution to form the same acylated imine salt (that would form by the more direct mechanism, or it can be isolated (in the case of enamines derived from aldehydes), or it may cleave in other ways.¹⁷⁹⁵

N-Alkylation can be a problem, particularly with enamines derived from aldehydes. An alternative method, which gives good yields of alkylation with primary and secondary halides, is alkylation of enamine *salts*, which are prepared by treating an imine with ethylmagnesium bromide in THF:¹⁷⁹⁶



The imines are prepared by the reaction of secondary amines with aldehydes or ketones, mainly ketones (**16-13**). The enamine salt method has also been used to give good yields of mono α alkylation of α,β -unsaturated ketones.¹⁷⁹⁷ Enamines prepared from aldehydes and

¹⁷⁸⁸ Katritzky, A.R.; Fang, Y.; Silina, A. *J. Org. Chem.* **1999**, *64*, 7622; Katritzky, A.R.; Huang, Z.; Fang, Y. *J. Org. Chem.* **1999**, *64*, 7625.

¹⁷⁸⁹ Britten, A.Z.; Owen, W.S.; Went, C.W. *Tetrahedron* **1969**, *25*, 3157.

¹⁷⁹⁰ See Hickmott, P.W. *Chem. Ind. (London)* **1974**, 731; Hünig, S.; Hoch, H. *Fortschr. Chem. Forsch.* **1970**, *14*, 235.

¹⁷⁹¹ Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkowicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

¹⁷⁹² Kuehne, M.E. *J. Am. Chem. Soc.*, **1959**, *81*, 5400.

¹⁷⁹³ Ziegenbein, W. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 358.

¹⁷⁹⁴ Baudoux, D.; Fuks, R. *Bull. Soc. Chim. Belg.* **1984**, *93*, 1009.

¹⁷⁹⁵ See Alt, G.H.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, **1988**, pp. 204–215.

¹⁷⁹⁶ Stork, G.; Dowd, S.R. *J. Am. Chem. Soc.*, **1963**, *85*, 2178.

¹⁷⁹⁷ Stork, G.; Benaim, J. *J. Am. Chem. Soc.*, **1971**, *93*, 5938.

butylisobutylamine can be alkylated by simple primary alkyl halides in good yields.¹⁷⁹⁸ N-Alkylation in this case is presumably prevented by steric hindrance.

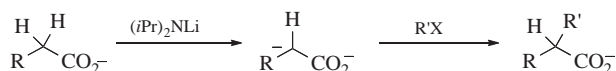
When the nitrogen of the substrate contains a chiral R group, both the *Stork enamine synthesis* and the enamine salt method can be used to perform enantioselective syntheses.¹⁷⁹⁹ The use of *S*-proline can generate a chiral enamine *in situ*, thus allowing alkylation to occur, giving alkylated product with good enantioselectivity. The reaction has been done intramolecularly.¹⁸⁰⁰

Conjugate addition (*Michael addition*) occurs when enamines react with conjugated ketones. This reaction is discussed in Reaction **15-24**.

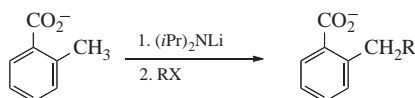
OS V, 533, 869; VI, 242, 496, 526; VII, 473.

10-70 Alkylation of Carboxylic Acid Salts

α -Carboxyalkyl-de-halogenation



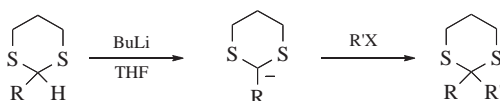
Carboxylic acids can be alkylated in the α position by conversion of their salts to dianions, which have resonance contributors,¹⁸⁰¹ by treatment with a strong base (e.g., LDA).¹⁸⁰² The use of Li^+ as the counterion increases the solubility of the dianionic salt. The reaction has been applied¹⁸⁰³ to primary alkyl, allylic, and benzylic halides, and to carboxylic acids of the form $\text{RCH}_2\text{CO}_2\text{H}$ and $\text{RR}^2\text{CHCO}_2\text{H}$.¹⁶⁹⁵ Alkylation occurs at carbon, the more nucleophilic site relative to the carboxylate oxygen anion (see Sec. 10.G.vii). This procedure is an alternative to the malonic ester synthesis (Reaction **10-67**) as a means of preparing carboxylic acids and has the advantage that acids of the form $\text{RR}'\text{R}^2\text{CCO}_2\text{H}$ can also be prepared. In a related reaction, methylated aromatic acids can be alkylated at the methyl group by a similar procedure.¹⁸⁰⁴



OS V, 526; VI, 517; VII, 249. See also, OS VII, 164.

10-71 Alkylation at a Position α to a Heteroatom

2-(2-Alkyl-thio) de-halogenation



¹⁷⁹⁸ Curphey, T.J.; Hung, J.C.; Chu, C.C.C. *J. Org. Chem.*, **1975**, *40*, 607. See also, Ho, T.; Wong, C.M. *Synth. Commun.*, **1974**, *4*, 147.

¹⁷⁹⁹ See Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, **1986**, pp. 248–255; Whitesell, J.K. *Acc. Chem. Res.* **1985**, *18*, 280; Bergbreiter, D.E.; Newcomb, M. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, **1983**, pp. 243–273.

¹⁸⁰⁰ Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.

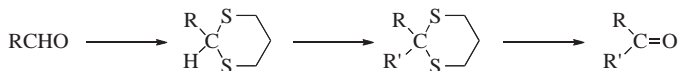
¹⁸⁰¹ Mladenova, M.; Blagoev, B.; Gaudemar, M.; Dardoize, F.; Lallemand, J.Y. *Tetrahedron* **1981**, *37*, 2153.

¹⁸⁰² Pfeffer, P.E.; Silbert, L.S.; Chirinko, Jr., J.M. *J. Org. Chem.* **1972**, *37*, 451.

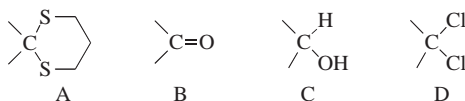
¹⁸⁰³ For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1717–1720ff.

¹⁸⁰⁴ Cregar, P.L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.

The presence of a sulfur atom on a carbon enhances the acidity of a proton on that carbon, and in dithioacetals and dithioketals that proton RSCH_2SR is even more acidic. 1,3-Dithianes can be alkylated¹⁸⁰⁵ if a proton is first removed by treatment with butyllithium in THF.¹⁸⁰⁶ Since 1,3-dithianes can be prepared by treatment of an aldehyde or its acetal (see OS VI, 556) with 1,3-propanedithiol (Reaction 16-11) and can be hydrolyzed (Reaction 10-7), this is a method for the conversion of an aldehyde to a ketone¹⁸⁰⁷ (see also, Reactions 10-68 and 18-9):



This is another example of Umpolung (see Reaction 10-68);¹⁷⁷³ the normally electrophilic carbon of the aldehyde is made to behave as a nucleophile. The reaction can be applied to the unsubstituted dithiane ($\text{R}=\text{H}$) and one or two alkyl groups can be introduced, so a wide variety of aldehydes and ketones can be made starting with formaldehyde.¹⁸⁰⁸ The R' group may be a primary or secondary alkyl or benzylic. Iodides give the best results. The reaction has been used to close rings.¹⁸⁰⁹ A similar synthesis of aldehydes can be performed starting with ethyl ethylthiomethyl sulfoxide ($\text{EtSOCH}_2\text{SEt}$).¹⁸¹⁰



Group **A** may be regarded as a structural equivalent for carbonyl group **B**, since introduction of **A** into a molecule is actually an indirect means of introducing **B**. It is convenient to have a word for units within molecules. Such a word is *synthon*, introduced by Corey,¹⁸¹¹ which is defined as a structural unit within a molecule that can be formed and/or assembled by known or conceivable synthetic operations. There are many other synthons equivalent to **A** and **B** (e.g., **C**; by Reactions 19-36 and 19-3) and **D** (by Reactions 10-2 and 16-23).¹⁸¹²

Carbanions generated from 1,3-dithianes also react with epoxides¹⁸¹³ to give the expected products. Reaction with epoxides leads to intermediates that undergo the *Brook rearrangement* (Reaction 18-44), which is synthetically useful in what is known as *anion relay chemistry*.

¹⁸⁰⁵ Seebach, D.; Corey, E.J. *J. Org. Chem.* **1975**, *40*, 231. See Page, P.C.B.; van Niel, M.B.; Prodger, J.C. *Tetrahedron* **1989**, *45*, 7643; Ager, D.J. in Hase, T.A. *Unpoled Synthons*, Wiley, NY, **1987**, pp. 19–37; Seebach, D. *Synthesis* **1969**, 17, especially pp. 24–27; Olsen, R.K.; Curriev, Jr., Y.O. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, **1974**, pp. 536–547.

¹⁸⁰⁶ See Lipshutz, B.H.; Garcia, E. *Tetrahedron Lett.* **1990**, *31*, 7261.

¹⁸⁰⁷ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1451–1454.

¹⁸⁰⁸ For a direct conversion of RX to RCHO , see Reaction 10-76.

¹⁸⁰⁹ See Seebach, D.; Jones, N.R.; Corey, E.J. *J. Org. Chem.* **1968**, *33*, 300; Hylton, T.; Boeckelheide, V. *J. Am. Chem. Soc.* **1968**, *90*, 6887; Ogura, K.; Yamashita, M.; Suzuki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1974**, 3653.

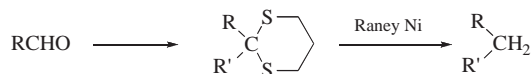
¹⁸¹⁰ Richman, J.E.; Herrmann, J.L.; Schlessinger, R.H. *Tetrahedron Lett.* **1973**, 3267. See also, Schill, G.; Jones, P.R. *Synthesis* **1974**, 117; Hori, I.; Hayashi, T.; Midorikawa, H. *Synthesis* **1974**, 705.

¹⁸¹¹ Corey, E.J. *Pure Appl. Chem.* **1967**, *14*, 19, pp. 20–23.

¹⁸¹² See Hase, T.A.; Koskimies, J.K. *Aldrichimica Acta* **1982**, *15*, 35.

¹⁸¹³ See Corey, E.J.; Seebach, D. *J. Org. Chem.* **1975**, *40*, 231.

Another useful application of this reaction stems from the fact that dithianes can be desulfurated with *Raney nickel* (Reaction **14-27**). Aldehydes can therefore be converted to chain-extended hydrocarbons:¹⁸¹⁴

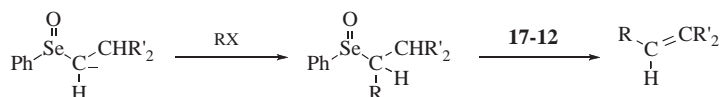


Similar reactions have been carried out with other thioacetals, as well as with compounds containing three thioether groups on a carbon.¹⁸¹⁵

If a stabilizing group other than sulfur is attached to the S—CH₂ unit of a thioether (RSCH₂X, where X is a stabilizing group), formation of the anion and alkylation can be facile. For example, benzylic and allylic thioethers (RSCH₂Ar and RSCH₂CH=CH₂)¹⁸¹⁶ and thioethers of the form RSCH₃ (R = tetrahydrofuranyl or 2-tetrahydropyranyl)¹⁸¹⁷ have been successfully alkylated at the carbon adjacent to the sulfur atom.¹⁸¹⁸ Stabilization by one thioether group has also been used in a method for the homologation of primary halides.¹⁸¹⁹ Thioanisole is treated with BuLi to give the corresponding anion,¹⁸²⁰ which reacts with the halide to give the thioether, which is then refluxed with a mixture of methyl iodide and sodium iodide in DMF to give the alkyl iodide as the final product (via an intermediate sulfonium salt). By this sequence, an alkyl halide (RX) is converted to its homologue RCH₂X by a pathway involving two laboratory steps (see also, Reaction **10-64**).

Vinylic sulfides containing an α hydrogen can also be alkylated¹⁸²¹ by alkyl halides or epoxides. This method is for converting an alkyl halide (RX) to an α,β-unsaturated aldehyde, which is the synthetic equivalent of the unknown [−]HC=CH—CHO ion.¹⁸²² Even simple alkyl aryl sulfides (RCH₂SAr and RR'CHSAr) have been alkylated α to the sulfur.¹⁸²³

Sulfones¹⁸²⁴ and sulfonic esters can also be alkylated in the α position if strong enough bases are used.¹⁸²⁵ Alkylation at the α position of selenoxides allows the formation of alkenes, since selenoxides easily undergo elimination (Reaction **17-12**).¹⁸²⁶



¹⁸¹⁴ See Hylton, T.; Boekelheide, V. *J. Am. Chem. Soc.* **1968**, *90*, 6887; Jones, J.B.; Grayshan, R. *Chem. Commun.* **1970**, 141, 741.

¹⁸¹⁵ See Lissel, M. *Liebigs Ann. Chem.* **1982**, 1589.

¹⁸¹⁶ Uemoto, K.; Kawahito, A.; Matsushita, N.; Skamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* **2001**, *42*, 905.

¹⁸¹⁷ Block, E.; Aslam, M. *J. Am. Chem. Soc.* **1985**, *107*, 6729.

¹⁸¹⁸ Biellmann, J.F.; Ducep, J.B. *Tetrahedron* **1971**, *27*, 5861. See also, Narasaka, K.; Hayashi, M.; Mukaiyama, T. *Chem. Lett.* **1972**, 259.

¹⁸¹⁹ Corey, E.J.; Jautelat, M. *Tetrahedron Lett.* **1968**, 5787.

¹⁸²⁰ Corey, E.J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097.

¹⁸²¹ Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2694.

¹⁸²² See Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* **1988**, *110*, 1290.

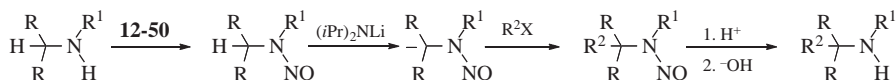
¹⁸²³ Dolak, T.M.; Bryson, T.A. *Tetrahedron Lett.* **1977**, 1961.

¹⁸²⁴ See Magnus, P.D. *Tetrahedron* **1977**, *33*, 2019, pp. 2022–2025; Hendrickson, J.B.; Sternbach, D.D.; Bair, K. *W. Acc. Chem. Res.* **1977**, *10*, 306.

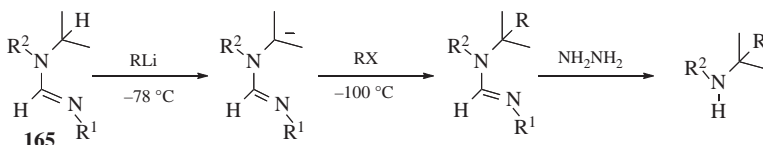
¹⁸²⁵ See Truce, W.E.; Hollister, K.R.; Lindy, L.B.; Parr, J.E. *J. Org. Chem.* **1968**, *33*, 43; Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* **1973**, 743, 746.

¹⁸²⁶ Reich, H.J.; Shah, S.K. *J. Am. Chem. Soc.* **1975**, *97*, 3250.

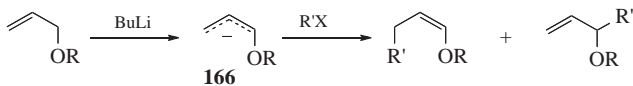
Alkylation can also be carried out, in certain compounds, at positions α to other heteroatoms,¹⁸²⁷ for example, at a position α to the nitrogen of tertiary amines.¹⁸²⁸ Alkylation α to the nitrogen of primary or secondary amines is not generally feasible because an NH hydrogen is usually more acidic than a CH hydrogen.



α-Lithiation of *N*-Boc amines has been accomplished and these react with halides in the presence of a Pd catalyst.¹⁸²⁹ Alkylation α to the nitrogen atom of a carbamate occurs when the carbamate is treated with a *Grignard reagent* under electrolysis conditions.¹⁸³⁰ α-Methoxy amides also react with allyl halides and zinc metal to give alkylation via replacement of the OMe unit.¹⁸³¹ It has been accomplished, however, by replacing the NH hydrogens with other (removable) groups.¹⁸³² In one example, a secondary amine is converted to its *N*-nitroso derivative (Reaction **12-50**).¹⁸³³ The *N*-nitroso product is easily hydrolyzed to the product amine (Reaction **19-51**).¹⁸³⁴ Alkylation of secondary and primary amines has also been accomplished with > 10 other protecting groups, involving conversion of amines to amides, carbamates,¹⁸³⁵ formamidines,¹⁸³⁶ and phosphoramides.¹⁸³¹ In the case of formamidines (**165**), use of a chiral R' leads to a chiral amine, in high ee, even when R is not chiral.¹⁸³⁷ The reaction of hydrazones with aryl halides, in the presence of a Pd catalyst leads to replacement of H with an aryl group (R'NH—N=CRH → R'NHC=NRR").¹⁸³⁸



A proton can be removed from an allylic ether by treatment with an alkyllithium at about -70°C (at higher temperatures the *Wittig rearrangement*, **18-22**, takes place) to give the ion **166**, which reacts with alkyl halides



¹⁸²⁷ See Krief, A. *Top. Curr. Chem.* **1987**, *135*, 1. Also see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, pp. 336–341.

¹⁸²⁸ Lepley, A.R.; Khan, W.A. *Chem. Commun.* **1967**, 1198; Lepley, A.R.; Giumanini, A.G. *J. Org. Chem.* **1966**, 31, 2055; Ahlbrecht, H.; Dollinger, H. *Tetrahedron Lett.* **1984**, 25, 1353.

¹⁸²⁹ Dieter, R.K.; Li, S. *Tetrahedron Lett.* **1995**, 36, 3613.

¹⁸³⁰ Suga, S.; Okajima, M.; Yoshida, J.-i. *Tetrahedron Lett.* **2001**, 42, 2173.

¹⁸³¹ Kise, N.; Yamazaki, H.; Mabuchi, T.; Shono, T. *Tetrahedron Lett.* **1994**, 35, 1561.

¹⁸³² For a review, see Beak, P.; Zajdel, W.J.; Reitz, D.B. *Chem. Rev.* **1984**, 84, 471.

¹⁸³³ Seebach, D.; Enders, D.; Renger, B. *Chem. Ber.* **1977**, *110*, 1852; Renger, B.; Kalinowski, H.; Seebach, D. *Chem. Ber.* **1977**, *110*, 1866. For a review, see Seebach, D.; Enders, D. *Angew. Chem. Int. Ed.* **1975**, *14*, 15.

¹⁸³⁴ Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* **1971**, *40*, 34, pp. 41–42.

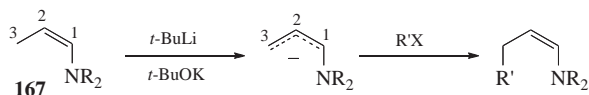
¹⁸³⁵ For the use of *tert*-butyl carbamates, see Beak, P.; Lee, W. *Tetrahedron Lett.* **1989**, 30, 1197.

¹⁸³⁶ For a review, see Meyers, A.I. *Aldrichimica Acta* **1985**, 18, 59.

¹⁸³⁷ Meyers, A.I.; Miller, D.B.; White, F. *J. Am. Chem. Soc.* **1988**, *110*, 4778; Gonzalez, M.A.; Meyers, A.I. *Tetrahedron Lett.* **1989**, *30*, 43, 47 and references cited therein.

¹⁸³⁸ Takemiya, A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2006**, *128*, 14800.

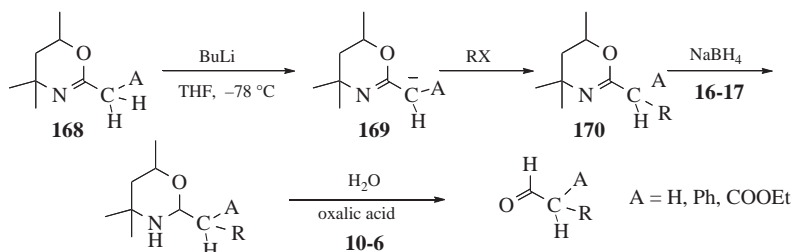
to give the two products shown.¹⁸³⁹ Similar reactions¹⁸⁴⁰ have been reported for allylic¹⁸⁴¹ and vinylic tertiary amines. In the latter case, enamines (**167**), treated with a strong base, are converted to anions that are then alkylated, generally at C-3.¹⁸⁴² (For direct alkylation of enamines at C-2, see Reaction **10-69**.)



It is also possible to alkylate a methyl, ethyl, or other primary group of an aryl ester (ArCO_2R), where Ar is a 2,4,6-trialkylphenyl group.¹⁸⁴³ Since esters can be hydrolyzed to alcohols, this constitutes an indirect alkylation of primary alcohols. Methanol has also been alkylated by converting it to $^-\text{CH}_2\text{O}^-$.¹⁸⁴⁴

OS VI, 316, 364, 542, 704, 869; VIII, 573.

10-72 Alkylation of Dihydro-1,3-Oxazine. The Meyers Synthesis of Aldehydes, Ketones, and Carboxylic Acids



A synthesis of aldehydes¹⁸⁴⁵ developed by Meyers et al.¹⁸⁴⁶ begins with the commercially available dihydro-1,3-oxazine derivatives (**168**; A = H, Ph, or COOEt).¹⁸⁴⁷ Removal of a proton from the indicated carbon in **168** leads to the resonance stabilized and bidentate anion (**169**). Alkylation occurs regioselectively at carbon using many alkyl bromides and iodides. The R group of RX can be primary or secondary alkyl, allylic, or benzylic and can carry another halogen or a CN group.¹⁸⁴⁸ The alkylated oxazine (**170**) is then reduced and hydrolyzed to give an aldehyde containing two more carbons than the starting RX. This method thus complements Reaction **10-71**, which converts RX to an aldehyde containing

¹⁸³⁹ Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* **1988**, *110*, 1290. See Hommes, H.; Verkruisje, H.D.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 113, and references cited therein.

¹⁸⁴⁰ See Biellmann, J.F.; Ducep, J. *Org. React.* **1982**, *27*, 1.

¹⁸⁴¹ Martin, S.F.; DuPriest, M.T. *Tetrahedron Lett.* **1977**, 3925 and references cited therein.

¹⁸⁴² For a review, see Ahlbrecht, H. *Chimia* **1977**, *31*, 391.

¹⁸⁴³ Beak, P.; Carter, L.G. *J. Org. Chem.* **1981**, *46*, 2363.

¹⁸⁴⁴ Seebach, D.; Meyer, N. *Angew. Chem. Int. Ed.* **1976**, *15*, 438.

¹⁸⁴⁵ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1461–1465.

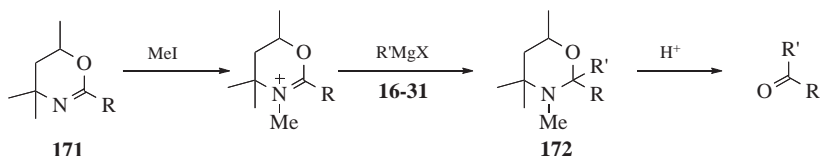
¹⁸⁴⁶ Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R.; Malone, G.R.; Kovelesky, A.C.; Nolen, R.L.; Portnoy, R.C. *J. Org. Chem.* **1973**, *38*, 36.

¹⁸⁴⁷ See Schmidt, R.R. *Synthesis* **1972**, 333; Collington, E.W. *Chem. Ind. (London)* **1973**, 987.

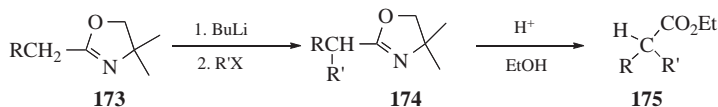
¹⁸⁴⁸ Meyers, A.I.; Malone, G.R.; Adickes, H.W. *Tetrahedron Lett.* **1970**, 3715.

one more carbon. Since A can be H, mono- or disubstituted acetaldehydes can be produced by this method.

The ion **169** also reacts with epoxides, to form γ -hydroxy aldehydes after reduction and hydrolysis,¹⁸⁴⁹ and with aldehydes and ketones (Reaction **16-38**). Similar aldehyde synthesis has also been carried out with thiazoles¹⁸⁵⁰ and thiazolines¹⁸⁵¹ (five-membered rings containing N and S in the 1 and 3 positions).



The reaction has been extended to the preparation of ketones:¹⁸⁵² Treatment of a dihydro-1,3-oxazine (**171**) with iodomethane forms the iminium salt (Reaction **10-31**) which, when treated with a *Grignard reagent* or organolithium compound (**16-31**), produces **172**, which can be hydrolyzed to a ketone. The R group can be alkyl, cycloalkyl, aryl, benzylic, and so on, and R' of the *Grignard reagent* can be alkyl, aryl, benzylic, or allylic. Note that the heterocycles **168**, **170**, or **171** do not react directly with *Grignard reagents*. In another procedure, 2-oxazolines¹⁸⁵³ (**173**) can be alkylated to give **174**,¹⁸⁵⁴ which are easily converted directly to the esters **175** by heating in 5–7% ethanolic sulfuric acid.



2-Oxazolines (**173** and **174**) are thus synthons for carboxylic acids; this is another indirect method for the α alkylation of a carboxylic acid,¹⁸⁵⁵ representing an alternative to the malonic ester synthesis (**10-67**) and to Reactions **10-70** and **10-73**. The method can be adapted to the preparation of optically active carboxylic acids by the use of a chiral reagent.¹⁸⁵⁶ Note that, unlike **168**, **173** can be alkylated even if R is alkyl. However, the C=N bond of **173** and **174** cannot be effectively reduced, so that aldehyde synthesis is not feasible here.¹⁸⁵⁷

OS VI, 905.

¹⁸⁴⁹ Adickes, H.W.; Politzer, I.R.; Meyers, A.I. *J. Am. Chem. Soc.* **1969**, 91, 2155.

¹⁸⁵⁰ Altman, L.J.; Richheimer, S.L. *Tetrahedron Lett.* **1971**, 4709.

¹⁸⁵¹ Meyers, A.I.; Durandetta, J.L. *J. Org. Chem.* **1975**, 40, 2021.

¹⁸⁵² Meyers, A.I.; Smith, E.M. *J. Org. Chem.* **1972**, 37, 4289.

¹⁸⁵³ For a review, see Meyers, A.I.; Mihelich, E.D. *Angew. Chem. Int. Ed.* **1976**, 15, 270.

¹⁸⁵⁴ Meyers, A.I.; Temple, Jr., D.L.; Nolen, R.L.; Mihelich, E.D. *J. Org. Chem.* **1974**, 39, 2778; Meyers, A.I.; Mihelich, E.D.; Nolen, R.L. *J. Org. Chem.* **1974**, 39, 2783; Meyers, A.I.; Mihelich, E.D.; Kamata, K. *J. Chem. Soc., Chem. Commun.* **1974**, 768.

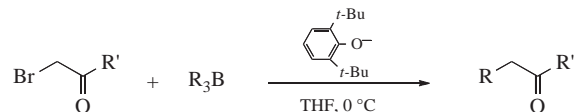
¹⁸⁵⁵ See Meyers, A.I. *Pure Appl. Chem.* **1979**, 51, 1255; *Acc. Chem. Res.* **1978**, 11, 375. See also, Hoobler, M.A.; Bergbreiter, D.E.; Newcomb, M. *J. Am. Chem. Soc.* **1978**, 100, 8182; Meyers, A.I.; Snyder, E.S.; Ackerman, J.J.H. *J. Am. Chem. Soc.* **1978**, 100, 8186.

¹⁸⁵⁶ See Lutomski, K.A.; Meyers, A.I. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, **1984**, pp. 213–274.

¹⁸⁵⁷ Meyers, A.I.; Temple Jr., D.L. *J. Am. Chem. Soc.* **1970**, 92, 6644, 6646.

10-73 Alkylation with Boranes, Boronic Acids, and Boronates

Alkyl-de-halogenation



Trialkylboranes react rapidly and in high yields with α -halo ketones,¹⁸⁵⁸ α -halo esters,¹⁸⁵⁹ α -halo nitriles,¹⁸⁶⁰ and α -halo sulfonyl derivatives (sulfones, sulfonic esters, sulfonamides)¹⁸⁶¹ in the presence of a base to give, respectively, alkylated ketones, esters, nitriles, and sulfonyl derivatives.¹⁸⁶² Potassium *tert*-butoxide is often a suitable base, but potassium 2,6-di-*tert*-butylphenoxide at 0 °C in THF gives better results in most cases, possibly because the large bulk of the two *tert*-butyl groups prevents the base from coordinating with the R_3B .¹⁸⁶³ The trialkylboranes are prepared by treatment of 3 equiv of an alkene with 1 equiv of BH_3 (Reaction 15-16).¹⁸⁶⁴ With appropriate boranes, the R group transferred to α -halo ketones, nitriles, and esters can be vinylic,¹⁸⁶⁵ or (for α -halo ketones and esters) aryl.¹⁸⁶⁶

The reaction can be extended to α,α -dihalo esters¹⁸⁶⁷ and α,α -dihalo nitriles.¹⁸⁶⁸ It is possible to replace just one halogen or both. In the latter case, the two alkyl groups can be the same or different. When dialkylation is applied to dihalo nitriles, the two alkyl groups can be primary or secondary, but with dihalo esters, dialkylation is limited to primary R. Another extension is the reaction of boranes (BR_3) with γ -halo- α,β -unsaturated esters.¹⁸⁶⁹ Alkylation takes place in the γ position, but the double bond migrates out of conjugation with the CO_2Et unit [$\text{BrCH}_2\text{CH}=\text{CHCO}_2\text{Et} \rightarrow \text{RCH}=\text{CHCH}_2\text{CO}_2\text{Et}$]. In this case, however, double-bond migration is an advantage, because nonconjugated β,γ -unsaturated esters are usually much more difficult to prepare than their α,β -unsaturated isomers.

The alkylation of activated halogen compounds is one of several reactions of trialkylboranes developed by H.C. Brown¹⁸⁷⁰ (see also, Reactions 15-16, 15-27, 18-31–18-40, etc.). These compounds are extremely versatile and can be used for the preparation of many types of compounds. In this reaction, for example, an alkene (via the BR_3) can be coupled to a ketone, a nitrile, a carboxylic ester, or a sulfonyl derivative. Note that this is still

¹⁸⁵⁸ Brown, H.C.; Rogic, M.M.; Rathke, M.W. *J. Am. Chem. Soc.* **1968**, 90, 6218.

¹⁸⁵⁹ Brown, H.C.; Rogic, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* **1968**, 90, 818.

¹⁸⁶⁰ Brown, H.C.; Nambu, H.; Rogic, M.M. *J. Am. Chem. Soc.* **1969**, 91, 6854.

¹⁸⁶¹ Truce, W.E.; Mura, L.A.; Smith, P.J.; Young, F. *J. Org. Chem.* **1974**, 39, 1449.

¹⁸⁶² See Negishi, E.; Idacavage, M.J. *Org. React.* **1985**, 33, 1, pp. 42–43, 143–150; Weill-Raynal, J. *Synthesis* **1976**, 633; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**, pp. 372–391, 404–409; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, **1973**, pp. 275–278, 283–287.

¹⁸⁶³ Brown, H.C.; Nambu, H.; Rogic, M.M. *J. Am. Chem. Soc.* **1969**, 91, 6852, 6854, 6855.

¹⁸⁶⁴ For an improved procedure, with 9-BBN (see Reaction 15-16), see Brown, H.C.; Rogic, M.M. *J. Am. Chem. Soc.* **1969**, 91, 2146; Brown, H.C.; Rogic, M.M.; Nambu, H.; Rathke, M.W. *J. Am. Chem. Soc.* **1969**, 91, 2147; Katz, J.; Dubois, J.E.; Lion, C. *Bull. Soc. Chim. Fr.* **1977**, 683.

¹⁸⁶⁵ Brown, H.C.; Bhat, N.G.; Campbell, Jr., J.B. *J. Org. Chem.* **1986**, 51, 3398.

¹⁸⁶⁶ Brown, H.C.; Rogic, M.M. *J. Am. Chem. Soc.* **1969**, 91, 4304.

¹⁸⁶⁷ Brown, H.C.; Rogic, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* **1968**, 90, 1911.

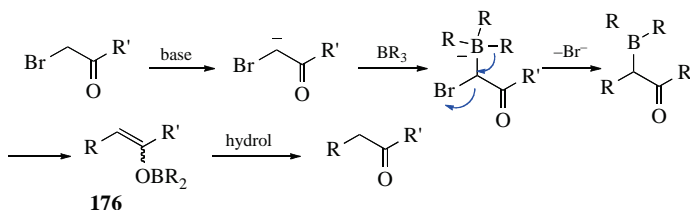
¹⁸⁶⁸ Nambu, H.; Brown, H.C. *J. Am. Chem. Soc.* **1970**, 92, 5790.

¹⁸⁶⁹ Brown, H.C.; Nambu, H. *J. Am. Chem. Soc.* **1970**, 92, 1761.

¹⁸⁷⁰ Brown, H.C. *Organic Syntheses via Boranes*, Wiley, NY, **1975**; *Hydroboration*, W.A. Benjamin, NY, **1962**; *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**.

another indirect way to alkylate a ketone (see Reaction 10-68) or a carboxylic acid (see Reaction 10-70), and provides an additional alternative to the malonic ester and acetoacetic ester syntheses (Reaction 10-67).

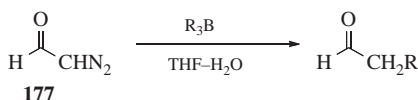
Although superficially this reaction resembles Reaction 10-57, it is likely that the mechanism is quite different, involving migration of an R group from boron to carbon (see also, Reactions 18-23–18-26). The mechanism is not known with certainty,¹⁸⁷¹ but it may be tentatively shown as (illustrated for an α -halo ketone):



The first step is removal of the acidic proton by the base to give an enolate anion that combines with the borane (Lewis acid–base reaction). An R group then migrates, displacing the halogen leaving group.¹⁸⁷² Another migration follows, this time of BR_2 from carbon to oxygen to give the enol borinate (**176**),¹⁸⁷³ which is hydrolyzed. Configuration at the alkyl group R is retained.¹⁸⁷⁴

Alkenylboranes ($\text{R}'_2\text{C}=\text{CHBZ}_2$; Z = various groups) couple in high yields with vinylic,¹⁸⁷⁵ alkynyl, aryl, benzylic, and allylic halides or triflates in the presence of a Pd catalyst and a base to give $\text{R}'_2\text{C}=\text{CHR}$.¹⁸⁷⁶ 9-Alkyl-9-BBN compounds (Reaction 15-16) also couple with vinylic and aryl halides,¹⁸⁷⁷ as well as with α -halo ketones, nitriles, and esters.¹⁸⁷⁸

The reaction has also been applied to compounds with other leaving groups. Diazo ketones, diazo esters, diazo nitriles, and diazo aldehydes (**177**)¹⁸⁷⁹ react with trialkylboranes in a similar manner.



The mechanism is probably also similar. In this case, a base is not needed, since the carbon already has an available pair of electrons. The reaction with diazo aldehydes¹⁸⁸⁰ is

¹⁸⁷¹ See Prager, R.H.; Reece, P.A. *Aust. J. Chem.* **1975**, 28, 1775.

¹⁸⁷² See Midland, M.M.; Zolopa, A.R.; Halterman, R.I. *J. Am. Chem. Soc.* **1979**, 101, 248. See also, Midland, M.M.; Preston, S.B. *J. Org. Chem.* **1980**, 45, 747.

¹⁸⁷³ Pasto, D.J.; Wojtkowski, P.W. *J. Org. Chem.* **1971**, 36, 1790.

¹⁸⁷⁴ Brown, H.C.; Rogic, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* **1969**, 91, 2150.

¹⁸⁷⁵ Occhiato, E.G.; Trabocchi, A.; Guarna, A. *Org. Lett.* **2000**, 2, 1241.

¹⁸⁷⁶ Sato, M.; Miyaoura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405; Rivera, I.; Soderquist, J.A. *Tetrahedron Lett.* **1991**, 32, 2311; and references cited therein. For a review, see Matteson, D.S. *Tetrahedron* **1989**, 45, 1859.

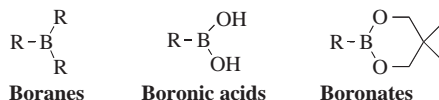
¹⁸⁷⁷ Miyaoura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, 111, 314. See also, Soderquist, J.A.; Santiago, B. *Tetrahedron Lett.* **1990**, 31, 5541.

¹⁸⁷⁸ Ishiyama, T.; Abe, S.; Miyaoura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691; Brown, H.C.; Joshi, N.N.; Pyun, C.; Singaram, B. *J. Am. Chem. Soc.* **1989**, 111, 1754. For another such coupling, see Matteson, D.S.; Tripathy, P.B.; Sarkar, A.; Sadhu, K.M. *J. Am. Chem. Soc.* **1989**, 111, 4399.

¹⁸⁷⁹ Mikhailov, B.M.; Gurskii, M.E. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1973**, 22, 2588.

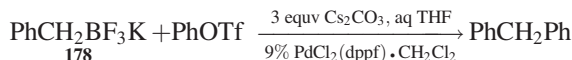
¹⁸⁸⁰ Hooz, J.; Morrison, G.F. *Can J. Chem.* **1970**, 48, 868.

especially notable, since successful reactions cannot be obtained with α -halo aldehydes.¹⁸⁸¹



Alkyl¹⁸⁸² and aryl¹⁸⁸³ boronic acids $[\text{RB}(\text{OH})_2]$ react with allylic acetates to give the alkylated product in the presence of a Pd catalyst.¹⁸⁸⁴ A cyclopropylboronic acid was coupled to an allylic bromide with silver oxide/KOH and a Pd catalyst.¹⁸⁸⁵ Arylboronic acids undergo a coupling reaction with epoxides in the presence of a Pd catalyst.¹⁸⁸⁶ Alkylboronic acids can also be coupled to aromatic compounds in the presence of $\text{Cu}(\text{OAc})_2$ and a Pd catalyst.¹⁸⁸⁷ The Pd catalyzed coupling of vinyl halides and alkylboronic acids,¹⁸⁸⁸ which gives substituted alkenes, is related to the *Suzuki coupling* (Reaction **13-12**). Vinyl zirconium reagents were coupled to alkyl halides with a Pd catalyst.¹⁸⁸⁹ Arylation of sp^3 C—H positions can be done using arylboronates and a Rh catalyst.¹⁸⁹⁰ In a related but metal-free reaction, activated epoxides and aziridines are opened by borates.¹⁸⁹¹

Potassium aryl- and 1-alkenyltrifluoroborates (ArBF_3K and RBF_3K) are easily prepared from organoboronic acids or esters. In general, the trifluoroborates have greater air stability and greater nucleophilicity¹⁸⁹² when compared to the corresponding organoboranes and organoboronic acid derivatives. Potassium alkyltrifluoroborates undergo the Pd catalyzed coupling reaction with arenediazonium tetrafluoroborates,¹⁸⁹³ diaryliodonium salts,¹⁸⁹⁴ aryl halides,¹⁸⁹⁵ as well as with aryl triflates. An example of the latter reaction converted **178** to diphenylmethane via coupling with phenyl triflate.¹⁸⁹⁶ Alkenyltrifluoroborates can be coupled to aryl halides.¹⁸⁹⁷



where dppf = bis(diphenylphosphino)ferrocene.

OS **VI**, 919; **IX**, 107.

¹⁸⁸¹ See Hooz, J.; Bridson, J.N.; Calzada, J.G.; Brown, H.C.; Midland, M.M.; Levy, A.B. *J. Org. Chem.* **1973**, *38*, 2574.

¹⁸⁸² Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* **2004**, *60*, 3813. For a variation involving a borate complex, see Zou, G.; Falck, J.R. *Tetrahedron Lett.* **2001**, *42*, 5817.

¹⁸⁸³ Nobre, S.M.; Monteiro, A.L. *Tetrahedron Lett.* **2004**, *45*, 8225; Langle, S.; Abarbri, M.; Duchêne, A. *Tetrahedron Lett.* **2003**, *44*, 9255.

¹⁸⁸⁴ Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276.

¹⁸⁸⁵ Chen, H.; Deng, M.-Z. *J. Org. Chem.* **2000**, *65*, 4444.

¹⁸⁸⁶ Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 6705.

¹⁸⁸⁷ Chen, X.; Goodhue, C.E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634.

¹⁸⁸⁸ Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 3851. See also, Yoshida, H.; Yamaryo, Y.; Oshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541.

¹⁸⁸⁹ Wiskur, S.L.; Lorte, A.; Fu, G.C. *J. Am. Chem. Soc.* **2004**, *126*, 82.

¹⁸⁹⁰ Pastine, S.J.; Gribkov, D.V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220.

¹⁸⁹¹ Pineschi, M.; Bertolini, F.; Haak, R.M.; Crotti, P.; Macchia, F. *Chem. Commun.* **2005**, 1426.

¹⁸⁹² Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* **2000**, 990.

¹⁸⁹³ Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875.

¹⁸⁹⁴ Xia, M.; Chen, Z.-C. *Synth. Commun.* **1999**, *29*, 2457.

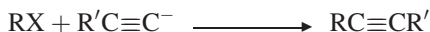
¹⁸⁹⁵ Molander, G.A.; Gormisky, P.E. *J. Org. Chem.* **2008**, *73*, 7481.

¹⁸⁹⁶ Molander, G.A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.

¹⁸⁹⁷ Molander, G.A.; Rivero, M.R. *Org. Lett.* **2002**, *4*, 107.

10-74 Alkylation at an Alkynyl Carbon

Alkynyl-de-halogenation



The reaction between alkyl halides and acetylide ions is useful, but of limited scope.¹⁸⁹⁸ Only primary halides unbranched in the β -position give good yields, although allylic halides can be used if CuI is present.¹⁸⁹⁹ If acetylene is the reagent, two different groups can be successively attached. Sulfates, sulfonates, and epoxides¹⁹⁰⁰ are sometimes used as substrates. The acetylide ion is often prepared by treatment of an alkyne with a strong base (e.g., NaNH₂). Magnesium acetylides (prepared as in Reaction 12-22) are also frequently used, although they react only with active substrates (e.g., allylic, benzylic, and propargylic halides) and not with primary alkyl halides. Alternatively, the alkyl halide can be treated with a lithium acetylide–ethylenediamine complex.¹⁹⁰¹ If 2 equiv of a very strong base are used, alkylation can be effected at a carbon α to a terminal triple bond: $\text{RCH}_2\text{C}\equiv\text{CH} + 2\text{BuLi} \rightarrow \text{RCHC}(\text{C}^- + \text{R}'\text{Br}) \rightarrow \text{RR}'\text{CHC}\equiv\text{C}^-$.¹⁹⁰² For another method of alkylating at an alkynyl carbon, see Reaction 18-26. An alternative method for generating an alkyne anion treated a trialkylsilyl alkyne with potassium carbonate in methanol, and then methyllithium/LiBr.¹⁹⁰³ In the presence of an alkyl iodide, alkylation at the alkynyl carbon occurred. Terminal alkynes react with alkylzinc reagents in the presence of a Pd catalyst.¹⁹⁰⁴

Other metalated terminal alkynes can be coupled to substrates with a leaving group, and even with other organometallics. In the presence of a Pd catalysts, an alkynyltin reagent reacts with an alkylzinc compound to give the corresponding alkyne.¹⁹⁰⁵ Terminal alkynes react with allylic bromides in the presence of a Ni catalyst.¹⁹⁰⁶ The reaction of a terminal alkyne with Zn(II) compounds allows reaction with silanes to give the 1-silylalkyne.¹⁹⁰⁷ A Re catalyzed C–H insertion reaction is known using terminal alkynes and an active methylene compound.¹⁹⁰⁸ Alkynylzinc compounds undergo Pd catalyzed cross-coupling reactions.¹⁹⁰⁹

1-Haloalkynes react with various substrates in the presence of a metal catalyst. 1-Haloalkynes (e.g., $\text{R}-\text{C}\equiv\text{C}-\text{X}$ react with ArSnBu_3 and CuI to give $\text{R}-\text{C}\equiv\text{C}-\text{Ar}$.¹⁹¹⁰ Organozirconium compounds react in a similar manner.¹⁹¹¹ Acetylene reacts with 2 equiv of iodobenzene, in the presence of a Pd catalyst and CuI, to give 1,2-diphenylethyne.¹⁹¹²

¹⁸⁹⁸ See Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, **1978**, pp. 790–800; Ziegenbein, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 185–206, 241–244. Also see Bernadou, F.; Mesnard, D.; Miginiac, L. *J. Chem. Res. (S)* **1978**, 106; **1979**, 190.

¹⁸⁹⁹ Jeffery, T. *Tetrahedron Lett.* **1989**, 30, 2225.

¹⁹⁰⁰ See Krause, N.; Seebach, D. *Chem. Ber.* **1988**, 121, 1315.

¹⁹⁰¹ Smith, W.N.; Beumel Jr., O.F. *Synthesis* **1974**, 441.

¹⁹⁰² Bhanu, S.; Scheinmann, F. *J. Chem. Soc. Perkin Trans. I*, **1979**, 1218; Quillinan, A.J.; Scheinmann, F. *Org. Synth.* **VI**, 595.

¹⁹⁰³ Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **2003**, 44, 9087.

¹⁹⁰⁴ Chen, M.; Zheng, X.; Li, W.; He, J.; Lei, A. *J. Am. Chem. Soc.* **2010**, 132, 4101.

¹⁹⁰⁵ Zhao, Y.; Wang, H.; Hou, X.; Hu, Y.; Lei, A.; Zhang, H.; Zhu, L. *J. Am. Chem. Soc.* **2006**, 128, 15048.

¹⁹⁰⁶ Nadal, M.L.; Bosch, J.; Vila, J.M.; Klein, G.; Ricart, S.; Moretó, J.M. *J. Am. Chem. Soc.* **2005**, 127, 10476.

¹⁹⁰⁷ Rahaim, Jr., R.J.; Shaw, J.T. *J. Org. Chem.* **2008**, 73, 2912.

¹⁹⁰⁸ Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, 7, 4823.

¹⁹⁰⁹ Qian, M.; Negishi, E. *Tetrahedron Lett.* **2005**, 46, 2927.

¹⁹¹⁰ Kang, S.-K.; Kim, W.-Y.; Jiao, X. *Synthesis* **1998**, 1252.

¹⁹¹¹ Liu, Y.; Xi, C.; Hara, R.; Nakajima, K.; Yamazaki, A.; Kotora, M.; Takahashi, T. *J. Org. Chem.* **2000**, 65, 6951.

¹⁹¹² Pal, M.; Kundu, N.G. *J. Chem. Soc. Perkin Trans I*, **1996**, 449. Also see, Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett.* **1996**, 37, 5527.

1-Trialkylsilyl alkynes react with 1-haloalkynes, in the presence of a CuCl catalyst, to give diynes¹⁹¹³ and with aryl triflates to give 1-aryl alkynes.¹⁹¹⁴ The enolate anion derived from a β -keto ester couples with 1-bromoalkynes to give the corresponding substitution product.¹⁹¹⁵ 1-Bromoalkynes react with nitrogen compounds (e.g., imidazole) in the presence of a Cu catalyst to give the corresponding alkyne.¹⁹¹⁶ 1-Bromoalkynes react with *Grignard* derived reagents in the presence of an Fe catalyst.¹⁹¹⁷

Alkynes couple with alkyl halides in the presence of SmI_2/Sm ,¹⁹¹⁸ or a copper catalyst.¹⁹¹⁹ Alkynes react with hypervalent iodine compounds¹⁹²⁰ and with reactive alkanes (e.g., adamantane) in the presence of AIBN.¹⁹²¹ The reaction of benzylic amines with terminal alkynes, in the presence of copper triflate and *tert*-butylhydroperoxide, leads to incorporation of the alkyne group α to the nitrogen.¹⁹²² A similar reaction occurs at a methyl group of *N,N*-dimethylaniline.¹⁹²³ α -Methoxycarbamates ($\text{MeO}-\text{CHR}-\text{NR}^1-\text{CO}_2\text{R}^2$) react with terminal alkynes and CuBr to give the alkynylamine.¹⁹²⁴ In the presence of GaCl_3 , $\text{ClC}\equiv\text{CSiMe}_3$ reacts with silyl enol ethers to give, after treatment with methanolic acid, an α -ethynyl ketone.¹⁹²⁵

In a related reaction, terminal alkynes react with silanes (R_3SiH) in the presence of an Ir catalyst¹⁹²⁶ or zinc triflate¹⁹²⁷ to give the 1-trialkylsilyl alkyne. Similar products are obtained when terminal alkynes react with *N*-trialkylsilylamines and ZnCl_2 .¹⁹²⁸

OS IV, 117; VI, 273, 564, 595; VIII, 415; IX, 117, 477, 688; 76, 263. Also see, OS IV, 801; VI, 925.

10-75 Preparation of Nitriles

Cyano-de-halogenation



The reaction between cyanide ion and alkyl halides is a convenient method for the preparation of nitriles.¹⁹²⁹ The reaction proceeds by a $\text{S}_{\text{N}}2$ mechanism,¹⁹³⁰ so primary, benzylic, and allylic halides give good yields of nitriles; secondary halides give

¹⁹¹³ Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, 39, 4075.

¹⁹¹⁴ See Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233.

¹⁹¹⁵ Poulsen, T.B.; Bernardi, L.; Alemán, J.; Overgaard, J.; Jørgensen, K.A. *J. Am. Chem. Soc.* **2007**, 129, 441.

¹⁹¹⁶ Laroche, C.; Li, J.; Freyer, M.W.; Kerwin, S.M. *J. Org. Chem.* **2008**, 73, 6462.

¹⁹¹⁷ Castagnolo, D.; Botta, M. *Eur. J. Org. Chem.* **2010**, 3224.

¹⁹¹⁸ Murakami, M.; Hayashi, M.; Ito, Y. *Synlett*, **1994**, 179.

¹⁹¹⁹ Bieber, L.W.; da Silva, M.F. *Tetrahedron Lett.* **2007**, 48, 7088.

¹⁹²⁰ Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Kim, W.-Y. *Synthesis* **1997**, 874.

¹⁹²¹ Xiang, J.; Jiang, W.; Fuchs, P.L. *Tetrahedron Lett.* **1997**, 38, 6635.

¹⁹²² Li, Z.; Li, C.-J. *Org. Lett.* **2004**, 6, 4997.

¹⁹²³ Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, 126, 11810.

¹⁹²⁴ Zhang, J.; Wei, C.; Lei, C.-J. *Tetrahedron Lett.* **2002**, 43, 5731.

¹⁹²⁵ Arisawa, M.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* **2002**, 4, 2209.

¹⁹²⁶ Shimizu, R.; Fuchikami, T. *Tetrahedron Lett.* **2000**, 41, 907.

¹⁹²⁷ Jiang, H.; Zhu, S. *Tetrahedron Lett.* **2005**, 46, 517.

¹⁹²⁸ Andreev, A.A.; Konshin, V.V.; Komarov, N.V.; Rubin, M.; Brouwer, C.; Gevorgyan, V. *Org. Lett.* **2004**, 6, 421.

¹⁹²⁹ See in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, **1983**, the articles by Fatiadi, A.J. pt. 2, pp. 1057–1303, and Friedrich, K. pt. 2, pp. 1343–1390; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 77–86.

¹⁹³⁰ For a discussion about the influence of solvent on this transition state, see Fang, Y.-r.; MacMillan, S.; Eriksson, J.; Kołodziejska-Huben, M.; Dybała-Defratyka, A.; Paneth, P.; Matsson, O.; Westaway, K.C. *J. Org. Chem.* **2006**, 71, 4742.

moderate yields. The reaction fails for tertiary halides, which give elimination under these conditions. Many other groups on the molecule do not interfere. A number of solvents have been used, but the high yields and short reaction times observed with DMSO make it a very good solvent for this reaction.¹⁹³¹ In general, polar aprotic solvents are the best choice. Other ways to obtain high yields under mild conditions are to use a phase-transfer catalyst,¹⁹³² in alternative solvents (e.g., PEG 400 (a polyethylene glycol)),¹⁹³³ or with ultrasound.¹⁹³⁴ This is an important way of increasing the length of a carbon chain by one carbon, since nitriles are easily hydrolyzed to carboxylic acids (Reaction 16-4).

The cyanide ion is an ambident nucleophile (it can react via N or via C) and isonitriles (also called isocyanides, $R-N\equiv C$) may be side products.¹⁹³⁵ If the preparation of isocyanides is desired (see Reaction 10-40), they can be made the main products by the use of reagents with more covalent metal-carbon bonds [e.g., silver or copper(I) cyanide,¹⁹³⁶ Sec. 10.G.vii, category 3]. However, the use of an excess of LiCN in acetone/THF gave the nitrile as the major product.¹⁹³⁷ Tosyl cyanide ($TOsO_2CN$) has been used in some cases.¹⁹³⁸ A radical cyanation of alkyl iodides has been reported using diethylphosphoryl cyanide¹⁹³⁹ (see Chap. 14).

Vinyl bromides can be converted to vinylic cyanides with $CuCN$,¹⁹⁴⁰ with KCN , a crown ether, and a Pd complex,¹⁹⁴¹ or with KCN and a $Ni(0)$ catalyst.¹⁹⁴² Halides can be converted to the corresponding nitriles by treatment with trimethylsilyl cyanide in the presence of catalytic amounts of $SnCl_4$: $R_3CCl + Me_3SiCN \rightarrow R_3CCN$.¹⁹⁴³ Primary, secondary, and tertiary alcohols are converted to nitriles in good yields by treatment with $NaCN$, Me_3SiCl , and a catalytic amount of NaI in $DMF-MeCN$.¹⁹⁴⁴ Lewis acids have been used in conjunction with $NaCN$ or KCN .¹⁹⁴⁵ α,β -Epoxy amides were opened to the β -cyano- α -hydroxyamide with Et_2AlCN .¹⁹⁴⁶ Cyanohydrins react with alkyl halides in some cases to give the nitrile.¹⁹⁴⁷

Substrates that react with cyanide may contain leaving groups other than halides (e.g., esters of sulfuric and sulfonic acids, sulfates and sulfonates, respectively). Vinylic triflates

¹⁹³¹ Smiley, R.A.; Arnold, C. J. *Org. Chem.* **1960**, 25, 257; Friedman, L.; Shechter, H. *J. Org. Chem.* **1960**, 25, 877.

¹⁹³² Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, **1978**, pp. 94–112; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, **1977**, pp. 96–108. See also, Bram, G.; Loupy, A.; Pedoussaut, M. *Tetrahedron Lett.* **1986**, 27, 4171; *Bull. Soc. Chim. Fr.* **1986**, 124.

¹⁹³³ Cao, Y.-Q.; Che, B.-H.; Pei, B.-G. *Synth. Commun.* **2001**, 31, 2203.

¹⁹³⁴ Ando, T.; Kawate, T.; Ichihara, J.; Hanafusa, T. *Chem. Lett.* **1984**, 725.

¹⁹³⁵ See Luanay, D.; Booth, S.; Clemens, I.; Merritt, A.; Bradley, M. *Tetrahedron Lett.* **2002**, 43, 7201.

¹⁹³⁶ See Jackson, H.L.; McKusick, B.C. *Org. Synth.* **IV**, 438.

¹⁹³⁷ Ciaccio, J.A.; Smrka, M.; Maio, W.A.; Rucando, D. *Tetrahedron Lett.* **2004**, 45, 7201.

¹⁹³⁸ Kim, S.; Song, H.-J. *Synlett* **2002**, 2110.

¹⁹³⁹ Cho, C.H.; Lee, J.Y.; Kim, S. *Synlett* **2009**, 81.

¹⁹⁴⁰ See Lapouyade, R.; Daney, M.; Lapenue, M.; Bouas-Laurent, H. *Bull. Soc. Chim. Fr.* **1973**, 720.

¹⁹⁴¹ Yamamura, K.; Murahashi, S. *Tetrahedron Lett.* **1977**, 4429.

¹⁹⁴² Procházka, M.; Siroky, M. *Collect. Czech. Chem. Commun.* **1983**, 48, 1765.

¹⁹⁴³ Zieger, H.E.; Wo, S. *J. Org. Chem.* **1994**, 59, 3838. See Tsuji, Y.; Yamada, N.; Tanaka, S. *J. Org. Chem.* **1993**, 58, 16 for a similar reaction with allylic acetates. See Hayashi, M.; Tamura, M.; Oguni, N. *Synlett*, **1992**, 663 for a similar reaction with epoxides using a Ti catalyst.

¹⁹⁴⁴ Camps, F.; Gasol, V.; Guerrero, A. *Synth. Commun.* **1988**, 18, 445.

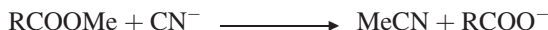
¹⁹⁴⁵ See Iranpoor, N.; Shekarriz, M. *Synth. Commun.* **1999**, 29, 2249.

¹⁹⁴⁶ Ruano, J.L.G.; Fernández-Ibáñez, M.Á.; Castro, A.M.M.; Ramos, J.H.R.; Flamarique, A.C.R. *Tetrahedron Asymmetry* **2002**, 13, 1321.

¹⁹⁴⁷ Dowd, P.; Wilk, B.K.; Wlostowski, M. *Synth. Commun.* **1993**, 23, 2323; Wilk, B.K. *Synth. Commun.* **1993**, 23, 2481 and see Ohno, H.; Mori, A.; Inoue, S. *Chem. Lett.* **1993**, 975 for similar reactions with epoxides.

give vinylic cyanides when treated with LiCN, a crown ether, and a Pd catalyst.¹⁹⁴⁸ Epoxides give β -hydroxy nitriles. The C-2-Selectivity was observed when NaCN and B(OMe)₃ were reacted with a disubstituted epoxide.¹⁹⁴⁹ The use of trimethylsilyl cyanide (Me₃SiCN) and a Lewis acid generates the *O*-TMS β -hydroxy nitrile, and the use of YbCl₃ and a salen complex gave good enantioselectivity.¹⁹⁵⁰ Tetrabutylammonium cyanide converted a primary alcohol to the corresponding nitrile in the presence of PPh₃/DDQ.¹⁹⁵¹ Alcohols are converted to cyanides by reaction with triphenylphosphine and cyanogen bromide.¹⁹⁵²

Sodium cyanide in HMPA selectively cleaves methyl esters in the presence of ethyl esters.¹⁹⁵³



OS **I**, 46, 107, 156, 181, 254, 256, 536; **II**, 292, 376; **III**, 174, 372, 557; **IV**, 438, 496, 576; **V**, 578, 614.

10-76 Direct Conversion of Alkyl Halides to Aldehydes and Ketones

Formyl-de-halogenation



The direct conversion of alkyl bromides to aldehydes, with an increase in the chain length by one carbon, can be accomplished¹⁹⁵⁴ by treatment with sodium tetracarbonylferrate(-2)¹⁹⁵⁵ (*Collman's reagent*) in the presence of triphenylphosphine and subsequent quenching of **179** with acetic acid. The reagent Na₂Fe(CO)₄ can be prepared by treatment of iron pentacarbonyl [Fe(CO)₅] with sodium amalgam in THF. Good yields are obtained from primary alkyl bromides; secondary bromides give lower yields. The reaction is generally not satisfactory for benzylic bromides, but a good yield of the ketone was obtained using benzyl chloride and aryl iodides.¹⁹⁵⁶ The initial species produced from RX and Na₂Fe(CO)₄ is the ion RFe(CO)₄⁻, which can be isolated,¹⁹⁵⁷ it then reacts with Ph₃P to give **179**.¹⁹⁵⁸

The synthesis can be extended to the preparation of ketones in six distinct ways.¹⁹⁵⁹ These include quenching **179** with a second alkyl halide (R'X) rather than acetic acid; omitting PPh₃ with first RX and then adding the second, R'X; treatment with RX in the presence of CO,¹⁹⁵⁵ followed by treatment with R'X'; treatment with an acyl halide followed by treatment with an alkyl halide or an epoxide, gives an α,β -unsaturated

¹⁹⁴⁸ Piers, E.; Fleming, F.F. *J. Chem. Soc., Chem. Commun.* **1989**, 756.

¹⁹⁴⁹ Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, 5, 1789.

¹⁹⁵⁰ Schaus, S.E.; Jacobsen, E.N. *Org. Lett.* **2000**, 2, 1001.

¹⁹⁵¹ Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi, N. *J. Org. Chem.* **2004**, 69, 2562.

¹⁹⁵² Tarrade-Matha, A.; Pillon, F.; Doris, E. *Synth. Commun.* **2010**, 40, 1646.

¹⁹⁵³ Müller, P.; Siegfried, B. *Helv. Chim. Acta* **1974**, 57, 987.

¹⁹⁵⁴ Cooke, Jr., M.P. *J. Am. Chem. Soc.* **1970**, 92, 6080.

¹⁹⁵⁵ See Collman, J.P. *Acc. Chem. Res.* **1975**, 8, 342. Also see Brunet, J. *Chem. Rev.* **1990**, 90, 1041.

¹⁹⁵⁶ Dolhem, E.; Barhdadi, R.; Folest, J.C.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* **2001**, 57, 525.

¹⁹⁵⁷ Siegl, W.O.; Collman, J.P. *J. Am. Chem. Soc.* **1972**, 94, 2516.

¹⁹⁵⁸ See Collman, J.P.; Finke, R.G.; Cawse, J.N.; Brauman, J.I. *J. Am. Chem. Soc.* **1978**, 100, 4766.

¹⁹⁵⁹ See Collman, J.P.; Hoffman, N.W. *J. Am. Chem. Soc.* **1973**, 95, 2689.

ketone.¹⁹⁶⁰ The final variations involve reaction of alkyl halides or tosylates with $\text{Na}_2\text{Fe}(\text{CO})_4$ in the presence of ethylene to give alkyl ethyl ketones,¹⁹⁶¹ when 1,4-dihalides are used, five-membered cyclic ketones are prepared.¹⁹⁶²

Yet another approach uses electrolysis conditions with the alkyl chloride, $\text{Fe}(\text{CO})_5$, and a Ni catalyst, which gives the ketone directly, in one step.¹⁹⁶³ In the first stage of methods 1, 2, and 3, primary bromides, iodides, and tosylates and secondary tosylates can be used. The second stage of the first-four methods requires more active substrates (e.g., primary iodides or tosylates or benzylic halides). Method 5 has been applied to primary and secondary substrates.

Other acyl organometallic reagents are known. An acyl zirconium reagent [e.g., $\text{RCOZr}(\text{Cl})\text{Cp}_2$] reacted with allylic bromide in the presence of CuI to give the corresponding ketone, but with allylic rearrangement.¹⁹⁶⁴

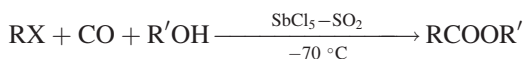
Symmetrical ketones (R_2CO) can be prepared by treatment of a primary alkyl or benzylic halide with $\text{Fe}(\text{CO})_5$ and a phase-transfer catalyst,¹⁹⁶⁵ or from a halide RX (R = primary alkyl, aryl, allylic, or benzylic) and CO by an electrochemical method involving a nickel complex.¹⁹⁶⁶ Aryl, benzylic, vinylic, and allylic halides have been converted to aldehydes by treatment with CO and Bu_3SnH , with a Pd catalyst.¹⁹⁶⁷ Various other groups do not interfere. Several procedures for the preparation of ketones are catalyzed by Pd complexes. Alkyl aryl ketones are formed in good yields by treatment of a mixture of an aryl iodide, an alkyl iodide, and a $\text{Zn}-\text{Cu}$ couple with CO ($\text{ArI} + \text{RI} + \text{CO} \rightarrow \text{RCOAr}$).¹⁹⁶⁸ Vinylic halides react with vinylic tin reagents in the presence of CO to give unsymmetrical divinyl ketones.¹⁹⁶⁹ Aryl, vinylic, and benzylic halides can be converted to methyl ketones ($\text{RX} \rightarrow \text{RCOMe}$) by reaction with (α -ethoxyvinyl)tributyltin [$\text{Bu}_3\text{SnC}(\text{OEt})=\text{CH}_2$].¹⁹⁷⁰ In addition, SmI_2 can be used to convert alkyl chlorides to ketones, in the presence of 50 atm of CO .¹⁹⁷¹

The conversion of alkyl halides to aldehydes and ketones can also be accomplished indirectly (Reaction 10-71). See also, Reaction 12-33.

OS VI, 807.

10-77 Carbonylation of Alkyl Halides, Alcohols, or Alkanes

Alkoxycarbonyl-de-halogenation



¹⁹⁶⁰ Yamashita, M.; Yamamura, S.; Kurimoto, M.; Suemitsu, R. *Chem. Lett.* **1979**, 1067.

¹⁹⁶¹ Cooke Jr., M.P.; Parlman, R.M. *J. Am. Chem. Soc.* **1975**, 97, 6863. However, see McMurtry, J.E.; Andrus, A. *Tetrahedron Lett.* **1980**, 21, 4687, and references cited therein.

¹⁹⁶² Yamashita, M.; Uchida, M.; Tashika, H.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* **1989**, 62, 2728.

¹⁹⁶³ Dolhem, E.; Ocafrain, M.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* **1997**, 53, 17089.

¹⁹⁶⁴ Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett.* **2000**, 41, 109.

¹⁹⁶⁵ des Abbayes, H.; Clément, J.; Laurent, P.; Tanguy, G.; Thilmont, N. *Organometallics* **1988**, 7, 2293.

¹⁹⁶⁶ Garnier, L.; Rollin, Y.; Périchon, J. *J. Organomet. Chem.* **1989**, 367, 347.

¹⁹⁶⁷ Baillargeon, V.P.; Stille, J.K. *J. Am. Chem. Soc.* **1986**, 108, 452. See also, Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1989**, 1816.

¹⁹⁶⁸ Tamaru, Y.; Ochiai, H.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1983**, 24, 3869.

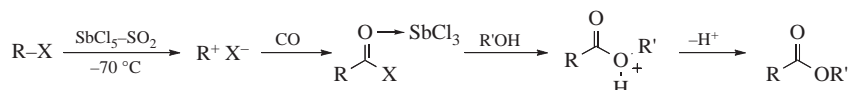
¹⁹⁶⁹ Goure, W.F.; Wright, M.E.; Davis, P.D.; Labadie, S.S.; Stille, J.K. *J. Am. Chem. Soc.* **1984**, 106, 6417. See Merrifield, J.H.; Godschalx, J.P.; Stille, J.K. *Organometallics* **1984**, 3, 1108.

¹⁹⁷⁰ Kosugi, M.; Sumiya, T.; Obara, Y.; Suzuki, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1987**, 60, 767.

¹⁹⁷¹ Ogawa, A.; Sumino, Y.; Nanke, T.; Ohya, S.; Sonoda, N.; Hirao, T. *J. Am. Chem. Soc.*, **1997**, 119, 2745.

A direct method for preparing a carboxylic acid treats an alkyl halide with NaNO_2 in acetic acid and DMSO.¹⁹⁷² Reaction of an alkyl halide with ClCOCO_2Me and $(\text{Bu}_3\text{Sn})_2$ under photochemical conditions leads to the corresponding methyl ester.¹⁹⁷³

Several methods, all based on carbon monoxide or metal carbonyls, have been developed for converting an alkyl halide to a carboxylic acid or an acid derivative with the chain extended by one carbon.¹⁹⁷⁴ When an alkyl halide is treated with $\text{SbCl}_5\text{—SO}_2$ at -70°C , it dissociates into the corresponding carbocation (Sec. 5.A.ii). If carbon monoxide and an alcohol are present, a carboxylic ester is formed by the following route:¹⁹⁷⁵



This has also been accomplished with concentrated H_2SO_4 saturated with CO .¹⁹⁷⁶ Not surprisingly, only tertiary halides perform satisfactorily; secondary halides give mostly rearrangement products. An analogous reaction takes place with alkanes possessing a tertiary hydrogen, using $\text{HF—SbF}_5\text{—CO}$.¹⁹⁷⁷

Carboxylic acids or esters are the products, depending on whether the reaction mixture is solvolyzed with water or an alcohol. Alcohols with more than seven carbons are cleaved into smaller fragments by this procedure.¹⁹⁷⁸ Similarly, tertiary alcohols¹⁹⁷⁹ react with H_2SO_4 and CO (which is often generated from HCOOH and the H_2SO_4 in the solution) to give trisubstituted acetic acids in a process called the *Koch–Haaf reaction* (see also, 15-35).¹⁹⁸⁰ If a primary or secondary alcohol is the substrate, the carbocation initially formed rearranges to a tertiary ion before reacting with the CO . Better results are obtained if trifluoromethanesulfonic acid ($\text{F}_3\text{CSO}_2\text{OH}$) is used instead of H_2SO_4 .¹⁹⁸¹ Iodo alcohols were transformed into lactones under radical conditions (AIBN , allylSnBu_3) and 45 atm of CO .¹⁹⁸²

Another method¹⁹⁸³ for the conversion of alkyl halides to carboxylic esters is treatment of a halide with nickel carbonyl $[\text{Ni}(\text{CO})_4]$ in the presence of an alcohol and its conjugate base.¹⁹⁸⁴ When R' is primary, RX may only be a vinylic or an aryl halide; retention of

¹⁹⁷² Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, 62, 234.

¹⁹⁷³ Kim, S.; Jon, S.Y. *Tetrahedron Lett.* **1998**, 39, 7317.

¹⁹⁷⁴ See Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, **1984**, pp. 199–204, 212–220, 234–235. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1684–1685, 1694–1698, 1702–1704.

¹⁹⁷⁵ Puzitskii, K.V.; Pirozhkov, S.D.; Ryabova, K.G.; Myshenkova, T.N.; Éidus, Ya.T. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1974**, 23, 192.

¹⁹⁷⁶ Takahashi, Y.; Yoneda, N. *Synth. Commun.* **1989**, 19, 1945.

¹⁹⁷⁷ Paatz, R.; Weisgerber, G. *Chem. Ber.* **1967**, 100, 984. See Akhrem, I.; Afanas'eva, L.; Petrovskii, P.; Vitt, S.; Orlinkov, A. *Tetrahedron Lett.* **2000**, 41, 9903.

¹⁹⁷⁸ Yoneda, N.; Takahashi, Y.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1986**, 59, 2819.

¹⁹⁷⁹ See Bahrmann, H.; Cornils, B. in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, **1980**, pp. 226–241; Piacenti, F.; Bianchi, M. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, **1977**, pp. 1–42.

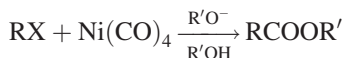
¹⁹⁸⁰ See Bahrmann, H. in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, **1980**, pp. 372–413.

¹⁹⁸¹ Booth, B.L.; El-Fekky, T.A. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2441.

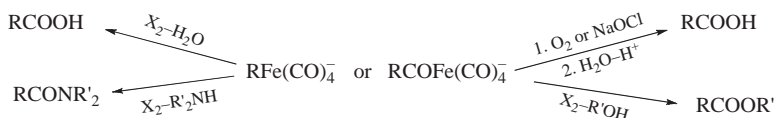
¹⁹⁸² Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* **2000**, 2, 389.

¹⁹⁸³ See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA, **1987**, pp. 749–768; Anderson, G.K.; Davies, J.A. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, pp. 335–359, pp. 348–356; Heck, R.F. *Adv. Catal.*, **1977**, 26, 323, p. 323; Cassar, L.; Chiusoli, G.P.; Guerrieri, F. *Synthesis* **1973**, 509.

configuration is observed at a vinylic R. Consequently, a carbocation intermediate is not involved here. When R' is tertiary, R may be primary alkyl as well as vinylic or aryl. This is thus one of the few methods for preparing esters of tertiary alcohols. Alkyl iodides give the best results, then bromides. In the presence of an amine, an amide can be isolated directly, at least in some instances.



Still another method for the conversion of halides to acid derivatives makes use of $\text{Na}_2\text{Fe}(\text{CO})_4$. As described in Reaction 10-76, primary and secondary alkyl halides and tosylates react with this reagent to give the ion $\text{RFe}(\text{CO})_4^-$ or, if CO is present, the ion $\text{RCOFe}(\text{CO})_4^-$. Treatment of $\text{RFe}(\text{CO})_4^-$ or $\text{RCOFe}(\text{CO})_4^-$ with oxygen or sodium hypochlorite gives, after hydrolysis, a carboxylic acid.¹⁹⁸⁵ Alternatively, $\text{RFe}(\text{CO})_4^-$ or $\text{RCOFe}(\text{CO})_4^-$ reacts with a halogen (e.g., I_2) in the presence of an alcohol to give a carboxylic ester,¹⁹⁸⁶ or in the presence of a secondary amine or water to give, respectively, the corresponding amide or free acid. Both $\text{RFe}(\text{CO})_4^-$ and $\text{RCOFe}(\text{CO})_4^-$, which are prepared from primary R, give high yields. With secondary R, the best results are obtained in the solvent THF by the use of $\text{RCOFe}(\text{CO})_4^-$ prepared from secondary tosylates. Ester and keto groups may be present in R without being affected. Carboxylic esters ($\text{RCO}_2\text{R'}$) have also been prepared by treating primary alkyl halides RX with alkoxides R'O^- in the presence of $\text{Fe}(\text{CO})_5$.¹⁹⁸⁷ Here $\text{RCOFe}(\text{CO})_4^-$ is presumably an intermediate.



Palladium complexes also catalyze the carbonylation of halides.¹⁹⁸⁸ Aryl (see Reaction 13-15),¹⁹⁸⁹ vinylic,¹⁹⁹⁰ benzylic, and allylic halides (especially iodides) can be converted to carboxylic esters with CO, an alcohol or alkoxide, and a Pd complex.¹⁹⁹¹ The Pd catalyzed carbonylation of organoindium compounds in the presence of methanol gives methyl esters.¹⁹⁹² Similar reactivity was reported with vinyl triflates.¹⁹⁹³ α -Halo ketones are converted to β -keto esters with CO, an alcohol, NBu_3 and a palladium catalyst at

¹⁹⁸⁵ Collman, J.P.; Winter, S.R.; Komoto, R.G. *J. Am. Chem. Soc.* **1973**, 95, 249.

¹⁹⁸⁶ Collman, J.P.; Winter, S.R.; Komoto, R.G. *J. Am. Chem. Soc.* **1973**, 95, 249.

¹⁹⁸⁷ Yamashita, M.; Mizushima, K.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Chem. Lett.* **1977**, 1355. See also, Tanguy, G.; Weinberger, B.; des Abbayes, H. *Tetrahedron Lett.* **1983**, 24, 4005.

¹⁹⁸⁸ See Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* **1988**, 57, 299, pp. 303–309; Heck, R. *F. Palladium Reagents in Organic Synthesis*, Academic Press, NY, **1985**, pp. 348–356, 366–370. See Kormos, C. M.; Leadbeater, N.E. *Synlett* **2007**, 2006.

¹⁹⁸⁹ See Bessard, Y.; Cretaz, R. *Heterocycles* **1999**, 51, 2589.

¹⁹⁹⁰ See Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, 26, 1109.

¹⁹⁹¹ Kiji, J.; Okano, T.; Higashimae, Y.; Kukui, Y. *Bull. Chem. Soc. Jpn.* **1996**, 69, 1029.

¹⁹⁹² Zhao, Y.; Jin, L.; Li, P.; Lei, A. *J. Am. Chem. Soc.* **2008**, 130, 9429.

¹⁹⁹³ Jutand, A.; Négri, S. *Synlett*, **1997**, 719.

110 °C.¹⁹⁹⁴ Use of an amine instead of the alcohol or alkoxide leads to an amide.¹⁹⁹⁵ Reaction with an amine, AIBN, CO, and a tetraalkyltin catalyst also leads to an amide.¹⁹⁹⁶ Benzylic and allylic halides were converted to carboxylic acids electrocatalytically, with CO and a Co-imine complex.¹⁹⁹⁷ Vinylic halides were similarly converted with CO and nickel cyanide, under phase-transfer conditions.¹⁹⁹⁸ Allylic *O*-phosphates were converted to allylic amides with CO and ClTi=NTMS, in the presence of a Pd catalyst.¹⁹⁹⁹ Terminal alkynes were converted to the alkynyl ester using CO, PdBr₂, CuBr₂ in methanol, and sodium bicarbonate.²⁰⁰⁰

Other organometallic reagents can be used to convert alkyl halides to carboxylic acid derivatives. Benzylic halides were converted to carboxylic esters with CO in the presence of a rhodium complex.²⁰⁰¹ Variations introduce the R' group via an ether (R'₂O),²⁰⁰² or an Al, Ti, or Zr alkoxide.²⁰⁰³ The reaction of an alkene, a primary alcohol, and CO, in the presence of a Rh catalyst, led to carbonylation of the alkene and formation of the corresponding ester.²⁰⁰⁴ Vinyl triflates were converted to the conjugated carboxylic acid with CO₂ and a Ni catalyst.²⁰⁰⁵ Reaction with an α,ω-diiodide, Bu₄NF, and Mo(CO)₆ gave the corresponding lactone.²⁰⁰⁶

A number of double carbonylations have been reported. In these reactions, two molecules of CO are incorporated in the product, leading to α-keto acids or their derivatives.²⁰⁰⁷ When the catalyst is a Pd complex, best results are obtained in the formation of α-keto amides.²⁰⁰⁸ The R group is usually aryl or vinylic.²⁰⁰⁹ The formation of α-keto acids²⁰¹⁰ or esters²⁰¹¹ requires more severe conditions. α-Hydroxy acids were obtained from aryl iodides when the reaction was carried out in the presence of an alcohol, which functioned as a reducing agent.²⁰¹² Cobalt catalysts have also been used and require lower CO pressures.²⁰⁰⁷

OS V, 20, 739.

¹⁹⁹⁴ Lapidus, A.L.; Eliseev, O.L.; Bondarenko, T.N.; Sizan, O.E.; Ostapenko, A.G.; Beletskaya, I.P. *Synthesis* **2002**, 317.

¹⁹⁹⁵ Schoenberg, A.; Heck, R.F. *J. Org. Chem.* **1974**, 39, 3327. See also, Cai, M.-Z.; Song, C.-S.; Huang, X. *Synth. Commun.* **1997**, 27, 361; Screttas, C.G.; Steele, B.R. *Org. Prep. Proceed. Int.* **1990**, 22, 271, pp. 288–314; Satoh, T.; Ikeda, M.; Kushino, Y.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, 62, 2662.

¹⁹⁹⁶ Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* **1998**, 1953.

¹⁹⁹⁷ Isse, A.A.; Gennaro, A. *Chem. Commun.* **2002**, 2798.

¹⁹⁹⁸ Alper, H.; Amer, I.; Vasapollo, G. *Tetrahedron Lett.* **1989**, 30, 2615. See also, Amer, I.; Alper, H. *J. Am. Chem. Soc.* **1989**, 111, 927.

¹⁹⁹⁹ Ueda, K.; Mori, M. *Tetrahedron Lett.* **2004**, 45, 2907. For an intramolecular carbonylation to generate a cyclic amide, see Trost, B.M.; Ameriks, M.K. *Org. Lett.* **2004**, 6, 1745.

²⁰⁰⁰ Li, J.; Jiang, H.; Chen, M. *Synth. Commun.* **2001**, 31, 199.

²⁰⁰¹ For an example, see Giroux, A.; Nadeau, C.; Han, Y. *Tetrahedron Lett.* **2000**, 41, 7601.

²⁰⁰² Buchan, C.; Hamel, N.; Woell, J.B.; Alper, H. *Tetrahedron Lett.* **1985**, 26, 5743.

²⁰⁰³ Woell, J.B.; Fergusson, S.B.; Alper, H. *J. Org. Chem.* **1985**, 50, 2134.

²⁰⁰⁴ Yokoa, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* **2003**, 5, 4329.

²⁰⁰⁵ Senboku, H.; Kanaya, H.; Tokuda, M. *Synlett* **2002**, 140.

²⁰⁰⁶ Imbeaux, M.; Mestdagh, H.; Moughamir, K.; Rolando, C. *J. Chem. Soc., Chem. Commun.* **1992**, 1678.

²⁰⁰⁷ For a review, see Collin, J. *Bull. Soc. Chim. Fr.* **1988**, 976.

²⁰⁰⁸ Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1982**, 233, C64; Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1984**, 3, 683.

²⁰⁰⁹ Son, T.; Yanagihara, H.; Ozawa, F.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1988**, 61, 1251.

²⁰¹⁰ Tanaka, M.; Kobayashi, T.; Sakakura, T. *J. Chem. Soc., Chem. Commun.* **1985**, 837.

²⁰¹¹ See Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1987**, 6, 1640.

²⁰¹² Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1987**, 28, 2721.

Aromatic Substitution, Electrophilic

Most substitutions at an aliphatic carbon are by nucleophiles. In aromatic systems the situation is reversed, because the high electron density at the aromatic ring leads to its reactivity as a Lewis base or a Brønsted–Lowry base, depending on the positive species. In electrophilic substitutions, a positive ion or the positive end of a dipole or induced dipole is attacked by the aromatic ring. The leaving group (the electrofuge) must necessarily depart without its electron pair. In nucleophilic substitution reactions, the chief leaving groups are those best able to carry the unshared pair: Br^- , H_2O , OTs^- , and so on (i.e., the weakest bases). In electrophilic substitution reactions, the most important leaving groups are those that can best exist without the pair of electrons necessary to fill the outer shell; that is, the weakest Lewis acids. The influence of solvents will vary with the reaction in many cases, and such details are discussed where appropriate in the reactions section (Sec. 11.F).¹

11.A. MECHANISMS

Electrophilic aromatic substitutions are unlike nucleophilic substitutions in that the large majority proceeds by just one mechanism with respect to the substrate.² In this mechanism, called the *arenium ion mechanism*, the electrophile, which can be viewed as a Lewis acid, is attacked by the π electrons of the aromatic ring, which can be viewed as a Lewis base, in the first step. This reaction leads to formation of a new C—X bond and a new sp^3 carbon in a positively charged intermediate called an arenium ion, where X is the electrophile. The positively charged intermediate (the arenium ion) is resonance stabilized, but not aromatic. Loss of a proton from the sp^3 carbon that is “adjacent” to the positive carbon in the arenium ion, in what is effectively an E1 process (see Sec. 17.A.ii) is driven by rearomatization of the ring from the arenium ion to give the aromatic substitution product. A proton therefore becomes the leaving group in this overall transformation, where X replaces H. The IUPAC designation for this mechanism is $\text{A}_\text{E} + \text{D}_\text{E}$. Another mechanism, much less common, consists of the opposite behavior: a leaving group departs *before* the electrophile arrives.

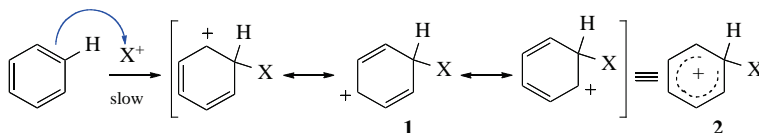
¹ For a review of electrophilic aromatic reactions in ionic liquids, see Borodkin, G.I.; Shubin, V.G. *Russ. J. Org. Chem.* **2006**, *42*, 1745.

² See Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, **1990**; Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, **1990**; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 1–406.

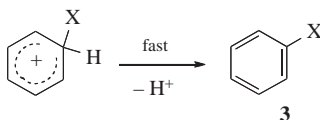
In this case, a substituent (*not* H) is attached to the aromatic ring, and the substituent is lost prior to incorporation of the electrophile. This mechanism, the S_E1 mechanism, corresponds to the S_N1 mechanism of nucleophilic substitution. Simultaneous attack and departure mechanisms (corresponding to S_N2) are not found at all. An addition–elimination mechanism has been postulated in one case (see Reaction 11-6).

11.A.i. The Arenium Ion Mechanism³

In the arenium ion mechanism, the electrophilic species may be produced in various ways, but when H is replaced by X conversion of the aromatic ring to an arenium ion it is basically the same in all cases. For this reason, most attention in the study of this mechanism centers on the identity of the electrophilic entity and how it is produced.



The electrophile may be a positive ion (X^+) or be a molecule that has a positive dipole. If it is a positive ion, it is attacked by the ring (a pair of electrons from the aromatic sextet is donated to the electrophile) and the product is a carbocation. This intermediate is a resonance hybrid, as shown in **1**, but is often represented as in **2**. The H atom to be replaced by X is shown in **1** for convenience. Ions of this type have been called⁴ *Wheland intermediates*, σ *complexes*, but nowadays they are called *arenium ions*.⁵ The inherent stability associated with aromaticity is no longer present in **1**, but the ion is stabilized by resonance. For this reason, the arenium ion is generally a highly reactive intermediate, although there are cases in which it has been isolated (see below).



Carbocations can react in various ways (see Sec. 5.A.iii), but for this type of ion the most likely pathway⁶ is loss of either X^+ or H^+ . In the second step of the mechanism, the reaction proceeds with loss of the proton and the aromatic sextet is restored in the final product (**3**). The second step is nearly always faster than the first, making the first rate determining, and the reaction is second order. If formation of the attacking species is slower still, the aromatic compound does not take part in the rate expression at all. If X^+ is lost, there is no net reaction, but if H^+ is lost, an aromatic substitution has taken place and a base (generally the counterion of the electrophilic species although solvents can also serve this purpose) is necessary to help remove it.

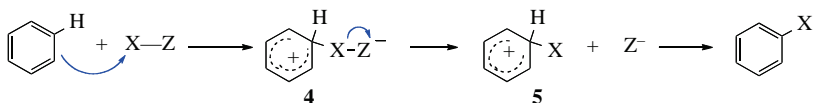
³ This mechanism is sometimes called the S_E2 mechanism because it is bimolecular, but in this book we reserve that name for aliphatic substrates (see Chap 12).

⁴ See Olah, G.A. *J. Am. Chem. Soc.* **1971**, 94, 808.

⁵ See Brouwer, D.M.; Mackor, E.L.; MacLean, C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, pp. 837–897; Perkampus, H. *Adv. Phys. Org. Chem.* **1966**, 4, 195.

⁶ Also see de la Mare, P.B.D. *Acc. Chem. Res.* **1974**, 7, 361.

If the electrophilic species is not an ion but a molecule with a polarized covalent bond, the product must have a negative charge unless part of the dipole, with its pair of electrons, is broken off somewhere in the process, as in the conversion of **4** to **5**. Note that when the aromatic ring attacks X, Z may be lost directly to give **5**.

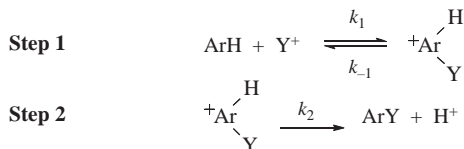


The electrophilic entities and how they are formed are discussed for each reaction in the reactions section of this chapter.

The evidence for the arenium ion mechanism is mainly of two kinds:

1. *Isotope Effects.* If the hydrogen ion departs before the arrival of the electrophile (S_E1 mechanism) or if the arrival and departure are simultaneous, there should be a substantial isotope effect (i.e., deuterated substrates should undergo substitution more slowly than non-deuterated compounds) because, in each case, the C—H bond is broken in the rate-determining step. However, in the arenium ion mechanism, the C—H bond is not broken in the rate-determining step, so no isotope effect should be found. Many such studies have been carried out and, in most cases, especially in the case of nitrations, there is no isotope effect.⁷ This result is incompatible with either the S_E1 or the simultaneous mechanism.

However, in many instances, isotope effects have been found. Since the values are generally much lower than expected for either the S_E1 or the simultaneous mechanisms (e.g., 1–3 for k_H/k_D instead of 6–7), there must be another explanation. For the case where hydrogen is the leaving group, the arenium ion mechanism can be summarized:

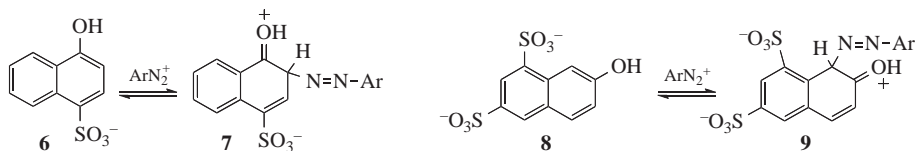


The small isotope effects found most likely arise from the reversibility of step 1 by a *partitioning effect*.⁸ The rate at which ArHY^+ reverts to ArH should be essentially the same as that at which ArDY^+ (or ArTY^+) reverts to ArD (or ArT), since the Ar—H bond is not cleaving. However, ArHY^+ should go to ArY faster than either ArDY^+ or ArTY^+ , since the Ar—H bond is broken in this step. If $k_2 \gg k_{-1}$, this does not matter; since a large majority of the intermediates go to product, the rate is determined only by the slow step ($k_2[\text{ArH}][\text{Y}^+]$) and no isotope effect is predicted. However, if $k_2 \leq k_{-1}$, reversion to starting materials is important. If k_2 for ArDY^+ (or ArTY^+) is $< k_2$ for ArHY^+ , but k_{-1} is the same, then a larger proportion of ArDY^+ reverts to starting compounds. That is, k_2/k_{-1} (the *partition factor*) for

⁷ Berglund-Larsson, U.; Melander, L. *Ark. Kemi* **1953**, 6, 219. See also, Zollinger, H. *Adv. Phys. Org. Chem.* **1964**, 2, 163.

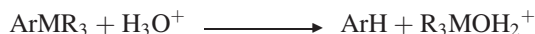
⁸ See Hammett, L.P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill, NY, **1970**, pp. 172–182.

ArDY^+ is less than that for ArHY^+ . Consequently, the reaction is slower for ArD than for ArH and an isotope effect is observed.



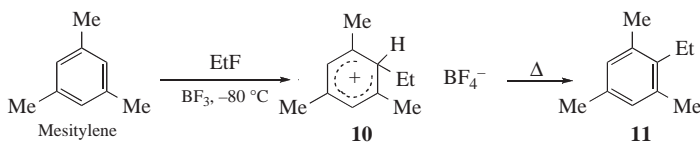
One circumstance that could affect the k_2/k_{-1} ratio is steric hindrance. Thus, diazonium coupling of **6** gave no isotope effect, while coupling of **8** gave a k_H/k_D ratio of 6.55.⁹ For steric reasons, it is much more difficult for **9** to lose a proton (it is harder for a base to approach) than it is for **7**, so k_2 is greater for the latter. Since no base is necessary to remove ArN_2^+ , k_{-1} does not depend on steric factors¹⁰ and is about the same for each. Thus the partition factor k_2/k_{-1} is sufficiently different for **7** and **9** that **8** exhibits a large isotope effect and **6** exhibits none.¹¹ Base catalysis can also affect the partition factor, since an increase in base concentration increases the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting materials. In some cases, isotope effects can be diminished or eliminated by a sufficiently high concentration of base.

Evidence for the arenium ion mechanism has also been obtained from other kinds of isotope-effect experiments, involving substitutions of the type



where M is Si, Ge, Sn, or Pb, and R is methyl or ethyl. In these reactions, the proton is the electrophile. If the arenium ion mechanism is operating, then the use of D_3O^+ should give rise to an isotope effect, since the D—O bond would be broken in the rate-determining step. Isotope effects of 1.55–0.05 were obtained,¹² in accord with the arenium ion mechanism.

2. *Isolation of Arenium Ion Intermediates.* Very strong evidence for the arenium ion mechanism comes from the isolation of arenium ions in a number of instances.¹³ For example, **7** was isolated as a solid with a



⁹ Zollinger, H. *Helv. Chim. Acta* **1955**, 38, 1597, 1617, 1623.

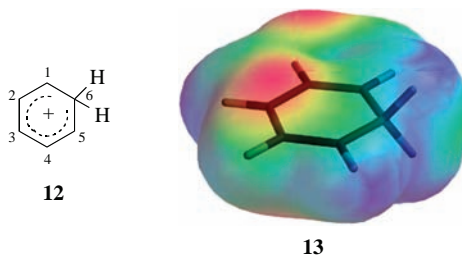
¹⁰ Snyckers, F.; Zollinger, H. *Helv. Chim. Acta* **1970**, 53, 1294.

¹¹ See Myhre, P.C.; Beug, M.; James, L.L. *J. Am. Chem. Soc.* **1968**, 90, 2105; Márton, J. *Acta Chem. Scand.* **1969**, 23, 3321, 3329.

¹² Bott, R.W.; Eaborn, C.; Greasley, P.M. *J. Chem. Soc.* **1964**, 4803.

¹³ See Koptug, V.A. *Top. Curr. Chem.* **1984**, 122, 1; *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1974**, 23, 1031; Shteingarts, V.D. *Russ. Chem. Rev.* **1981**, 50, 735; Farcasiu, D. *Acc. Chem. Res.* **1982**, 15, 46.

melting point of -15°C from treatment of mesitylene with ethyl fluoride and the catalyst BF_3 at -80°C . When **10** was heated, the normal substitution product (**11**) was obtained.¹⁴ Even the simplest such ion, the benzenonium ion (**12**) has been prepared in $\text{HF}-\text{SbF}_5-\text{SO}_2\text{ClF}-\text{SO}_2\text{F}_2$ at -134°C , where it could be studied



spectrally.¹⁵ The ^{13}C NMR spectra of the benzenonium ion¹⁶ and the pentamethylbenzenonium ion¹⁷ give graphic evidence for the charge distribution shown in **12** (see the electron density map for the arenium ion, **13**). According to this, the 1, 3, and 5 carbons, each of which bears a positive charge of about $+1/3$ [note that C-1,-3,-5 (numbering from **12**) are lighter, indicating less electron density in **13**, whereas C-2,-4 are darker for higher electron density], should have a greater chemical shift in the NMR than the 2 and 4 carbon atoms, which are uncharged. The spectra bear this out. For example, ^{13}C NMR chemical shifts for **12** are C-3: 178.1; C-1 and C-5: 186.6; C-2 and C-4: 136.9, and C-6: 52.2.¹⁶

In Chapter 3, it was mentioned that positive ions can form addition complexes with π systems. Since the initial step of electrophilic substitution involves attack of a positive ion by an aromatic ring, it has been suggested¹⁸ that such a complex, called a π -complex (represented as **14**), is formed first, and then is converted to the arenium ion (**15**).¹⁹ Stable solutions of arenium ions or π complexes (e.g., with Br_2 , I_2 , picric acid, Ag^+ , or HCl) can be formed.²⁰ For example, π -complexes are formed when aromatic hydrocarbons are treated with HCl alone, but the use of HCl plus a Lewis acid (e.g., AlCl_3) gives arenium ions. The two types of solution have very different properties. For example, a solution of an arenium ion is colored and conducts electricity, which shows that positive and negative ions are present, while a π complex formed from HCl and benzene is colorless and does not conduct a current. Furthermore, when DCl is used to form a π complex, no deuterium exchange takes place (because there is no covalent bond between the electrophile and the ring), while formation of an arenium ion with DCl and AlCl_3 gives deuterium exchange. The relative stabilities of some methylated arenium ions and π complexes are shown in Table 11.1. The arenium ion stabilities listed were

¹⁴ Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* **1958**, *80*, 6541. See Effenberger, F. *Acc. Chem. Res.* **1989**, *22*, 27.

¹⁵ Olah, G.A.; Schlosberg, R.H.; Porter, R.D.; Mo, Y.K.; Kelly, D.P.; Mateescu, G.D. *J. Am. Chem. Soc.* **1972**, *94*, 2034.

¹⁶ Olah, G.A.; Staral, J.S.; Asencio, G.; Liang, G.; Forsyth, D.A.; Mateescu, G.D. *J. Am. Chem. Soc.* **1978**, *100*, 6299.

¹⁷ Lyster, J.R.; Yannoni, C.S.; Bruck, D.; Fyfe, C.A. *J. Am. Chem. Soc.* **1979**, *101*, 4770.

¹⁸ Dewar, M.J.S. *Electronic Theory of Organic Chemistry*; Clarendon Press: Oxford, **1949**.

¹⁹ See Hubig, S.M.; Kochi, J.K. *J. Org. Chem.* **2000**, *65*, 6807.

²⁰ See Gallivan, J.P.; Dougherty, D.A. *Org. Lett.* **1999**, *1*, 103; Rosokha, S.V.; Kochi, J.K. *J. Org. Chem.* **2002**, *67*, 1727.

TABLE 11.1 Relative Stabilities of Arenium Ions, π -Complexes, and Relative Rates of Chlorination and Nitration^a

Substituents	Relative Arenium Ion Stability ^b	Relative π -Complex Stability ^b	Rate of Chlorination ^c	Rate of Nitration ^d
None (benzene)	0.09	0.61	0.0005	0.51
Me	0.63	0.92	0.157	0.85
<i>p</i> -di-Me ₃	1.00	1.00	1.00	1.00
<i>o</i> -di-Me ₃	1.1	1.13	2.1	0.89
<i>m</i> -di-Me ₃	26	1.26	200	0.84
1,2,4-Tri-Me ₃	63	1.36	340	
1,2,3-Tri-Me ₃	69	1.46	400	
1,2,3,4-tetra-Me ₃	400	1.63	2,000	
1,2,3,5-tetra-Me ₃	16,000	1.67	240,000	
Penta-Me ₃	29,900		360,000	

Reprinted with permission Kilpatrick, M.; Luborsky, F.E. *J. Am. Chem. Soc.* **1953**, 75, 577. Copyright © 1953 American Chemical Society.

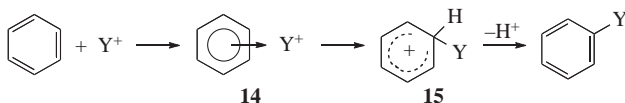
^aIn each case, *p*-xylene = 1.00.

^bSee Ref. 21.

^cSee Ref. 22.

^dSee Ref. 27.

determined by the relative basicity of the substrate toward HF.²¹ The π -complex stabilities are relative equilibrium constants for the reaction²² between the aromatic hydrocarbon and HCl. As shown in Table 11.1, the relative stabilities of the two types of species are very different: The π complex stability changes very little with methyl substitution, but the arenium ion stability changes a great deal. Note that stable arenium ions have been obtained from large methylene-bridged polycyclic aromatic hydrocarbons.²³



How can we tell if **14** is present on the reaction path? If it is present, there are two possibilities: (1) The formation of **14** is rate determining (the conversion of **14** to **15** is much faster), or (2) the formation of **14** is rapid, and the conversion **14** to **15** is rate determining. One way to ascertain which species is formed in the rate-determining step in a given reaction is to use the stability information given in Table 11.1. We measure the relative rates of reaction of a given electrophile with the series of compounds listed in Table 11.1. If the relative rates resemble the arenium ion stabilities, we conclude that the arenium ion is formed in the slow step; but if they resemble the stabilities of the π

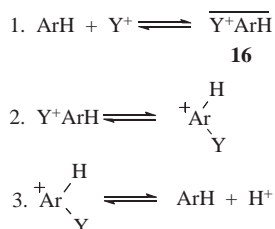
²¹ Kilpatrick, M.; Luborsky, F.E. *J. Am. Chem. Soc.* **1953**, 75, 577.

²² Brown, H.C.; Brady, J.D. *J. Am. Chem. Soc.* **1952**, 74, 3570.

²³ Laali, K.K.; Okazaki, T.; Harvey, R.G. *J. Org. Chem.* **2001**, 66, 3977.

complexes, the latter are formed in the slow step.²⁴ When such experiments are carried out, it is found in most cases that the relative rates are similar to the arenium ion and not to the π complex stabilities. For example, Table 11.1 lists chlorination rates.²² Similar results were obtained in room temperature bromination with Br_2 in acetic acid²⁵ and in acetylation with $\text{CH}_3\text{CO}^+ \text{SbF}_6^-$.²⁶ It is clear that in these cases the π complex either does not form at all, or if it does, its formation is not rate determining (unfortunately, it is very difficult to distinguish between these two possibilities).

On the other hand, in nitration with the powerful electrophile NO_2^+ (in the form of $\text{NO}_2^+ \text{BF}_4^-$), the relative rates resembled π complex stabilities much more than arenium ion stabilities (Table 11.1).²⁷ Similar results were obtained for bromination with Br_2 and FeCl_3 in nitromethane. These results were taken to mean²⁸ that in these cases π complex formation is rate determining. However, graphical analysis of the NO_2^+ data showed that a straight line could not be drawn when the nitration rate was plotted against π -complex stability,²⁹ which casts doubt on the rate-determining formation of a π complex in this case.³⁰ There is other evidence, from positional selectivities (discussed in Sec. 11.D), that *some* intermediate is present before the arenium ion is formed, whose formation can be rate determining with powerful electrophiles. Not much is known about this intermediate, which is given the nondescriptive name *encounter complex* and generally depicted as **16**. The arenium complex mechanism is therefore written as:³¹



For the reason given above and for other reasons, it is unlikely that the encounter complex is a π complex, but just what kind of attraction exists between Y^+ and ArH is not known, other than the presumption that they are together within a solvent cage (see also, Sec. 11.D). There is evidence (from isomerizations occurring in the alkyl group, as well as other observations) that π complexes are present on the pathway from substrate to arenium ion in the gas-phase protonation of alkylbenzenes.³²

²⁴ Condon, F.E. *J. Am. Chem. Soc.* **1952**, *74*, 2528.

²⁵ Brown, H.C.; Stock, L.M. *J. Am. Chem. Soc.* **1957**, *79*, 1421.

²⁶ Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* **1964**, *86*, 2203.

²⁷ Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* **1961**, *83*, 4571, 4581.

²⁸ Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* **1964**, *86*, 1039, 1044.

²⁹ Rys, P.; Skrabal, P.; Zollinger, H. *Angew. Chem. Int. Ed.* **1972**, *11*, 874. See also, DeHaan, F.P.; Covey, W.D.; Delker, G.L.; Baker, N.J.; Feigon, J.F.; Miller, K.D.; Stelter, E.D. *J. Am. Chem. Soc.* **1979**, *101*, 1336; Santiago, C.; Houk, K.N.; Perrin, C.L. *J. Am. Chem. Soc.* **1979**, *101*, 1337.

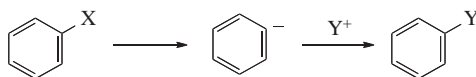
³⁰ See Ridd, J.H. *Acc. Chem. Res.* **1971**, *4*, 248; Taylor, R.; Tewson, T.J. *J. Chem. Soc., Chem. Commun.* **1973**, 836; Naidenov, S.V.; Guk, Yu.V.; Golod, E.L. *J. Org. Chem. USSR* **1982**, *18*, 1731. Also see Olah, G.A. *Acc. Chem. Res.* **1971**, *4*, 240; Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* **1974**, *96*, 2892; Sedaghat-Herati, M.R.; Sharifi, T. *J. Organomet. Chem.* **1989**, *363*, 39; Banthorpe, D.V. *Chem. Rev.* **1970**, *70*, 295, especially Sections VI and IX.

³¹ See Stock, L.M. *Prog. Phys. Org. Chem.* **1976**, *12*, 21; Ridd, J.H. *Adv. Phys. Org. Chem.* **1978**, *16*, 1.

³² Holman, R.W.; Gross, M.L. *J. Am. Chem. Soc.* **1989**, *111*, 3560.

11.A.ii. The S_E1 Mechanism

The S_E1 mechanism (*substitution electrophilic unimolecular*) is rare, being found only in certain cases in which carbon is the leaving atom (see Reactions **11-33** and **11-35**) or when a very strong base is present (see Reactions **11-1**, **11-10**, and **11-39**).³³ It consists of two steps with an intermediate carbanion. The IUPAC designation is D_E + A_E.



Reactions **12-41**, **12-45**, and **12-46** also take place by this mechanism when applied to aryl substrates.

11.B. ORIENTATION AND REACTIVITY

11.B.i. Orientation and Reactivity in Monosubstituted Benzene Rings³⁴

When an electrophilic substitution reaction is performed on a monosubstituted benzene, the new group may be directed primarily to the ortho, meta, or para position and the substitution may be slower or faster than with benzene itself.³⁵ The group already on the ring determines which position the new group will take and whether the reaction will be slower or faster than with benzene. Groups that increase the reaction rate are called *activating* and those that slow it are *deactivating*. Some groups are predominantly meta directing; all of these are deactivating. Others are mostly ortho–para directing; while some of these (e.g., halogens) are deactivating too, most are activating. Groups direct *predominantly*, but usually not *exclusively*. For example, nitration of nitrobenzene gave 93% *m*-dinitrobenzene, 6% of the ortho, and 1% of the para isomer.

The orientation and reactivity effects are explained on the basis of resonance and field effects of each group on the stability of the intermediate arenium ion. To understand why we can use this approach, it is necessary to know that in these reactions the product is usually kinetically and not thermodynamically controlled (see Sec. 6.F). Some of the reactions are irreversible and the others are usually stopped well before equilibrium is reached. *Therefore, which of the three possible intermediates is formed is dependent not on the thermodynamic stability of the products, but on the activation energy necessary to form each of the three intermediates.* It is not easy to predict which of the three activation energies is lowest, but it is necessary to make the assumption that the free energy profile resembles either Fig. 6.2a or b. In either case, the transition state is closer in energy to the arenium ion intermediate than to the starting compounds. Invoking the *Hammond postulate* (Sec. 6.G), assume that the geometry of the transition state also resembles that of the intermediate and that anything that increases the stability of the intermediate will

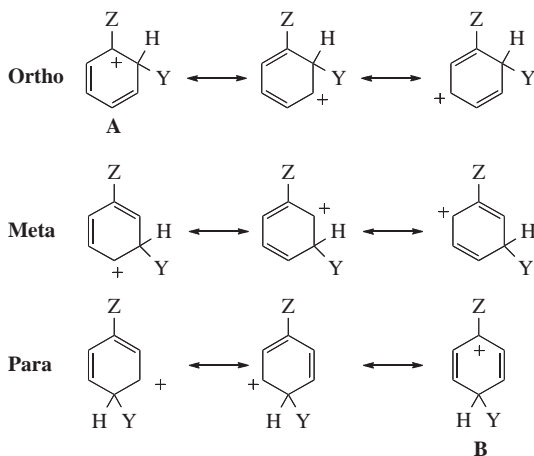
³³ Also see Eaborn, C.; Hornfeld, H.L.; Walton, D.R.M. *ccqBunnett, J.F.; Miles J.H.; Nahabedian, K* **1967**, 1036.

³⁴ See Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, **1971**, pp. 122–145, 163–220.

³⁵ For a computational approach to evaluate substituent constants, see Galabov, B.; Ilieva, S.; Schaefer III, H.F. *J. Org. Chem.* **2006**, 71, 6382.

also lower the activation energy necessary to attain it. Since the intermediate, once formed, is rapidly converted to products, the relative stabilities of the three intermediates can be used as guides to predict which products will predominantly form. Of course, if reversible reactions are allowed to proceed to equilibrium, product ratios that are quite different may be obtained. For example, the sulfonation of naphthalene at 80 °C, where the reaction does not reach equilibrium, gives mostly α -naphthalenesulfonic acid,³⁶ while at 160 °C, where equilibrium is attained, the β isomer predominates³⁷ (the α isomer is thermodynamically less stable because of steric interaction between the SO_3H group and the hydrogen at the 8 position).

The three possible ions from incorporation of Y at the ortho, meta, and para positions are shown below, and each arenium ion obviously has a positive charge in the ring. It is therefore possible to predict that any group Z that has an electron-donating field effect ($+I$, Z will have a δ^- charge or a δ^- dipole in most cases) should stabilize all three ions (relative to **1**), since electron donation to a positive center is stabilizing. On the other hand, electron-withdrawing groups ($-I$, Z will have a δ^+ charge or a δ^+ dipole in most cases) will increase the positive charge on the ring (like charges repel), and destabilize the arenium ion. Formation of a stabilized ion should be faster than benzene, which generates **1**, or activating, but formation of a destabilized ion should be slower, or deactivating. Such field effects should taper off with distance and are thus strongest at the carbon connected to the group Z (known as the ipso carbon). Of the three arenium ions, only the ortho and para have any positive charge at this carbon. None of the canonical forms of the meta ion has a positive charge at the ipso carbon. Therefore, $+I$ groups should stabilize all three ions, but mostly the ortho and para, so they should be not only activating but ortho-para-directing as well. On the other hand, $-I$ groups, by removing electron density, should destabilize all three ions, but mostly the ortho and para, and should be not only deactivating but also meta directing.



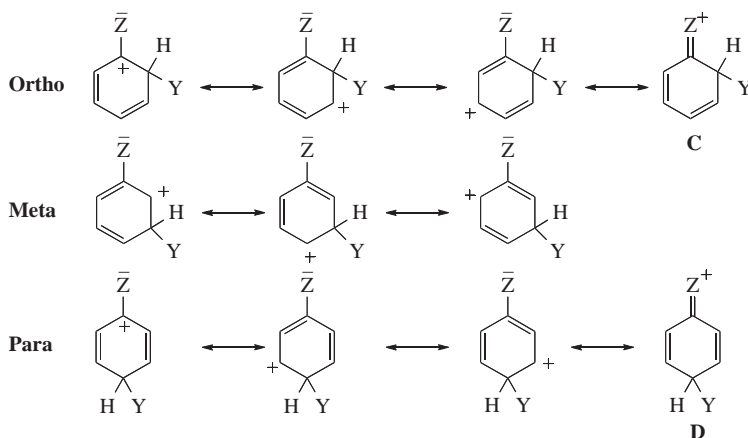
These conclusions are correct as far as they go, but they do not lead to the proper results in all cases. In many cases, there is *resonance interaction* between Z and the ring; this also

³⁶ Fierz, H.E.; Weissenbach, P. *Helv. Chim. Acta* **1920**, 3, 312.

³⁷ Witt, O.N. *Ber.* **1915**, 48, 743.

affects the relative stability, in some cases in the same direction as the field effect, in others differently.

Some substituents have a pair of electrons (usually unshared) that may be contributed *toward* the ring. Two of the three (ortho and para) arenium ions would then have a fourth resonance contributor as shown. For each ion, the same three canonical forms can be drawn as before, but now we can draw an extra form for the ortho and para ions. The stability of these two ions is increased by the extra form not only because it is another canonical form, but also because it is more stable than the others and makes a greater contribution to the hybrid. Every atom (except, of course, hydrogen) in these forms (**C** and **D**) has a complete octet, while all the other forms have one carbon atom with a sextet. No corresponding form can be drawn for the meta isomer. The inclusion of this form in the hybrid lowers the energy not only because of rule 6 (Sec. 2.E), but also because it spreads the positive charge over a larger area, out onto group Z. Groups with a pair of electrons (e.g., the halogens) to contribute would be expected, then, in the absence of field effects, not only to direct ortho and para, but also to activate these positions for electrophilic attack.



On the basis of these discussions, we can distinguish three types of groups.

1. *Groups that Contain an Unshared Pair of Electrons on the Atom Connected to the Ring.* In this category are O^- , NR_2 , NHR , NH_2 ,³⁸ OH , OR , $NHCOR$, $OCOR$, SR , and the four halogens.³⁹ The halogens deactivate the aromatic ring to substitution (the rate of reaction is slower than that of benzene), and this effect may arise from the unique energy level of the halogen lone-pair orbital, which is higher than the

³⁸ It must be remembered that in acid solution amines are converted to their conjugate acids, which for the most part are meta directing (type 2). However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, ortho-para direction is often found even under acidic conditions.

³⁹ See Chuchani, G. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, **1968**, pp. 250–265; for ether groups see Kohnstam, G.; Williams, D.L.H. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, **1967**, pp. 132–150.

adjacent π molecular orbital of benzene (π_1).⁴⁰ The widely held explanation for this, however, is that the halogens have a $-I$ effect. The SH group would probably belong here too, except that in the case of thiophenols, electrophiles usually attack the sulfur rather than the ring, and ring substitution is not feasible with these substrates.⁴¹ The resonance explanation predicts that all these groups should be ortho-para directing, and they are, though all except O^- are electron withdrawing by the field effect (Sec. 11.I). Therefore, for these groups, resonance is more important than the field effect. This result is especially true for NR_2 , NHR , NH_2 , and OH , which are *strongly* activating, as is O^- . The other groups are mildly activating, except for the halogens, which are deactivating. Fluorine⁴² is the least deactivating, and fluorobenzenes usually show a reactivity approximating that of benzene itself. The other three halogens deactivate about equally. In order to explain why chlorine, bromine, and iodine deactivate the ring, even though they direct ortho-para, assume that the canonical forms **C** and **D** make such great contributions to the respective hybrids that they make the ortho and para arenium ions more stable than the meta, even though the $-I$ effect of the halogen is withdrawing sufficient electron density from the ring to deactivate it. The three halogens make the ortho and para ions more stable than the meta, but less stable than the unsubstituted arenium ion (**1**). For the other groups that contain an unshared pair, the ortho and para ions are more stable than either the meta or the unsubstituted ion. For most of the groups in this category, the meta ion is more stable than **1**, so that groups, such as NH_2 and OH , activate the meta positions too, but not as much as the ortho and para positions (see also, the discussion in Sec. 11.C).

2. *Groups that Lack an Unshared Pair on the Atom Connected to the Ring and that Are $-I$.* In this category are, in approximate order of decreasing deactivating ability, NR_3^+ , NO_2 , CF_3 ,⁴³ CN , SO_3H , CHO , COR , CO_2H , CO_2R , $CONH_2$, CCl_3 , and NH_3^+ . Also in this category are all other groups with a positive charge on the atom directly connected to the ring⁴⁴ (SR_2^+ , PR_3^+ , etc.) and many groups with positive charges on atoms farther away, since often these are still powerful $-I$ groups. The field-effect explanation predicts that these should all be meta directing and deactivating, and (except for NH_3^+) this is the case. The NH_3^+ group is an anomaly, since this group directs para about as much as or a little more than it directs meta.⁴⁵ The NH_2Me^+ , $NHMe_2^+$, and NMe_3^+ groups all give more meta than para substitution, the percentage of para product decreasing with the increasing number of methyl groups.⁴⁶

⁴⁰ Tomoda, S.; Takamatsu, K.; Iwaoka, M. *Chem. Lett.* **1998**, 581.

⁴¹ Tarbell, D.S.; Herz, A.H.J. *Am. Chem. Soc.* **1953**, 75, 4657. Ring substitution is possible if the SH group is protected. See Walker, D. *J. Org. Chem.* **1966**, 31, 835.

⁴² Carroll, T.X.; Thomas, T.D.; Bergersen, H.; Børve, K.J.; Sæthre, L.J. *J. Org. Chem.* **2006**, 71, 1961.

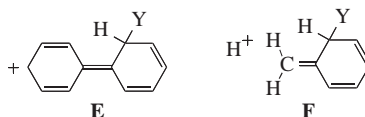
⁴³ See Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* **2002**, 8, 799.

⁴⁴ See Gilow, H.M.; De Shazo, M.; Van Cleave, W.C. *J. Org. Chem.* **1971**, 36, 1745; Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, **1971**, pp. 167–176.

⁴⁵ Hartshorn, S.R.; Ridd, J.H. *J. Chem. Soc. B* **1968**, 1063. Also see Ridd, J.H. in *Aromaticity*, *Chem. Soc. Spec. Publ.*, no. 21, **1967**, pp. 149–162.

⁴⁶ Brickman, M.; Utley, J.H.P.; Ridd, J.H. *J. Chem. Soc.* **1965**, 6851.

3. *Groups that Lack an Unshared pair on the Atom connected to the Ring and that Are ortho–para Directing.* In this category are alkyl groups,⁴⁷ aryl groups, and the COO^- group,⁴⁸ all of which activate the ring. Since aryl groups are $-I$ groups, they might seem to belong to category 2. They are nevertheless ortho–para directing and activating. This can be explained in a similar manner as in category 1, with a pair of electrons from the aromatic sextet playing the part played by the unshared pair, so that forms like **E** are generated. The effect of negatively charged groups like CO_2^- is easily explained by the field effect (negatively charged groups are of course electron donating), since there is no resonance interaction between the group and the ring. The effect of alkyl groups can be explained in the same way, but, in addition, canonical forms can be drawn, even though there is no unshared pair. These, of course, are hyperconjugation forms like **F** (see above). This effect, like the field effect, predicts activation and ortho–para direction, so that it is not possible to say how much each effect contributes to the result. Another way of looking at the effect of alkyl groups, which sums up both field and hyperconjugation effects, is that (for $Z = R$) the ortho and para arenium ions are more stable because each contains a form (**A** and **B**) that is a tertiary carbocation, while all the canonical forms for the meta ion and for **1** are secondary carbocations. In activating ability, alkyl groups usually follow the *Baker–Nathan order* (Sec. 2.M), but not always.⁴⁹



11.B.ii. The Ortho/Para Ratio⁵⁰

When an ortho–para directing group is on a ring, it is usually difficult to predict how much of the product will be the ortho isomer and how much is the para isomer. Indeed, these proportions can depend greatly on the reaction conditions. For example, chlorination of toluene gives an ortho/para ratio anywhere from 62:38 to 34:66.⁵¹ Nevertheless, certain points can be made. On a purely statistical basis there would be 67% ortho and 33% para, since there are two ortho positions and only one para. However, the phenonium ion (**12**), which arises from protonation of benzene, has the approximate charge distribution shown⁵² (see **13** as well). If this model were accepted for the arenium ion in aromatic substitution, a para substituent would have a greater stabilizing effect on the adjacent carbon than an ortho substituent. If other effects are absent, this would mean that >33% para and <67% ortho substitution would be found. In hydrogen exchange (Reaction 11-1), where other effects are absent, it has been found for a number of

⁴⁷ For a discussion of the substituents effect of the methyl group, see Myrseth, V.; Sæthre, L.J.; Børve, K.J.; Thomas, T.D. *J. Org. Chem.* **2007**, 72, 5715.

⁴⁸ Spryskov, A.A.; Golubkin, L.N. *J. Gen. Chem. USSR* **1961**, 31, 833. Since the CO_2^- group is present only in alkaline solution, where electrophilic substitution is not often done, it is seldom encountered.

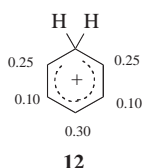
⁴⁹ See, however, Schubert, W.M.; Gurka, D.F. *J. Am. Chem. Soc.* **1969**, 91, 1443; Himoe, A.; Stock, L.M. *J. Am. Chem. Soc.* **1969**, 91, 1452.

⁵⁰ See Effenberger, F.; Maier, A.J. *J. Am. Chem. Soc.* **2001**, 123, 3429.

⁵¹ Stock, L.M.; Himoe, A. *J. Am. Chem. Soc.* **1961**, 83, 4605.

⁵² Olah, G.A. *Acc. Chem. Res.* **1970**, 4, 240, p. 248.

substituents that the average ratio of the logarithms of the partial rate factors for these positions (see Sec. 11.C for a definition of partial rate factor) was close to 0.865,⁵³ which is not far from the value predicted from the ratio of charge densities in **12**. This picture is further supported by the fact that meta-directing groups, which destabilize a positive charge, give ortho/para ratios $>67:33$ ⁵⁴ (of course, the total amount of ortho and para substitution with these groups is small, but the *ratios* are generally $>67:33$). Another important factor is the steric effect. If either the group on the attacking ring or the group on the electrophile is large, steric hindrance inhibits formation of the ortho product and increases the amount of the para isomer. An example may be seen in the nitration, under the same conditions, of toluene and *tert*-butylbenzene. The former gave 58% of the ortho compound and 37% of the para, while the more bulky *tert*-butyl group gave 16% of the ortho product and 73% of the para.⁵⁵ Some groups are so large that they direct almost entirely para.



When the ortho–para directing group is one with an unshared pair (this of course applies to most of them), there is another effect that increases the amount of para product at the expense of the ortho. A comparison of the intermediates involved (see above) shows that **C** is a canonical form with an *ortho*-quinoid structure, while **D** has a *para*-quinoid structure. *para*-Quinones are more stable than the ortho isomers, so it seems reasonable to assume that **D** is more stable than **C**, and therefore contributes more to the hybrid and increases its stability compared to the ortho intermediate.

It has been shown that it is possible to compel regiospecific para substitution by enclosing the substrate molecules in a cavity from which only the para position projects. Anisole was chlorinated in solutions containing a cyclodextrin, a molecule in which the anisole is almost entirely enclosed (see Fig. 3.4). With a high enough concentration of cyclodextrin, it was possible to achieve a para/ortho ratio of 21.6⁵⁶ (in the absence of the cyclodextrin the ratio was only 1.48). This behavior is a model for the regioselectivity found in the action of enzymes.

11.B.iii. Ipso Attack

Orientation has been discussed previously in the case of monosubstituted benzenes entirely in terms of attachment at the ortho, meta, and para positions, but attachment at

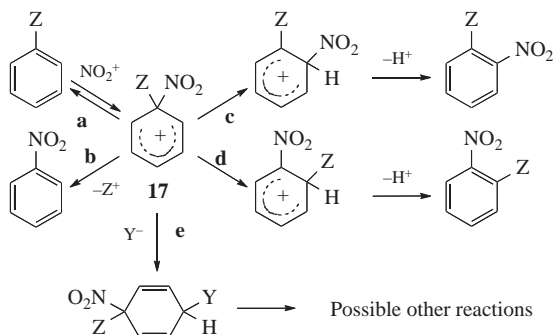
⁵³ Ansell, H.V.; Le Guen, J.; Taylor, R. *Tetrahedron Lett.* **1973**, 13.

⁵⁴ Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, **1971**, pp. 176–180.

⁵⁵ Nelson, K.L.; Brown, H.C. *J. Am. Chem. Soc.* **1951**, 73, 5605. See Baas, J.M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* **1972**, 91, 285, 517, 831.

⁵⁶ Breslow, R.; Campbell, P. *J. Am. Chem. Soc.* **1969**, 91, 3085; *Bioorg. Chem.* **1971**, 1, 140. See also, Komiyama, M.; Hirai, H. *J. Am. Chem. Soc.* **1983**, 105, 2018; **1984**, 106, 174; Chênevert, R.; Ampleman, G. *Can. J. Chem.* **1987**, 65, 307; Komiyama, M. *Polym. J. (Tokyo)* **1988**, 20, 439.

the position bearing the substituent (called the *ipso position*⁵⁷) can also be important. Ipso attack has mostly been studied for nitration.⁵⁸ When attack of NO_2^+ leads to incorporation at the ipso position there are at least five possible fates for the resulting arenium ion (**17**).



Path a. The arenium ion can lose NO_2^+ and revert to the starting compounds. This results in no net reaction and is often undetectable.

Path b. The arenium ion can lose Z^+ , in which case this is simply aromatic substitution with a leaving group other than H (see Reactions **11-33–11-41**).

Path c. The electrophilic group (in this case NO_2^+) can undergo a 1,2-migration, followed by loss of the proton. The product in this case is the same as that obtained by direct attachment of NO_2^+ at the ortho position of PhZ . It is not always easy to tell how much of the ortho product in any individual case arises from this pathway,⁵⁹ though there is evidence that it can be a considerable proportion. Because of this possibility, many of the reported conclusions about the relative reactivity of the ortho, meta, and para positions are cast into doubt, since some of the product may have arisen not from direct attachment at the ortho position, but from attachment at the ipso position followed by rearrangement.⁶⁰

Path d. The ipso substituent (Z) can undergo 1,2-migration, which also produces the ortho product (although the rearrangement would become apparent if there were other substituents present). The evidence is that this pathway is very minor, at least when the electrophile is NO_2^+ .⁶¹

Path e. Attack of a nucleophile on **17**. In some cases, the products of such an attack (cyclohexadienes) have been isolated⁶² (this is 1,4-addition to the aromatic ring), but further reactions are also possible.

⁵⁷ Perrin, C.L.; Skinner, G.A. *J. Am. Chem. Soc.* **1971**, 93, 3389; Traynham, J.G. *J. Chem. Educ.* **1983**, 60, 937.

⁵⁸ See Moodie, R.B.; Schofield, K. *Acc. Chem. Res.* **1976**, 9, 287. See also, Fischer, A.; Henderson, G.N.; RayMahasay, S. *Can. J. Chem.* **1987**, 65, 1233, and other papers in this series.

⁵⁹ See Gibbs, H.W.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. Perkin Trans. 2* **1978**, 1145.

⁶⁰ This was first pointed out by Myhre, P.C. *J. Am. Chem. Soc.* **1972**, 94, 7921.

⁶¹ See Hartshorn, M.P.; Readman, J.M.; Robinson, W.T.; Sies, C.W.; Wright, G.J. *Aust. J. Chem.* **1988**, 41, 373.

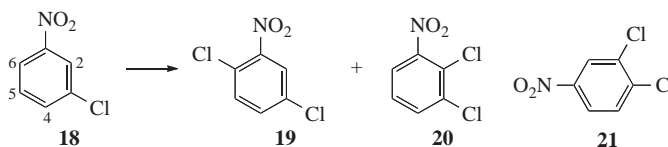
⁶² See Banwell, T.; Morse, C.S.; Myhre, P.C.; Vollmar, A. *J. Am. Chem. Soc.* **1977**, 99, 3042; Fischer, A.; Greig, C. *Can. J. Chem.* **1978**, 56, 1063.

11.B.iv. Orientation in Benzene Rings with More Than One Substituent⁶³

It is often possible in these cases to predict the correct isomer. In many cases, the groups already on the ring reinforce each other. Thus, 1,3-dimethylbenzene is substituted at the 4 position (ortho to one group and para to the other), but not at the 5 position (meta to both). Likewise, the incoming group in *p*-chlorobenzoic acid goes to the position ortho to the chloro and meta to the carboxyl group.

When the groups oppose each other, predictions may be more difficult, as in *N*-acetyl-2-methoxyaniline. In a case such as where two groups of about equal directing ability are in competing positions, all four products can be expected, and it is not easy to predict the proportions, except that steric hindrance should probably reduce the yield of substitution ortho to the acetamido group, especially for large electrophiles. Mixtures of about equal proportions are frequent in such cases. Nevertheless, even when groups on a ring oppose each other, there are some regularities.

1. If a strong activating group competes with a weaker one or with a deactivating group, the former controls. Thus *o*-cresol gives substitution mainly ortho and para to the *hydroxyl* group and not to the methyl. For this purpose, we can arrange the groups in the following order: NH_2 , OH , NR_2 , $\text{O}^- > \text{OR}$, OCOR , $\text{NHCOR} > \text{R}$, $\text{Ar} > \text{halogen} > \text{meta-directing groups}$.
2. All other things being equal, a third group is least likely to enter between two groups in the meta relationship. This is the result of steric hindrance and increases in importance with the size of the groups on the ring and with the size of the attacking species.⁶⁴
3. When a meta-directing group is meta to an ortho-para directing group, the incoming group primarily goes ortho to the meta-directing group rather than para. For example, chlorination of **18** gives mostly **19**. The importance of this effect is underscored by the fact that **20**, which is in violation of the preceding rule, is formed in smaller amounts, but **21** is not formed at all. This is called the *ortho effect*,⁶⁵ and many such examples are known.⁶⁶ Another is the nitration of *p*-bromotoluene, which gives 2,3-dinitro-4-bromotoluene. In this case, once the first nitro group came in, the second was directed ortho to it rather than para, even though this means that the group has to come in between two groups in the meta position. There is no good explanation yet for the ortho effect, though possibly there is intramolecular assistance from the meta-directing group.



⁶³ For a quantitative discussion, see Section 11.C.

⁶⁴ See Kruse, L.I.; Cha, J.K. *J. Chem. Soc., Chem. Commun.* **1982**, 1333.

⁶⁵ This is not the same as the ortho effect mentioned at the end of Section 9.C.

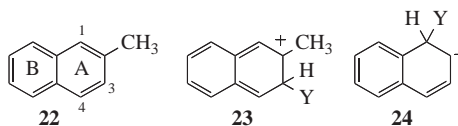
⁶⁶ See Hammond, G.S.; Hawthorne, M.F. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, **1956**, pp. 164–200, 178–182.

It is interesting that chlorination of **18** illustrates all three rules. Of the four positions open to the electrophile, the 5 position violates rule 1, the 2 position rule 2, and the 4 position rule 3. The principal attachment is therefore at position 6.

11.B.v. Orientation in Other Ring Systems⁶⁷

In fused ring systems, the positions are not equivalent and there is usually a preferred orientation, even in the unsubstituted hydrocarbon. The preferred positions may often be predicted as for benzene rings. Thus it is possible to draw more canonical forms for the arenium ion when attack by naphthalene leads to attachment of the electrophile at the α position than when attack by naphthalene leads to attachment of the electrophile at the β position. Therefore, the α position is the preferred site of attachment,⁶⁸ although, as previously mentioned (Sec. 11.B.i), the isomer formed by substitution at the β -position is thermodynamically more stable and is the product if the reaction is reversible and equilibrium is reached. Because of the more extensive delocalization of charges in the corresponding arenium ions, naphthalene is more reactive than benzene and substitution is faster at both positions. Similarly, anthracene, phenanthrene, and other fused polycyclic aromatic hydrocarbons are also substituted faster than benzene.

Heterocyclic compounds, too, have nonequivalent positions, and the principles are similar,⁶⁹ in terms of mechanism, and rate data is available.⁷⁰ Furan, thiophene, and pyrrole are chiefly substituted at the 2 position, and all are substituted faster than benzene.⁷¹ Pyrrole is particularly reactive, with a reactivity approximating that of aniline or the phenoxide ion. For pyridine,⁷² it is not the free base that must attack the electrophile but the conjugate acid (the pyridinium ion),⁷³ making the reactivity much less than that of benzene, being similar to that of nitrobenzene. The 3 position is most reactive in electrophilic substitution reactions of pyridine. However, groups can be introduced into the 4 position of a pyridine ring indirectly, by performing the reaction on the corresponding pyridine *N*-oxide.⁷⁴ Note that calculations show that the 2-pyridyl and 2-pyrimidyl cations are best represented as *ortho*-hetaryonium ions, being more stable than their positional, nonconjugated isomers by as much as 18–28 kcal mol⁻¹ (75–117 kJ mol⁻¹).⁷⁵



⁶⁷ See Hafner, H.; Moritz, K.L. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 4, Wiley, NY, **1965**, pp. 127–183; Bublitz, D.E.; Rinehart, Jr., K.L. *Org. React.* **1969**, 17, 1.

⁶⁸ See de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution Nitration and Halogenation*, Academic Press, NY, **1959**, pp. 169–209.

⁶⁹ See Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, **1990**.

⁷⁰ Katritzky, A.R.; Fan, W.-Q. *Heterocycles* **1992**, 34, 2179.

⁷¹ See Marino, G. *Adv. Heterocycl. Chem.* **1971**, 13, 235.

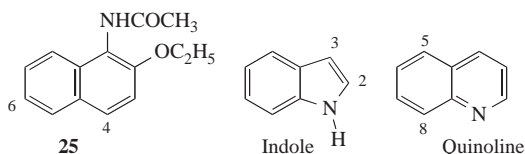
⁷² See Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, 44, 199; Katritzky, A.R.; Johnson, C.D. *Angew. Chem. Int. Ed.* **1967**, 6, 608; Abramovitch, R.A.; Saha, J.G. *Adv. Heterocycl. Chem.* **1966**, 6, 229. Also see Anderson, H.J.; Loader, C.E. *Synthesis* **1985**, 353.

⁷³ Katritzky, A.R.; Kingsland, M. *J. Chem. Soc. B* **1968**, 862.

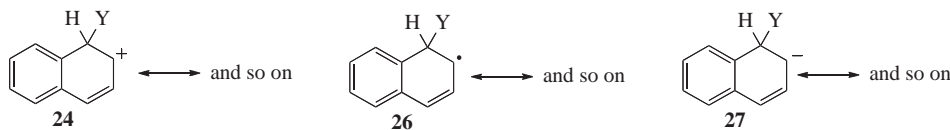
⁷⁴ Jaffé, H.H. *J. Am. Chem. Soc.* **1954**, 76, 3527.

⁷⁵ Gozzo, F. C.; Eberlin, M. N. *J. Org. Chem.* **1999**, 64, 2188.

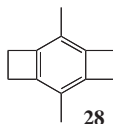
When fused ring systems contain substituents, successful predictions can often be made by using a combination of the above principles. Thus, ring A of 2-methylnaphthalene (**22**) is activated by the methyl group; ring B is not (although the presence of a substituent in a fused ring system affects all the rings,⁷⁶ the effect is generally greatest on the ring to which it is attached). Substitution is therefore expected in ring A. The methyl group activates positions 1 and 3, which are ortho to itself, but not position 4, which is meta to it. However, substitution at the 3 position gives rise to an arenium ion for which it is impossible to write a low-energy canonical form in which ring B has a complete sextet. Only forms like **23** are possible, in which the sextet is no longer intact. In contrast, substitution at the 1 position gives rise to a more stable arenium ion, for which two canonical forms (one of them is **24**) can be written in which ring B is benzenoid. We thus predict predominant substitution at C-1, and that is what is generally found.⁷⁷ However, in some cases predictions are much harder to make. For example, chlorination or nitration of **25** gives mainly the 4 derivative, but bromination yields chiefly the 6 compound.⁷⁸



For fused heterocyclic systems too, predictions can be made based on the above principles, although many exceptions are known. Thus, indole is chiefly substituted in the pyrrole ring (at position 3) and reacts faster than benzene, while quinoline generally reacts in the benzene ring, at the 5 and 8 positions, and slower than benzene, though faster than pyridine.



In alternant hydrocarbons (Sec. 2.J), the reactivity at a given position is similar for electrophilic, nucleophilic, and free radical substitution, because the same kind of resonance can be shown in all three types of intermediate (cf. **24**, **26**, and **27**). Attachment of the electrophile at the position that will best delocalize a positive charge will also best delocalize a negative charge or an unpaired electron. Most results are in accord with these predictions. For example, naphthalene is attacked primarily at the 1 position by NO_2^+ , NH_2^- , and Ph^\cdot , and always more readily than benzene.



⁷⁶ See Ansell, H.V.; Sheppard, P.J.; Simpson, C.F.; Stroud, M.A.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1979**, 381.

⁷⁷ See Kim, J.B.; Chen, C.; Krieger, J.K.; Judd, K.R.; Simpson, C.C.; Berliner, E. *J. Am. Chem. Soc.* **1970**, 92, 910. Also see Gore, P.H.; Siddiquei, A.S.; Thorburn, S. *J. Chem. Soc. Perkin Trans. 1* **1972**, 1781.

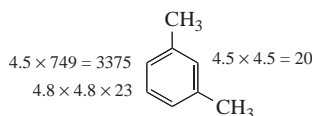
⁷⁸ Bell, F. *J. Chem. Soc.* **1959**, 519.

When strain due to a ring fused on an aromatic ring deforms that ring out of planarity, the molecule is more reactive to electrophilic aromatic substitution.⁷⁹ This has been explained by the presence of a shortened bond for the sp^2 hybridized carbon, increasing the strain at that position. This finding is known as the *Mills–Nixon effect*.⁸⁰ There is EPR evidence (see Sec. 5.C.i) for 3,6-dimethyl-1,2,4,5-tetrahydrobenzo-bis-cyclobutene (**28**), which supports the *Mills–Nixon effect*,⁸¹ and a theoretical study, which supports this.⁸² However, *ab initio* studies of triannelated benzene rings shows *no evidence* for the *Mills–Nixon effect*, and a new motif for bond-alternating benzenes was proposed.⁸³ Indeed, it is argued that the *Mills–Nixon effect* is not real.⁸⁴

11.C. QUANTITATIVE TREATMENTS OF REACTIVITY IN THE SUBSTRATE

Quantitative rate studies of aromatic substitutions are complicated by the fact that there are usually several hydrogen atoms that can leave, so that measurements of overall rate ratios do not give a complete picture as they do in nucleophilic substitutions, where it is easy to compare substrates that have only one possible leaving group in a molecule. What is needed is not, say, the overall rate ratio for acetylation of toluene versus that for benzene, but the *rate ratio at each position*. These can be calculated from the overall rates and a careful determination of the proportion of isomers formed, provided that the products are kinetically controlled, as is usually the case. The *partial rate factor* may be defined for a given group and a given reaction as the rate of substitution at a single position relative to a single position in benzene. For example, for acetylation of toluene the partial rate factors follow: for the ortho position $o_f^{\text{Me}} = 4.5$, for the meta $m_f^{\text{Me}} = 4.8$, and for the para $p_f^{\text{Me}} = 749$.⁸⁵ This means that toluene is acetylated at the ortho position 4.5 times as fast as a single position in benzene, or 0.75 times as fast as the overall rate of acetylation of benzene. A partial rate factor >1 for a given position indicates that the group in question activates that position for the given reaction. Partial rate factors differ from one reaction to another and are even different, though less so, for the same reaction under different conditions.

Once the partial rate factors are known, the proportions of isomers to be obtained when two or more groups are present on a ring can be predicted, *if the assumption is made that the effect of substituents is independent*. For example, if the two methyl groups in *m*-xylene have the same effect as the methyl group in toluene, the theoretical partial rate factors at each position can be calculated by multiplying those from toluene, so they should be as indicated.



⁷⁹ Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, Chichester, **1990**, p. 53.

⁸⁰ Mills, W.H.; Nixon, I.G. *J. Chem. Soc.* **1930**, 2510.

⁸¹ Davies, A.G.; Ng, K.M. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1857.

⁸² Eckert-Maksić, M.; Maksić, Z.B.; Klessinger, M. *J. Chem. Soc. Perkin Trans. 2* **1994**, 285.

⁸³ Baldrige, K.K.; Siegel, J.J. *J. Am. Chem. Soc.* **1992**, *114*, 9583.

⁸⁴ Siegel, J.S. *Angew. Chem. Int. Ed.* **1994**, *33*, 1721.

⁸⁵ Brown, H.C.; Marino, G.; Stock, L.M. *J. Am. Chem. Soc.* **1959**, *81*, 3310.

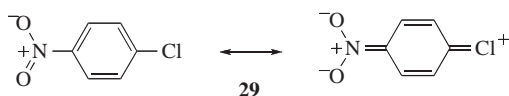
TABLE 11.2 Calculated and Experimental Isomer Distributions in the Acetylation of *m*-Xylene^a

Position	Isomer Distribution (%)	
	Calculated	Observed
2	0.30	0
4	9.36	97.5
5	0.34	2.5

Reprinted with permission Marino G.; Brown, H.C. *J. Am. Chem. Soc.* **1959**, *81*, 5929.
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^aSee Ref. 86.

From this, it is possible to calculate the overall theoretical rate ratio for acetylation of *m*-xylene relative to benzene, since this is one-sixth the sum of the partial rate factors (in this case 1130), and the isomer distribution if the reaction is kinetically controlled. The overall rate ratio actually is 347⁸⁶ and the calculated and observed isomer distributions are listed in Table 11.2.⁸⁶ In this case, and in many others, agreement is fairly good, but many cases are known where the effects are not additive (as in Sec. 11.B.ii).⁸⁷ For example, this treatment predicts that for 1,2,3-trimethylbenzene there should be 35% 5 substitution and 65% 4 substitution, but acetylation gave 79% 5 substitution and 21% of the 4 isomer. The treatment is thrown off by steric effects (e.g., those mentioned earlier, Sec. 11.B.iv), by products arising from ipso attack (Sec. 11.B.ii) and by resonance interaction *between* groups (e.g., **29**), which must make the results deviate from simple additivity of the effects of the groups.



Another approach that avoids the problem created by having competing leaving groups present in the same substrate is the use of substrates that contain only one leaving group. This is most easily accomplished by the use of a leaving group other than hydrogen. By this means, overall rate ratios can be measured for specific positions.⁸⁸ Results obtained in this way⁸⁹ give a reactivity order quite consistent with that for hydrogen as leaving group.

A quantitative scale of reactivity for aromatic substrates (fused, heterocyclic, and substituted rings) has been devised, based on the HSAB concept (Sec. 8.E).⁹⁰ From MO theory, a quantity called *activation hardness* can be calculated for each position of an aromatic ring. The smaller the activation hardness, the faster the attachment at that position; hence the treatment predicts the most likely orientations for incoming groups.

⁸⁶ Marino, G.; Brown, H.C. *J. Am. Chem. Soc.* **1959**, *81*, 5929.

⁸⁷ See Cook, R.S.; Phillips, R.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* **1974**, 1166. For a theoretical treatment of why additivity fails, see Godfrey, M. *J. Chem. Soc. B* **1971**, 1545.

⁸⁸ See Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43.

⁸⁹ See Eaborn, C.; Jackson, P.M. *J. Chem. Soc. B* **1969**, 21.

⁹⁰ Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* **1990**, *112*, 5720.

11.D. A QUANTITATIVE TREATMENT OF REACTIVITY OF THE ELECTROPHILE: THE SELECTIVITY RELATIONSHIP

Not all electrophiles are equally reactive. The nitronium ion is attacked not only by benzene but also by aromatic rings that contain a strongly deactivating group. On the other hand, diazonium ions couple only with rings containing a powerful activating group. Attempts have been made to correlate the influence of substituents with the reactivity of the group being attacked. The most obvious way to do this is with the *Hammett equation* (Sec. 8.G):

$$\log(k, k_0) = \rho \sigma$$

For aromatic substitution,⁹¹ k_0 is divided by 6 and, for meta substitution, k is divided by 2, so that comparisons are made for only one position (consequently, k/k_0 for, say, the methyl group at a para position is identical to the partial rate factor p_f^{Me}). It was soon found that, while this approach worked fairly well for electron-withdrawing groups, it failed for those that are electron donating. However, if the equation is modified by the insertion of the Brown σ^+ values instead of the Hammett σ values (because a positive charge develops during the transition state), more satisfactory correlations can be made, even for electron-donating groups (see Table 9.4 for a list of σ^+ values).⁹² Groups with a negative value of σ_p^+ or σ_m^+ are activating for that position; groups with a positive value are deactivating. The ρ values correspond to the susceptibility of the reaction to stabilization or destabilization by the Z group and to the reactivity of the electrophile. The ρ values vary not only with the electrophile, but also with conditions. A large negative value of ρ means an electrophile of relatively low reactivity. Of course, this approach is completely useless for ortho substitution, since the Hammett equation does not apply there.

A modification of the Hammett approach, suggested by Brown, called the *selectivity relationship*,⁹³ is based on the principle that reactivity of a species varies inversely with selectivity. Table 11.3 shows how electrophiles can be arranged in order of selectivity as measured by two indexes: (1) their selectivity in attacking toluene rather than benzene, and (2) their selectivity between the meta and para positions in toluene.⁹³ As the table shows, an

TABLE 11.3 Relative Rates and Product Distributions in Some Electrophilic Substitutions on Toluene and Benzene^a

Reaction	Relative Rate	Product Distribution, (%)	
	$k_{\text{toluene}}/k_{\text{benzene}}$	<i>m</i>	<i>p</i>
Bromination	605	0.3	66.8
Chlorination	350	0.5	39.7
Benzoylation	110	1.5	89.3
Nitration	23	2.8	33.9
Mercuriation	7.9	9.5	69.5
Isopropylation	1.8	25.9	46.2

^aSee Ref. 93.

⁹¹ See Exner, O.; Böhm, S. *J. Org. Chem.* **2002**, 67, 6320.

⁹² See Koptiyug, V.A.; Salakhutdinov, N.F.; Detsina, A.N. *J. Org. Chem. USSR* **1984**, 20, 1039.

⁹³ Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* **1963**, 1, 35.

electrophile more selective in one respect is also more selective in the other. In many cases, electrophiles known to be more stable (hence less reactive) than others show a higher selectivity, as would be expected. For example, the *tert*-butyl cation is more stable and more selective than the isopropyl (Sec. 5.A.ii), and Br₂ is more selective than Br⁺. However, deviations from the relationship are known.⁹⁴ Selectivity depends not only on the nature of the electrophile, but also on the temperature. As expected, it normally decreases with increasing temperature.

Brown assumed that a good measurement of selectivity was the ratio of the para and meta partial rate factors in toluene. He defined the selectivity S_f of a reaction as:

$$S_f = \log \left(\frac{p_f^{\text{Me}}}{m_f^{\text{Me}}} \right)$$

That is, the more reactive the reactive species, the less preference it has for the para position compared to the meta. If we combine the Hammett–Brown $\sigma^+ \rho$ relationship with the linearity between $\log S_f$ and $\log p_f^{\text{Me}}$ and between $\log S_f$ and $\log m_f^{\text{Me}}$, it is possible to derive the following expressions:

$$\begin{aligned} \log p_f^{\text{Me}} &= \left(\frac{\sigma_p^+}{\sigma_p^+ - \sigma_m^+} \right) S_f \\ \log m_f^{\text{Me}} &= \left(\frac{\sigma_m^+}{\sigma_p^+ - \sigma_m^+} \right) S_f \end{aligned}$$

S_f is related to ρ by $S_f = \rho(\sigma_p^+ - \sigma_m^+)$

The general validity of these equations is supported by a great deal of experimental data on aromatic substitution reactions of toluene. Examples of values for some reactions obtained from these equations are given in Table 11.4.⁹⁵ For other substituents, the treatment works well with groups that, like methyl, are not very polarizable. For more polarizable groups the correlations are sometimes satisfactory and sometimes not, probably because each electrophile in the transition state makes a different demand on the electrons of the substituent group.

Not only are there substrates for which the treatment is poor, but it also fails with very powerful electrophiles. This is the reason why it is necessary to postulate the encounter complex mentioned in Section 11.A.i. For example, relative rates of nitration of *p*-xylene,

TABLE 11.4 Values of m_f^{Me} , p_f^{Me} , S_f , and ρ for Three Reactions of Toluene^a

Reaction	m_f^{Me}	p_f^{Me}	S_f	ρ
PhMe + EtBr $\xrightarrow[\text{benzene, 25}^\circ\text{C}]{\text{GaBr}_3}$	1.56	6.02	0.587	−2.66
PhMe + HNO ₃ $\xrightarrow[45^\circ\text{C}]{90\% \text{ HOAc}}$	2.5	58	1.366	−6.04
PhMe + Br ₂ $\xrightarrow[25^\circ\text{C}]{85\% \text{ HOAc}}$	5.5	2420	2.644	−11.40

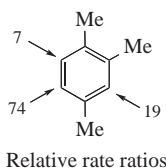
^aSee Ref. 95.

⁹⁴ See Olah, G.A.; Olah, J.A.; Ohyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 5284.

⁹⁵ Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35 presents many tables of these kinds of data. See also, DeHaan, F.P.; Chan, W.H.; Chang, J.; Ferrara, D.M.; Wainschel, L.A. *J. Org. Chem.* **1986**, *51*, 1591, and other papers in this series.

1,2,4-trimethylbenzene, and 1,2,3,5-tetramethylbenzene were 1.0, 3.7, and 6.4,⁹⁶ though the extra methyl groups should enhance the rates much more (*p*-xylene itself reacted 295 times faster than benzene). The explanation is that with powerful electrophiles the reaction rate is so rapid (reaction taking place at virtually every encounter⁹⁷ between an electrophile and substrate molecule)⁹⁸ that the presence of additional activating groups can no longer increase the rate.⁹⁹

Given this behavior (little selectivity in distinguishing between different substrate molecules), the selectivity relationship would predict that positional selectivity should also be very small. However, it is not. For example, under conditions where nitration of *p*-xylene and 1,2,4-trimethylbenzene takes place at about equal rates, there was no corresponding lack of selectivity at positions *within* the latter.¹⁰⁰ Although steric effects are about the same at both positions, >10 times as much 5-nitro product was formed as 6-nitro product. It is clear that the selectivity relationship has broken down and it becomes necessary to explain why such an extremely rapid reaction should occur with positional selectivity. The explanation offered is that the rate-determining step is formation of an encounter complex (**12**, Sec. 11.B.ii).¹⁰¹ Since the position of attachment is not determined in the rate-determining step, the 5:6 ratio is not related to the reaction rate. Essentially the same idea was suggested earlier¹⁰² and for the same reason (failure of the selectivity relationship in some cases), but the earlier explanation specifically pictured the complex as a π complex, and we have seen (Sec. 11.B.ii) that there is evidence against this.



One interesting proposal¹⁰³ is that the encounter pair is a radical pair $\text{NO}_2^\bullet \text{ArH}^{+\bullet}$ formed by an electron transfer (SET), which would explain why the electrophile, once in the encounter complex, can acquire the selectivity that the free NO_2^+ lacked (it is not proposed that a radical pair is present in all aromatic substitutions; only in those that do not obey the selectivity relationship). The radical pair subsequently collapses to the arenium ion. There is evidence¹⁰⁴ both for and against this proposal.¹⁰⁵

⁹⁶ Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* **1974**, *96*, 2892.

⁹⁷ See Moodie, R.B.; Schofield, K.; Thomas, P.N. *J. Chem. Soc. Perkin Trans. 2* **1978**, 318.

⁹⁸ See Ridd, J.H. *Adv. Phys. Org. Chem.* **1978**, *16*, 1.

⁹⁹ Manglik, A.K.; Moodie, R.B.; Schofield, K.; Dedeoglu, E.; Dutly, A.; Rys, P. *J. Chem. Soc. Perkin Trans. 2* **1981**, 1358.

¹⁰⁰ Barnett, J.W.; Moodie, R.B.; Schofield, K.; Taylor, P.G.; Weston, J.B. *J. Chem. Soc. Perkin Trans. 2* **1979**, 747.

¹⁰¹ See Sheats, G.F.; Strachan, A.N. *Can. J. Chem.* **1978**, *56*, 1280. Also see Attinà, M.; Cacace, F.; de Petris, G. *Angew. Chem. Int. Ed.* **1987**, *26*, 1177.

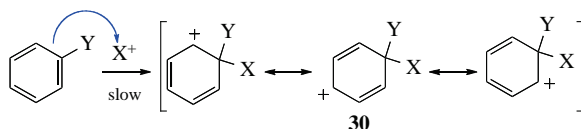
¹⁰² Olah, G.A. *Acc. Chem. Res.* **1971**, *4*, 240.

¹⁰³ Perrin, C.L. *J. Am. Chem. Soc.* **1977**, *99*, 5516.

¹⁰⁴ See Sankararaman, S.; Haney, W.A.; Kochi, J.K. *J. Am. Chem. Soc.* **1987**, *109*, 5235; Keumi, T.; Hamanaka, K.; Hasegawa, K.; Minamide, N.; Inoue, Y.; Kitajima, H. *Chem. Lett.* **1988**, 1285; Johnston, J.F.; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* **1989**, 244. For evidence against it, see Eberson, L.; Radner, F. *Acc. Chem. Res.* **1987**, *20*, 53; Baciocchi, E.; Mandolini, L. *Tetrahedron* **1987**, *43*, 4035.

¹⁰⁵ See Morkovnik, A.S. *Russ. Chem. Rev.* **1988**, *57*, 144.

11.E. THE EFFECT OF THE LEAVING GROUP



In the vast majority of aromatic electrophilic substitutions, the leaving group is H^+ as indicated above, and very little work has been done on the relative electrofugal ability of other leaving groups. However, the following orders of leaving-group ability have been suggested¹⁰⁶: (1) for leaving groups that depart without assistance ($\text{S}_{\text{N}}1$ process with respect to the leaving group), $\text{NO}_2^+^{107} < i\text{Pr}^+ \sim \text{SO}_3 < t\text{-Bu}^+ \sim \text{ArN}_2^+ < \text{ArCHOH}^+ < \text{NO}^+ < \text{CO}_2$; (2) for leaving groups that depart with assistance from an outside nucleophile ($\text{S}_{\text{N}}2$ process), $\text{Me}^+ < \text{Cl}^+ < \text{Br}^+ < \text{D}^+ \sim \text{RCO}^+ < \text{H}^+ \sim \text{I}^+ < \text{Me}_3\text{Si}^+$. We can use this kind of list to help predict which group, X or Y, will cleave from an arenium ion **30** (see **1**, where $\text{Y} = \text{H}$) once it has been formed, and so obtain an idea of which electrophilic substitutions are feasible. However, a potential leaving group can also affect a reaction in another way: by influencing the rate at which attack of the original electrophile leads to attachment directly at the ipso position. Partial rate factors for electrophilic attack at a position substituted by a group other than hydrogen are called ipso partial rate factors (i_f^X).⁵⁷ Such factors for the nitration of *p*-haloanisoles are 0.18, 0.08, and 0.06, for *p*-iodo-, *p*-bromo-, and *p*-chloroanisole, respectively.¹⁰⁸ This means, for example, that attack at the electrophile in this case leads to attachment at the 4 position of 4-iodoanisole 0.18 times as fast as a single position of benzene. Note that this is far slower than attachment at the 4 position resulting from attack of anisole itself so that the presence of the iodo group greatly slows the reaction at that position. A similar experiment on *p*-cresol showed that ipso attack at the methyl position was 6.8 times slower than attack of phenol leading to attachment at the para position.¹⁰⁹ Thus, in these cases, both an iodo and a methyl group deactivate the ipso position.¹¹⁰

11.F. REACTIONS

The reactions in this chapter are classified according to leaving group. Hydrogen replacements are treated first, and then rearrangements in which the attacking entity is first cleaved from another part of the molecule (hydrogen is also the leaving group in these cases), and finally replacements of other leaving groups.

¹⁰⁶ Perrin, C.L. *J. Org. Chem.* **1971**, 36, 420.

¹⁰⁷ See Bullen, J.V.; Ridd, J.H.; Sabek, O. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1681, and other papers in this series.

¹⁰⁸ Perrin, C.L.; Skinner, G.A. *J. Am. Chem. Soc.* **1971**, 93, 3389. See also, Fischer, P.B.; Zollinger, H. *Helv. Chim. Acta* **1972**, 55, 2139.

¹⁰⁹ Tee, O.; Iyengar, N.R.; Bennett, J.M. *J. Org. Chem.* **1986**, 51, 2585.

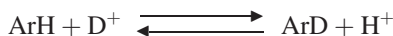
¹¹⁰ See Clemens, A.H.; Hartshorn, M.P.; Richards, K.E.; Wright, G.J. *Aust. J. Chem.* **1977**, 30, 103, 113.

11.F.i. Hydrogen as the Leaving Group in Simple Substitution Reactions

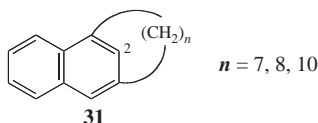
A. Hydrogen as the Electrophile

11-1 Hydrogen Exchange

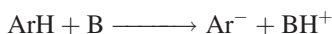
Deuterio-de-hydrogenation or Deuteration



Aromatic compounds can exchange hydrogen atoms when treated with acids. The reaction is used chiefly to study mechanistic questions¹¹¹ (including substituent effects), but can also be useful to deuterate (add ^2H) or tritiate (add ^3H) aromatic rings selectively. The usual directive effects apply and, for example, phenol treated with D_2O gives slow exchange on heating, with only ortho and para hydrogen atoms being exchanged.¹¹² Strong acids, of course, exchange faster with aromatic substrates, and this exchange must be taken into account when studying the mechanism of any aromatic substitution catalyzed by acids. There is a great deal of evidence that exchange takes place by the ordinary arenium ion mechanism. Among the evidence are the orientation effects noted above and the finding that the reaction is general acid catalyzed, which means that a proton is transferred in the slow step¹¹³ (Sec. 8.D). Furthermore, many examples have been reported of stable solutions of arenium ions formed by attack of a proton on an aromatic ring.⁵ Simple aromatic compounds can be extensively deuterated in a convenient fashion by treatment with D_2O and BF_3 .¹¹⁴ It has been shown that tritium exchange takes place readily at the 2 position of **31**, despite the fact that this position is hindered by the bridge. The rates were not very different from the comparison compound 1,3-dimethylnaphthalene.¹¹⁵



Hydrogen exchange can also be effected with strong bases¹¹⁶ (e.g., NH_2^-). In these cases, the slow step is the proton transfer:¹¹⁷



so the $\text{S}_{\text{E}}1$ mechanism and not the usual arenium ion mechanism is operating.¹¹⁸ Aromatic rings can also be deuterated by treatment with D_2O and a Rh(III) chloride¹¹⁹ or Pt¹²⁰ catalyst

¹¹¹ See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 194–277.

¹¹² Small, P.A.; Wolfenden, J.H. *J. Chem. Soc.* **1936**, 1811.

¹¹³ See Kresge, A.J.; Chiang, Y.; Sato, Y. *J. Am. Chem. Soc.* **1967**, 89, 4418; Gruen, L.C.; Long, F.A. *J. Am. Chem. Soc.* **1967**, 89, 1287; Butler, A.B.; Hendry, J.B. *J. Chem. Soc. B* **1970**, 852.

¹¹⁴ Larsen, J.W.; Chang, L.W. *J. Org. Chem.* **1978**, 43, 3602.

¹¹⁵ Laws, A.P.; Neary, A.P.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1033.

¹¹⁶ See Elvidge, J.A.; Jones, J.R.; O'Brien, C.; Evans, E.A.; Sheppard, H.C. *Adv. Heterocycl. Chem.* **1974**, 16, 1.

¹¹⁷ For a discussion of the aromatic character of this transition state, see Bernasconi, C.F. *Pure Appl. Chem.* **2009**, 81, 649.

¹¹⁸ Shatenshtein, A.I. *Tetrahedron* **1962**, 18, 95.

¹¹⁹ Lockley, W.J.S. *Tetrahedron Lett.* **1982**, 23, 3819; *J. Chem. Res. (S)* **1985**, 178.

¹²⁰ See Blake, M.R.; Garnett, J.L.; Gregor, I.K.; Hannan, W.; Hoa, K.; Long, M.A. *J. Chem. Soc., Chem. Commun.* **1975**, 930. See also, Parshall, G.W. *Acc. Chem. Res.* **1975**, 8, 113.

or with C_6D_6 and an alkylaluminum dichloride catalyst,¹²¹ though rearrangements may take place during the latter procedure. Tritium (^3H , abbreviated T) can be introduced by treatment with T_2O and an alkylaluminum dichloride catalyst.¹²¹ Tritiation at specific sites (e.g., >90% para in toluene) has been achieved with T_2 gas and a microporous aluminophosphate catalyst.¹²²

B. Nitrogen Electrophiles

11-2 Nitration or Nitro-de-hydrogenation



Most aromatic compounds, whether of high or low reactivity, can be nitrated, because a wide variety of nitrating agents is available.¹²³ For benzene, the simple alkylbenzenes, and less reactive compounds, the most common reagent is a mixture of concentrated nitric and sulfuric acids,¹²⁴ but for active substrates, the reaction can be carried out with nitric acid alone,¹²⁵ or in water, acetic acid, acetic anhydride, or chloroform.¹²⁶ Milder conditions are necessary for active compounds (e.g., amines, phenols, and pyrroles), since reaction with mixed nitric and sulfuric acids would oxidize these substrates. With active substrates, (e.g., anilines¹²⁷ and phenols,¹²⁸ nitration can be accomplished by nitrosation under oxidizing conditions with a mixture of dilute nitrous and nitric acids.¹²⁹ Trimethoxybenzenes were nitrated easily with ceric ammonium nitrate on silica gel,¹³⁰ and mesitylene was nitrated in an ionic liquid using nitric acid–acetic anhydride.¹³¹ Phenol can also be nitrated in an ionic liquid.¹³² An alternative route for the nitration of activated aromatic compounds (e.g., anisole), used a nitrate ester (RONO_2) with triflic acid in an ionic liquid for ortho-selective nitration.¹³³

¹²¹ Long, M.A.; Garnett, J.L.; West, J.C. *Tetrahedron Lett.* **1978**, 4171.

¹²² Garnett, J.L.; Kennedy, E.M.; Long, M.A.; Than, C.; Watson, A.J. *J. Chem. Soc., Chem. Commun.* **1988**, 763.

¹²³ See Esteves, P.M.; de M. Carneiro, J.W.; Cardoso, S.P.; Barbosa, A.G.H.; Laali, K.K.; Rasul, G.; Prakash, G.K.S.; Olah, G.A. *J. Am. Chem. Soc.* **2003**, *125*, 4836; Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration: Methods and Mechanisms*, VCH, NY, **1989**; Schofield, K. *Aromatic Nitration*, Cambridge University Press, Cambridge, **1980**; Hoggett, J.H.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, **1971**; Weaver, W.M. in Feuer, H. *Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, **1970**, pp. 1–48; de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution Nitration and Halogenation*, Academic Press, NY, **1959**, pp. 48–93. For a review of side reactions, see Suzuki, H. *Synthesis* **1977**, 217. Also see, Bosch, E.; Kochi, J.K. *J. Org. Chem.* **1994**, *59*, 3314; Olah, G.A.; Wang, Q.; Li, X.; Bucsi, I. *Synthesis* **1992**, 1085; Olah, G.A.; Reddy, V.P.; Prakash, G.K.S. *Synthesis* **1992**, 1087.

¹²⁴ Ramana, M.M.V.; Malik, S.S.; Parihar, J.A. *Tetrahedron Lett.* **2004**, *45*, 8681.

¹²⁵ See Parac-Vogt, T.N.; Binnemans, K. *Tetrahedron Lett.* **2004**, *45*, 3137.

¹²⁶ See Tasneem, Ali, M.M.; Rajanna, K.C.; Saiparakash, P.K. *Synth. Commun.* **2001**, *31*, 1123.

¹²⁷ See Yang, X.; Xi, C. *Synth. Commun.* **2007**, *37*, 3381.

¹²⁸ Calcium nitrate can be used for the microwave nitration of phenolic compounds. See Bose, A.K.; Ganguly, S.N.; Manhas, M.S.; Rao, S.; Speck, J.; Pekelny, U.; Pombo-Villars, E. *Tetrahedron Lett.* **2006**, *47*, 1885. Also see Anuradha, V.; Srinivas, P.V.; Aparna, P.; Rao, J.M. *Tetrahedron Lett.* **2006**, *47*, 4933; Shi, M.; Cui, S.-C.; Yin, W.-P. *Eur. J. Org. Chem.* **2005**, 2379.

¹²⁹ See Ridd, J.H. *Chem. Soc. Rev.* **1991**, *20*, 149.

¹³⁰ Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* **1999**, *29*, 1195.

¹³¹ Lancaster, N.L.; Llopis-Mestre, V. *Chem. Commun.* **2003**, 2812.

¹³² Rajogopal, R.; Srinivasan, K.V. *Synth. Commun.* **2004**, *34*, 961.

¹³³ Laali, K.K.; Gettewert, V.J. *J. Org. Chem.* **2001**, *66*, 35.

For nitration reactions of “normal” aromatic compounds, representative nitrating agents are NaNO_2 and trifluoroacetic acid,¹³⁴ $\text{N}_2\text{O}_4/\text{O}_2$ and a catalytic amount of zeolite H β ,¹³⁵ $\text{Yb}(\text{OTf})_3$,¹³⁶ $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$,¹³⁷ ceric ammonium nitrate,¹³⁸ urea nitrate and nitrourea,¹³⁹ and nitronium salts.¹⁴⁰ A mixture of NO_2 and ozone has also been used.¹⁴¹ Nitric acid, in the presence of P_2O_5 supported on SiO_2 , is useful for the nitration of aromatic compounds under solvent-free conditions.¹⁴² Nitration of styrene poses a problem since addition occurs at the $\text{C}=\text{C}$ unit to give a 1-nitroethyl aryl.¹⁴³ Deactivated aromatic rings, as in acetophenone, were nitrated with N_2O_5 and $\text{Fe}(\text{acac})_2$ ($\text{acac}=\text{acetylacetone}$).¹⁴⁴ Heterocycles (e.g., pyridine) are nitrated with N_2O_5 and SO_2 .¹⁴⁵

When anilines are nitrated under strong acid conditions, meta orientation is generally observed, because the ammonium salt is the species undergoing nitration, which is the conjugate acid of the amine. If the conditions are less acidic, the free amine is nitrated and the orientation is ortho–para. Although the free base may be present in much smaller amounts than the conjugate acid, it is far more susceptible to aromatic substitution (see also, Sec. 11.B.i). Because of these factors and because they are vulnerable to oxidation by nitric acid, primary aromatic amines are often protected before nitration by treatment with acetyl chloride (Reaction 16-72) or acetic anhydride (Reaction 16-73). Nitration of the resulting acetanilide derivative avoids all these problems. There is evidence that when the reaction takes place on the free amine, it is the nitrogen that is attacked to give an *N*-nitro compound ($\text{Ar}-\text{NH}-\text{NO}_2$), which rapidly undergoes rearrangement (see Reaction 11-28) to give the product.¹⁴⁶

Since the nitro group is deactivating, it is usually easy to stop the reaction after one group has entered the ring, but a second and a third group can be introduced if desired, especially when an activating group is also present. Even *m*-dinitrobenzene can be nitrated if vigorous conditions are applied. This has been accomplished with $\text{NO}_2^+ \text{BF}_4^-$ in FSO_3H at 150 °C.¹⁴⁷

¹³⁴ Uemura, S.; Toshimitsu, A.; Okano, M. *J. Chem. Soc. Perkin Trans. 1* **1978**, 1076; Zolfigol, M.A.; Ghaemi, E.; Madrakian, E. *Synth. Commun.* **2000**, 30, 1689; Zolfigol, M.A.; Bagherzadeh, M.; Madrakian, E.; Gaemi, E.; Taqian-Nasab, A. *J. Chem. Res. (S)* **2001**, 140.

¹³⁵ Smith, K.; Almeer, S.; Black, S.J. *Chem. Commun.* **2000**, 1571. See also, Smith, K.; Musson, A.; DeBoos, G. *A. J. Org. Chem.* **1998**, 63, 8448.

¹³⁶ Barrett, A.G.M.; Braddock, D.C.; Ducray, R.; McKinnell, R.M.; Waller, F.J. *Synlett* **2000**, 57.

¹³⁷ Sun, H.-B.; Hua, R.; Yin, Y. *J. Org. Chem.* **2005**, 70, 9071.

¹³⁸ Yang, X.; Xi, C.; Jiang, Y. *Tetrahedron Lett.* **2005**, 46, 8781.

¹³⁹ Almog, J.; Klein, A.; Sokol, A.; Sasson, Y.; Sonenfeld, D.; Tamiri, T. *Tetrahedron Lett.* **2006**, 47, 8651.

¹⁴⁰ Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* **1962**, 84, 3684. Also see Iranpoor, N.; Firouzabadi, H.; Heydari, R. *Synth. Commun.* **1999**, 29, 3295; Guk, Yu. V.; Ilyushin, M.A.; Golod, E.L.; Gidasov, B.V. *Russ. Chem. Rev.* **1983**, 52, 284.

¹⁴¹ Nose, M.; Suzuki, H.; Suzuki, H. *J. Org. Chem.* **2001**, 66, 4356; Peng, X.; Suzuki, H. *Org. Lett.* **2001**, 3, 3431.

¹⁴² Hajipour, A.R.; Ruoho, A.E. *Tetrahedron Lett.* **2005**, 46, 8307.

¹⁴³ Lewis, R.J.; Moodie, R.B. *J. Chem. Soc. Perkin Trans. 2* **1997**, 563.

¹⁴⁴ Bak, R.R.; Smallridge, A.J. *Tetrahedron Lett.* **2001**, 42, 6767.

¹⁴⁵ Arnestad, B.; Bakke, J.M.; Hegbom, I.; Ranes, E. *Acta Chem. Scand. B* **1996**, 50, 556.

¹⁴⁶ Ridd, J.H.; Scriven, E.F.V. *J. Chem. Soc., Chem. Commun.* **1972**, 641. See also, Helsby, P.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1191.

¹⁴⁷ Olah, G.A.; Lin, H.C. *Synthesis* **1974**, 444.

With most of the reagents mentioned, the attacking species is the nitronium ion (NO_2^+). Among the ways in which this ion is formed are

1. In concentrated sulfuric acid, by an acid–base reaction in which nitric acid is the base:



This ionization is essentially complete.

2. In concentrated nitric acid alone,¹⁴⁸ by a similar acid–base reaction in which one molecule of nitric acid is the acid and another the base:



This equilibrium lies to the left ($\sim 4\%$ ionization), but enough NO_2^+ is formed for nitration to occur.

3. The equilibrium just mentioned occurs to a small extent even in organic solvents.
4. With N_2O_5 in CCl_4 , there is spontaneous dissociation:



but in this case there is evidence that some nitration also takes place with undissociated N_2O_5 as the electrophile.

5. When nitronium salts are used, NO_2^+ is of course present to begin with. Esters and acyl halides of nitric acid ionize to form NO_2^+ .

There is a great deal of evidence that NO_2^+ is present in most nitration reactions and that it is the attacking entity,¹⁴⁹ for example,

1. Nitric acid has a peak in the Raman spectrum. When nitric acid is dissolved in concentrated sulfuric acid, the peak disappears and two new peaks appear, one at 1400 cm^{-1} attributable to NO_2^+ and one at 1050 cm^{-1} due to HSO_4^- .¹⁵⁰
2. On addition of nitric acid, the freezing point of sulfuric acid is lowered about four times the amount expected if no ionization has taken place.¹⁵¹ This means that the addition of one molecule of nitric acid results in the production of four particles, which is strong evidence for the ionization reaction between nitric and sulfuric acids given above.
3. The fact that nitronium salts in which nitronium ion is known to be present (by X-ray studies) nitrate aromatic compounds shows that this ion does attack the ring.
4. The rate of the reaction with most reagents is proportional to the concentration of NO_2^+ , not to that of other species.¹⁵² When the reagent produces this ion in small

¹⁴⁸ See Belson, D.J.; Strachan, A.N. *J. Chem. Soc. Perkin Trans. 2* **1989**, 15.

¹⁴⁹ Hughes, E.D.; Ingold, C.K. in a series of several papers with several different coworkers, see *J. Chem. Soc.* **1950**, 2400.

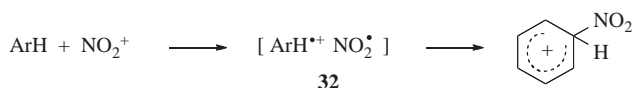
¹⁵⁰ Ingold, C.K.; Millen, D.J.; Poole, H.G. *J. Chem. Soc.* **1950**, 2576.

¹⁵¹ Gillespie, R.J.; Graham, J.; Hughes, E.D.; Ingold, C.K.; Peeling, E.R.A. *J. Chem. Soc.* **1950**, 2504.

¹⁵² See Ross, D.S.; Kuhlmann, K.F.; Malhotra, R. *J. Am. Chem. Soc.* **1983**, 105, 4299.

amounts, the attack is slow and only active substrates can be nitrated. In concentrated and aqueous mineral acids, the kinetics are second order: first order each in aromatic substrate and in nitric acid (unless pure nitric acid is used in which case there are pseudo-first-order kinetics). But in organic solvents (e.g., nitromethane, acetic acid, and CCl_4), the kinetics are first order in nitric acid alone and zero order in aromatic substrate, because the rate-determining step is formation of NO_2^+ and the substrate does not take part in this.

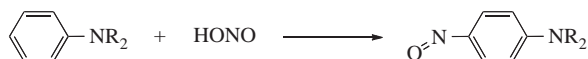
In a few cases, depending on the substrate and solvent, there is evidence that the arenium ion is not formed directly, but via the intermediacy of a radical pair (see Sec. 11.D), such as **32**.¹⁵³



Arylboronic acids have been shown to react with ammonium nitrate and trifluoroacetic acid to give the corresponding nitrobenzene.¹⁵⁴

OS **I**, 372, 396, 408 (see also, OS **53**, 129); **II**, 254, 434, 438, 447, 449, 459, 466; **III**, 337, 644, 653, 658, 661, 837; **IV**, 42, 364, 654, 711, 722, 735; **V**, 346, 480, 829, 1029, 1067.

11-3 Nitrosation or Nitroso-de-hydrogenation



Ring nitrosation¹⁵⁵ with nitrous acid is normally carried out only with active substrates (e.g., amines and phenols). However, primary aromatic amines give diazonium ions (Reaction **13-19**) when treated with nitrous acid,¹⁵⁶ and secondary amines tend to give *N*-nitroso rather than *C*-nitroso compounds (Reaction **12-50**); hence this reaction is normally limited to phenols and tertiary aromatic amines. Nevertheless, secondary aromatic amines can be *C*-nitrosated in two ways. The *N*-nitroso compound first obtained can be isomerized to a *C*-nitroso compound (Reaction **11-29**), or it can be treated with another equivalent of nitrous acid to give an *N,C*-dinitroso compound. Also, a successful nitrosation of anisole has been reported, where the solvent was $\text{CF}_3\text{COOH}-\text{CH}_2\text{Cl}_2$.¹⁵⁷

Much less work has been done on the mechanism of this reaction than on Reaction **11-2**.¹⁵⁸ In some cases, the attacking entity is NO^+ , but in others it is apparently NOCl , NOBr , N_2O_3 , and so on, in each of which there is a carrier of NO^+ . Both NOCl and NOBr are formed during the normal process of making nitrous acid (the treatment of sodium nitrite with HCl or HBr). Nitrosation requires active substrates because NO^+ is much

¹⁵³ See Ridd, J.H. *Chem. Soc. Rev.* **1991**, 20, 149; Kochi, J.K. *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, 1, 53.

¹⁵⁴ Prakash, G.K.S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N.A.; Olah, G.A. *Org. Lett.* **2004**, 6, 2205.

¹⁵⁵ See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, **1988**, pp. 58–76. Also see, Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc. Perkin Trans. 2* **1997**, 663.

¹⁵⁶ See Hoefnagel, M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* **1989**, 108, 97.

¹⁵⁷ Radner, F.; Wall, A.; Loncar, M. *Acta Chem. Scand.* **1990**, 44, 152.

¹⁵⁸ See Williams, D.L.H. *Adv. Phys. Org. Chem.* **1983**, 19, 381. See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, **1988**, pp. 58–76; Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc. Perkin Trans. 2* **1997**, 663.

less reactive than NO_2^+ . Kinetic studies have shown that NO^+ is at least 10^{14} times less reactive than NO_2^+ .¹⁵⁹ A consequence of the relatively high stability of NO^+ is that this species is easily cleaved from the arenium ion, so that k_{-1} competes with k_2 (Sec. 11.A.i) and isotope effects are found.¹⁶⁰ With phenols, there is evidence that nitrosation may first take place at the OH group, after which the nitrite ester thus formed rearranges to the C-nitroso product.¹⁶¹ Tertiary aromatic amines substituted in the ortho position generally do not react with HONO, probably because the ortho substituent prevents planarity of the dialkylamino group, without which the ring is no longer activated. This is an example of steric inhibition of resonance (Sec. 2.F).

OS I, 214, 411, 511; II, 223; IV, 247.

11-4 Diazonium Coupling

Arylazo-de-hydrogenation



Aromatic diazonium ions normally couple only with active substrates (e.g., amines and phenols).¹⁶² Many of the products of this reaction are used as dyes (*azo dyes*).¹⁶³ Presumably because of the size of the species attacked by the aromatic ring, substitution is mostly para to the activating group, unless that position is already occupied, in which case ortho substitution takes place. The pH of the solution is important both for phenols and amines. For amines, the solutions may be mildly acidic or neutral. The fact that amines give ortho and para products shows that even in mildly acidic solution they react in their un-ionized form. If the acidity is too high, the reaction does not occur, because the concentration of free amine becomes too small. Phenols must be coupled in slightly alkaline solution where they are converted to the more reactive phenoxide ions, because phenols themselves are not active enough for the reaction. However, neither phenols nor amines react in moderately alkaline solution, because the diazonium ion is converted to a diazo hydroxide ($\text{Ar}-\text{N}=\text{N}-\text{OH}$). Primary and secondary amines face competition from attack at the nitrogen.¹⁶⁴ However, the resulting *N*-azo compounds (aryl triazenes) can be isomerized to *C*-azo compounds (Reaction 11-30). In at least some cases, even when the *C*-azo compound is isolated, it is the result of initial *N*-azo compound formation followed by isomerization. It is therefore possible to synthesize the *C*-azo compound directly in one laboratory step.¹⁶⁵ Acylated amines and phenolic ethers and esters are ordinarily not active enough for this reaction, though it is sometimes possible to couple them (as well as such polyalkylated benzenes as mesitylene and pentamethylbenzene) to diazonium ions containing electron-withdrawing groups in the para position, since such groups increase the concentration of the positive charge and thus the electrophilicity of the ArN_2^+ . Some coupling reactions that are otherwise very slow

¹⁵⁹ Challis, B.C.; Higgins, R.J.; Lawson, A.J. *J. Chem. Soc. Perkin Trans. 2* **1972**, 1831; Challis, B.C.; Higgins, R.J. *J. Chem. Soc. Perkin Trans. 2* **1972**, 2365.

¹⁶⁰ Challis, B.C.; Higgins, R.J. *J. Chem. Soc. Perkin Trans. 2* **1973**, 1597.

¹⁶¹ Gosney, A.P.; Page, M.I. *J. Chem. Soc. Perkin Trans. 2* **1980**, 1783.

¹⁶² See Szele, I.; Zollinger, H. *Top. Curr. Chem.* **1983**, 112, 1; Hegarty, A.F. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, **1978**, pp. 545–551.

¹⁶³ See Zollinger, H. *Color Chemistry*, VCH, NY, **1987**, pp. 85–148; Gordon, P.F.; Gregory, P. *Organic Chemistry in Colour*, Springer, NY, **1983**, pp. 95–162.

¹⁶⁴ See Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* **1981**, 64, 1717, 1728.

¹⁶⁵ Kelly, R.P.; Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* **1982**, 65, 122.

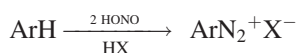
(in cases where the coupling site is crowded) are catalyzed by pyridine for reasons discussed in Section 11.A.i. Phase-transfer catalysis has also been used.¹⁶⁶

Coupling of a few aliphatic diazonium compounds to aromatic rings has been reported. All the examples reported so far involve cyclopropanediazonium ions and bridgehead diazonium ions, in which loss of N₂ would lead to very unstable carbocations.¹⁶⁷ Azobenzenes have been prepared by Pd catalyzed coupling of aryl hydrazides with aryl halides, followed by direct oxidation.¹⁶⁸

The mechanism of (*Z/E*) isomerization in Ar—N=NAr systems has been studied.¹⁶⁹ OS I, 49, 374; II, 35, 39, 145.

11-5 Direct Introduction of the Diazonium Group

Diazonation or Diazonio-de-hydrogenation



Diazonium salts can be prepared directly by replacement of an aromatic hydrogen without the necessity of going through the amino group.¹⁷⁰ The reaction is essentially limited to active substrates (amines and phenols), since otherwise poor yields are obtained. Since the reagents and the substrate are the same as in Reaction 11-3, the first species formed is the nitroso compound. In the presence of excess nitrous acid, this is converted to the diazonium ion.¹⁷¹ The reagent (azidochloromethylene)dimethylammonium chloride [Me₂N=C(Cl)N₃ Cl[−]] can also introduce the diazonium group directly into a phenol.¹⁷² A synthesis of solid aryldiazonium chlorides is now available.¹⁷³

11-6 Amination or Amino-de-hydrogenation¹⁷⁴



Aromatic compounds can be converted to primary aromatic amines in 10–65% yields, by treatment with hydrazoic acid (HN₃) in the presence of AlCl₃ or H₂SO₄.¹⁷⁵ Higher yields (>90%) have been reported with trimethylsilyl azide (Me₃SiN₃) and triflic acid (F₃CSO₂OH).¹⁷⁶ Treatment of an aromatic compound with tetramethylhydrazonium iodide and then ammonium also gives the aryl amine.¹⁷⁷ Tertiary amines have been prepared in ~50–90% yields by treatment of aromatic hydrocarbons with *N*-chlorodialkylamines; by heating in 96% sulfuric acid; or with AlCl₃ or FeCl₃ in nitroalkane solvents; or

¹⁶⁶ Hashida, Y.; Kubota, K.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* **1988**, 61, 905.

¹⁶⁷ See Szele, I.; Zollinger, H. *Top. Curr. Chem.* **1983**, 112, 1, see pp. 3–6.

¹⁶⁸ Lim, Y.-K.; Lee, K.-S.; Cho, C.-G. *Org. Lett.* **2003**, 5, 979.

¹⁶⁹ Asano, T.; Furuta, H.; Hofmann, H.-J.; Cimiraglia, R.; Tsuno, Y.; Fujio, M. *J. Org. Chem.* **1993**, 58, 4418.

¹⁷⁰ Tedder, J.M. *J. Chem. Soc.* **1957**, 4003.

¹⁷¹ Kamalova, F.R.; Nazarova, N.E.; Solodova, K.V.; Yaskova, M.S. *J. Org. Chem. USSR* **1988**, 24, 1004.

¹⁷² Kokel, B.; Viehe, H.G. *Angew. Chem. Int. Ed.* **1980**, 19, 716.

¹⁷³ Mohamed, S.K.; Gomaa, M.A.-M.; El-Din, A.M.N. *J. Chem. Res. (S)* **1997**, 166.

¹⁷⁴ See Kovacic, P. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 1493–1506.

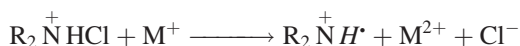
¹⁷⁵ Kovacic, P.; Russell, R.L.; Bennett, R.P. *J. Am. Chem. Soc.* **1964**, 86, 1588.

¹⁷⁶ Olah, G.A.; Ernst, T.D. *J. Org. Chem.* **1989**, 54, 1203.

¹⁷⁷ Rozhkov, V.V.; Shevlev, S.A.; Chervin, I.T.; Mitchel, A.R.; Schmidt, R.D. *J. Org. Chem.* **2003**, 68, 2498.

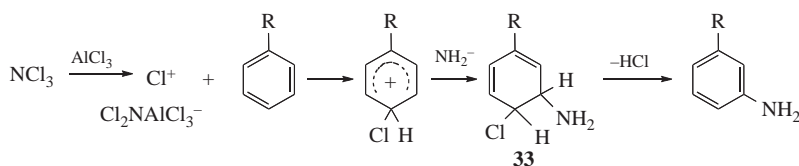
by irradiation.¹⁷⁸ Treatment of an aryl halide with an amine and a Pd catalyst leads to the aniline derivative.¹⁷⁹

Tertiary (and to a lesser extent, secondary) aromatic amines can also be prepared in moderate-to-high yields by amination with an *N*-chlorodialkylamine (or an *N*-chloroalkylamine) and a metallic-ion catalyst (e.g., Fe²⁺, Ti³⁺, Cu⁺, Cr²⁺) in the presence of sulfuric acid.¹⁸⁰ The attacking species in this case is the aminium radical ion (R₂NH^{•+}) formed by¹⁸¹



Because attack is by a positive species (even though it is a free radical), orientation is similar to that in other electrophilic substitutions (e.g., phenol and acetanilide give ortho and para substitution, mostly para). When an alkyl group is present, attack at the benzylic position competes with ring substitution. Aromatic rings containing only meta-directing groups do not give the reaction at all. Fused-ring systems react well.¹⁸²

Unusual orientation has been reported for amination with haloamines and with NCl₃ in the presence of AlCl₃. For example, toluene gave predominately meta amination.¹⁸³ It has been suggested that initial attack in this case is by Cl⁺ and that a nitrogen nucleophile (whose structure is not known but is represented here as NH₂[−] for simplicity) adds to the resulting arenium ion, so that the initial reaction is addition to a carbon–carbon double bond followed by elimination of HCl from **33**.¹⁸⁴



According to this suggestion, the electrophilic attack is at the para position (or the ortho, which leads to the same product) and the meta orientation of the amino group arises indirectly. This mechanism is called the *σ*-substitution mechanism.

Diphenyliodonium salts react with amines in the presence of a Cu catalyst. Diphenyliodonium tetrafluoroborate, (Ph₂I⁺ BF₄[−]), reacts with indole in DMF at 150 °C with a Cu (OAc)₂ catalyst (e.g., to give *N*-phenylindole).¹⁸⁵

Aromatic compounds that do not contain meta-directing groups can be converted to diarylamines by treatment with aryl azides in the presence of phenol at −60 °C: ArH + Ar'N₃ → ArNHAr'.¹⁸⁶ Diarylamines are also obtained by the reaction of

¹⁷⁸ Bock, H.; Kompa, K. *Angew. Chem. Int. Ed.* **1965**, 4, 783; *Chem. Ber.* **1966**, 99, 1347, 1357, 1361.

¹⁷⁹ Guram, A.S.; Rennels, R.A.; Buchwald, S.L. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1348.

¹⁸⁰ See Minisci, F. *Top. Curr. Chem.* **1976**, 62, 1, see pp. 6–16, *Synthesis* **1973**, 1, see pp. 2–12, Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* **1972**, 4, 203, pp. see 213–238.

¹⁸¹ See Chow, Y.L. *React. Intermed. (Plenum)* **1980**, 1, 151.

¹⁸² See Citterio, A.; Gentile, A.; Minisci, F.; Navarrini, V.; Serravalle, M.; Ventura, S. *J. Org. Chem.* **1984**, 49, 4479.

¹⁸³ See Strand, J.W.; Kovacic, P. *J. Am. Chem. Soc.* **1973**, 95, 2977 and references cited therein.

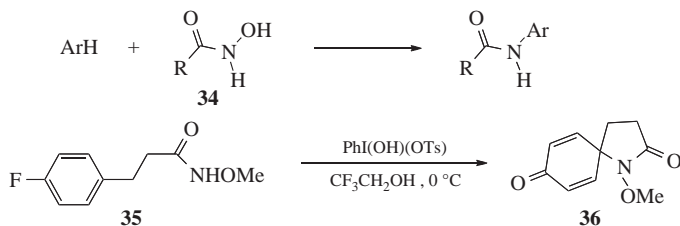
¹⁸⁴ Kovacic, P.; Levisky, J.A. *J. Am. Chem. Soc.* **1966**, 88, 1000.

¹⁸⁵ Zhou, T.; Chen, Z.-C. *Synth. Commun.* **2002**, 32, 903.

¹⁸⁶ Nakamura, K.; Ohno, A.; Oka, S. *Synthesis* **1974**, 882. See also, Takeuchi, H.; Takano, K. *J. Chem. Soc. Perkin Trans. 1* **1986**, 611.

N-arylhydroxylamines with aromatic compounds (benzene, toluene, anisole) in the presence of F_3CCO_2H : $ArH + Ar'NHOH \rightarrow ArNHA r'$.¹⁸⁷

Direct *amidation* can be carried out if an aromatic compound is heated with a hydroxamic acid (**34**) in polyphosphoric acid, but the scope is essentially limited to phenolic ethers.¹⁸⁸ Naphthol reacted with a substituted hydrazine to give the 1-amino derivative.¹⁸⁹ The formation of hydroindole derivatives was accomplished by reaction of a *N*-carbamoyl phenylethylamine derivative with phenyliodine (**III**) diacetate, followed by Bu_4NF .¹⁹⁰ Direct amidation via ipso substitution by nitrogen was accomplished when a *N*-methoxy aryylethylamide (**35**) was treated with [hydroxyl(tosyloxy)iodo]benzene (HTIB) in 2,2,2-trifluoroethanol, giving a *N*-methoxy spirocyclic amide (**36**).¹⁹¹

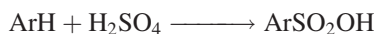


Aromatic compounds add to DEAD, in the presence of $InCl_3-SiO_2$ and microwave irradiation, to give the *N*-aryldiamino compound $[ArN(CO_2Et)-NHCO_2Et]$.¹⁹² An interesting variation in the alkylation reaction used 5 equiv of aluminum chloride in a reaction of *N*-methyl-*N*-phenylhydrazine and benzene to give *N*-methyl-4-phenylaniline.¹⁹³

Also see, Reactions **13-5** and **13-16**.

C. Sulfur Electrophiles

11-7 Sulfonation or Sulfo-de-hydrogenation



The sulfonation reaction is very broad in scope and many aromatic hydrocarbons (including fused-ring systems), aryl halides, ethers, carboxylic acids, amines,¹⁹⁴ acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated.¹⁹⁵ Phenols can also be successfully sulfonated, but attack at oxygen may compete.¹⁹⁶ Sulfonation is often accomplished with concentrated sulfuric acid, but it can also be done with fuming H_2SO_4 ,

¹⁸⁷ Shudo, K.; Ohta, T.; Okamoto, T. *J. Am. Chem. Soc.* **1981**, 103, 645.

¹⁸⁸ March, J.; Engenito, Jr., J.S. *J. Org. Chem.* **1981**, 46, 4304. Also see, Cablewski, T.; Gurr, P.A.; Rander, K.D.; Strauss, C.R. *J. Org. Chem.* **1994**, 59, 5814.

¹⁸⁹ Tang, Q.; Zhang, C.; Luo, M. *J. Am. Chem. Soc.* **2008**, 130, 5840.

¹⁹⁰ Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* **2002**, 67, 3425.

¹⁹¹ Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* **2003**, 68, 5429.

¹⁹² Yadav, J.S.; Subba Reddy, B.V.; Kumar, G.M.; Madan, C. *Synlett* **2001**, 1781.

¹⁹³ Ohwada, A.; Nara, S.; Sakamoto, T.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3064.

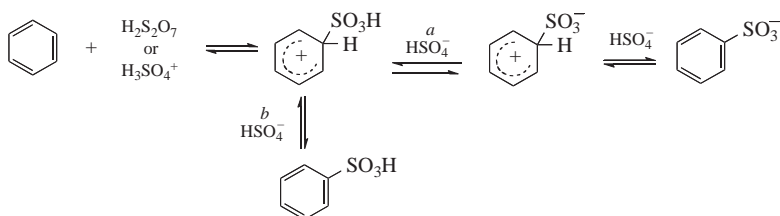
¹⁹⁴ See Khelevin, R.N. *J. Org. Chem. USSR* **1987**, 23, 1709; **1988**, 24, 535 and references cited therein.

¹⁹⁵ See Nelson, K.L. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 1355–1392; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, **1965**, pp. 62–83, 87–124.

¹⁹⁶ See de Wit, P.; Woldhuis, A.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1988**, 107, 668.

SO_3 , ClSO_2OH , $\text{ClSO}_2\text{NMe}_2/\text{In}(\text{OTf})_3$,¹⁹⁷ or other reagents.¹⁹⁸ A FeCl_3 based ionic liquid has been used for the sulfonation of aromatic compounds.¹⁹⁹ As with nitration (Reaction 11-2), reagents of a wide variety of activity are available to suit both highly active and highly inactive substrates. Since this reaction is reversible (see Reaction 11-38), it may be necessary to drive the reaction to completion. However, at low temperatures the reverse reaction is very slow and the forward reaction is practically irreversible.²⁰⁰ Sulfur trioxide reacts much more rapidly than sulfuric acid with benzene (it is nearly instantaneous). Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see Reaction 11-36).

A great deal of work has been done on the mechanism, chiefly by Cerfontain and co-workers.²⁰¹ Mechanistic study is made difficult by the complicated nature of the solutions. Indications are that the electrophile varies with the reagent, though SO_3 is involved in all cases, either free or combined with a carrier. In aq H_2SO_4 solutions, the electrophile is thought to be H_3SO_4^+ (or a combination of H_2SO_4 and H_3O^+) at concentrations below $\sim 80\text{--}85\%$ H_2SO_4 , and $\text{H}_2\text{S}_2\text{O}_7$ (or a combination of H_2SO_4 and SO_3) at concentrations higher than this²⁰² (the changeover point varies with the substrate²⁰³). Evidence for a change in electrophile is that in both the dilute and the concentrated solutions the rate of the reaction was proportional to the activity of H_3SO_4^+ and $\text{H}_2\text{S}_2\text{O}_7$, respectively. Further evidence is that with toluene as substrate the two types of solution gave very different ortho/para ratios. The mechanism is essentially the same for both electrophiles and may be shown as²⁰²:



The other product of the first step is HSO_4^- or H_2O from $\text{H}_2\text{S}_2\text{O}_7$ or H_3SO_4^+ , respectively. Path *a* is the principal route, except at very high H_2SO_4 concentrations, when path *b* becomes important. With H_3SO_4^+ the first step is rate determining under all conditions, but with $\text{H}_2\text{S}_2\text{O}_7$ the first step is the slow step only up to $\sim 96\%$ H_2SO_4 , when a subsequent proton transfer becomes partially rate determining.²⁰⁴ The $\text{H}_2\text{S}_2\text{O}_7$ is more reactive than H_3SO_4^+ . In fuming sulfuric acid (H_2SO_4 containing excess SO_3), the electrophile is

¹⁹⁷ Frost, C.G.; Hartley, J.P.; Griffin, D. *Synlett* **2002**, 1928.

¹⁹⁸ See Hajipour, A.R.; Mirjalili, B.B.F.; Zarei, A.; Khazdooz, L.; Ruoho, A.E. *Tetrahedron Lett.* **2004**, 45, 6607.

¹⁹⁹ Bahrami, K.; Khodei, M.M.; Shahbazi, F. *Tetrahedron Lett.* **2008**, 49, 3931.

²⁰⁰ Spryskov, A.A. *J. Gen. Chem. USSR* **1960**, 30, 2433.

²⁰¹ See Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, **1968**. For reviews, see Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1985**, 104, 153; Cerfontain, H.; Kort, C.W.F. *Int. J. Sulfur Chem. C* **1971**, 6, 123; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 56–77.

²⁰² Cerfontain, H.; Lambrechts, H.J.A.; Schaasberg-Nienhuis, Z.R.H.; Coombes, R.G.; Hadjigeorgiou, P.; Tucker, G.P. *J. Chem. Soc. Perkin Trans. 2* **1985**, 659 and references cited therein.

²⁰³ See Kaandorp, A.W.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1969**, 88, 725.

²⁰⁴ Kort, C.W.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1967**, 86, 865.

thought to be $\text{H}_3\text{S}_2\text{O}_7^+$ (protonated $\text{H}_2\text{S}_2\text{O}_7$) up to $\sim 104\%$ H_2SO_4 and $\text{H}_2\text{S}_4\text{O}_{13}$ ($\text{H}_2\text{SO}_4 + 3 \text{SO}_3$) beyond this concentration.²⁰⁵ Finally, when pure SO_3 is the reagent in aprotic solvents, SO_3 itself is the actual electrophile.²⁰⁶ Free SO_3 is the most reactive of all these species, so that attack here is generally fast and a subsequent step is usually rate determining, at least in some solvents.

OS II, 42, 97, 482, 539; III, 288, 824; IV, 364; VI, 976.

11-8 Halosulfonation or Halosulfo-de-hydrogenation



Aromatic sulfonyl chlorides can be prepared directly, by treatment of aromatic rings with chlorosulfuric acid.²⁰⁷ Since sulfonic acids can also be prepared by the same reagent (Reaction 11-7), it is likely that they are intermediates, being converted to the halides by excess chlorosulfuric acid.²⁰⁸ The reaction has also been effected with bromo- and fluorosulfuric acids. Sulfinyl chlorides (ArSOCl) have been prepared by the reaction of thionyl chloride and an aromatic compound on Montmorillonite K-10 clay.²⁰⁹

OS I, 8, 85.

11-9 Sulfonylation

Alkylsulfonylation or Alkylsulfo-de-hydrogenation



Diaryl sulfoxides can be prepared by the reaction of aromatic compounds with thionyl chloride and triflic acid.²¹⁰ Diaryl sulfones have also been prepared using thionyl chloride with the ionic liquid $[\text{bmim}]\text{Cl} \cdot \text{AlCl}_3$.²¹¹ Diaryl sulfones can be formed by treatment of aromatic compounds with aryl sulfonyl chlorides and a *Friedel–Crafts catalyst*.²¹² This reaction is analogous to *Friedel–Crafts acylation* with carboxylic acid halides (Reaction 11-17). In a better procedure, the aromatic compound is treated with an aryl sulfonic acid and P_2O_5 in polyphosphoric acid.²¹³ Still another method uses an arylsulfonic trifluoromethanesulfonic anhydride ($\text{ArSO}_2\text{OSO}_2\text{CF}_3$) (generated *in situ* from ArSO_2Br and $\text{CF}_3\text{SO}_3\text{Ag}$) without a catalyst.²¹⁴ Indium tris(triflate)²¹⁵ and indium trichloride²¹⁶ leads to sulfonation of aromatic compounds with sulfonyl chlorides. Indium bromide was used

²⁰⁵ Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* **1973**, 633.

²⁰⁶ Lammertsma, K.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* **1980**, 28 and references cited therein.

²⁰⁷ For a review, see Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, **1965**, pp. 84–87.

²⁰⁸ See van Albada, M.P.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* **1977**, 1548, 1557.

²⁰⁹ Karade, N.N.; Kate, S.S.; Adude, R.N. *Synlett* **2001**, 1573.

²¹⁰ Olah, G.A.; Martinez, E.R.; Prakash, G.K.S. *Synlett* **1999**, 1397.

²¹¹ See Mohile, S.S.; Potdar, M.K.; Salunkhe, M.M. *Tetrahedron Lett.* **2003**, 44, 1255.

²¹² See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 77–83; Jensen, F.R.; Goldman, G. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 1319–1347.

²¹³ Sipe, Jr., H.J.; Clary, D.W.; White, S.B. *Synthesis* **1984**, 283. See also, Ueda, M.; Uchiyama, K.; Kano, T. *Synthesis* **1984**, 323.

²¹⁴ Effenberger, F.; Huthmacher, K. *Chem. Ber.* **1976**, 109, 2315. For similar methods, see Ono, M.; Nakamura, Y.; Sato, S.; Itoh, I. *Chem. Lett.* **1988**, 395.

²¹⁵ Frost, C.G.; Hartley, J.P.; Whittle, A.J. *Synlett* **2001**, 830.

²¹⁶ Garzya, V.; Forbes, I.T.; Lauru, S.; Maragni, P. *Tetrahedron Lett.* **2004**, 45, 1499.

with indoles.²¹⁷ A ferric chloride catalyzed reaction with microwave irradiation has also been reported,²¹⁸ as has the use of zinc metal with microwave irradiation.²¹⁹ The reaction can be extended to the preparation of alkyl aryl sulfones by the use of a sulfonyl fluoride.²²⁰

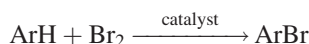
Direct formation of diaryl sulfones from benzenesulfonic acid and benzene was accomplished using Nafion-H.²²¹ Aryl halides react with sulfinic acid salts, via a proline-promoted CuI catalyzed coupling reaction.²²² Arylboronic acids (see Reaction 10-73) are sulfonated in ionic liquids, using a Cu catalyst.²²³

OS X, 147.

D. Halogen Electrophiles

11-10 Halogenation²²⁴

Halo-de-hydrogenation



1. *Chlorine*²²⁵ and *Bromine*.²²⁶ Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst.²²⁷ For amines and phenols the reaction is so rapid that it is carried out with a dilute solution of Br₂ or Cl₂ in water at room temperature, or with aqueous HBr in DMSO.²²⁸ Typically, it is not possible to stop the reaction with anilines before all the available ortho and para positions are substituted, because the initially formed haloamines are weaker bases than the original amines and are less likely to be protonated by the liberated HX.²²⁹ For this reason, the corresponding anilides are used if monosubstitution is desired. With phenols it is possible to stop after one group has entered.²³⁰ The rapid room temperature reaction with amines and phenols is often used as a test for these compounds. In general, for active substrates including anilines, phenols, naphthalene, and polyalkylbenzenes²³¹ (e.g., mesitylene and isodurene), no catalyst is needed. The overall effectiveness of reagents in aromatic substitution is Cl₂ >

²¹⁷ Yadav, J.S.; Reddy, B.V.S.; Krishna, A.D.; Swamy, T. *Tetrahedron Lett.* **2003**, 44, 6055.

²¹⁸ Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N.; Desmurs, J.-R. *J. Org. Chem.* **2001**, 66, 421.

²¹⁹ Bandgar, B.P.; Kasture, S.P. *Synth. Commun.* **2001**, 31, 1065.

²²⁰ Hyatt, J.A.; White, A.W. *Synthesis* **1984**, 214.

²²¹ Olah, G.A.; Mathew, T.; Prakash, G.K.S. *Chem. Commun.* **2001**, 1696.

²²² Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, 70, 2696.

²²³ Kantam, M.L.; Neelima, B.; Sreedhar, B.; Chakravarti, R. *Synlett* **2008**, 1455.

²²⁴ See de la Mare, P.B.D. *Electrophilic Halogenation*, Cambridge University Press, Cambridge, **1976**; Buehler, C.A.; Pearson, D.E. *Survey of Organic Synthesis*, Wiley, NY, **1970**, pp. 392–404; Braendlin, H.P.; McBee, E.T. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 1517–1593; Eisch, J.J. *Adv. Heterocycl. Chem.* **1966**, 7, 1. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 619–628.

²²⁵ For electrophilicities of chlorinating agents, see Duan, X.-H.; Mayr, H. *Org. Lett.* **2010**, 12, 2238.

²²⁶ For a computational study of the electrophilic affinity for the bromination of arenes, see Galabov, B.; Koleva, G.; Schaefer, III H.F.; Schleyer, P.v.R. *J. Org. Chem.* **2010**, 75, 2813.

²²⁷ For a site-directed bromination using an electrochemical method, see Raju, T.; Kulangiappar, K.; Kulandainathan, M.A.; Malini, U.U.R.; Muthukumaran, A. *Tetrahedron Lett.* **2006**, 47, 4581.

²²⁸ Srivastava, S.K.; Chauhan, P.M.S.; Bhaduri, A.P. *Chem. Commun.* **1996**, 2679.

²²⁹ See Berthelot, J.; Guette, C.; Desbène, P.; Basselier, J.; Chaquin, P.; Masure, D. *Can. J. Chem.* **1989**, 67, 2061. For another procedure, see Onaka, M.; Izumi, Y. *Chem. Lett.* **1984**, 2007.

²³⁰ See Brittain, J.M.; de la Mare, P.B.D. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, **1983**, pp. 522–532.

²³¹ See Baciocchi, E.; Illuminati, G. *Prog. Phys. Org. Chem.* **1967**, 5, 1.

$\text{BrCl} > \text{Br}_2 > \text{ICl} > \text{I}_2$. A mixture of ZnBr_2 /diazene has been suggested for the regioselective para-bromination of activated aromatic substrates.²³²

When chlorination or bromination is carried out at high temperatures (e.g., 300–400 °C), ortho–para directing groups direct meta and vice versa.²³³ A different mechanism operates here, which is not completely understood. It is also possible for bromination to take place by the $\text{S}_{\text{E}}1$ mechanism, for example, in the *t*-BuOK catalyzed bromination of 1,3,5-tribromobenzene.²³⁴

For less activated aromatic rings, iron was commonly used at one time for halogenation, but the real catalyst was shown not to be the iron itself, but rather the ferric bromide or chloride formed in small amounts from the reaction between iron and the reagent. Indeed, ferric chloride and other Lewis acids are typically directly used as catalysts, as is iodine. Many Lewis acids can be used, including thallium(III) acetate, which promotes bromination with high regioselectivity para to an ortho–para directing group.²³⁵ A mixture of $\text{Mn}(\text{OAc})_3$ and acetyl chloride, with ultrasound, chlorinates anisole with high selectivity.²³⁶

Other reagents can be used to promote chlorination or bromination. copper(II)-catalyzed chlorination has been reported using dioxygen as an oxidant.²³⁷ *N*-Bromosuccinimide under photochemical conditions²³⁸ brominates aromatic compounds, as does pyridinium bromide perbromide,²³⁹ and NBS in acetic acid with ultrasound is effective.²⁴⁰ Both NCS and NBS with aq BF_3 gave the respective chloride or bromide.²⁴¹ The NBS in an ionic liquid²⁴² gave the brominated aromatic, and para-bromination of aniline was reported by mixing aniline with the ionic liquid, bmim Br_2 .²⁴³ Similarly, hmim Br_3 ²⁴⁴ without another reagent is a brominating agent. Bromine on silica gel²⁴⁵ or with SO_2Cl_2 ²⁴⁶ gave good yields of the brominated aromatic compound. Majetich et al.²⁴⁷ reported the use of HBr/DMSO for the remarkably selective bromination of aniline. Highly para-selective bromination was accomplished using dioxane dibromide, under solvent free conditions.²⁴⁸

²³² Stropnik, T.; Bombek, S.; Kočevár, M.; Polanc, S. *Tetrahedron Lett.* **2008**, 49, 1729.

²³³ See Kooyman, E.C. *Pure. Appl. Chem.* **1963**, 7, 193.

²³⁴ Mach, M.H.; Bunnett, J.F. *J. Am. Chem. Soc.* **1974**, 96, 936.

²³⁵ McKillop, A.; Bromley, D.; Taylor, E.C. *J. Org. Chem.* **1972**, 37, 88.

²³⁶ Prokes, I.; Toma, S.; Luche, J.-L. *J. Chem. Res. (S)* **1996**, 164.

²³⁷ Chen, X.; Hao, X.-S.; Goodhue, C.E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, 128, 6790.

²³⁸ Chhattise, P.K.; Ramaswamy, A.V.; Waghmode, S.B. *Tetrahedron Lett.* **2008**, 49, 189.

²³⁹ Reeves, W.P.; Lu, C.V.; Schulmeier, B.; Jonas, L.; Hatlevik, O. *Synth. Commun.* **1998**, 28, 499. Also see, Bisarya, S.C.; Rao, R. *Synth. Commun.* **1993**, 23, 779.

²⁴⁰ Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Synth. Commun.* **1995**, 25, 2401.

²⁴¹ Prakash, G.K.S.; Mathew, T.; Hoole, D.; Esteves, P.M.; Wang, Q.; Rasul, G.; Olah, G.A. *J. Am. Chem. Soc.* **2004**, 126, 15770. Also see Andersh, B.; Murphy, D.L.; Olson, R.J. *Synth. Commun.* **2000**, 30, 2091. For an Au catalyzed halogenation see Mo, F.; Yan, J.M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2010**, 49, 2028.

²⁴² See Rajagopal R.; Jarikote, D.V.; Lahoti, R.J.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* **2003**, 44, 1815. For a reaction in Bu_4NBr , see Ganguly, N.C.; De, P.; Dutta, S. *Synthesis* **2005**, 1103.

²⁴³ See Lei, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* **2004**, 2809.

²⁴⁴ See Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* **2004**, 2536.

²⁴⁵ Ghiaci, M.; Asghari, J. *Bull. Chem. Soc. Jpn.* **2001**, 74, 1151.

²⁴⁶ Gnaim, J.M.; Sheldon, R.A. *Tetrahedron Lett.* **2005**, 46, 4465.

²⁴⁷ Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* **1997**, 62, 4321.

²⁴⁸ Chaudhuri, S.K.; Roy, S.; Saha, M.; Bhar, S. *Synth. Commun.* **2007**, 37, 581.

Other reagents have been used for chlorination and bromination. If the substrate contains alkyl groups, side-chain halogenation (Reaction **14-1**) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible. Sulfuryl chloride (SO_2Cl_2) in acetic acid chlorinates anisole derivatives,²⁴⁹ and acetyl chloride with a catalytic amount of ceric ammonium nitrate also converted aromatic compounds to the corresponding chlorinated derivative.²⁵⁰ A mixture of KCl and Oxone[®] chlorinated activated aromatic compounds.²⁵¹ Oxone and KBr gave good para-bromination of anisole,²⁵² as does NH_4Br /Oxone.²⁵³ Dibromoisocyanuric acid in H_2SO_4 is a very good brominating agent²⁵⁴ for substrates with strongly deactivating substituents.²⁵⁵ *N*-Chlorosuccinimide in isopropyl alcohol²⁵⁶ chlorinates aniline derivatives, and $\text{KBr}/\text{NaBO}_3 \cdot 4 \text{H}_2\text{O}$ has been used for the bromination of aniline derivatives.²⁵⁷ Conversion of aniline to the *N*- SnMe_3 derivative allowed *in situ* bromination with bromine, with high para selectivity after conversion to the free amine with aq KF.²⁵⁸ Pyridinium bromochromate converted phenolic derivatives to brominated phenols.²⁵⁹

Predominant ortho chlorination²⁶⁰ of phenols has been achieved with chlorinated cyclohexadienes,²⁶¹ while para chlorination of phenols, phenolic ethers, and amines can be accomplished with *N*-chloroamines²⁶² and with *N*-chlorodimethylsulfonium chloride ($\text{Me}_3\text{S}^+\text{Cl}^-$).²⁶³ The last method is also successful for bromination when *N*-bromodimethylsulfonium bromide is used. Highly selective ortho chlorination of acetanilides has been reported, using a combination of P and Cu catalysts.²⁶⁴ Iridium-catalyzed borylation of arenes leads to meta-halogenation.²⁶⁵ Certain alkylated phenols can be brominated in the meta positions with Br_2 in the superacid solution $\text{SbF}_5\text{—HF}$.²⁶⁶ It is likely that meta orientation is the result of conversion by the superacid of the OH group to the OH_2^+ group, which should be meta-directing because of its positive charge. Bromination and the *Sandmeyer reaction* (**14-20**) can be carried out in one laboratory step to give **37**

²⁴⁹ Yu, G.; Mason, H.J.; Wu, X.; Endo, M.; Douglas, J.; Macor, J.E. *Tetrahedron Lett.* **2001**, 42, 3247.

²⁵⁰ Roy, S.C.; Rana, K.K.; Guin, C.; Banerjee, B. *Synlett* **2003**, 221.

²⁵¹ Narender, N.; Srinivasu, P.; Kulkarni, S.J.; Raghavan, K.V. *Synth. Commun.* **2002**, 32, 279.

²⁵² Tamhankar, B.V.; Desai, U.V.; Mane, R.B.; Wadgaonkar, P.P.; Bedekar, A.V. *Synth. Commun.* **2001**, 31, 2021.

²⁵³ Arun Kumar, M.; Rohitha, C.N.; Kulkarni, S.J.; Narender, N. *Synthesis* **2010**, 1629.

²⁵⁴ Nitrobenzene is pentabrominated in 1 min with this reagent in 15% oleum at room temperature.

²⁵⁵ Gottardi, W. *Monatsh. Chem.* **1968**, 99, 815; **1969**, 100, 42.

²⁵⁶ Zanka, A.; Kubota, A. *Synlett* **1999**, 1984.

²⁵⁷ Roche, D.; Prasad, K.; Repic, O.; Blacklock, T.J. *Tetrahedron Lett.* **2000**, 41, 2083.

²⁵⁸ Smith, M.B.; Guo, L.; Okeyo, S.; Stenzel, J.; Yanella, J.; La Chapelle, E. *Org. Lett.* **2002**, 4, 2321. A polymeric Sn reagent has been developed for this purpose, see Chrétien, J.-M.; Zammattio, F.; Le Grogne, E.; Paris, M.; Cahingt, B.; Montavon, G.; Quintard, J.-P. *J. Org. Chem.* **2005**, 70, 2870.

²⁵⁹ Patwari, S.B.; Baseer, M.A.; Vibhute, Y.B.; Bhusare, S.R. *Tetrahedron Lett.* **2003**, 44, 4893.

²⁶⁰ See Kamigata, N.; Satoh, T.; Yoshida, M.; Matsuyama, H.; Kameyama, M. *Bull. Chem. Soc. Jpn.* **1988**, 61, 2226; de la Vega, F.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 653.

²⁶¹ Lemaire, M.; Guy, A.; Guette, J. *Bull. Soc. Chim. Fr.* **1985**, 477.

²⁶² Lindsay Smith, J.R.; McKeer, L.C.; Taylor, J.M. *J. Chem. Soc. Perkin Trans. 2* **1989**, 1529, 1537. See also, Minisci, F.; Vismara, E.; Fontana, F.; Platone, E.; Faraci, G. *J. Chem. Soc. Perkin Trans. 2* **1989**, 123.

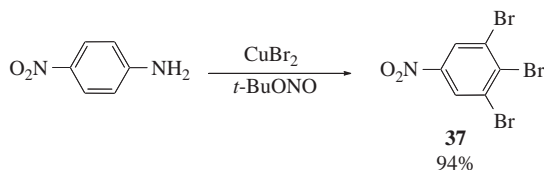
²⁶³ Olah, G.A.; Ohannesian, L.; Arvanaghi, M. *Synthesis* **1986**, 868.

²⁶⁴ Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, 128, 7416.

²⁶⁵ Murphy, J.M.; Liao, X.; Hartwig, J.F. *J. Am. Chem. Soc.* **2007**, 129, 15434.

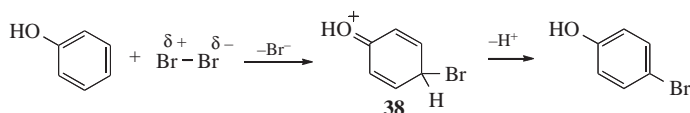
²⁶⁶ Jacquesy, J.; Jouannetaud, M.; Makani, S. *J. Chem. Soc., Chem. Commun.* **1980**, 110.

by treatment of an aromatic primary amine with CuBr_2 and *tert*-butyl nitrite, for example,²⁶⁷



With deactivated aromatic derivatives, NBS and H_2SO_4 is an effective reagent, giving the meta-brominated product.²⁶⁸ Bromination at C-6 of 2-aminopyridine was accomplished with NBS.²⁶⁹ An alternative route reacted pyridine *N*-oxide with POCl_3 and triethylamine to give 2-chloropyridine.²⁷⁰

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 that has been polarized by the ring.²⁷¹



Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into Cl^+ and Cl^- , the addition of chloride should decrease the rate and the addition of acids should increase it. Intermediate **38** has been detected spectrally in the aqueous bromination of phenol.²⁷²

When a Lewis acid catalyst²⁷³ is used with chlorine or bromine, the attacking entity may be Cl^+ or Br^+ , formed by $\text{FeCl}_3 + \text{Br}_2 \rightarrow \text{FeCl}_3\text{Br}^- + \text{Br}^+$, or it may be Cl_2 or Br_2 , polarized by the catalyst. With other reagents, the attacking entity in brominations may be Br^+ or a species (e.g., H_2OBr^+ , the conjugate acid of HOBr), in which H_2O is a carrier of Br^+ .²⁷⁴ With HOCl in water the electrophile may be Cl_2O , Cl_2 , or H_2OCl^+ ; in acetic acid it is generally AcOCl . All these species are more reactive than HOCl itself.²⁷⁵ It is extremely doubtful that Cl^+ is a significant electrophile in chlorinations by HOCl .²⁷⁵ It has been demonstrated in the reaction between *N*-methylaniline and calcium hypochlorite that the chlorine entity is

²⁶⁷ Doyle, M.P.; Van Lente, M.A.; Mowat, R.; Fobare, W.F. *J. Org. Chem.* **1980**, *45*, 2570.

²⁶⁸ Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K.K. *J. Org. Chem.* **2007**, *72*, 5867.

²⁶⁹ Cañibano, V.; Rodríguez, J.F.; Santos, M.; Sanz-Tejedor, A.; Carreño, M.C.; González, G.; García-Ruano, J.L. *Synthesis* **2001**, 2175.

²⁷⁰ Jung, J.-C.; Jung, Y.-J.; Park, O.-S. *Synth. Commun.* **2001**, *31*, 2507.

²⁷¹ See de la Mare, P.B.D., *Electrophilic Halogenation*, Cambridge University Press, Cambridge, **1976**; de la Mare, P.B.D.; Swedlund, B.E. in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 1, Wiley, NY, **1973**; pp. 490–536; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 83–139. See also, Keefer, R.M.; Andrews, L.J. *J. Am. Chem. Soc.* **1977**, *99*, 5693; Tee, O.S.; Paventi, M.; Bennett, J.M. *J. Am. Chem. Soc.* **1989**, *111*, 2233.

²⁷² Tee, O.S.; Iyengar, N.R.; Paventi, M. *J. Org. Chem.* **1983**, *48*, 759. See also, Tee, O.S.; Iyengar, N.R. *Can. J. Chem.* **1990**, *68*, 1769.

²⁷³ See also, Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, 2837.

²⁷⁴ See Rao, T.S.; Mali, S.I.; Dangat, V.T. *Tetrahedron* **1978**, *34*, 205.

²⁷⁵ Swain, C.G.; Crist, D.R. *J. Am. Chem. Soc.* **1972**, *94*, 3195.

attacked by the *nitrogen* to give *N*-chloro-*N*-methylaniline, which rearranges (as in Reaction 11-31) to give a mixture of ring-chlorinated *N*-methylanilines in which the ortho isomer predominates.²⁷⁶ In addition to hypohalous acids and metal hypohalites, organic hypohalites are reactive. An example is *tert*-butylhypobromite (*t*-BuOBr), which brominated toluene in the presence of zeolite (HNaX).²⁷⁷

Furan and thiophene are known to polymerize in the presence of strong acid, both Brønsted–Lowry and Lewis. For such highly reactive heteroaromatic systems, alternative halogenating reagents are commonly used. Furan was converted to 2-bromofuran with a bromine•dioxane complex (e.g., at <0 °C.²⁷⁸ 3-Butylthiophene reacted with NBS/acetic acid to give 2-bromo-3-butylthiophene.²⁷⁹ *N*-Methylpyrrole reacted with NBS and a catalytic amount of PBr₃, at –78 °C → –10 °C, to give *N*-methyl-3-bromopyrrole.²⁸⁰

2. *Iodine*. Iodine is the least reactive of the halogens in aromatic substitution.²⁸¹ Except for active substrates, an oxidizing agent must normally be present to oxidize I₂ to a better electrophile.²⁸² Examples of such oxidizing agents used with I₂ are HNO₃, SO₃, hypervalent iodine compounds [e.g., PhI(OTf)₂,²⁸³ NaIO₄,²⁸⁴ ammonium iodide and H₂O₂,²⁸⁵ ceric ammonium nitrate,²⁸⁶ peroxydisulfates,²⁸⁷ and a mixture of NaIO₄/KI/NaCl].²⁸⁸ A solvent-free iodination used I₂ and AgNO₃.²⁸⁹ The reagent ICl is a better iodinating agent than iodine itself.²⁹⁰ A mixture of ICl/In(OTf)₃ has also been used.²⁹¹ Iodination can also be accomplished by treatment of the substrate with NCI and H₂SO₄,²⁹² *N*-Iodosuccinamide and trifluoroacetic acid,²⁹³ KI/KIO₃ in aq methanol,²⁹⁴ KI and H₂O₂,²⁹⁵ and NaI with an iron catalyst.²⁹⁶ Sodium periodate and iodine was used to iodinate β-carbolines.²⁹⁷ A solvent-free iodination was accomplished using NaICl₂ and

²⁷⁶ Paul, D.F.; Haberfield, P. *J. Org. Chem.* **1976**, *41*, 3170.

²⁷⁷ Smith, K.; El-Hiti, G.A.; Hammond, M.E.W.; Bahzad, D.; Li, Z.; Siquet, C. *J. Chem. Soc., Perkin Trans. I* **2000**, 2745.

²⁷⁸ See Baciocchi, E.; Clementi, S.; Sebastiani, G.V. *J. Chem. Soc., Chem. Commun.* **1975**, 875.

²⁷⁹ Hoffmann, K.J.; Carlsen, P.H.J. *Synth. Commun.* **1999**, *29*, 1607.

²⁸⁰ Dvornikova, E.; Kamienska-Trela, K. *Synlett* **2002**, 1152.

²⁸¹ See Pizey, J.S. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, **1977**, pp. 227–276. For a review of aromatic iodination, see Merkushev, E.B. *Synthesis* **1988**, 923.

²⁸² Butler, A.R. *J. Chem. Educ.* **1971**, *48*, 508.

²⁸³ Panunzi, B.; Rotiroli, L.; Tingoli, M. *Tetrahedron Lett.* **2003**, *44*, 8753.

²⁸⁴ Lulinski, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 951.

²⁸⁵ Narender, N.; Reddy, K.S.R.; Krishna Mohan, K.V.V.; Kulkarni, S.J. *Tetrahedron Lett.* **2007**, *48*, 6124.

²⁸⁶ Das, B.; Krishnaiah, M.; Venkateswarlu, K.; Reddy, V.S. *Tetrahedron Lett.* **2007**, *48*, 81.

²⁸⁷ Tajik, H.; Esmaceli, A.A.; Mohammadpoor-Baltork, I.; Ershadi, A.; Tajmehri, H. *Synth. Commun.* **2003**, *33*, 1319.

²⁸⁸ Emmanuvel, L.; Shukla, R.K.; Sudalai, A.; Gurunath, S.; Sivaram, S. *Tetrahedron Lett.* **2006**, *47*, 4793.

²⁸⁹ Yusubov, M.S.; Tveryakova, E.N.; Krasnokutskaya, E.A.; Perederyna, I.A.; Zhdankin, V.V. *Synth. Commun.* **2007**, *37*, 1259.

²⁹⁰ See McClelland, C.W. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, **1983**, pp. 85–164; Mukaiyama, T.; Kitagawa, H.; Matsuo, J.-i. *Tetrahedron Lett.* **2000**, *41*, 9383.

²⁹¹ Johnsson, R.; Meijer, A.; Ellervik, U. *Tetrahedron* **2005**, *61*, 11657.

²⁹² Chaikovskii, V.K.; Shorokhodov, V.I.; Filimonov, V.D. *Russ. J. Org. Chem.* **2001**, *37*, 1503.

²⁹³ Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* **2002**, *43*, 5047.

²⁹⁴ Adimurthy, S.; Ramachandiraiah, G.; Ghosh, P.K.; Bedekar, A.V. *Tetrahedron Lett.* **2003**, *44*, 5099.

²⁹⁵ Reddy, K.S.K.; Narender, N.; Rohitha, C.N.; Kulkarni, S.J. *Synth. Commun.* **2008**, *38*, 3894.

²⁹⁶ Firouzabadi, H.; Iranpoor, N.; Shiri, M. *Tetrahedron Lett.* **2003**, *44*, 8781.

²⁹⁷ Bonesi, S.M.; Erra-Balsells, R. *J. Heterocyclic Chem.* **2001**, *38*, 77.

an *N*-bromoammonium salt.²⁹⁸ Another solvent-free iodination used I₂ with Bi(NO₃)₃ on silica gel.²⁹⁹ A mixture of iodine/pyridine/dioxane leads to selective para-iodination of aniline derivatives.³⁰⁰ Selective ortho cyanation allows the reaction with iodine to give the corresponding aryl iodide.³⁰¹ Iodination of activated aromatics has been reported using KI and ammonium peroxodisulfate.³⁰² *N*-Iodosuccinimide and *p*-toluenesulfonic acid give regioselective iodination of phenol and related compounds.³⁰³

The actual attacking species is less clear than with bromine or chlorine. Iodine itself is too unreactive, except for active species (e.g., phenols), where there is good evidence that I₂ is the attacking entity.³⁰⁴ There is evidence that AcOI may be the reactive entity when peroxyacetic acid is the oxidizing agent,³⁰⁵ and I₃⁺ when SO₃ or HIO₃ is the oxidizing agent.³⁰⁶ The I⁺ ion has been implicated in several procedures.³⁰⁷ For an indirect method for accomplishing aromatic iodination see (Reaction 12-31).

3. *Fluorine*. Direct fluorination of aromatic rings with F₂ is not feasible at room temperature, because of the extreme reactivity of F₂.³⁰⁸ It has been accomplished at low temperatures (e.g., -70 to -20 °C, depending on the substrate),³⁰⁹ but the reaction is not yet of preparative significance. Fluorination has also been reported with acetyl hypofluorite (CH₃CO₂F, generated from F₂ and sodium acetate),³¹⁰ and with an *N*-fluoroperfluoroalkyl sulfonamide [e.g., (CF₃SO₂)₂NF].³¹¹ Pyridine has been converted to 2-fluoropyridine with F₂/I₂/NEt₃ in 1,1,2-trichloro-1,2,2-trifluoroethane.³¹² However, none of these methods seems likely to displace the *Schiemann reaction* (13-23; heating diazonium tetrafluoroborates) as the most common method for introducing fluorine into aromatic rings.

OS I, 111, 121, 123, 128, 207, 323; II, 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; III, 132, 134, 138, 262, 267, 575, 796; IV, 114, 166, 256, 545, 547, 872, 947; V, 117, 147, 206, 346; VI, 181, 700; VIII, 167; IX, 121, 356. Also see, OS II, 128.

²⁹⁸ Hajipour, A.R.; Ruoho, A.E. *Org. Prep. Proceed. Int.* **2002**, 34, 647.

²⁹⁹ Alexander, V.M.; Khandekar, A.C.; Samant, S.D. *Synlett* **2003**, 1895.

³⁰⁰ Monnereau, C.; Blart, E.; Odobel, F. *Tetrahedron Lett.* **2005**, 46, 5421.

³⁰¹ Usui, S.; Hashimoto, Y.; Morey, J.V.; Wheatley, A.E.H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, 129, 15102.

³⁰² Ganguly, N.C.; Barik, S.K.; Dutta, S. *Synthesis* **2010**, 1467.

³⁰³ Bovonsombat, P.; Leykajarakul, J.; Khan, C.; Pla-on, K.; Krause, M.M.; Khanthapura, P.; Ali, R.; Doowa, N. *Tetrahedron Lett.* **2009**, 50, 2664.

³⁰⁴ Grovenstein, Jr., E.; Aprahamian, N.S.; Bryan, C.J.; Gnanapragasam, N.S.; Kilby, D.C.; McKelvey, Jr., J.M.; Sullivan, R.J. *J. Am. Chem. Soc.* **1973**, 95, 4261.

³⁰⁵ Ogata, Y.; Urasaki, I. *J. Chem. Soc. C* **1970**, 1689.

³⁰⁶ Arotzky, J.; Butler, R.; Darby, A.C. *J. Chem. Soc. C* **1970**, 1480.

³⁰⁷ Galli, C. *J. Org. Chem.* **1991**, 56, 3238.

³⁰⁸ See German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, **1989**; Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* **1986**, 86, 997. Also see Hewitt, C.D.; Silvester, M.J. *Aldrichimica Acta* **1988**, 21, 3.

³⁰⁹ Stavber, S.; Zupan, M. *J. Org. Chem.* **1983**, 48, 2223. See also, Purrington, S.T.; Woodard, D.L. *J. Org. Chem.* **1991**, 56, 142.

³¹⁰ See Visser, G.W.M.; Bakker, C.N.M.; van Halteren, B.W.; Herscheid, J.D.M.; Brinkman, G.A.; Hoekstra, A. *J. Org. Chem.* **1986**, 51, 1886.

³¹¹ Singh, S.; DesMarteau, D.D.; Zuberi, S.S.; Witz, M.; Huang, H. *J. Am. Chem. Soc.* **1987**, 109, 7194.

³¹² Chambers, R.D.; Parsons, M.; Sandford, G.; Skinner, C.J.; Atherton, M.J.; Moilliet, J.S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 803.

E. Carbon Electrophiles

A new carbon–carbon bond is formed in the reactions in this section. With respect to the aromatic ring, they are electrophilic substitutions, because a positive species attacks the ring. We treat them in this manner because it is customary. However, with respect to the electrophile, most of these reactions are nucleophilic substitutions, and what was said in Chapter 10 is pertinent to them.

11-11 Friedel–Crafts Alkylation

Alkylation or Alkyl-de-hydrogenation



The alkylation of aromatic rings, called *Friedel–Crafts alkylation*, is a reaction of very broad scope.³¹³ Catalytic asymmetric Friedel–Crafts alkylation reactions are known.³¹⁴ The most important reagents are alkyl halides, alkenes, and alcohols, but other types of reagent have also been employed.³¹³ Tertiary halides are particularly good substrates since they form relatively stable tertiary carbocations. When alkyl halides are used, the reactivity order is $\text{F} > \text{Cl} > \text{Br} > \text{I}$.³¹⁵ This trend can be seen in reactions of dihalo compounds (e.g., $\text{FCH}_2\text{CH}_2\text{CH}_2\text{Cl}$), which react with benzene to give $\text{PhCH}_2\text{CH}_2\text{CH}_2\text{Cl}$ ³¹⁶ when the catalyst is BCl_3 . By the use of this catalyst, it is therefore possible to place a haloalkyl group on a ring (see also, Reaction 11-14).³¹⁷ Di- and trihalides, when all the halogens are the same, usually react with more than one molecule of an aromatic compound; it is usually not possible to stop the reaction earlier.³¹⁸ Thus, benzene with CH_2Cl_2 gives not PhCH_2Cl , but Ph_2CH_2 ; benzene with CHCl_3 gives Ph_3CH . With CCl_4 , however, the reaction stops when only three rings have been substituted to give Ph_3CCl . Functionalized alkyl halides [e.g., $\text{ClCH}(\text{SEt})\text{CO}_2\text{Et}$] undergo Friedel–Crafts alkylation.³¹⁹ Montmorillonite clay-(K10) is an effective medium for alkylation reactions.³²⁰

Alkenes are especially good alkylating agents, generally proceeding by formation of an intermediate carbocation that reacts with the electron-rich aromatic ring, and the final product (39) incorporates a H and Ar from ArH to a $\text{C}=\text{C}$ double bond. Many variations are possible. This reaction has been accomplished in an ionic liquid, using $\text{Sc}(\text{OTf})_3$ as the catalyst.³²¹ Other catalysts include $\text{Sm}(\text{OTf})_3$.³²² Intramolecular versions lead to

³¹³ See Roberts, R.M.; Khalaf, A.A. *Friedel–Crafts Alkylation Chemistry*, Marcel Dekker, NY, **1984**. For a treatise on Friedel–Crafts reactions in general, see Olah, G.A. *Friedel–Crafts and Related Reactions*, Wiley, NY, **1963–1965**. See Olah, G.A. *Friedel–Crafts Chemistry*, Wiley, NY, **1973**.

³¹⁴ Poulsen, T.B.; Jørgensen, K.A. *Chem. Rev.* **2008**, *108*, 2903; Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156; Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292; Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484; Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaoli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403; Adachi, S.; Tanaka, F.; Watanabe, K.; Watada, A.; Harada, T. *Synthesis* **2010**, 2652; Faita, G.; Mella, M.; Toscanini, M.; Desimoni, G. *Tetrahedron* **2010**, *66*, 3024.

³¹⁵ See Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* **1955**, *77*, 5584.

³¹⁶ Olah, G.A.; Kuhn, S.J. *J. Org. Chem.* **1964**, *29*, 2317.

³¹⁷ See Olah, G.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, **1963**, pp. 881–905. This review also covers the case of alkylation versus acylation.

³¹⁸ See Belen'kii, L.I.; Brokhovetsky, D.B.; Krayushkin, M.M. *Chem. Scr.*, **1989**, *29*, 81.

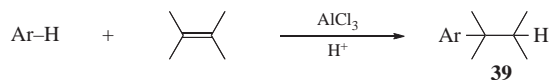
³¹⁹ See Sinha, S.; Mandal, B.; Chandrasekaran, S. *Tetrahedron Lett.* **2000**, *41*, 9109.

³²⁰ Sieskind, O.; Albrecht, P. *Tetrahedron Lett.* **1993**, *34*, 1197.

³²¹ See Song, C.E.; Shim, W.H.; Roh, E.J.; Choi, J.H. *Chem. Commun.* **2000**, 1695.

³²² Hajra, S.; Maji, B.; Bar, S. *Org. Lett.* **2007**, *9*, 2783.

polycyclic aromatic compounds.³²³ Benzene reacted with 1,2,3,6-tetrahydropyridine in the presence of trifluoromethanesulfonic acid to give 4-phenylpiperidine.³²⁴



When 4-methoxyphenol reacted with isobutylene (electrolysis with 3 M LiClO₄ in nitromethane and acetic acid), initial reaction with the phenolic oxygen generated an ether moiety and the resulting carbocation was attacked by the aromatic ring to form a benzofuran.³²⁵ Enantioselective alkylations have been reported for pyrroles and indoles, using a chiral Pybox–Cu complex.³²⁶

Acetylene reacts with 2 mol of aromatic compound to give 1,1-diarylethanes, and phenylacetylene reacted to give 1,1-diarylethenes with a Sc(OTf)₃ catalyst.³²⁷ Variations are possible here as well. Phenol reacted with trimethylsilylethyne, in the presence of SnCl₄ and 50% BuLi, at 105 °C, to give the 2-vinyl phenolic derivative.³²⁸ A Ru catalyzed intramolecular reaction with a pendant alkyne unit led to a dihydronaphthalene derivative,³²⁹ and a Rh catalyzed reaction led to indanone derivatives.³³⁰ An acidic fluoroantimonate(V) ionic liquid has been used as a catalyst.³³¹

Alcohols are more active than alkyl halides, but if a Lewis acid catalyst is used more catalyst is required, since the catalyst complexes with the OH group. However, proton acids (e.g., H₂SO₄) are often used to catalyze alkylation with alcohols. An intramolecular cyclization was reported from an allylic alcohol, using P₂O₅, to give indene derivatives.³³² Secondary alcohols are coupled to aromatic compounds using a heterobimetallic Ir–Sn complex.³³³ Molecular iodine has been used to catalyze benzylation of arenes with benzylic alcohols.³³⁴ A “contra Friedel–Crafts” *tert*-butylation has been reported.³³⁵ Diastereoselective alkylation is possible from alcohol precursors. High facial diastereoselectivity was reported with “chiral benzylic cations”, for example.³³⁶

³²³ See Youn, S.W.; Pastine, S.J.; Sames, D. *Org. Lett.* **2004**, *6*, 581.

³²⁴ Klumpp, D.A.; Beauchamp, P.S.; Sanchez Jr., G.V.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* **2001**, *42*, 5821.

³²⁵ Chiba, K.; Fukuda, M.; Kim, S.; Kitano, Y.; Toda, M. *J. Org. Chem.* **1999**, *64*, 7654; Abe, H.; Koshiba, N.; Yamasaki, A.; Harayama, T. *Heterocycles* **1999**, *51*, 2301. See also, Shen, Y.; Atobe, M.; Fuchigami, T. *Org. Lett.* **2004**, *6*, 2441.

³²⁶ Palomo, C.; Oiarbide, M.; Kardak, B.G.; García, J.M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154.

³²⁷ Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573.

³²⁸ Kobayashi, K.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 241.

³²⁹ Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913; Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414; Nishizawa, M.; Takao, H.; Yadav, V.K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563; Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett.* **2004**, *6*, 2361. See also, Fillion, E.; Carson, R.J.; Trépanier, V.E.; Goll, J.M.; Remorova, A.A. *J. Am. Chem. Soc.* **2004**, *126*, 15354.

³³⁰ Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 2872; Yamabe, H.; Mizuno, A.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 3248; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2071.

³³¹ Choi, D.S.; Kim, J.H.; Shin, U.S.; Deshmukh, R.R.; Song, C.E. *Chem. Commun.* **2007**, 3482.

³³² Basavaiah, D.; Bakthadoss, M.; Reddy, G.J. *Synthesis* **2001**, 919; Nishibayashi, Y.; Joshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846.

³³³ Podder, S.; Choudhury, J.; Roy, S. *J. Org. Chem.* **2007**, *72*, 3129.

³³⁴ Sun, G.; Wang, Z. *Tetrahedron Lett.* **2008**, *49*, 4929.

³³⁵ Clayden, J.; Stimson, C.C.; Keenan, M. *Chem. Commun.* **2006**, 1393.

³³⁶ Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* **2005**, *127*, 9348.

When carboxylic esters are the reagents, there is competition between alkylation and acylation (Reaction 11-17). This competition can often be controlled by choice of catalyst, and alkylation is usually favored, but carboxylic esters are not often employed in Friedel–Crafts reactions. Other alkylating agents are ethers,³³⁷ thiols, sulfates, sulfonates, alkyl nitro compounds,³³⁸ and even alkanes and cycloalkanes, under conditions where these are converted to carbocations. Notable here are ethylene oxide, which puts the CH₂CH₂OH group onto the ring,³³⁹ and cyclopropyl³⁴⁰ units. For all types of reagent, the reactivity order is allylic ~ benzylic > tertiary > secondary > primary. Alkyl mesylates undergo alkylation reaction with benzene rings in the presence of Sc(OTf)₃.³⁴¹ Allylic acetates undergo alkylation with Mo(CO)₆,³⁴² and allylic chlorides react in the presence of ZnCl₂/SiO₂.³⁴³

Naphthalene and other fused ring compounds are so reactive that they react with the catalyst, and therefore tend to give poor yields in Friedel–Crafts alkylation. Heterocyclic rings also tend to be poor substrates for the reaction. Although some furans and thiophenes have been alkylated, polymerization is quite common, and a true alkylation of a pyridine or a quinoline has never been described.³⁴⁴ *N*-Methylpyrrole reacted with the C=C unit of methacrolein in the presence of a chiral catalyst (a chiral Friedel–Crafts catalyst) to give the 2-alkylated pyrrole, with good enantioselectivity.³⁴⁵ Alkylation at C-5 of 2-trimethylsilylfuran was accomplished using the carbocation [(*p*-MeOC₆H₄)₂CH⁺ OTf] and Proton Sponge (see Sec. 8.F, category 6).³⁴⁶ The reaction of isoquinoline with ClCO₂Ph and AgOTf, followed by reaction with an allylic silane, led to a 2-allylic dihydroisoquinoline.³⁴⁷

Regardless of which reagent is used, a catalyst is nearly always required.³⁴⁸ Lewis acid catalysts (e.g., aluminum chloride and boron trifluoride) are the most common, but many other Lewis acids have been used,³⁴⁹ and also proton acids (e.g., HF and H₂SO₄).³⁵⁰ Calcium has been used to catalyze Friedel–Crafts alkylation reactions, at room temperature.³⁵¹ For active halides, a trace of a less active catalyst (e.g., ZnCl₂) may be enough. For an unreactive halide (e.g., chloromethane), a more powerful catalyst (e.g., AlCl₃) is needed, and in larger amounts. In some cases, especially with alkenes, a Lewis acid catalyst causes reaction only if a small amount of proton-donating cocatalyst is present. Catalysts have been arranged in the following order of overall reactivity: AlBr₃ > AlCl₃ > GaCl₃

³³⁷ See Podder, S.; Roy, S. *Tetrahedron* **2007**, 63, 9146.

³³⁸ Bonvino, V.; Casini, G.; Ferappi, M.; Cingolani, G.M.; Pietroni, B.R. *Tetrahedron* **1981**, 37, 615.

³³⁹ Taylor, S.K.; Dickinson, M.G.; May, S.A.; Pickering, D.A.; Sadek, P.C. *Synthesis* **1998**, 1133. See also, Brandänge, S.; Bäckvall, J.-E.; Leijonmarck, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2051.

³⁴⁰ Patra, P.K.; Patro, B.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1993**, 34, 3951.

³⁴¹ Singh, R.P.; Kamble, R.M.; Chandra, K.L.; Saravanani, P.; Singh, V.K. *Tetrahedron* **2001**, 57, 241.

³⁴² Shimizu, I.; Sakamoto, T.; Kawaragi, S.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* **1997**, 137.

³⁴³ Kodomari, M.; Nawa, S.; Miyoshi, T. *J. Chem. Soc. Chem. Commun.* **1995**, 1895.

³⁴⁴ Drahowzal, F.A. in Olah, G.A., *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, **1964**, p. 433.

³⁴⁵ Paras, N.A.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2001**, 123, 4370.

³⁴⁶ Herrlich, M.; Hampel, N.; Mayr, H. *Org. Lett.* **2001**, 3, 1629.

³⁴⁷ Yamaguchi, R.; Nakayasu, T.; Hatano, B.; Nagura, T.; Kozima, S.; Fujita, K.-i. *Tetrahedron* **2001**, 57, 109.

³⁴⁸ See Stang, P.J.; Anderson, A.G. *J. Am. Chem. Soc.* **1978**, 100, 1520.

³⁴⁹ See Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2004**, 44, 238.

³⁵⁰ See Olah, G.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, **1963**, pp. 201–366, 853–881. A reusable catalyst derived from a heteropoly acid has been reported; see Okumura, K.; Yamashita, K.; Hirano, M.; Niwa, M. *Chem. Lett.* **2005**, 34, 716.

³⁵¹ Niggemann, M.; Meel, M.J. *Angew. Chem. Int. Ed.* **2010**, 49, 3684.

$> \text{FeCl}_3 > \text{SbCl}_5^{352} > \text{ZrCl}_4, \text{SnCl}_4 > \text{BCl}_3, \text{BF}_3, \text{SbCl}_3^{353}$; but the reactivity order in each case depends on the substrate, reagent, and conditions. Other Lewis acids have been used, of course, including SeCl_2 ,³⁵⁴ InCl_3 ,³⁵⁵ and enantiopure cycloalkyldialkylsilyl triflimide catalysts.³⁵⁶

Friedel–Crafts alkylation is unusual among the principal aromatic substitutions in that the entering group is activating (the product is more reactive than the starting aromatic substrate), and di- and polyalkylation are frequently observed. However, the activating effect of simple alkyl groups (e.g., ethyl and isopropyl) is only ~ 1.5 –3 times as fast as benzene for *Friedel–Crafts alkylations*,³⁵⁷ so it is often possible to obtain high yields of monoalkyl product.³⁵⁸ Actually, the fact that di- and polyalkyl derivatives are frequently obtained is not due to the small difference in reactivity, but to the circumstance that alkylbenzenes are preferentially soluble in the catalyst layer, where the reaction actually takes place.³⁵⁹ This factor can be removed by the use of a suitable solvent, by high temperatures, or by high-speed stirring.

It is important to note that the OH, OR, NH_2 , and so on, groups do not facilitate the reaction, since most Lewis acid catalysts coordinate with these basic groups. Although phenols give the usual *Friedel–Crafts reactions*, orienting ortho and para, the reaction is very poor for aniline derivatives. However, amines can undergo the reaction if alkenes are used as reagents and aluminum anilides as catalysts.³⁶⁰ In this method, the catalyst is prepared by treating the amine to be alkylated with one-third equiv of AlCl_3 . A similar reaction can be performed with phenols, though here the catalyst is $\text{Al}(\text{OAr})_3$.³⁶¹ Primary aromatic amines (and phenols) can be methylated regioselectively in the ortho position by an indirect method (see Reaction 11-23). For an indirect method for regioselective ortho methylation of phenols, see Reaction 15-65.

In most cases, meta-directing groups make the ring too inactive for alkylation. Nitrobenzene cannot be alkylated, and there are only a few reports of successful *Friedel–Crafts alkylations* when electron-withdrawing groups are present.³⁶² This is not because the attacking species is not powerful enough; indeed we have seen (Sec. 11.D) that alkyl cations are among the most powerful of electrophiles. The difficulty is caused by the fact that, with inactive substrates, degradation and polymerization of the electrophile occurs before it can attack the ring. However, if an activating and a deactivating group are both present on a ring, *Friedel–Crafts alkylation* can be accomplished.³⁶³ Aromatic nitro compounds can be methylated by a nucleophilic mechanism (Reaction 13-17).

³⁵² See Yakobson, G.G.; Furin, G.G. *Synthesis* **1980**, 345.

³⁵³ Russell, G.A. *J. Am. Chem. Soc.* **1959**, *81*, 4834.

³⁵⁴ Potapov, V.A.; Khuriganova, O.I.; Amosova, S.V. *Russ. J. Org. Chem.* **2009**, *45*, 1569.

³⁵⁵ Kaneko, M.; Hayashi, R.; Cook, G.R. *Tetrahedron Lett.* **2007**, *48*, 7085.

³⁵⁶ See Tang, Z.; Mathieu, B.; Tinant, B.; Dive, G.; Ghosez, L. *Tetrahedron* **2007**, *63*, 8449.

³⁵⁷ Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* **1962**, *84*, 1688.

³⁵⁸ See Davister, M.; Laszlo, P. *Tetrahedron Lett.* **1993**, *34*, 533 for examples of paradoxical selectivity in Friedel–Crafts alkylation.

³⁵⁹ Francis, A.W. *Chem. Rev.* **1948**, *43*, 257.

³⁶⁰ See Stroh, R.; Ebersberger, J.; Haberland, H.; Hahn, W. *Newer Methods Prep. Org. Chem.* **1963**, *2*, 227.

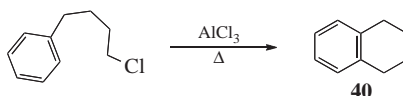
³⁶¹ Koshchii, V.A.; Kozlikovskii, Ya.B.; Matyusha, A.A. *J. Org. Chem. USSR* **1988**, *24*, 1358; Laan, J.A.M.; Giesen, F.L.L.; Ward, J.P. *Chem. Ind. (London)* **1989**, 354. See Stroh, R.; Seydel, R.; Hahn, W. *Newer Methods Prep. Org. Chem.* **1963**, *2*, 337.

³⁶² Shen, Y.; Liu, H.; Chen, Y. *J. Org. Chem.* **1990**, *55*, 3961.

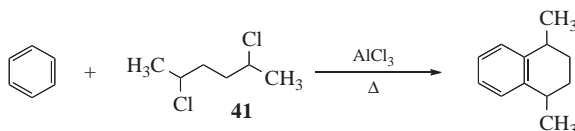
³⁶³ Olah, G.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, **1963**, p. 34.

The intermediate for *Friedel–Crafts alkylation* is a carbocation, and rearrangement to a more stable cation can be quite facile. Therefore, rearrangement of the alkyl substrate occurs frequently and is an important synthetic limitation of *Friedel–Crafts alkylation*. For example, benzene treated with *n*-propyl bromide gives mostly isopropylbenzene (cumene) and much less *n*-propylbenzene. Rearrangement is usually in the order primary \rightarrow secondary \rightarrow tertiary and usually occurs by migration of the smaller group on the adjacent carbon. Therefore, in the absence of special electronic or resonance influences on the migrating group (e.g., phenyl), H migrates before methyl, which migrates before ethyl, and so on (see discussion of rearrangement mechanisms in Chap 18). It is therefore not usually possible to put a primary alkyl group (other than methyl³⁶⁴ and ethyl) onto an aromatic ring by *Friedel–Crafts alkylation*. Because of these rearrangements, *n*-alkylbenzenes are often prepared by *acylation* (Reaction 11-17), followed by reduction (Reaction 19-61).

An important use of the *Friedel–Crafts alkylation* reaction is to effect ring closure,³⁶⁵ via an intramolecular process.³⁶⁶ The most common method is to heat an aromatic compound with aluminum chloride having a halogen, hydroxy, or alkene group in the proper position, as, for example, in the preparation of tetralin (**40**).



Another way of effecting ring closure through *Friedel–Crafts alkylation* is to use a reagent containing two groups (e.g., **41**). These reactions are most successful for the preparation of six-membered rings,³⁶⁷ though five- and seven-membered rings have also been closed in this manner. For other *Friedel–Crafts* ring-closure reactions, see Reactions 11-15, 11-13, and 11-17. An interesting variation in this reaction showed that *N*-acyl aniline derivatives, upon treatment with $\text{Et}_2\text{P}(=\text{O})\text{H}$ in water and a water soluble initiator (V-501) led to an intramolecular alkylation reaction to give an amide.³⁶⁸



As mentioned above, the electrophile in *Friedel–Crafts alkylation* is a carbocation, at least in most cases.³⁶⁹ This is in accord with the knowledge that carbocations rearrange in the direction primary \rightarrow secondary \rightarrow tertiary (see Chap 18). In each case, the cation is

³⁶⁴ See Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* **2000**, 41, 7555.

³⁶⁵ See Barclay, L.R.C. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, **1964**, pp. 785–977.

³⁶⁶ See Stashenko, E.E.; Martínez, J.R.; Tafurt-García, G.; Palma, A.; Bofill, J.M. *Tetrahedron* **2008**, 64, 7407.

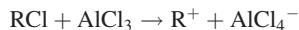
³⁶⁷ See Khalaf, A.A.; Roberts, R.M. *J. Org. Chem.* **1966**, 31, 89.

³⁶⁸ Khan, T.A.; Tripoli, R.; Crawford, J.T.; Martin, C.G.; Murphy, J.A. *Org. Lett.* **2003**, 5, 2971.

³⁶⁹ See Taylor, R. *Electrophilic Aromatic Substitution, Electrophilic Aromatic Substitution*, Wiley, NY, **1990**, pp. 188–213.

formed from the attacking reagent and the catalyst. For the three most important types of reagent these reactions are

From alkyl halides



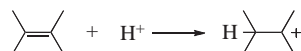
From alcohols³⁷⁰ and Lewis acids



From alcohols and protonic acids



From alkenes (a supply of protons is usually required)



There is direct evidence, from IR and NMR spectra, that the *tert*-butyl cation is quantitatively formed when *tert*-butyl chloride reacts with AlCl_3 in anhydrous liquid HCl .³⁷¹ In the case of alkenes, *Markovnikov's rule* (Sec. 15.B.ii) is followed. Carbocation formation is particularly easy from some reagents, because of the stability of the cations. Triphenylmethyl chloride³⁷² and 1-chloroadamantane³⁷³ alkylate activated aromatic rings (e.g., phenols and amines) with no catalyst or solvent. Ions as stable as this are less reactive than other carbocations and often attack only active substrates. The tropylium ion, for example, alkylates anisole, but not benzene.³⁷⁴ Note in Section 10.F that relatively stable vinylic cations can be generated from certain vinylic compounds. These have been used to introduce vinylic groups into aryl substrates.³⁷⁵ Lewis acids (e.g., BF_3 ³⁷⁶ or AlEt_3 ³⁷⁷ can also be used for alkylation of aromatic rings with alkene units.

There is considerable evidence that many *Friedel–Crafts alkylations*, especially with primary reagents, do not go through a completely free carbocation. The ion may exist as a tight ion pair with, say, AlCl_4^- as the counterion or as a complex. Among the evidence is that methylation of toluene by methyl bromide and methyl iodide gave different ortho/para/meta ratios,³⁷⁸ although the same ratios are expected if the same species are attacked in each case. Other evidence is that, in some cases, the reaction kinetics are third order; first order each in aromatic substrate, attacking reagent, and catalyst.³⁷⁹ In these instances, a mechanism in which the carbocation is slowly formed and then rapidly attacked by the aromatic ring is ruled out since, in such a mechanism, the substrate would not appear in the rate expression. Since it is known that free carbocations, once formed, are rapidly attacked by the ring (acting as a nucleophile), there are no free carbocations here. Another possibility (with alkyl halides) is that some alkylations take place by an $\text{S}_{\text{N}}2$ mechanism (with respect to the halide), in which case no carbocations would be involved at all. However, a completely $\text{S}_{\text{N}}2$ mechanism requires inversion of configuration. Most investigations of *Friedel–Crafts stereochemistry*, even where an $\text{S}_{\text{N}}2$ mechanism might most be expected, have resulted in total racemization, or at best a few percent inversion.

³⁷⁰ See Bijoy, P.; Subba Rao, G.S.R. *Tetrahedron Lett.* **1994**, 35, 3341.

³⁷¹ Kalchschmid, F.; Mayer, E. *Angew. Chem. Int. Ed.* **1976**, 15, 773.

³⁷² See Chuchani, G.; Zabicky, J. *J. Chem. Soc. C* **1966**, 297.

³⁷³ Takaku, M.; Taniguchi, M.; Inamoto, Y. *Synth. Commun.* **1971**, 1, 141.

³⁷⁴ Bryce-Smith, D.; Perkins, N.A. *J. Chem. Soc.* **1962**, 5295.

³⁷⁵ Kitamura, T.; Kobayashi, S.; Taniguchi, H.; Rappoport, Z. *J. Org. Chem.* **1982**, 47, 5503.

³⁷⁶ Majetich, G.; Liu, S.; Siesel, D. *Tetrahedron Lett.* **1995**, 36, 4749.

³⁷⁷ Majetich, G.; Zhang, Y.; Liu, S. *Tetrahedron Lett.* **1994**, 35, 4887.

³⁷⁸ Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* **1956**, 78, 2182.

³⁷⁹ See Choi, S.U.; Brown, H.C. *J. Am. Chem. Soc.* **1963**, 85, 2596.

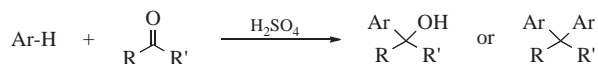
A few exceptions have been found,³⁸⁰ most notably where the reagent was optically active propylene oxide, in which case 100% inversion was reported.³⁸¹

Rearrangement is possible even with a non-carbocation mechanism. The rearrangement could occur *before* the attack on the ring takes place. It has been shown that treatment of $\text{CH}_3^{14}\text{CH}_2\text{Br}$ with AlBr_3 in the absence of any aromatic compound gave a mixture of the starting material and $^{14}\text{CH}_3\text{CH}_2\text{Br}$.³⁸² Similar results were obtained with $\text{PhCH}_2^{14}\text{CH}_2\text{Br}$, in which case the rearrangement was so fast that the rate could be measured only below -7° .³⁸³ Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see Reaction 11-33).³⁸⁴

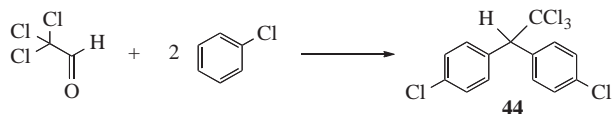
See Reaction 11-17 for *Friedel–Crafts acylation*. See Reaction 14-17 and 14-19 for free radical alkylation.

OS I, 95, 548; II, 151, 229, 232, 236, 248; III, 343, 347, 504, 842; IV, 47, 520, 620, 665, 702, 898, 960; V, 130, 654; VI, 109, 744.

11-12 Hydroxyalkylation or Hydroxyalkyl-de-hydrogenation



When an aldehyde, ketone, or other carbonyl-containing substrate is treated with a protonic or Lewis acid, an oxygen-stabilized cation is generated. In the presence of an aromatic ring, *Friedel–Crafts type alkylation* occurs. The condensation of aromatic rings with aldehydes or ketones is called *hydroxyalkylation*.³⁸⁵ The reaction can be used to prepare alcohols,³⁸⁶ though more often the alcohol initially produced reacts with another molecule of aromatic compound (Reaction 11-11) to give diarylation. For this the reaction is quite useful, an example being the preparation of 1,1,1-trichloro-2,2'-bis(*p*-chlorophenyl)ethane DDT, 44:



The diarylation reaction is especially common with phenols (the diaryl product here is called a bisphenol). The reaction is normally carried out in alkaline solution on the phenolate ion.³⁸⁷ Another variation involved *Friedel–Crafts coupling* of an aldehyde to an activated aromatic compound (an aniline derivative) to give diaryl carbinols that exhibited

³⁸⁰ Some instances of retention of configuration have been reported; a neighboring-group mechanism is likely in these cases: see Effenberger, F.; Weber, T. *Angew. Chem. Int. Ed.* **1987**, 26, 142.

³⁸¹ Nakajima, T.; Suga, S.; Sugita, T.; Ichikawa, K. *Tetrahedron* **1969**, 25, 1807. For cases of almost complete inversion, with acyclic reagents, see Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. *J. Org. Chem.* **1991**, 56, 183.

³⁸² Adema, E.H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* **1962**, 81, 323, 336.

³⁸³ See Roberts, R.M.; Gibson, T.L. *Isot. Org. Chem.* **1980**, 5, 103.

³⁸⁴ See Lee, C.C.; Hamblin, M.C.; Uthe, J.F. *Can. J. Chem.* **1964**, 42, 1771.

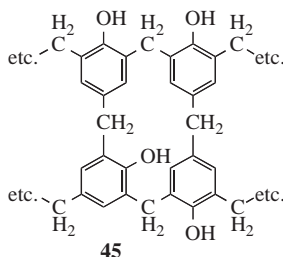
³⁸⁵ See Hofmann, J.E.; Schriesheim, A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, **1963**, pp. 597–640.

³⁸⁶ See Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G. *Synthesis* **1980**, 124.

³⁸⁷ For a review, see Schnell, H.; Krimm, H. *Angew. Chem. Int. Ed.* **1963**, 2, 373.

atropisomerism (see Sec. 4.C, category 5).³⁸⁸ When the reaction was done with a chiral aluminum complex, modest enantioselectivity was observed.

The hydroxymethylation of phenols with formaldehyde is called the *Lederer–Manasse reaction*. This reaction must be carefully controlled,³⁸⁹ since it is possible for the para and both ortho positions to be substituted and for each of these to be rearylated, so that a polymeric structure (**45**) is produced. However, such polymers, which are of the Bakelite type (phenol–formaldehyde resins, **45**), are of considerable commercial importance.



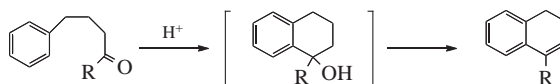
The attacking species is the carbocation ($R_2(OH)C^+$) formed from the aldehyde or ketone and the acid catalyst, except when the reaction is carried out in basic solution.

When an aromatic ring is treated with diethyl oxomalonate $[(EtOOC)_2C=O]$, the product is an arylmalonic acid derivative $[ArC(OH)(COOEt)_2]$, which can be converted to an arylmalonic acid $[ArCH(COOEt)_2]$.³⁹⁰ This is therefore a way of applying the malonic ester synthesis (Reaction **10-67**) to an aryl group (see also, Reaction **13-14**). Of course, the opposite mechanism applies here: The aryl species is the nucleophile.

Two methods, both involving boron-containing reagents, have been devised for the regioselective ortho hydroxymethylation of phenols or aromatic amines.³⁹¹ Conjugated aldehydes undergo *Friedel–Crafts alkylation* with aryltrifluoroborate salts, in the presence of a catalytic amount of an imidazolidinone.³⁹²

OS **III**, 326; **V**, 422; **VI**, 471, 856; **VIII**, 75, 77, 80. Also see, OS **I**, 214.

11-13 Cyclodehydration of Carbonyl-Containing Compounds



As described in Reaction **11-12**, the reaction of carbonyl-containing functional groups with protonic or Lewis acids lead to oxygen-stabilized carbocations. When generated in the presence of an aromatic ring, *Friedel–Crafts alkylation* occurs to give an alcohol or an alkene, if dehydration occurs under the reaction conditions. When an

³⁸⁸ Gothelf, A.S.; Hansen, T.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 854.

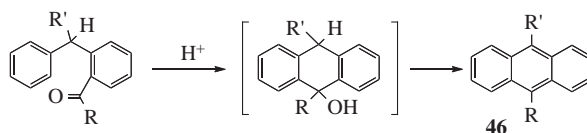
³⁸⁹ See Casiraghi, G.; Casnati, G.; Pochini, A.; Puglia, G.; Ungaro, R.; Sartori, G. *Synthesis* **1981**, 143.

³⁹⁰ Ghosh, S.; Pardo, S.N.; Salomon, R.G. *J. Org. Chem.* **1982**, 47, 4692.

³⁹¹ Sugawara, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, 100, 4842; Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, 365.

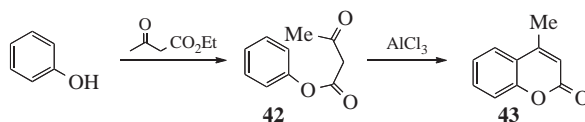
³⁹² Lee, S.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2007**, 129, 15438.

aromatic compound contains an aldehyde or ketone function in a position suitable for closing a suitably sized ring, treatment with acid results in cyclodehydration. The reaction is a special case of **11-12**, but in this case dehydration almost always takes place to give a double bond conjugated with the aromatic ring.³⁹³ The method is very general and is widely used to close both carbocyclic and heterocyclic rings.³⁹⁴ Polyphosphoric acid is a common reagent, but other acids have also been used. In a variation known as the *Bradsher reaction*,³⁹⁵ diarylmethanes, which contain a carbonyl group in the ortho position, can be cyclized to anthracene derivatives (**46**). In this case, 1,4-dehydration takes place, at least formally.



An intramolecular cyclization of an aryl ether to the carbonyl of a pendant aryl ketone, on clay with microwave irradiation, led to a benzofuran via *Friedel–Crafts cyclization* and elimination of water.³⁹⁶

A variation of this reaction involves acylation of a β -keto ester, followed by *Friedel–Crafts cyclization* of the ketone moiety. The product is a coumarin (**43**), in what is known as the *Pechmann condensation*.³⁹⁷ Isolation of esters (e.g., **42**) is not always necessary, and protonic acids can be used rather than Lewis acids. The *Pechmann condensation* is facilitated by the presence of hydroxyl (OH), dimethylamino (NMe₂), and alkyl groups meta to the hydroxyl of the phenol.³⁹⁸ The reaction has been accomplished using microwave irradiation on graphite/Montmorillonite K-10.³⁹⁹ *Pechmann condensation* in an ionic liquid using ethyl acetate has also been reported.⁴⁰⁰



The carbonyl unit involved in the cyclization process is not restricted to aldehydes and ketones. The carbonyl of acid derivatives (e.g., amides) also can be utilized. One of the more important cyclodehydration reactions is applied to the formation of heterocyclic systems via cyclization of β -aryl amides, in what is called the *Bischler–Napieralski reaction*.⁴⁰¹ In this reaction, amides of the type **47** are cyclized with phosphorous oxychloride or other reagents, including polyphosphoric acid, sulfuric acid, or phosphorus

³⁹³ See Bonnet-Delpon, D.; Charpentier-Morize, M.; Jacquot, R. *J. Org. Chem.* **1988**, 53, 759.

³⁹⁴ See Bradsher, C.K. *Chem. Rev.* **1987**, 87, 1277.

³⁹⁵ Bradsher, C.K. *Chem. Rev.* **1987**, 87, 1277, see pp. 1287–1294.

³⁹⁶ Meshram, H.M.; Sekhar, K.C.; Ganesh, Y.S.S.; Yadav, J.S. *Synlett* **2000**, 1273.

³⁹⁷ von Pechmann, H.; Duisberg, C. *Ber.* **1883**, 16, 2119; Sethna, S.; Phadke, R. *Org. React.* **1953**, 7, 1. For a Pechmann condensation in ionic liquids, see Kumar, V.; Tomar, S.; Patel, R.; Yousaf, A.; Parmar, V.S.; Malhotra, S.V. *Synth. Commun.* **2008**, 38, 2646.

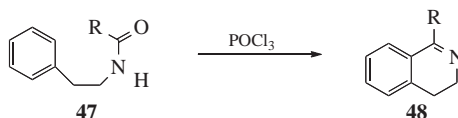
³⁹⁸ Miyano, M.; Dorn, C.R. *J. Org. Chem.* **1972**, 37, 259.

³⁹⁹ Frère, S.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2001**, 42, 2791.

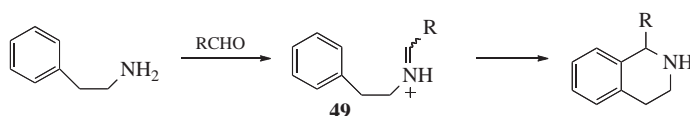
⁴⁰⁰ See Potdar, M.K.; Mohile, S.S.; Salunkhe, M.M. *Tetrahedron Lett.* **2001**, 42, 9285.

⁴⁰¹ See Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, 36, 1279.

pentoxide, to give a dihydroisoquinoline (**48**). The *Bischler–Napieralski reaction* has been done in ionic liquids using POCl_3 .⁴⁰² The reaction has also been done using solid-phase (see Sec. 9.D.iv) techniques.⁴⁰³



If the starting compound contains a hydroxyl group in the α position, an additional dehydration takes place and the product is an isoquinoline.⁴⁰⁴ Higher yields can be obtained if the amide is treated with PCl_3 to give an imino chloride ($\text{ArCH}_2\text{CH}_2\text{N}=\text{CR}-\text{Cl}$), which is isolated and then cyclized by heating.⁴⁰⁵ In this latter case, a nitrilium ion ($\text{ArCH}_2\text{CH}_2^+\text{N}\equiv\text{CR}$) is an intermediate.



Another useful variation is the *Pictet–Spengler isoquinoline synthesis*, also known as the *Pictet–Spengler reaction*.⁴⁰⁶ The reactive intermediate is an iminium ion (**49**) rather than an oxygen-stabilized cation, but attack at the electrophilic carbon of the $\text{C}=\text{N}$ unit (see Reaction **16-31**) leads to an isoquinoline derivative. When a β -arylamine reacts with an aldehyde, the product is an iminium salt, which cyclizes with an aromatic ring to complete the reaction and generate a tetrahydroisoquinoline.⁴⁰⁷ Metal-catalyzed reactions are known, including the use of $\text{AuCl}_3/\text{AgOTf}$.⁴⁰⁸ A variety of aldehydes can be used, and substitution on the aromatic ring leads to many derivatives. When the reaction is done in the presence of a chiral catalyst, good enantioselectivity was observed.⁴⁰⁹

Another variation in this basic procedure leads to tetrahydroisoquinolines. When phenethylamine was treated with *N*-hydroxymethylbenzotriazole and then AlCl_3 in chloroform, cyclization occurred, and reduction with sodium borohydride gave the 1,2,3,4-tetrahydro-*N*-methyloisoquinoline.⁴¹⁰

OS **I**, 360, 478; **II**, 62, 194; **III**, 281, 300, 329, 568, 580, 581; **IV**, 590; **V**, 550; **VI**, 1. Also see, OS **I**, 54.

⁴⁰² See Judeh, Z.M.A.; Ching, C.B.; Bu, J.; McCluskey, A. *Tetrahedron Lett.* **2002**, 43, 5089.

⁴⁰³ Chern, M.-S.; Li, W.R. *Tetrahedron Lett.* **2004**, 45, 8323.

⁴⁰⁴ Wang, X.-j.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* **1998**, 39, 6609.

⁴⁰⁵ Fodor, G.; Gal, G.; Phillips, B.A. *Angew. Chem. Int. Ed.* **1972**, 11, 919.

⁴⁰⁶ Pictet, A.; Spengler, T. *Ber.* **1911**, 44, 2030; Cox, E.D.; Cook, J.M. *Chem. Rev.* **1995**, 95, 1797. See also, Whaley, W.M.; Govindachari, T.R. *Org. React.* **1951**, 6, 74; Youn, S.W. *Org. Prep. Proceed. Int.* **2006**, 38, 505.

⁴⁰⁷ Ong, H.H.; May, E.L. *J. Heterocyclic Chem.* **1971**, 8, 1007.

⁴⁰⁸ Youn, S.W. *J. Org. Chem.* **2006**, 71, 2521.

⁴⁰⁹ Seayad, J.; Seayad, A.M.; List, B. *J. Am. Chem. Soc.* **2006**, 128, 1086; Raheem, I.T.; Thiara, P.S.; Peterson, E.A.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2007**, 129, 13404; Sewgobind, N.V.; Wanner, M.J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J.H.; Hiemstra, H. *J. Org. Chem.* **2008**, 73, 6405.

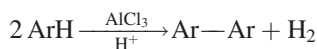
⁴¹⁰ Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 179.

11-14 Haloalkylation or Haloalkyl-de-hydrogenation

When certain aromatic compounds are treated with formaldehyde and HCl, the CH_2Cl group is introduced into the ring in a reaction called *chloromethylation*. The reaction has also been carried out with other aldehydes and with HBr and HI. The more general term *haloalkylation* covers these cases.⁴¹¹ The reaction is successful for benzene, and alkyl-, alkoxy-, and halobenzenes. It is greatly hindered by meta-directing groups, which reduce yields or completely prevent the reactions. Amines and phenols are too reactive and usually give polymers unless deactivating groups are also present, but phenolic ethers and esters successfully undergo the reaction. Compounds of lesser reactivity can often be chloromethylated with chloromethyl methyl ether (ClCH_2OMe) or methoxyacetyl chloride ($\text{MeOCH}_2\text{COCl}$).⁴¹² Zinc chloride is the most common catalyst, but other Friedel–Crafts catalysts are also employed. As with Reaction 11-12 and for the same reason, an important side product is the diaryl compound Ar_2CH_2 (from formaldehyde).

Apparently, the initial step involves reaction of the aromatic compound with the aldehyde to form the hydroxyalkyl compound, exactly as in Reaction 11-12, and then the HCl converts this to the chloroalkyl compound.⁴¹³ The acceleration of the reaction by ZnCl_2 has been attributed⁴¹⁴ to the raising of the acidity of the medium, causing an increase in the concentration of HOCH_2^+ ions.

OS III, 195, 197, 468, 557; IV, 980.

11-15 Friedel–Crafts Arylation: The Scholl Reaction**De-hydrogen-coupling**

The coupling of two aromatic molecules by treatment with a Lewis and a proton acid is called the *Scholl reaction*.⁴¹⁵ Yields are low and the synthesis is seldom useful. High temperatures and strong-acid catalysts are required, and the reaction fails for substrates that are destroyed by these conditions. The reaction becomes important with large fused-ring systems, so ordinary *Friedel–Crafts reactions* (11-11) on these systems are rare. For example, naphthalene gives binaphthyl under *Friedel–Crafts conditions*. Yields can be

⁴¹¹ See Belen'kii, L.I.; Vol'kenshtein, Yu.B.; Karmanova, I.B. *Russ. Chem. Rev.* **1977**, 46, 891; Olah, G.A.; Tolgyesi, W.S. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, **1963**, pp. 659–784.

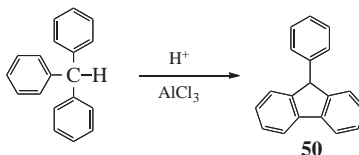
⁴¹² McKillop, A.; Madjdabadi, F.A.; Long, D.A. *Tetrahedron Lett.* **1983**, 24, 1933.

⁴¹³ Ogata, Y.; Okano, M. *J. Am. Chem. Soc.* **1956**, 78, 5423. See also, Olah, G.A.; Yu, S.H. *J. Am. Chem. Soc.* **1975**, 97, 2293.

⁴¹⁴ Lyushin, M.M.; Mekhtiev, S.D.; Guseinova, S.N. *J. Org. Chem. USSR* **1970**, 6, 1445.

⁴¹⁵ See Kovacic, P.; Jones, M.B. *Chem. Rev.* **1987**, 87, 357; Balaban, A.T.; Nenitzescu, C.D. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, **1964**, pp. 979–1047.

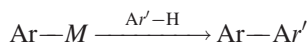
increased by the addition of a salt (e.g., CuCl_2 or FeCl_3), which acts as an oxidant.⁴¹⁶ Rhodium⁴¹⁷ and Ru catalysts⁴¹⁸ have also been used.



Intramolecular *Scholl reactions* (e.g., formation of **50** from triphenylmethane) are much more successful than the intermolecular reaction. The mechanism is not clear, but it may involve attack by a proton to give an arenium ion of type **12** (Sec. 11.A.i, category 2), which would be the electrophile that attacks the other ring.⁴¹⁹ Sometimes arylations have been accomplished by treating aromatic substrates with particularly active aryl halides, especially fluorides. For free radical arylations, see Reactions **12-15**, **13-26**, **13-27**, **13-10**, **14-17**, and **14-18**.

OS IV, 482; X, 359. Also see, OS V, 102, 952.

11-16 Arylation of Aromatic Compounds by Metalated Aryls



Many metalated aryl compounds are known to couple with aromatic compounds. Aniline derivatives react with $\text{ArPb}(\text{OAc})_3$, for example, to give the 2-arylaniline.⁴²⁰ Phenolic anions also react to form biaryls, with modest enantioselectivity in the presence of brucine.⁴²¹ A Mn(III) mediated synthesis of biaryls used microwave irradiation for the coupling reaction.⁴²² The homocoupling reaction of aryl *Grignard reagents* in the presence of TEMPO is known.⁴²³

Phenylboronates $[\text{ArB}(\text{OR})_2]$ react with electron-deficient aromatic compounds (e.g., acetophenone) to give the biaryl.⁴²⁴ Arylboronates also react with π -allyl Pd complexes to form the alkylated aromatic compound.⁴²⁵ Arylboronic acids are also coupled in the presence of metal catalysts.⁴²⁶ Organoborates can be coupled using an oxovanadium catalyst,⁴²⁷ and potassium phenyltrifluoroborates can be coupled to aromatics using a combination of Pd and Cu catalysts.⁴²⁸

⁴¹⁶ For examples with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 77–84; Sartori, G.; Maggi, R.; Bigi, F.; Grandi, M. *J. Org. Chem.* **1993**, 58, 7271.

⁴¹⁷ Barrett, A.G.M.; Itoh, T.; Wallace, E.M. *Tetrahedron Lett.* **1993**, 34, 2233. For a microwave promoted reaction, see Lewis, J.C.; Wu, J.Y.; Bergman, R.G.; Ellman, J.A. *Angew. Chem. Int. Ed.* **2006**, 45, 1589.

⁴¹⁸ Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2005**, 127, 6632. For a coupling reaction of pyridines, see Kawashima, T.; Takao, T.; Suzuki, H. *J. Am. Chem. Soc.* **2007**, 129, 11006.

⁴¹⁹ See Clowes, G.A. *J. Chem. Soc. C* **1968**, 2519.

⁴²⁰ Saito, S.; Kano, T.; Ohyabu, Y.; Yamamoto, H. *Synlett* **2000**, 1676.

⁴²¹ Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, 124, 5365.

⁴²² Demir, A.S.; Findik, H.; Saygili, N.; Subasi, N.T. *Tetrahedron* **2010**, 66, 1308.

⁴²³ Maji, M.S.; Studer, A. *Synthesis* **2009**, 2467.

⁴²⁴ Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, 125, 1698.

⁴²⁵ Ortar, G. *Tetrahedron Lett.* **2003**, 44, 4311.

⁴²⁶ Basl, O.; Li, C.-J. *Org. Lett.* **2008**, 10, 3661.

⁴²⁷ Mizuno, H.; Sakurai, H.; Amaya, T.; Hirao, T. *Chem. Commun.* **2006**, 5042.

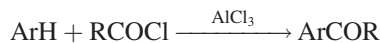
⁴²⁸ Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, 73, 7428.

A Cu catalyzed coupling reaction with hypervalent arylated iodine derivatives is known.⁴²⁹

See Reactions **13-9**, **13-11**, and **13-12**.

11-17 Friedel–Crafts Acylation

Acylation or Acyl-de-hydrogenation



The most important method for the preparation of aryl ketones is known as *Friedel–Crafts acylation*.⁴³⁰ The reaction is of wide scope. Reagents other than acyl halides can be used,⁴³¹ including carboxylic acids,⁴³² anhydrides, and ketenes. Oxalyl chloride has been used to give diaryl 1,2-diketones.⁴³³ Carboxylic esters usually give alkylation as the predominant product (see Reaction **11-11**).⁴³⁴ *N*-Carbamoyl β -lactams reacted with naphthalene in the presence of trifluoromethanesulfonic acid to give the keto-amide.⁴³⁵

The alkyl group (R in RCOCl) may be aryl as well as alkyl.⁴³⁶ The major disadvantages of *Friedel–Crafts alkylation*, polyalkylation, and rearrangement of the intermediate carbocation, are not a problem in *Friedel–Crafts acylation*. Rearrangement of the alkyl group (R in RCOCl) is never found because the intermediate is an acylium ion (an acyl cation, $\text{RC}\equiv\text{O}^+$, see below), which is stabilized by resonance. Because the RCO group is deactivating, the reaction stops cleanly after one group is introduced. All four acyl halides can be used, though chlorides are most commonly employed. The order of activity is usually, but not always, $\text{I} > \text{Br} > \text{Cl} > \text{F}$.⁴³⁷ Catalysts are Lewis acids,⁴³⁸ similar to those in Reaction **11-11**, but in acylation a little >1 equiv of catalyst is required per mole of reagent, because the first mole coordinates with the oxygen of the reagent [as in $\text{R}(\text{Cl})\text{C}=\text{O}^{+-}\text{AlCl}_3$].⁴³⁹ A reusable catalyst $[\text{Ln}(\text{OTf})_3-\text{LiClO}_4]$ has been developed.⁴⁴⁰ Ferric chloride in an ionic liquid has

⁴²⁹ Phipps, R.J.; Grimster, N.P.; Gaunt, M.J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

⁴³⁰ See Olah, G.A. *Friedel–Crafts and Related Reactions*, Wiley, NY, **1963–1964**, as follows: Vol. 1, Olah, G.A. pp. 91–115; Vol. 3, Gore, P.H. pp. 1–381; Peto, A.G. pp. 535–910; Sethna, S. pp. 911–1002; Jensen, F.R.; Goldman, G. pp. 1003–1032. Also see Gore, P.H. *Chem. Ind. (London)* **1974**, 727; *Advances in Friedel–Crafts Acylation Reactions: Catalytic and Green Processes*, Sartori, G.; Maggi, R., CRC Press, Boca Raton, FL, **2009**.

⁴³¹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1423–1426.

⁴³² Kawamura, M.; Cui, D.-M.; Hayashi, T.; Shimada, S. *Tetrahedron Lett.* **2003**, *44*, 7715. See Kaur, J.; Kozhevnikov, I.V. *Chem. Commun.* **2002**, 2508.

⁴³³ Taber, D.F.; Sethuraman, M.R. *J. Org. Chem.* **2000**, *65*, 254.

⁴³⁴ See Hwang, J.P.; Prakash, G.K.S.; Olah, G.A. *Tetrahedron* **2000**, *56*, 7199.

⁴³⁵ Anderson, K.W.; Tepe, J. *Org. Lett.* **2002**, *4*, 459.

⁴³⁶ For a discussion of the relationship between electrophilicity of the substituting agents and substrate selectivity, see Meneses, L.; Fuentealba, P.; Contreras, R. *Tetrahedron* **2005**, *61*, 831.

⁴³⁷ Yamase, Y. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 480; Corriu, R. *Bull. Soc. Chim. Fr.* **1965**, 821.

⁴³⁸ See Pearson, D.E.; Buehler, C.A. *Synthesis* **1972**, 533. Examples include, $\text{Ga}(\text{ONF})_3$, where Nf = non-afluorobutanesulfonate; Matsu, J.-i.; Odashima, K.; Kobayashi, S. *Synlett* **2000**, 403. $\text{In}(\text{OTf})_3$ with LiClO_4 ; Chapman, C.J.; Frost, C.G.; Hartley, J.P.; Whittle, A.J. *Tetrahedron Lett.* **2001**, *42*, 773. InCl_3 ; Choudhary, V.R.; Jana, S.K.; Patil, N.S. *Tetrahedron Lett.* **2002**, *43*, 1105. $\text{Sc}(\text{OTf})_3$; Kawada, A.; Mitamura, S.; Matsuo, J.-i.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2325. $\text{Yb}[\text{C}(\text{SO}_2\text{C}_4\text{F}_4)_3]_3$; Barrett, A.G.M.; Boulloc, N.; Braddock, D.C.; Chadwick, D.; Henderson, D.A. *Synlett* **2002**, 1653. BiOCl_3 ; Répichet, S.; Le Roux, C.; Roques, N.; Dubac, J. *Tetrahedron Lett.* **2003**, *44*, 2037. ZnO ; Sarvari, M.H.; Sharghi, H. *J. Org. Chem.* **2004**, *69*, 6953.

⁴³⁹ See Chevrier, B.; Weiss, R. *Angew. Chem. Int. Ed.* **1974**, *13*, 1.

⁴⁴⁰ Kawada, A.; Mitamura, S.; Kobayashi, S. *Chem. Commun.* **1996**, 183. Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett*, **1994**, 545; Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 409.

also been used.⁴⁴¹ The HY-Zeolite has also been used to facilitate the reaction with acetic anhydride.⁴⁴² Catalysts include a Pd catalyst, which was used with acetic anhydride,⁴⁴³ TiCl_4 ,⁴⁴⁴ SnI_2 ,⁴⁴⁵ In metal,⁴⁴⁶ acetyl chloride, and zinc powder with microwave irradiation.⁴⁴⁷ *Friedel–Crafts acylation* using a carboxylic acid with a catalyst called Envirocac-EPIC (an acid-treated clay-based material) was reported.⁴⁴⁸ *Friedel–Crafts acylation* was reported in an ionic liquid.⁴⁴⁹ An interesting acylation reaction was reported that coupled trichlorophenylmethane to benzene, giving benzophenone in the presence of the ionic liquid $\text{AlCl}_3\text{--BPC}$.⁴⁵⁰ (butylpyridiniumchloroaluminate = BPC). Acylation has been accomplished in carbon disulfide.⁴⁵¹ An interesting variation couples a conjugated acid chloride with benzene, in the presence of AlCl_3 and microwave irradiation, to give an indanone.⁴⁵²

Protonic acids can be used as catalysts when the reagent is a carboxylic acid.⁴⁵³ Triflic anhydride promotes dehydrative acylation of carboxylic acids,⁴⁵⁴ as does $\text{P}_2\text{O}_5/\text{SiO}_2$.⁴⁵⁵ An aryl carboxylic acid can be converted to the acid chloride *in situ* with cyanuric chloride and AlCl_3 , leading to *Friedel–Crafts acylation*.⁴⁵⁶ A solvent-free method is also available using tosic acid/graphite.⁴⁵⁷

The mixed carboxylic sulfonic anhydrides ($\text{RCOOSO}_2\text{CF}_3$) are extremely reactive acylating agents and can smoothly acylate benzene without a catalyst.⁴⁵⁸ With active substrates (e.g., aryl ethers, fused-ring systems, thiophenes), *Friedel–Crafts acylation* can be carried out with very small amounts of catalyst, often just a trace, or even sometimes with no catalyst at all.

The reaction is quite successful for many types of substrate, including fused ring systems, which give poor results in Reaction 11-11. Compounds containing ortho–para directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the para products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from *N*- or *O*-acylation; however, *O*-acylated phenols can be converted to *C*-acylated phenols by the *Fries rearrangement* (Reaction 11-27). *Friedel–Crafts acylation* is usually prevented by meta-directing (deactivating) groups.

⁴⁴¹ Khodaei, M.M.; Bahrami, K.; Shahbazi, F. *Chem. Lett.* **2008**, 37, 844.

⁴⁴² Sreekumar, R.; Padmukumar, R. *Synth. Commun.* **1997**, 27, 777. See Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* **1994**, 35, 2601.

⁴⁴³ Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D.; Reetz, M.T. *Org. Lett.* **2001**, 3, 417.

⁴⁴⁴ Bensari, A.; Zaveri, N.T. *Synthesis* **2003**, 267.

⁴⁴⁵ Soueidan, M.; Collin, J.; Gil, R. *Tetrahedron Lett.* **2006**, 47, 5467.

⁴⁴⁶ Jang, D.O.; Moon, K.S.; Cho, D.H.; Kim, J.-G. *Tetrahedron Lett.* **2006**, 47, 6063.

⁴⁴⁷ Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* **2003**, 2877.

⁴⁴⁸ Bandgar, B.P.; Sadavarte, V.S. *Synth. Commun.* **1999**, 29, 2587.

⁴⁴⁹ See Gmouth, S.; Yang, H.; Vaultier, M. *Org. Lett.* **2003**, 5, 2219.

⁴⁵⁰ See Rebeiro, G.L.; Khadilkar, B.M. *Synth. Commun.* **2000**, 30, 1605.

⁴⁵¹ Georgakilas, V.; Perdikomatis, G.P.; Triantafyllou, A.S.; Siskos, M.G.; Zarkadis, A.K. *Tetrahedron* **2002**, 58, 2441.

⁴⁵² Yin, W.; Ma, Y.; Xu, J.; Zhao, Y. *J. Org. Chem.* **2006**, 71, 4312.

⁴⁵³ See Kawamura, M.; Cui, D.-M.; Shimada, S. *Tetrahedron* **2006**, 62, 9201. Also see Posternak, A.G.; Garlyauskayte, R.Yu.; Yagupolskii, L.M. *Tetrahedron Lett.* **2009**, 50, 446.

⁴⁵⁴ Khodaei, M.M.; Alizadeh, A.; Nazari, E. *Tetrahedron Lett.* **2007**, 48, 4199.

⁴⁵⁵ Zarei, A.; Hajipour, A.R.; Khazdooz, L. *Tetrahedron Lett.* **2008**, 49, 6715.

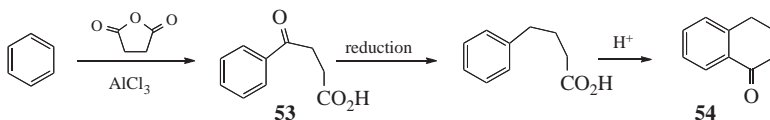
⁴⁵⁶ Kangani, C.O.; Day, B.W. *Org. Lett.* **2008**, 10, 2645.

⁴⁵⁷ Sarvari, M.H.; Sharghi, H. *Helv. Chim. Acta* **2005**, 88, 2282.

⁴⁵⁸ Effenberger, F.; Sohn, E.; Eppe, G. *Chem. Ber.* **1983**, 116, 1195. See also, Keumi, T.; Yoshimura, K.; Shimada, M.; Kitajima, H. *Bull. Chem. Soc. Jpn.* **1988**, 44, 455.

Indeed, nitrobenzene is often used as a solvent for the reaction. Many heterocyclic systems, including furans, thiophenes, pyrans, and pyrroles⁴⁵⁹ but not pyridines or quinolines, can be acylated in good yield. Initial reaction of indole with Et_2AlCl ⁴⁶⁰ or SnCl_4 ,⁴⁶¹ followed by acetyl chloride leads to 3-acetylindole. By comparison, the reaction of *N*-acetylindole with acetic anhydride and AlCl_3 gave *N*,6-diacetylindole.⁴⁶² Acetylation at C-3 was also accomplished with acetyl chloride in the ionic liquid $\text{emimcl}-\text{AlCl}_3$.⁴⁶³ Gore, in Ref. 430 (pp. 36–100; with tables, pp. 105–321), presents an extensive summary of the substrates to which this reaction has been applied.

Friedel–Crafts acylation can be carried out with cyclic anhydrides,⁴⁶⁴ in which case the product contains a carboxyl group in the side chain (**53**). When succinic anhydride is used, the product is $\text{ArCOCH}_2\text{CH}_2\text{CO}_2\text{H}$. This can be reduced (Reaction **19-61**) to $\text{ArCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, and can then be cyclized by an internal *Friedel–Crafts acylation* to give **54**. The total process is called the *Haworth reaction*.⁴⁶⁵



When a mixed-anhydride ($\text{RCOOCOR}'$) is the reagent, two products are possible: ArCOR and ArCOR' . Which product predominates depends on two factors. If *R* contains electron-withdrawing groups, then ArCOR' is chiefly formed, but if this factor is approximately constant in *R* and *R'*, the ketone with the larger *R* group predominantly forms.⁴⁶⁶ This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid (HCOOCOR).

An important use of the *Friedel–Crafts acylation* is to effect ring closure.⁴⁶⁷ This closure can be accomplished if an acyl halide, anhydride, or carboxylic acid⁴⁶⁸ group is in the proper position. An example is the conversion of **51** to **52**. The reaction is used mostly to close six-membered rings, but has also been done for five- and seven-membered rings, which close less readily. Even larger rings can be closed by high-dilution techniques.⁴⁶⁹ Tricyclic and larger systems are often made by using substrates containing one of the acyl groups on a ring. Many fused-ring systems are made in this manner. If the bridging group is CO, the product is a quinone.⁴⁷⁰ One of the most

⁴⁵⁹ Yadav, J.S.; Reddy, B.V.S.; Kondaji, G.; Rao, R.S.; Kumar, S.P. *Tetrahedron Lett.* **2002**, 43, 8133.

⁴⁶⁰ Zhang, Z.; Yang, Z.; Wong, H.; Zhu, J.; Meanwell, N.A.; Kadow, J.F.; Wang, T. *J. Org. Chem.* **2002**, 67, 6226.

⁴⁶¹ Ottoni, O.; de V.F. Neder, A.; Dias, A.K.B.; Cruz, R.P.A.; Aquino, L.B. *Org. Lett.* **2001**, 3, 1005.

⁴⁶² Cruz, R.P.A.; Ottoni, O.; Abella, C.A.M.; Aquino, L.B. *Tetrahedron Lett.* **2001**, 42, 1467. See Pal, M.; Dakarapu, R.; Padakanti, S. *J. Org. Chem.* **2004**, 69, 2913.

⁴⁶³ See Yeung, K.-S.; Farkas, M.E.; Qiu, Z.; Yang, Z. *Tetrahedron Lett.* **2002**, 43, 5793.

⁴⁶⁴ See Peto, A.G. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, p. 535.

⁴⁶⁵ See Agranat, I.; Shih, Y. *J. Chem. Educ.* **1976**, 53, 488.

⁴⁶⁶ Edwards, Jr., W.R.; Sibelle, E.C. *J. Org. Chem.* **1963**, 28, 674.

⁴⁶⁷ See Sethna, S. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 911–1002. For examples with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1427–1431.

⁴⁶⁸ See Cui, D.-M.; Zhang, C.; Kawamura, M.; Shimada, S. *Tetrahedron Lett.* **2004**, 45, 1741.

⁴⁶⁹ See Schubert, W.M.; Sweeney, W.A.; Latourette, H.K. *J. Am. Chem. Soc.* **1954**, 76, 5462.

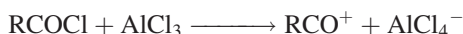
⁴⁷⁰ See Naruta, Y.; Maruyama, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, **1988**, pp. 325–332; Thomson, R.H. in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, **1974**, pp. 136–139.

common catalysts for intramolecular *Friedel–Crafts acylation* is polyphosphoric acid⁴⁷¹ (because of its high potency), but AlCl_3 , H_2SO_4 , and other Lewis and proton acids are also used, though acylations with acyl halides are not generally catalyzed by proton acids.



Thioesters are coupled to arylboronic acids in the presence of a Pd catalyst, in a *Friedel–Crafts acylation*-type coupling.⁴⁷² Acyl halides are coupled to arylboronic acids under microwave irradiation.⁴⁷³

The mechanism of *Friedel–Crafts acylation* is not completely understood,⁴⁷⁴ but at least two mechanisms probably operate, depending on conditions.⁴⁷⁵ In most cases, the attacking species is the acyl cation, either free or as an ion pair, formed by⁴⁷⁶



If R is tertiary, RCO^+ may lose CO to give R^+ , so that the alkyl arene ArR is often a side product or even the main product. This kind of cleavage is much more likely with relatively unreactive substrates, where the acylium ion has time to break down. For example, pivaloyl chloride (Me_3CCOCl) gives the normal acyl product with anisole, but yields the alkyl product (Me_3CPh) with benzene. In the other mechanism, an acyl cation is not involved, but the 1:1 complex (**55**) attacks directly.⁴⁷⁷ Free-ion attack is more likely for sterically hindered R.⁴⁷⁸ The ion CH_3CO^+ has been detected (by IR spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents (e.g., nitrobenzene); but in nonpolar solvents (e.g., as chloroform) only the complex and not the free ion is present.⁴⁷⁹ In any event, 1 molar equivalent of catalyst certainly remains complexed to the product at the end of the reaction. When the reaction is performed with $\text{RCO}^+ \text{SbF}_6^-$, no catalyst is required and the free ion⁴⁸⁰ (or ion pair) is undoubtedly the attacking entity.⁴⁸¹ The use of LiClO_4 on the metal triflate catalyzed *Friedel–Crafts acylation* of methoxynaphthalene derivatives has been examined. The presence of the lithium salt leads to acylation in the ring containing the methoxy unit, whereas reaction occurs in the other ring in the absence of lithium salts.⁴⁸² Note that lithium perchlorate

⁴⁷¹ See Rowlands, D.A. in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, **1985**, pp. 156–414.

⁴⁷² Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L.S. *J. Am. Chem. Soc.* **2007**, *129*, 1132.

⁴⁷³ Poláčková, V.; Toma, Š.; Augustínová, I. *Tetrahedron* **2006**, *62*, 11675.

⁴⁷⁴ See Effenberger, F.; Eberhard, J.K.; Maier, A.H. *J. Am. Chem. Soc.* **1996**, *118*, 12572.

⁴⁷⁵ See Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, **1990**, pp. 222–237.

⁴⁷⁶ After 2 min, exchange between PhCOCl and $\text{Al}(^{36}\text{Cl})_3$ is complete: Oulevey, G.; Susz, P.B. *Helv. Chim. Acta* **1964**, *47*, 1828.

⁴⁷⁷ See Tan, L.K.; Brownstein, S. *J. Org. Chem.* **1983**, *48*, 302.

⁴⁷⁸ Gore, P.H. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1627; Satchell, D.P.N. *J. Chem. Soc.* **1961**, 5404.

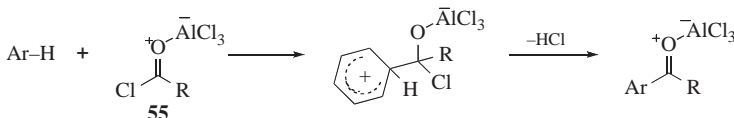
⁴⁷⁹ Cassimatis, D.; Bonnin, J.P.; Theophanides, T. *Can. J. Chem.* **1970**, *48*, 3860.

⁴⁸⁰ See Chevrier, B.; Le Carpentier, J.; Weiss, R. *Acta Crystallogr., Sect. B*, **1972**, *28*, 2673; *J. Am. Chem. Soc.* **1972**, *94*, 5718.

⁴⁸¹ Olah, G.A.; Lin, H.C.; Germain, A. *Synthesis* **1974**, 895. Also see Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* **1990**, *22*, 1.

⁴⁸² Kobayashi, S.; Komoto, I. *Tetrahedron* **2000**, *56*, 6463.

forms a complex with acetic anhydride, which can be used for the *Friedel–Crafts acetylation* of activated aromatic compounds.⁴⁸³



A related reaction couples an acid chloride with an aromatic compound in the presence of a Rh catalyst, but the coupling reaction involves a decarbonylation to give a biaryl.⁴⁸⁴

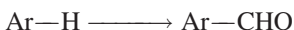
OS **I**, 109, 353, 476, 517; **II**, 3, 8, 15, 81, 156, 169, 304, 520, 569; **III**, 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; **IV**, 8, 34, 88, 898, 900; **V**, 111; **VI**, 34, 618, 625 **X**, 125.

Reaction **11-18** is a direct formylation of the ring.⁴⁸⁵ Reaction **11-17** has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 h at -6° ,⁴⁸⁶ but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in solution, but has not been isolated.⁴⁸⁷ Mixed anhydrides of formic and other acids are known⁴⁸⁸ and can be used to formylate amines (see Reaction **16-73**) and alcohols, but no formylation takes place when they are applied to aromatic rings. See Reaction **13-17** for a nucleophilic method for the formylation of aromatic rings.

A related reaction involves a biaryl, where one ring is a phenol. Treatment with BCl_3 and an AlCl_3 catalyst, followed by reaction with CO and $\text{Pd}(\text{OAc})_2$, led to carbonylation and acylation to give the corresponding lactone.⁴⁸⁹ Carbonylation of aromatic compounds can lead to aryl ketones. Heating an aromatic compound with $\text{Ru}(\text{CO})_{12}$, ethylene and 20 atm. of CO gave the corresponding aryl ethyl ketone.⁴⁹⁰

11-18 Formylation

Formylation or Formyl-de-hydrogenation



The reaction with disubstituted formamides ($\text{R}_2\text{N-CHO}$) and phosphorus oxychloride, called the *Vilsmeier* or the *Vilsmeier–Haack reaction*,⁴⁹¹ is the most common method

⁴⁸³ Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinalde, S.; Sambri, L. *Tetrahedron Lett.* **2002**, 43, 6331.

⁴⁸⁴ Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, 130, 8136.

⁴⁸⁵ See Olah, G.A.; Kuhn, S.J.; Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 1153–1256; Olah, G.A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, 87, 671. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1423–1426.

⁴⁸⁶ Staab, H.A.; Datta, A.P. *Angew. Chem. Int. Ed.* **1964**, 3, 132.

⁴⁸⁷ Olah, G.A.; Vankar, Y.D.; Arvanaghi, M.; Sommer, J. *Angew. Chem. Int. Ed.* **1979**, 18, 614.

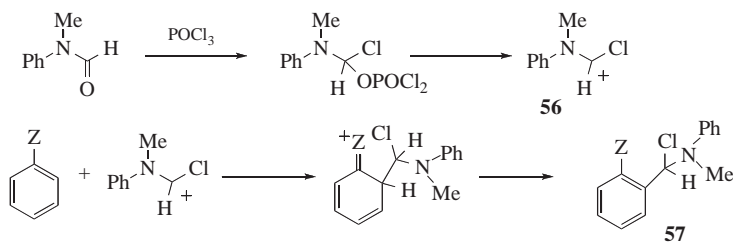
⁴⁸⁸ Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* **1964**, 83, 863.

⁴⁸⁹ Zhou, Q.J.; Worm, K.; Dolle, R.E. *J. Org. Chem.* **2004**, 69, 5147.

⁴⁹⁰ Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D.R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, 65, 1475.

⁴⁹¹ See Blaser, D.; Calmes, M.; Daunis, J.; Natt, F.; Tardy-Delassus, A.; Jacquier, R. *Org. Prep. Proceed. Int.* **1993**, 25, 338 for improvements in this reaction.

for the formylation of aromatic rings.⁴⁹² However, it is applicable only to active substrates (e.g., amines and phenols). An intramolecular version is also known.⁴⁹³ Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes and ferrocenes). Although *N*-phenyl-*N*-methylformamide is a common reagent, other arylalkyl amides and dialkyl amides are also used.⁴⁹⁴ Phosgene (COCl₂) has been used in place of POCl₃. The reaction has also been carried out with other amides to give ketones (actually an example of Reaction 11-17), but not often. The attacking species⁴⁹⁵ is **56**,⁴⁹⁶ and the mechanism is probably that shown to give **57**, which is unstable and easily hydrolyzes to the product. Either formation of **56** or the reaction of **56** with the substrate can be rate determining, depending on the reactivity of the substrate.⁴⁹⁷



When (CF₃SO₂)₂O was used instead of POCl₃, the reaction was extended to some less-active compounds, including naphthalene and phenanthrene.⁴⁹⁸

In a related reaction, paraformaldehyde can be used, with MgCl₂-NEt₃, to convert phenol to phenol 2-carbaldehyde.⁴⁹⁹ Another variation treated acetanilide with POCl₃—DMF and generated 2-chloroquinoline-3-carboxaldehyde.⁵⁰⁰ Used in conjunction with conjugated hydroxylamines, a tandem *Vilsmeier–Beckman reaction* (see Reaction 18-17 for the *Beckman rearrangement*) leads to pyridines (2-chloro-3-carboxaldehyde).⁵⁰¹ A chain-extension variation has been reported in which an aryl alkyl ketone is treated with POCl₃/DMF on silica with microwave irradiation to give a conjugated aldehyde [ArC(=O)R → ArC(Cl)=CHCHO].⁵⁰²

OS I, 217; **III**, 98, **IV**, 331, 539, 831, 915.



Formylation with Zn(CN)₂ and HCl is called the *Gatterman reaction*⁵⁰³ and can be applied to alkylbenzenes, phenols and their ethers, as well as many heterocyclic

⁴⁹² See Jutz, C. *Adv. Org. Chem.* **1976**, 9, pt. 1, 225.

⁴⁹³ Meth-Cohn, O.; Goon, S. *J. Chem. Soc. Perkin Trans. 1* **1997**, 85.

⁴⁹⁴ See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, **1974**, pp. 1–99.

⁴⁹⁵ For a review of such species, see Kantelehnner, W. *Adv. Org. Chem.* **1979**, 9, pt. 2, 5.

⁴⁹⁶ See Jugie, G.; Smith, J.A.S.; Martin, G.J. *J. Chem. Soc. Perkin Trans. 2* **1975**, 925.

⁴⁹⁷ Alunni, S.; Linda, P.; Marino, G.; Santini, S.; Savelli, G. *J. Chem. Soc. Perkin Trans. 2* **1972**, 2070.

⁴⁹⁸ Martínez, A.G.; Alvarez, R.M.; Barcina, J.O.; Cerero, S. de la M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *J. Chem. Soc., Chem. Commun.* **1990**, 1571.

⁴⁹⁹ Hofsløkken, N.U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, 53, 258.

⁵⁰⁰ Ali, M.M.; Tasneem, Rajanna, K.C.; Prakash, P.K.S. *Synlett* **2001**, 251. Also see Akila, S.; Selvi, S.; Balasubramanian, K. *Tetrahedron* **2001**, 57, 3465.

⁵⁰¹ Amaresh, R.R.; Perumal, P.T. *Synth. Commun.* **2000**, 30, 2269.

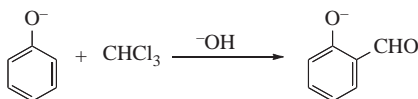
⁵⁰² Paul, S.; Gupta, M.; Gupta, R. *Synlett* **2000**, 1115.

⁵⁰³ See Truce, W.E. *Org. React.* **1957**, 9, 37; Tanaka, M.; Fujiwara, M.; Ando, H. *J. Org. Chem.* **1995**, 60, 2106 for rate studies.

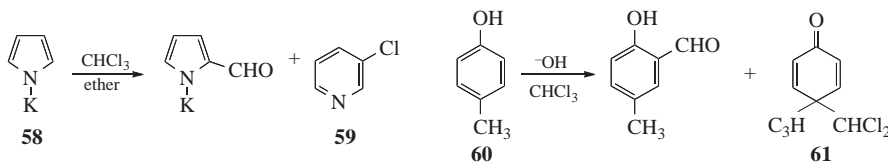
compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction, the substrate was treated with HCN, HCl, and ZnCl₂, but the use of Zn(CN)₂ and HCl (HCN and ZnCl₂ are generated *in situ*) makes the reaction more convenient to carry out and yields are not diminished. The mechanism of the *Gatterman reaction* has not been investigated very much, but it is known that an initially formed, but not isolated nitrogen-containing product, is hydrolyzed to aldehyde. This product is presumed to be ArCH=NH₂⁺Cl[−], as shown. When benzene was treated with NaCN under superacid conditions (F₃CSO₂OH–SbF₅, see Sec. 5.A.ii), a good yield of product was obtained, leading to the conclusion that the electrophile in this case was ⁺C(H)=N⁺H₂.⁵⁰⁴ The *Gatterman reaction* may be regarded as a special case of Reaction 11-24.

Another method, formylation with CO and HCl in the presence of AlCl₃ and CuCl⁵⁰⁵ (the *Gatterman–Koch reaction*), is limited to benzene and alkylbenzenes.⁵⁰⁶ Aryl halides are converted to aryl aldehydes with CO/H₂ in the presence of a Pd catalyst.⁵⁰⁷

OS II, 583; III, 549.



In the *Reimer–Tiemann reaction*, aromatic rings are formylated by reaction with chloroform and hydroxide ion.⁵⁰⁸ The method is useful only for phenols and certain heterocyclic compounds (e.g., pyrroles and indoles). Unlike the previous formylation methods (Reaction 11-18), this one is conducted in basic solution. Yields are generally low, seldom rising >50%.⁵⁰⁹ The incoming group is directed ortho, unless both ortho positions are filled, in which case the attack is para.⁵¹⁰ Certain substrates have been shown to give abnormal products instead of or in addition to the normal ones. For example, **58** and **60** gave, respectively, **59** and **61**, as well as the normal aldehyde products. From the nature of the reagents and



from the kind of abnormal products obtained, it is clear that the reactive entity in this reaction is dichlorocarbene (CCl₂).⁵¹¹ This product is known to be produced by treatment of chloroform with bases (see Reaction 10-3); it is an electrophilic reagent and is known to

⁵⁰⁴ Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1991**, 113, 691.

⁵⁰⁵ See, however, Toniolo, L.; Graziani, M. *J. Organomet. Chem.* **1980**, 194, 221.

⁵⁰⁶ See Crounse, N.N. *Org. React.* **1949**, 5, 290.

⁵⁰⁷ Sergeev, A.G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2008**, 130, 15549.

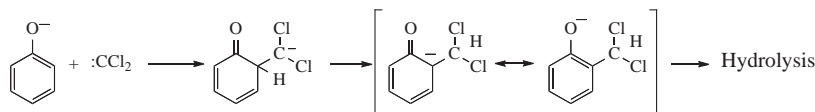
⁵⁰⁸ See Wynberg, H.; Meijer, E.W. *Org. React.* **1982**, 28, 1.

⁵⁰⁹ See Cochran, J.C.; Melville, M.G. *Synth. Commun.* **1990**, 20, 609.

⁵¹⁰ See, however, Neumann, R.; Sasson, Y. *Synthesis* **1986**, 569.

⁵¹¹ See Kulinkovich, O.G. *Russ. Chem. Rev.* **1989**, 58, 711.

give ring expansion of aromatic rings (see Reaction 15-64), accounting for products like 58. The mechanism of the normal reaction is thus something like⁵¹²:



The formation of 61 in the case of 60 can be explained by attack of some of the CCl_2 ipso to the CH_3 group. Since this position does not contain a hydrogen, normal proton loss cannot take place and the reaction ends when the CCl_2^- moiety acquires a proton.

A method closely related to the *Reimer-Tiemann reaction* is the *Duff reaction*, in which hexamethylenetetramine $[(\text{CH}_2)_6\text{N}_4]$ is used instead of chloroform. This reaction can be applied only to phenols and amines; ortho substitution is generally observed and yields are low. A mechanism⁵¹³ has been proposed that involves initial aminoalkylation (Reaction 11-22) to give ArCH_2NH_2 , followed by dehydrogenation to $\text{ArCH}=\text{NH}$ and hydrolysis of this to the aldehyde product. When $(\text{CH}_2)_6\text{N}_4$ is used in conjunction with $\text{F}_3\text{CCO}_2\text{H}$, the reaction can be applied to simple alkylbenzenes; yields are much higher and a high degree of regioselectively para substitution is found.⁵¹⁴ In this case too, an imine seems to be an intermediate.

OS III, 463; IV, 866



Besides Reaction 11-18, several other formylation methods are known.⁵¹⁵ In one of these, dichloromethyl methyl ether formylates aromatic rings with *Friedel-Crafts catalysts*.⁵¹⁶ The ArCHClOMe compound is probably an intermediate. Orthoformates have also been used.⁵¹⁷ In another method, aromatic rings are formylated with formyl fluoride (HCOF) and BF_3 .⁵¹⁸ Unlike formyl chloride, formyl fluoride is stable enough for this purpose. This reaction was successful for benzene, alkylbenzenes, PhCl , PhBr , and naphthalene. Phenols can be regioselectively formylated in the ortho position in high yields by treatment with 2 molar equivalents of paraformaldehyde in aprotic solvents in the presence of SnCl_4 and a tertiary amine.⁵¹⁹ Phenols have also been formylated indirectly by conversion to the aryllithium reagent followed by treatment with *N*-formyl piperidine.⁵²⁰ See also, the indirect method mentioned at Reaction 11-23. Aryl halides are converted to the corresponding aldehyde in a related reaction.⁵²¹

OS V, 49; VII, 162.

Reactions 11-19 and 11-20 are direct carboxylations⁵²² of aromatic rings.⁵²³

⁵¹² Robinson, E.A. *J. Chem. Soc.* **1961**, 1663; Hine, J.; van der Veen, J.M. *J. Am. Chem. Soc.* **1959**, *81*, 6446. See also, Langlois, B.R. *Tetrahedron Lett.* **1991**, *32*, 3691.

⁵¹³ Ogata, Y.; Kawasaki, A.; Sugiura, F. *Tetrahedron* **1968**, *24*, 5001.

⁵¹⁴ Smith, W.E. *J. Org. Chem.* **1972**, *37*, 3972.

⁵¹⁵ See Nishino, H.; Tsunoda, K.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 545.

⁵¹⁶ Lewin, A.H.; Parker, S.R.; Fleming, N.B.; Carroll, F.I. *Org. Prep. Proceed. Int.* **1978**, *10*, 201.

⁵¹⁷ Gross, H.; Rieche, A.; Matthey, G. *Chem. Ber.* **1963**, *96*, 308.

⁵¹⁸ Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* **1960**, *82*, 2380.

⁵¹⁹ Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1862.

⁵²⁰ Hardcastle, I.R.; Quayle, P.; Ward, E.L.M. *Tetrahedron Lett.* **1994**, *35*, 1747.

⁵²¹ Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Groß, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *45*, 154.

⁵²² See Fujiwara, Y.; Kawata, I.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1982**, 132.

⁵²³ See Olah, G.A.; Olah, J.A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 1257-1273.

11-19 Carboxylation with Carbonyl Halides

Carboxylation or Carboxy-de-hydrogenation



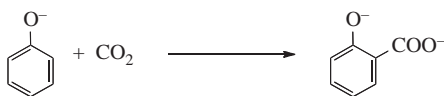
Phosgene, in the presence of *Friedel–Crafts catalysts*, can carboxylate the ring. This process is analogous to Reaction **11-17**, but the ArCOCl initially produced hydrolyzes to the carboxylic acid. However, in most cases the reaction does not take this course, but instead the ArCOCl is attacked by another ring to give a ketone ArCOAr . A number of other reagents have been used to get around this difficulty, including oxalyl chloride, urea hydrochloride, chloral (Cl_3CCHO),⁵²⁴ carbamoyl chloride (H_2NCOCl), and *N,N*-diethylcarbamoyl chloride.⁵²⁵ With carbamoyl chloride the reaction is called the *Gatterman amide synthesis* and the product is an amide. Among compounds carboxylated by one or another of these reagents are benzene, alkylbenzenes, and fused ring systems.⁵²⁶

Although mechanistically different, other methods are available to convert aromatic compounds to aromatic carboxylic acids. The Pd catalyzed reaction of aromatic compounds and formic acid leads to benzoic acid derivatives.⁵²⁷ Diphenyliodonium tetrafluoroborate ($\text{Ph}_2\text{I}^+ \text{BF}_4^-$) reacts with CO and In in DMF, with a Pd catalyst, to give benzophenone.⁵²⁸

OS V, 706; VII, 420.

11-20 Carboxylation with Carbon Dioxide: The Kolbe–Schmitt Reaction

Carboxylation or Carboxy-de-hydrogenation



Sodium phenoxides can be carboxylated, mostly in the ortho position, by CO_2 (the *Kolbe–Schmitt reaction*). The mechanism is not clearly understood, but apparently some kind of a complex is formed between the reactants,⁵²⁹ making the carbon of the CO_2 more positive and putting it in a good position to attack the ring. Potassium phenoxide, which is less likely to form such a complex, is chiefly attacked in the para position. There is evidence that, in the complex formed from potassium salts, the bonding is between the aromatic compound and the carbon atom of CO_2 .⁵³⁰ At least part of the potassium *p*-hydroxybenzoate that forms comes from a rearrangement of initially formed potassium salicylate (sodium salicylate does not rearrange).⁵³¹ Carbon tetrachloride can be used instead of CO_2 under *Reimer–Tiemann* (Reaction **11-18**) conditions.

⁵²⁴ Menegheli, P.; Rezende, M.C.; Zucco, C. *Synth. Commun.* **1987**, 17, 457.

⁵²⁵ Naumov, Yu.A.; Isakova, A.P.; Kost, A.N.; Zakharov, V.P.; Zvolinskii, V.P.; Moiseikina, N.F.; Nikeryasova, S.V. *J. Org. Chem. USSR* **1975**, 11, 362.

⁵²⁶ See Sartori, G.; Casnati, G.; Bigi, F.; Bonini, G. *Synthesis* **1988**, 763.

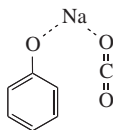
⁵²⁷ Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* **2004**, 6, 2437.

⁵²⁸ Zhou, T.; Chen, Z.-C. *Synth. Commun.* **2002**, 32, 3431.

⁵²⁹ Hales J.L.; Jones, J.I.; Lindsey, A.S. *J. Chem. Soc.* **1954**, 3145.

⁵³⁰ See Hirao, I.; Kito, T. *Bull. Chem. Soc. Jpn.* **1973**, 46, 3470.

⁵³¹ See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 344–348. See also, Ota, K. *Bull. Chem. Soc. Jpn.* **1974**, 47, 2343.



Sodium or potassium phenoxide can be carboxylated regioselectively in the para position in high yield by treatment with sodium or potassium carbonate and carbon monoxide.⁵³² The ¹⁴C labeling showed that it is the carbonate carbon that appears in the *p*-hydroxybenzoic acid product.⁵³³ The CO is converted to sodium or potassium formate. Carbon monoxide has also been used to carboxylate aromatic rings with Pd compounds as catalysts.⁵³⁴ In addition, a Pd catalyzed reaction has been used directly to prepare acyl fluorides $\text{ArH} \rightarrow \text{ArCOF}$.⁵³⁵ Molybdovanadophosphates have been used for anisole in the presence of CO and O₂.⁵³⁶ A Pd catalyzed carboxylation has been reported using Ag₂CO₃ and CO.⁵³⁷

An enzymatic carboxylation was reported, in supercritical CO₂ (see Sec. 9.D.ii), in which exposure of pyrrole to *Bacillus megaterium* PYR2910 and KHCO₃ gave the potassium salt of pyrrole 2-carboxylic acid.⁵³⁸

OS II, 557.

11-21 Amidation

N-Alkylcarbamoyl-de-hydrogenation



N-Substituted amides can be prepared by direct attack of isocyanates on aromatic rings.⁵³⁹ The R group may be alkyl or aryl, but if the latter, dimers and trimers are also obtained. Isothiocyanates similarly give thioamides.⁵⁴⁰ The reaction has been carried out intramolecularly both with aralkyl isothiocyanates and acyl isothiocyanates.⁵⁴¹ In the latter case, the product is easily hydrolyzable to a dicarboxylic acid; this is a way of putting a carboxyl group on a ring ortho to one already there (62 is prepared by treatment of the acyl halide with lead thiocyanate). The reaction gives better yields with substrates of the type $\text{ArCH}_2\text{CONCS}$, where six-membered rings are formed. An intramolecular reaction of 2-amido biaryls leads to carbazoles in the presence of Pd and Cu catalysts.⁵⁴²

⁵³² Yasuhara, Y.; Nogi, T. *J. Org. Chem.* **1968**, 33, 4512; *Chem. Ind. (London)* **1969**, 77.

⁵³³ Yasuhara, Y.; Nogi, T.; Saisho, H. *Bull. Chem. Soc. Jpn.* **1969**, 42, 2070.

⁵³⁴ See Jintoku, T.; Taniguchi, H.; Fujiwara, Y. *Chem. Lett.* **1987**, 1159; Ugo, R.; Chiesa, A. *J. Chem. Soc. Perkin Trans. 1* **1987**, 2625.

⁵³⁵ Sakakura, T.; Chaisupakitsin, M.; Hayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1987**, 334, 205.

⁵³⁶ Ohashi, S.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2005**, 486.

⁵³⁷ Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, 130, 14082. See also, Sakakibara, K.; Yamashita, M.; Nozaki, K. *Tetrahedron Lett.* **2005**, 46, 959.

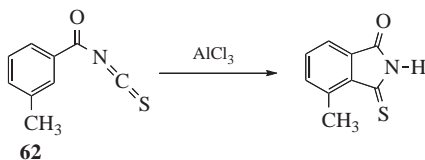
⁵³⁸ Matsuda, T.; Ohashi, Y.; Harada, T.; Yanagihara, R.; Nagasawa, T.; Nakamura, K. *Chem. Commun.* **2001**, 2194.

⁵³⁹ Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E.; Citterio, A. *Tetrahedron* **1986**, 42, 885.

⁵⁴⁰ Jagodzinski, T. *Synthesis* **1988**, 717.

⁵⁴¹ Smith, P.A.S.; Kan, R.O. *J. Org. Chem.* **1964**, 29, 2261.

⁵⁴² Tsang, W.C.P.; Zheng, N.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, 127, 14560.



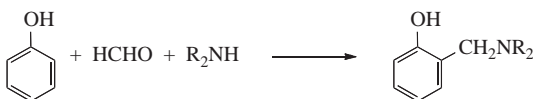
There are interesting transition metal catalyzed reactions that lead to aryl amides. The use of POCl_3 and DMF, with a Pd catalyst, converts aryl iodides to benzamides.⁵⁴³ Carbonylation is another method that generates amides. When an aryl iodide was treated with a secondary amine and $\text{Mo}(\text{CO})_6$, in the presence of 3 equiv of DBU, 10% $\text{Pd}(\text{OAc})_2$, with microwave irradiation at 100°C , the corresponding benzamide was obtained.⁵⁴⁴ Aminocarbonylation is accomplished with microwave irradiation using hydroxylamine as an ammonia equivalent.⁵⁴⁵

OS V, 1051; VI, 465.

Reactions **11-12–11-23** involve the introduction of a CH_2Z group, where Z is halogen, hydroxyl, amino, or alkylthio. They are all *Friedel–Crafts reactions* of aldehydes and ketones and, with respect to the carbonyl compound, additions to the $\text{C}=\text{O}$ double bond. They follow mechanisms discussed in Chapter 16.

11-22 Aminoalkylation and Amidoalkylation

Dialkylaminoalkylation or Dialkylamino-de-hydrogenation



Phenols, secondary and tertiary aromatic amines,⁵⁴⁶ pyrroles, and indoles can be aminomethylated by treatment with formaldehyde and a secondary amine. Other aldehydes have sometimes been employed. Aminoalkylation is a special case of the *Mannich reaction* (**16-19**). When phenols and other activated aromatic compounds are treated with *N*-hydroxymethylchloroacetamide, *amidomethylation* takes place⁵⁴⁷ to give **63**, which is often hydrolyzed *in situ* to the aminoalkylated product. Other *N*-hydroxyalkyl and *N*-chlorinated compounds have also been used.³⁷⁹ Nitroethane in polyphosphoric acid can be used for the acetamidation of aromatic compounds.⁵⁴⁸

⁵⁴³ Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* **2002**, 4, 2849. Also see Schnyder, A.; Beller, M.; Mehlretter, G.; Nsenda, T.; Studer, M.; Indolese, A.F. *J. Org. Chem.* **2001**, 66, 4311. See also, Schnyder, A.; Indolese, A.F. *J. Org. Chem.* **2002**, 67, 594.

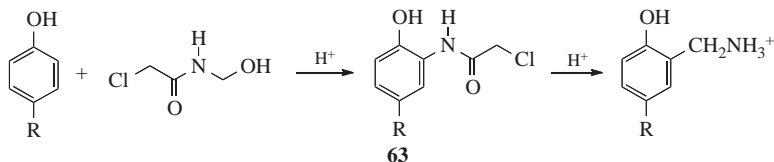
⁵⁴⁴ Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, 68, 5750.

⁵⁴⁵ Wu, X.; Wannberg, J.; Larhed, M. *Tetrahedron* **2006**, 62, 4665.

⁵⁴⁶ Miocque, M.; Vierfond, J. *Bull. Soc. Chim. Fr.* **1970**, 1896, 1901, 1907.

⁵⁴⁷ For a review, see Zaug, H.E. *Synthesis* **1984**, 85.

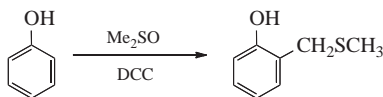
⁵⁴⁸ Aksenov, A.V.; Aksenov, N.A.; Nadein, O.N.; Aksenova, I.V. *Synlett* **2010**, 2628.



Aryl halides are aminomethylated with potassium organotrifluoroborates.⁵⁴⁹ OS I, 381; IV, 626; V, 434; VI, 965; VII, 162.

11-23 Thioalkylation

Alkylthioalkylation or Alkylthioalkyl-de-hydrogenation

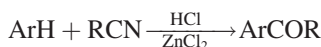


A methylthiomethyl group can be inserted into the ortho position of phenols by heating with DMSO and 1,3-dicyclohexylcarbodiimide (DCC).⁵⁵⁰ Other reagents can be used instead of DCC, among them SOCl_2 ,⁵⁵¹ or acetic anhydride.⁵⁵² Alternatively, the phenol can be treated with DMS and NCS, followed by triethylamine.⁵⁵³ The reaction can be applied to amines (to give $o\text{-NH}_2\text{C}_6\text{H}_4\text{CH}_2\text{SMe}$) by treatment with *t*-BuOCl, Me_2S , and NaOMe in CH_2Cl_2 .⁵⁵⁴ Aromatic hydrocarbons have been thioalkylated with ethyl α -(chloromethylthio)acetate ($\text{ClCH}_2\text{SCH}_2\text{CO}_2\text{Et}$) to give $\text{ArCH}_2\text{SCH}_2\text{CO}_2\text{Et}$,⁵⁵⁵ and with methyl methylsulfinylmethyl sulfide ($\text{MeSCH}_2\text{SOMe}$) or methylthiomethyl *p*-tolyl sulfone ($\text{MeSCH}_2\text{SO}_2\text{C}_6\text{H}_4\text{Me}$) to give ArCH_2SMe ,⁵⁵⁶ in each case with a Lewis acid catalyst.

OS VI, 581, 601.

11-24 Acylation with Nitriles: The Hoesch Reaction

Acylation or Acyl-de-hydrogenation



Friedel–Crafts acylation with nitriles and HCl is called the *Hoesch* or the *Houben–Hoesch reaction*.⁵⁵⁷ In most cases, a Lewis acid is necessary; zinc chloride is the most common. The reaction is generally useful only with phenols, phenolic ethers, and some reactive heterocyclic compounds (e.g., pyrrole), but it can be extended to aromatic amines

⁵⁴⁹ Molander, G.A.; Sandrock, D.L. *Org. Lett.* **2007**, 9, 1597.

⁵⁵⁰ Olofson, R.A.; Marino, J.P. *Tetrahedron* **1971**, 27, 4195.

⁵⁵¹ Sato, K.; Inoue, S.; Ozawa, K.; Tazaki, M. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2715.

⁵⁵² Hayashi, Y.; Oda, R. *J. Org. Chem.* **1967**, 32, 457; Pettit, G.H.; Brown, T.H. *Can. J. Chem.* **1967**, 45, 1306; Claus, P. *Monatsh. Chem.* **1968**, 99, 1034.

⁵⁵³ Gassman, P.G.; Amick, D.R. *J. Am. Chem. Soc.* **1978**, 100, 7611.

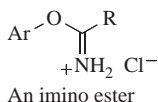
⁵⁵⁴ Gassman, P.G.; Gruetzmacher, G. *J. Am. Chem. Soc.* **1973**, 95, 588; Gassman, P.G.; van Bergen, T.J. *J. Am. Chem. Soc.* **1973**, 95, 590, 591.

⁵⁵⁵ Tamura, Y.; Tsugoshi, T.; Annoura, H.; Ishibashi, H. *Synthesis* **1984**, 326.

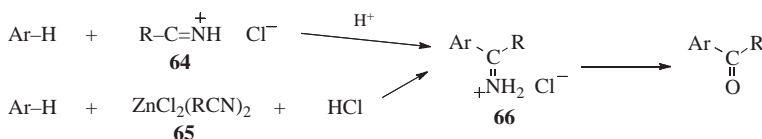
⁵⁵⁶ Torisawa, Y.; Satoh, A.; Ikegami, S. *Tetrahedron Lett.* **1988**, 29, 1729.

⁵⁵⁷ See Ruske, W. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 383–497.

by the use of BCl_3 .⁵⁵⁸ Acylation in the case of aniline derivatives is regioselectively ortho. Monohydric phenols, however, generally do not give ketones⁵⁵⁹ but are attacked at the oxygen to produce imino esters. Many nitriles have been used. Even aryl nitriles give good yields if they are first treated with HCl and ZnCl_2 , and then the substrate added at 0°C .⁵⁶⁰ In fact, this procedure increases yields with any nitrile. If thiocyanates (RSCN) are used, thiol esters (ArCOSR) can be obtained. The *Gatterman reaction* (Reaction 11-18) is a special case of the *Hoesch synthesis*.

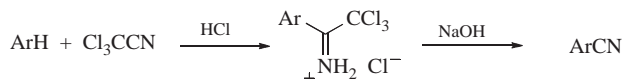


The reaction mechanism is complex and not completely settled.⁵⁶¹ The first stage consists of an attack on the substrate by a species containing the nitrile and HCl (and the Lewis acid, if present) to give an imine salt (**66**). Among the possible reactive species are **64** and **65**. In the second stage, the salts are hydrolyzed to the products, first the iminium salt, and then the ketone. Ketones can also be obtained by treating phenols or phenolic ethers with a nitrile in the presence of $\text{F}_3\text{CSO}_2\text{OH}$.⁵⁶² The mechanism in this case is different.



OS II, 522.

11-25 Cyanation or Cyano-de-hydrogenation



Aromatic hydrocarbons (including benzene), phenols, and phenolic ethers can be cyanated with trichloroacetonitrile, BrCN , or mercury fulminate $[\text{Hg}(\text{ONC})_2]$.⁵⁶³ In the case of Cl_3CCN , the actual attacking entity is probably $\text{Cl}_3\text{C}-\text{C}^+=\text{NH}$, formed by addition of a proton to the cyano nitrogen. Secondary aromatic amines (ArNHR), as well as phenols, can be cyanated in the ortho position with Cl_3CCN and BCl_3 .⁵⁶⁴

Note that aryl triflates are converted to the aryl nitrile by treatment with $\text{Zn}(\text{CN})_2$ and a Pd catalyst.⁵⁶⁵

OS III, 293.

⁵⁵⁸ Sugawara, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* **1979**, *44*, 578.

⁵⁵⁹ For an exception, see Toyoda, T.; Sasakura, K.; Sugawara, T. *J. Org. Chem.* **1981**, *46*, 189.

⁵⁶⁰ Zil'berman, E.N.; Rybakova, N.A. *J. Gen. Chem. USSR* **1960**, *30*, 1972.

⁵⁶¹ See Ruske, W. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, p. 383; Jeffery, E.A.; Satchell, D.P.N. *J. Chem. Soc. B* **1966**, 579.

⁵⁶² Amer, M.I.; Booth, B.L.; Noori, G.F.M.; Proença, M.F.J.R.P. *J. Chem. Soc. Perkin Trans. 1* **1983**, 1075.

⁵⁶³ Olah, G.A. in Olah, G.A. in Olah, *Friedel-Crafts and Related Reactions*, Vol. 1, Wiley, NY, **1963**, pp. 119-120.

⁵⁶⁴ Adachi, M.; Sugawara, T. *Synth. Commun.* **1990**, *20*, 71.

⁵⁶⁵ Kubota, H.; Rice, K.C. *Tetrahedron Lett.* **1998**, *39*, 2907.

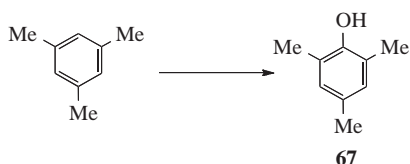
F. Oxygen Electrophiles

Oxygen electrophiles are very uncommon, since oxygen does not bear a positive charge very well. However, there is one reaction that can be mentioned.

11-26 Hydroxylation or Hydroxy-de-hydrogenation



There have been only a few reports of direct hydroxylation⁵⁶⁶ by an electrophilic process (see, however, **14-5**).⁵⁶⁷ In general, poor results are obtained, partly because the introduction of an OH group activates the ring, which suppresses further reaction. Quinone formation is common. However, alkyl-substituted benzenes (e.g., mesitylene or durene) can be hydroxylated in good yield with trifluoroperacetic acid and boron trifluoride.⁵⁶⁸ In the case of mesitylene, the product (**67**) is not subject to further attack.



In a related procedure, even benzene and substituted benzenes (e.g., PhMe, PhCl, and xylenes) can be converted to phenols in good yields with sodium perborate–F₃CSO₂OH.⁵⁶⁹ Aromatic amines, *N*-acyl amines, and phenols were hydroxylated with H₂O₂ in SbF₅–HF.⁵⁷⁰ Pyridine and quinoline were converted to their 2-acetoxy derivatives in high yields with acetyl hypofluorite (AcOF) at –75 °C.⁵⁷¹

Another hydroxylation reaction is the *Elbs reaction*.⁵⁷² In this method, phenols can be oxidized to *p*-diphenols with K₂S₂O₈ in alkaline solution.⁵⁷³ Primary, secondary, or tertiary aromatic amines give predominant or exclusive ortho substitution unless both ortho positions are blocked, in which case para substitution is found. The reaction with amines is called the *Boylan–Sims oxidation*. Yields are low with either phenols or amines, generally <50%. The mechanisms are not clear,⁵⁷⁴ but for the *Boylan–Sims oxidation* there is evidence that the S₂O₈^{2–} ion attacks at the ipso position, and then a migration follows.⁵⁷⁵

⁵⁶⁶ For a list of hydroxylation reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 977–978.

⁵⁶⁷ See Jacquesy, J.; Gesson, J.; Jouannetaud, M. *Rev. Chem. Intermed.* **1988**, 9, 1, see pp. 5–10; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1985**, pp. 173–176, 347–350.

⁵⁶⁸ Hart, H.; Buehler, C.A. *J. Org. Chem.* **1964**, 29, 2397. See also, Hart, H. *Acc. Chem. Res.* **1971**, 4, 337.

⁵⁶⁹ Prakash, G.K.S.; Krass, N.; Wang, Q.; Olah, G.A. *Synlett* **1991**, 39.

⁵⁷⁰ Berrier, C.; Carreyre, H.; Jacquesy, J.; Joannetaud, M. *New J. Chem.* **1990**, 14, 283, and cited references.

⁵⁷¹ Rozen, S.; Hebel, D.; Zamir, D. *J. Am. Chem. Soc.* **1987**, 109, 3789.

⁵⁷² See Behrman, E.J. *Org. React.* **1988**, 35, 421.

⁵⁷³ See Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1982**, 23, 1573, 1577.

⁵⁷⁴ Walling, C.; Camaioni, D.M.; Kim, S.S. *J. Am. Chem. Soc.* **1978**, 100, 4814.

⁵⁷⁵ Srinivasan, C.; Perumal, S.; Arumugam, N. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1855.

Electrolysis of benzene, in the presence of trifluoroacetic acid and triethylamine, leads to a 73% yield of phenol.⁵⁷⁶ Photolytic hydroxylation of benzene has been reported in the presence of mesoporous TiO₂.⁵⁷⁷ Deactivated rings (e.g., nitrobenzene) are selectively ortho hydroxylated by molecular oxygen in the presence of H₅PV₂Mo₁₀O₄₀ polyoxometalate.⁵⁷⁸ Nitrous oxide has been used as an oxidant, in the presence of FeAlPO catalysts.⁵⁷⁹

G. Metal Electrophiles

Reactions in which a metal replaces the hydrogen of an aromatic ring are considered along with their aliphatic counterparts in Chapter 12 (Reactions 12-22 and 12-23).

11.F.ii. Hydrogen as the Leaving Group in Rearrangement Reactions

In these reactions, a group is detached from a *side chain* and then reattached the ring, but in other aspects they resemble the reactions already treated in this chapter.⁵⁸⁰ Since a group moves from one position to another in a molecule, these are rearrangements (also see Chap 18). In all these reactions, the question arises as to whether the group that cleaves from a given molecule is attacked by the same molecule or another one; that is, Is the reaction intramolecular or intermolecular? For intermolecular reactions, the mechanism is the same as ordinary aromatic substitution, but for intramolecular cases the migrating group could never be completely free, or else it would be able to react with another molecule. Since the migrating species in intramolecular rearrangements is thus likely to remain near the atom from which it cleaved, it has been suggested that intramolecular reactions are more likely to lead to ortho products than are the intermolecular type. This characteristic has been used, among others, to help decide whether a given rearrangement is inter- or intramolecular, though there is evidence that at least in some cases, an intermolecular mechanism can still result in a high degree of ortho migration.⁵⁸¹

The *Claisen* (Reaction 18-33) and *benzidine* (Reaction 18-36) rearrangements, which superficially resemble those in this section, have different mechanisms and are treated in Chapter 18.

A. Groups Cleaving from Oxygen

11-27 The Fries Rearrangement

1/C-Hydro,5/O-acyl-interchange⁵⁸²



⁵⁷⁶ Fujimoto, K.; Tokuda, Y.; Maekawa, H.; Matsubara, Y.; Mizuno, T.; Nishiguchi, I. *Tetrahedron* **1996**, 52, 3889.

⁵⁷⁷ Shiraishi, Y.; Saito, N.; Hirai, T. *J. Am. Chem. Soc.* **2005**, 127, 12820. Also see Mita, S.; Sakamoto, T.; Yamada, S.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, 46, 7729; Tani, M.; Sakamoto, T.; Mita, S.; Sakaguchi, S.; Ishii, Y. *Angew. Chem. Int. Ed.* **2005**, 44, 2586.

⁵⁷⁸ Khenkin, A.M.; Weiner, L.; Neumann, R. *J. Am. Chem. Soc.* **2005**, 127, 9988.

⁵⁷⁹ Shiju, N.R.; Fiddy, S.; Sonntag, O.; Stockenhuber, M.; Sankar, G. *Chem. Commun.* **2006**, 4955.

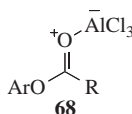
⁵⁸⁰ See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**; Williams, D.L.H.; Buncl, I.M. *Isot. Org. Chem.* **1980**, 5, 147; Williams, D.L.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 433–486.

⁵⁸¹ See Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1601.

⁵⁸² This is the name for the para migration. For the ortho migration, the name is 1/C-hydro,3/O-acyl-interchange.

Phenolic esters can be rearranged by heating with *Friedel–Crafts catalysts* in a synthetically useful reaction known as the *Fries rearrangement*.⁵⁸³ Both *o*- and *p*-acylphenols can be produced, and it is often possible to select conditions so that either one predominates. The ortho/para ratio is dependent on the temperature, solvent, and amount of catalyst used. Exceptions are known, but low temperatures generally favor the para product and high temperatures favor the ortho product. The R group may be aliphatic or aromatic. Any meta-directing substituent on the ring interferes with the reactions, as might be expected for a *Friedel–Crafts* process. In the case of aryl benzoates treated with $\text{F}_3\text{CSO}_2\text{OH}$, the *Fries rearrangement* was shown to be reversible and an equilibrium was established.⁵⁸⁴ Transition metal catalyzed *Fries rearrangements* have been reported.⁵⁸⁵

Questions remain about the exact mechanism.⁵⁸⁶ Opinions have been expressed that it is completely intermolecular,⁵⁸⁷ completely intramolecular,⁵⁸⁸ and partially inter- and intramolecular.⁵⁸⁹ One way to decide between inter- and intramolecular processes is to run the reaction of the phenolic ester in the presence of another aromatic compound, say, toluene. If some of the toluene is acylated, the reaction must be, at least in part, intermolecular. If the toluene is not acylated, the presumption is that the reaction is intramolecular, though this is not certain, for it may be that the toluene is not attacked because it is less active than the other. A number of such experiments (called *crossover experiments*) have been carried out; sometimes crossover products have been found and sometimes not. As in Reaction 11-17, an initial complex (**68**) is formed between the substrate and the catalyst, so that a catalyst/substrate molar ratio of at least 1:1 is required. In the presence of aluminum chloride, the *Fries rearrangement* can be induced with microwave irradiation.⁵⁹⁰ Simply heating phenyl acetate with microwave irradiation gives the *Fries rearrangement*.⁵⁹¹ The *Fries rearrangement* has been carried out in ionic melts.⁵⁹²



⁵⁸³ See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 72–82, 365–368; Gerecs, A. in Olah, G.A. in Olah, G. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 499–533. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, p. 1310.

⁵⁸⁴ Effenberger, F.; Gutmann, R. *Chem. Ber.* **1982**, *115*, 1089.

⁵⁸⁵ With $\text{Hf}(\text{OTf})_4$ see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 2053. With $\text{Sc}(\text{OTf})_3$, see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 4183; with ZrCl_4 see Harrowven, D.C.; Dainty, R.F. *Tetrahedron Lett.* **1996**, *37*, 7659.

⁵⁸⁶ See Sharghi, H.; Eshghi, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 135.

⁵⁸⁷ Martin, R.; Gavard, J.; Delfly, M.; Demerseman, P.; Tromelin, A. *Bull. Soc. Chim. Fr.* **1986**, 659 and cited references.

⁵⁸⁸ Ogata, Y.; Tabuchi, H. *Tetrahedron* **1964**, *20*, 1661.

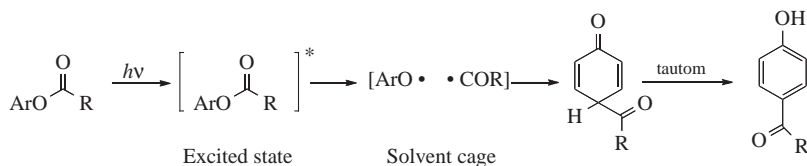
⁵⁸⁹ Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1601.

⁵⁹⁰ Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* **1999**, *29*, 1195.

⁵⁹¹ Paul, S.; Gupta, M. *Synthesis* **2004**, 1789.

⁵⁹² Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* **2001**, *42*, 1979.

The *Fries rearrangement* can also be carried out with UV light, in the absence of a catalyst.⁵⁹³ This reaction, called the *photo-Fries rearrangement*,⁵⁹⁴ is predominantly an intramolecular free radical process. Both ortho and para migration are observed.⁵⁹⁵ Unlike the Lewis acid catalyzed *Fries rearrangement*, the *photo-Fries reaction* can be accomplished, though often in low yields, when meta-directing groups are on the ring. The available evidence strongly suggests the following mechanism involving formation of the excited state⁵⁹⁷ followed by dissociation to a radical pair⁵⁹⁶ for the *photo-Fries rearrangement*⁵⁹⁷ (illustrated for para attack).



The phenol ArOH is always a side product, resulting from some ArO• that leaks from the solvent cage and abstracts a hydrogen atom from a neighboring molecule. When the reaction was performed on phenyl acetate in the gas phase, where there are no solvent molecules to form a cage (but in the presence of isobutane as a source of abstractable hydrogen atoms), phenol was the chief product and virtually no *o*- or *p*-hydroxyacetophenone was found.⁵⁹⁸ Other evidence⁵⁹⁹ for the mechanism is that CIDNP has been observed during the course of the reaction⁶⁰⁰ and that the ArO• radical has been detected by flash photolysis⁶⁰¹ and by nanosecond time-resolved Raman spectroscopy.⁶⁰²

A LDA-mediated *anionic Fries rearrangement* of aryl carbamates has been reported.⁶⁰³ The so-called *anionic Snieckus–Fries rearrangement* has also been discussed.⁶⁰⁴

Treatment of *O*-arylsulfonate esters with AlCl₃–ZnCl₂, on silica with microwave irradiation, leads to 2-sulfonyl phenols in a *thia-Fries rearrangement*.⁶⁰⁵ A similar reaction was reported with *O*-arylsulfonamides.⁶⁰⁶

OS II, 543; III, 280, 282.

⁵⁹³ Finnegan, R.A.; Matice, J.J. *Tetrahedron* **1965**, 21, 1015.

⁵⁹⁴ See Bellus, D. *Adv. Photochem.* **1971**, 8, 109; Bellus, D.; Hrdlovic, P. *Chem. Rev.* **1967**, 67, 599. See Cui, C.; Wang, X.; Weiss, R.G. *J. Org. Chem.* **1996**, 61, 1962.

⁵⁹⁵ The migration can be made almost entirely ortho by cyclodextrin encapsulation (see Sec. 3.C.iv): Syamala, M.S.; Rao, B.N.; Ramamurthy, V. *Tetrahedron* **1988**, 44, 7234. See also, Veglia, A.V.; Sanchez, A.M.; de Rossi, R.H. *J. Org. Chem.* **1990**, 55, 4083.

⁵⁹⁶ Proposed by Kobsa, H. *J. Org. Chem.* **1962**, 27, 2293.

⁵⁹⁷ It has been suggested that a second mechanism, involving a four-center transition state, is also possible: Sander, M.R.; Hedaya, E.; Trecker, D.J. *J. Am. Chem. Soc.* **1968**, 90, 7249; Bellus, D. *Adv. Photochem.* **1971**, 8, 109.

⁵⁹⁸ Meyer, J.W.; Hammond, G.S. *J. Am. Chem. Soc.* **1972**, 94, 2219.

⁵⁹⁹ See Shine, H.J.; Subotkowski, W. *J. Org. Chem.* **1987**, 52, 3815.

⁶⁰⁰ Adam, W. *J. Chem. Soc., Chem. Commun.* **1974**, 289.

⁶⁰¹ Kalmus, C.E.; Hercules D.M. *J. Am. Chem. Soc.* **1974**, 96, 449.

⁶⁰² Beck, S.M.; Brus, L.E. *J. Am. Chem. Soc.* **1982**, 104, 1805.

⁶⁰³ For a discussion of the role of aggregates and mixed aggregates in this reaction, see Singh, K.J.; Collum, D.B. *J. Am. Chem. Soc.* **2006**, 128, 13753.

⁶⁰⁴ Riggs, J.C.; Singh, K.J.; Yun, M.; Collum, D.B. *J. Am. Chem. Soc.* **2008**, 130, 13709.

⁶⁰⁵ Moghaddam, F.M.; Dakamin, M.G. *Tetrahedron Lett.* **2000**, 41, 3479.

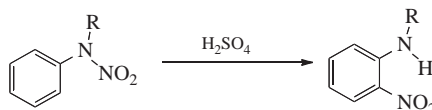
⁶⁰⁶ Benson, G.A.; Maughan, P.J.; Shelly, D.P.; Spillane, W.J. *Tetrahedron Lett.* **2001**, 42, 8729.

B. Groups Cleaving from Nitrogen⁶⁰⁷

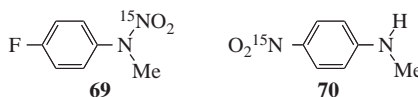
It has been shown that PhNH_2D rearranges to *o*- and *p*-deuterioaniline.⁶⁰⁸ The migration of OH, formally similar to Reactions **11-28**–**11-32**, is a nucleophilic substitution and is treated in Chapter 13 (**13-32**).

11-28 Migration of the Nitro Group

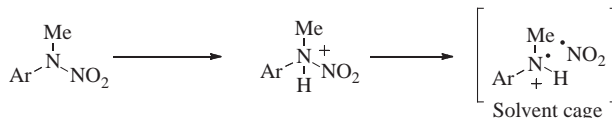
1/ *C*-Hydro,3/*N*-nitro-interchange



N-Nitro aromatic amines rearrange on treatment with acids to *o*- and *p*-nitroamines with the ortho compounds predominating.⁶⁰⁹ Aside from this indication of an intramolecular process, there is also the fact that virtually no meta isomer is produced in this reaction,⁶¹⁰ although direct nitration of an aromatic amine generally gives a fair amount of meta product. Thus a mechanism in which NO_2^+ is dissociated from the ring and then is attacked by another molecule must be ruled out. Further results indicating an intramolecular process include the observation that rearrangement of several substrates in the presence of K^{15}NO_3 gave products containing no ^{15}N ,⁶¹¹ and that rearrangement of a mixture of $\text{PhNH}^{15}\text{NO}_2$ and unlabeled *p*- $\text{MeC}_6\text{H}_4\text{NHNO}_2$ gave 2-nitro-4-methylaniline containing no ^{15}N .⁶¹² On the other hand, rearrangement of



69 in the presence of unlabeled PhNMeNO_2 gave labeled **70**, which did not arise by displacement of F.⁶¹³ The R group may be hydrogen or alkyl. Two principal mechanisms have been suggested, one involving cyclic attack by the oxygen of the nitro group at the ortho position before the group cleaves,⁶¹⁴ and the other involving a cleavage into a radical and a radical ion held together in a solvent cage.⁶¹⁵ Among the evidence



⁶⁰⁷ See Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, **1973**, pp. 192–199.

⁶⁰⁸ Okazaki, N.; Okumura, A. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 989.

⁶⁰⁹ See Williams, D.L.H. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, **1982**, pp. 127–153; White, W.N. *Mech. Mol. Migr.* **1971**, *3*, 109–143; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 235–249.

⁶¹⁰ Hughes, E.D.; Jones, G.T. *J. Chem. Soc.* **1950**, 2678.

⁶¹¹ Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* **1965**, 6135.

⁶¹² Geller, B.A.; Dubrova, L.N. *J. Gen. Chem. USSR* **1960**, *30*, 2627.

⁶¹³ White, W.N.; Golden, J.T. *J. Org. Chem.* **1970**, *35*, 2759.

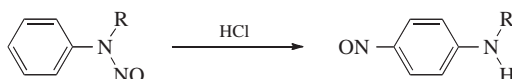
⁶¹⁴ Banthorpe, D.V.; Thomas, J.A. *J. Chem. Soc.* **1965**, 7149, 7158. Also see, Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* **1965**, 6135.

⁶¹⁵ White, W.N.; White, H.S.; Fentiman, A. *J. Org. Chem.* **1976**, *41*, 3166.

for the latter view⁶¹⁶ are the effects of substituents on the rate of the reaction,⁶¹⁷ ^{15}N and ^{14}C kinetic isotope effects that show nonconcertedness,⁶¹⁸ and the fact that both *N*-methylaniline and nitrous acid are produced in sizable and comparable amounts in addition to the normal products *o*- and *p*-nitro-*N*-methylaniline.⁶¹⁹ These side products are formed when the radicals escape from the solvent cage.

11-29 Migration of the Nitroso Group: The Fischer–Hepp Rearrangement

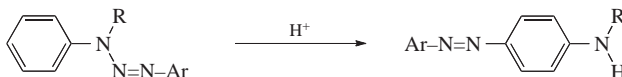
1/*C*-Hydro-5/*N*-nitroso-interchange



The migration of a nitroso group, formally similar to Reaction 11-28, is important because *p*-nitroso secondary aromatic amines cannot generally be prepared by direct *C*-nitrosation of secondary aromatic amines (see Reaction 12-50). The reaction, known as the *Fischer–Hepp rearrangement*,⁶²⁰ is brought about by treatment of *N*-nitroso secondary aromatic amines with HCl. Other acids give poor or no results. In benzene systems, the para product is usually formed exclusively.⁶²¹ The mechanism of the rearrangement is not completely understood. The fact that the reaction takes place in a large excess of urea⁶²² shows that it is intramolecular⁶²³ since, if NO^+ , NOCl , or some similar species were free in the solution, it would be captured by the urea, preventing the rearrangement.

11-30 Migration of an Arylazo Group

1/*C*-Hydro-5/*N*-arylazo-interchange



Rearrangement of aryl triazenes can be used to prepare azo derivatives of primary and secondary aromatic amines.⁶²⁴ These are first diazotized at the amino group (see Reaction 11-4) to give triazenes, which are then rearranged by treatment with acid. The rearrangement always gives the para isomer, unless that position is occupied.

⁶¹⁶ See White, W.N.; Klink, J.R. *J. Org. Chem.* **1977**, *42*, 166; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* **1982**, 261.

⁶¹⁷ White, W.N.; Klink, J.R. *J. Org. Chem.* **1970**, *35*, 965.

⁶¹⁸ Shine, H.J.; Zygmunt, J.; Brownawell, M.L.; San Filippo, Jr., J. *J. Am. Chem. Soc.* **1984**, *106*, 3610.

⁶¹⁹ White, W.N.; White, H.S. *J. Org. Chem.* **1970**, *35*, 1803.

⁶²⁰ See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, **1988**, pp. 113–128; Williams, D.L.H. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, **1982**, Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 231–235.

⁶²¹ See Titova, S.P.; Arinich, A.K.; Gorelik, M.V. *J. Org. Chem. USSR* **1986**, *22*, 1407.

⁶²² Morgan, T.D.B.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* **1972**, 74.

⁶²³ See also, Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* **1982**, 801.

⁶²⁴ See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 212–221.

11-31 Migration of Halogen: The Orton Rearrangement

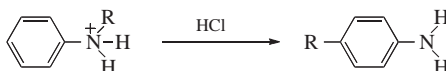
1/C-Hydro-5/N-halo-interchange



Migration of a halogen from a nitrogen side chain to the ring by treatment with HCl is called the *Orton rearrangement*.⁶²⁵ The main product is the para isomer, though some ortho product may also be formed. The reaction has been carried out with *N*-chloro- and *N*-bromoamines and less often with *N*-iodo compounds. The amine must be acylated, except that PhNCl_2 gives 2,4-dichloroaniline. The reaction is usually performed in water or acetic acid. There is considerable evidence (cross-halogenation, labeling, etc.) that this is an intermolecular process.⁶²⁶ First, the HCl reacts with the starting material to give ArNHCOCH_3 and Cl_2 ; then the chlorine halogenates the ring as in Reaction 11-10. Among the evidence is that chlorine has been isolated from the reaction mixture. The *Orton rearrangement* can also be brought about photochemically⁶²⁷ and by heating in the presence of benzoyl peroxide.⁶²⁸ These are free radical processes.

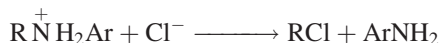
11-32 Migration of an Alkyl Group⁶²⁹

1/C-Hydro-5/N-alkyl-interchange



When HCl salts of arylalkylamines are heated at $\sim 200\text{--}00^\circ\text{C}$, migration occurs in what is called the *Hofmann–Martius reaction*. It is an intermolecular reaction, since crossing is found. For example, methylanilinium bromide gave not only the normal products *o*- and *p*-toluidine, but also aniline and di- and trimethylanilines.⁶³⁰ As would be expected for an intermolecular process, there is isomerization when R is primary.

With primary R, the reaction probably goes through the alkyl halide formed initially in an $\text{S}_{\text{N}}2$ reaction:



Evidence for this view is that alkyl halides have been isolated from the reaction mixture and that Br^- , Cl^- , and I^- gave different ortho/para ratios, which indicates that the halogen is involved in the reaction.⁶³⁰ Further evidence is that the alkyl halides isolated are not rearranged (as would be expected if they are formed by an $\text{S}_{\text{N}}2$ mechanism), even though the alkyl groups in the ring are rearranged. Once the alkyl halide is formed, it reacts with the substrate by a normal *Friedel–Crafts alkylation* process (Reaction 11-11), accounting

⁶²⁵ See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 221–230, 362–364; Bieron, J.F.; Dinan, F.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 263–269.

⁶²⁶ See Golding, P.D.; Reddy, S.; Scott, J.M.W.; White, V.A.; Winter, J.G. *Can. J. Chem.* **1981**, 59, 839.

⁶²⁷ See Hodges, F.W. *J. Chem. Soc.* **1933**, 240.

⁶²⁸ See Coulson, J.; Williams, G.H.; Johnston, K.M. *J. Chem. Soc. B* **1967**, 174.

⁶²⁹ See Grillot, G.F. *Mech. Mol. Migr.* **1971**, 3 237; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 249–257.

⁶³⁰ Ogata, Y.; Tabuchi, H.; Yoshida, K. *Tetrahedron* **1964**, 20, 2717.

for the rearrangement. When R is secondary or tertiary, carbocations may be directly formed so that the reaction does not go through the alkyl halides.⁶³¹

It is also possible to carry out the reaction by heating the amine (not the salt) at a temperature between 200 and 350 °C with a metal halide (e.g., CoCl₂, CdCl₂, or ZnCl₂). When this is done, the reaction is called the *Reilly–Hickinbottom rearrangement*. Primary R groups larger than ethyl give both rearranged and unrearranged products.⁶³² The reaction is not generally useful for secondary and tertiary R groups, which are usually cleaved to alkenes under these conditions.

When acylated arylamines are photolyzed, migration of an acyl group takes place⁶³³ in a process that resembles the photo-Fries reaction (11-27).

11.F.iii. Other Leaving Groups

Three types of reactions are considered in this section.

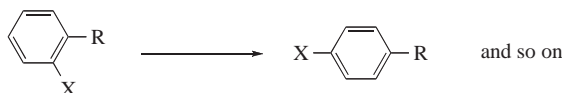
1. Reactions in which hydrogen replaces another leaving group:



2. Reactions in which an electrophile other than hydrogen replaces another leaving group:



3. Reactions in which a group (other than hydrogen) migrates from one position in a ring to another. Such migrations can be either inter- or intramolecular:

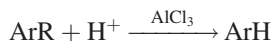


The three types are not treated separately, but reactions are classified by leaving group.

A. Carbon Leaving Groups

11-3 Reversal of Friedel–Crafts Alkylation

Hydro-de-alkylation or Dealkylation



Alkyl groups can be cleaved from aromatic rings by treatment with proton and/or Lewis acids. Tertiary R groups are the most easily cleaved; because this is true, the *tert*-butyl group is occasionally introduced into a ring, used to direct another group, and then removed.⁶³⁴ For example, 4-*tert*-butyltoluene (**71**) reacted with benzoyl chloride and AlCl₃ to give the acylated product, and subsequent treatment with AlCl₃ led to loss of the *tert*-butyl group to give **72**.⁶³⁵

Secondary R groups are harder to cleave, and primary R harder still. Because of this reaction, care must be taken when using *Friedel–Crafts catalysts* (Lewis or proton acids)

⁶³¹ Hart, H.; Kosak, J.R. *J. Org. Chem.* **1962**, 27, 116.

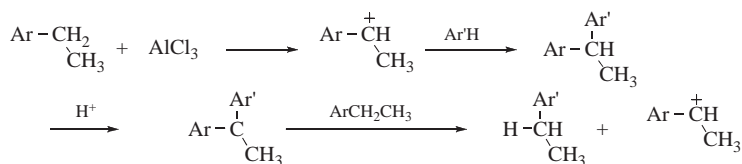
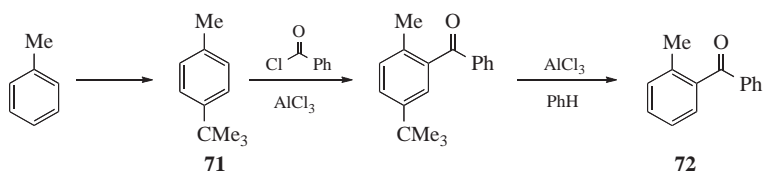
⁶³² See Birchall, J.M.; Clark, M.T.; Goldwhite, H.; Thorpe, D.H. *J. Chem. Soc. Perkin Trans. 1* **1972**, 2579.

⁶³³ See Nassetta, M.; de Rossi, R.H.; Cosa, J.J. *Can. J. Chem.* **1988**, 66, 2794.

⁶³⁴ See Tashiro, M. *Synthesis* **1979**, 921; Tashiro, M.; Fukata, G. *Org. Prep. Proced. Int.* **1976**, 8, 51.

⁶³⁵ Hofman, P.S.; Reidling, D.J.; Nauta, W.T. *Recl. Trav. Chim. Pays-Bas* **1960**, 79, 790.

on aromatic compounds containing alkyl groups. True cleavage, in which the R becomes an alkene, occurs only at high temperatures, $>400^\circ\text{C}$.⁶³⁶ At ordinary temperatures, the R group attacks another ring, so that the bulk of the product may be dealkylated, but there is a residue of heavily alkylated material. The isomerization reaction, in which a group migrates from one position in a ring to another or to a different ring, is therefore more important than true cleavage. In these reactions, the meta isomer is generally the most favored product among the dialkylbenzenes; and the 1,3,5-product the most favored among the trialkylbenzenes, because they have the highest thermodynamic stabilities. Alkyl migrations can be inter- or intramolecular, depending on the conditions and on the R group. The following experiments can be cited: Ethylbenzene treated with HF and BF_3 gave, almost completely, benzene and diethylbenzenes⁶³⁷ (entirely intermolecular); propylbenzene labeled in the β position gave benzene, propylbenzene, and di- and tripropylbenzenes, but the propylbenzene recovered was partly labeled in the α position and not at all in the γ position⁶³⁸ (both intra- and intermolecular); *o*-xylene treated with HBr and AlBr_3 gave a mixture of *o*- and *m*- but no *p*-xylene, while *p*-xylene gave *p*- and *m*- but no *o*-xylene, and no trimethyl compounds could be isolated in these experiments⁶³⁹ (exclusively intramolecular rearrangement). Apparently, methyl groups migrate only intramolecularly, while other groups may follow either path.⁶⁴⁰



The mechanism⁶⁴¹ of intermolecular rearrangement can involve free alkyl cations, but there is much evidence to show that this is not necessarily the case. For example, many of them occur without rearrangement within the alkyl group. The following mechanism has been proposed for intermolecular rearrangement without the involvement of carbocations that are separated from the ring.⁶⁴²

Evidence for this mechanism is that optically active PhCHDCH_3 labeled in the ring with ^{14}C and treated with GaBr_3 in the presence of benzene gave ethylbenzene containing no deuterium and two deuterium atoms and that the rate of loss of radioactivity was about equal

⁶³⁶ Olah, G.A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 1, Wiley, NY, **1963**, pp. 36–38.

⁶³⁷ McCaulay, D.A.; Lien, A.P. *J. Am. Chem. Soc.* **1953**, 75, 2407. For similar results, see Bakoss, H.J.; Roberts, R. M.G.; Sadri, A.R. *J. Org. Chem.* **1982**, 47, 4053.

⁶³⁸ Roberts, R.M.G.; Douglass, J.E. *J. Org. Chem.* **1963**, 28, 1225.

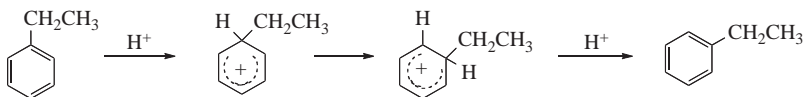
⁶³⁹ Allen, R.H.; Yats, L.D. *J. Am. Chem. Soc.* **1959**, 81, 5289.

⁶⁴⁰ Allen, R.H. *J. Am. Chem. Soc.* **1960**, 82, 4856.

⁶⁴¹ See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 1–55.

⁶⁴² Streitwieser, Jr., A.; Reif, L. *J. Am. Chem. Soc.* **1964**, 86, 1988.

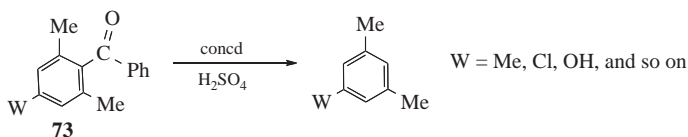
to the rate of loss of optical activity.⁶⁴² The mechanism of intramolecular rearrangement is not very clear. 1,2 shifts of this kind have been proposed:⁶⁴³



There is evidence from ¹⁴C labeling that intramolecular migration occurs only through 1,2-shifts.⁶⁴⁴ Any 1,3- or 1,4-migration takes place by a series of two or more 1,2-shifts.

Phenyl groups have also been found to migrate. Thus *o*-terphenyl, heated with AlCl₃—H₂O, gave a mixture containing 7% *o*-, 70% *m*-, and 23% *p*-terphenyl.⁶⁴⁵ Alkyl groups have also been replaced by groups other than hydrogen (nitro groups).

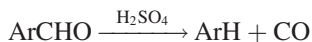
Unlike alkylation, *Friedel–Crafts acylation* has been generally considered to be irreversible, but a number of instances of electrofugal acyl groups have been reported,⁶⁴⁶ especially where there are two ortho substituents (e.g., the hydro-debenzoylation of **73**).⁶⁴⁷



OS V, 332. Also see, OS III, 282, 653; V, 598.

11-34 Decarbonylation of Aromatic Aldehydes

Hydro-de-formylation or Deformylation



The decarbonylation of aromatic aldehydes with sulfuric acid⁶⁴⁸ is the reverse of the *Gatterman–Koch reaction* (**11-18**). It has been carried out with trialkyl- and trialkoxybenzaldehydes. The reaction takes place by the ordinary arenium ion mechanism: The attacking species is H⁺ and the leaving group is HCO⁺, which can lose a proton to give CO or combine with OH[−] from the water solvent to give formic acid.⁶⁴⁹ Aromatic aldehydes

⁶⁴³ Olah, G.A.; Meyer, M.W.; Overchuk, N.A. *J. Org. Chem.* **1964**, 29, 2313.

⁶⁴⁴ See Steinberg, H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* **1962**, 81, 185; Koptug, V.A.; Isaev, I.S.; Vorozhtsov, Jr., N.N. *Doklad. Akad. Nauk SSSR*, **1963**, 149, 100.

⁶⁴⁵ Olah, G.A.; Meyer, M.W. *J. Org. Chem.* **1962**, 27, 3682.

⁶⁴⁶ See Keumi, T.; Morita, T.; Ozawa, Y.; Kitajima, H. *Bull. Chem. Soc. Jpn.* **1989**, 62, 599; Giordano, C.; Villa, M.; Annunziata, R. *Synth. Commun.* **1990**, 20, 383.

⁶⁴⁷ Al-Ka'bi, J.; Farooqi, J.A.; Gore, P.H.; Moonga, B.S.; Waters, D.N. *J. Chem. Res. (S)* **1989**, 80.

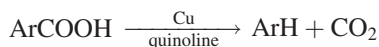
⁶⁴⁸ See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 316–323; Schubert, W.M.; Kintner, R.R. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 695–760.

⁶⁴⁹ Burkett, H.; Schubert, W.M.; Schultz, F.; Murphy, R.B.; Talbott, R. *J. Am. Chem. Soc.* **1959**, 81, 3923.

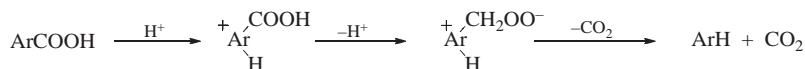
have also been decarbonylated with basic catalysts.⁶⁵⁰ When basic catalysts are used, the mechanism is probably similar to the S_E1 process of Reaction **11-35** (see also, Reaction **14-32**).

11-35 Decarboxylation of Aromatic Acids

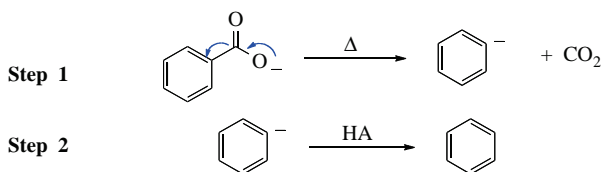
Hydro-de-carboxylation or Decarboxylation



The decarboxylation of aromatic acids is most often carried out by heating with copper and quinoline. However, two other methods can be used with certain substrates. In one method, the salt of the acid (ArCOO[−]) is heated, and in the other the carboxylic acid is heated with a strong acid, often sulfuric. The latter method is accelerated by the presence of electron-donating groups in ortho and para positions and by the steric effect of groups in the ortho positions; in benzene systems it is generally limited to substrates that contain such groups. In this method, decarboxylation takes place by the arenium ion mechanism,⁶⁵¹ with H⁺ as the electrophile and CO₂ as the leaving group.⁶⁵² Evidently, the order of electrofugal ability is CO₂ > H⁺ > COOH⁺, so that it is necessary, at least in most cases, for the COOH to lose a proton before it can cleave.



When carboxylate *ions* are decarboxylated, the mechanism is entirely different, being of the S_E1 type. Evidence for this mechanism is that the reaction is first order and that electron-withdrawing groups, which would stabilize a carbanion, facilitate the reaction.⁶⁵³



Despite its synthetic importance, the mechanism of the copper–quinoline method has been studied very little, but it has been shown that the actual catalyst is cuprous ion.⁶⁵⁴ In fact, the reaction proceeds much faster if the acid is heated in quinoline with cuprous oxide instead of copper, provided that atmospheric oxygen is rigorously excluded. A mechanism has been suggested in which it is the cuprous salt of the acid that actually undergoes the decarboxylation.⁶⁵⁴ It has been shown that cuprous salts of aromatic acids

⁶⁵⁰ Bunnett, J.F.; Miles J.H.; Nahabedian, K.V. *J. Am. Chem. Soc.* **1961**, 83, 2512; Forbes, E.J.; Gregory, M.J. *J. Chem. Soc. B* **1968**, 205.

⁶⁵¹ See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 303–316; Willi, A.V. *Isot. Org. Chem.* **1977**, 3, 257.

⁶⁵² See Willi, A.V.; Cho, M.H.; Won, C.M. *Helv. Chim. Acta* **1970**, 53, 663.

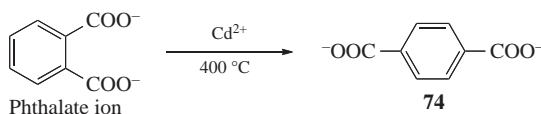
⁶⁵³ See Segura, P.; Bunnett, J.F.; Villanova, L. *J. Org. Chem.* **1985**, 50, 1041.

⁶⁵⁴ Cohen, T.; Schambach, R.A. *J. Am. Chem. Soc.* **1970**, 92, 3189. See also, Aalten, H.L.; van Koten, G.; Tromp, J.; Stam, C.H.; Goubitz, K.; Mak, A.N.S. *Recl. Trav. Chim. Pays-Bas* **1989**, 108, 295.

are easily decarboxylated by heating in quinoline⁶⁵⁵ and that arylcopper compounds are intermediates that can be isolated in some cases.⁶⁵⁶ Metallic silver has been used in place of copper, with higher yields.⁶⁵⁷ Silver acetate has also been used to promote decarboxylation.⁶⁵⁸ A photolytic decarboxylation also has been reported, under a dioxygen atmosphere in the presence of HgF_2 .⁶⁵⁹

In certain cases, the carboxyl group can be replaced by electrophiles other than hydrogen (e.g., NO ,⁶⁵⁷ I ,⁶⁶⁰ Br ,⁶⁶¹ or Hg).⁶⁶² Although closely related to reactions in Chapter 13 (Reactions **13-9**, **13-11**, and **13-12**), a decarboxylative coupling reaction of aryl halides and arylcarboxylic acids has been reported, using Pd and Cu catalysts, to give the corresponding biaryl.⁶⁶³

Rearrangements are also known to take place. For example, when the phthalate ion is heated with a catalytic amount of cadmium, the terphthalate ion (**74**) is produced:⁶⁶⁴

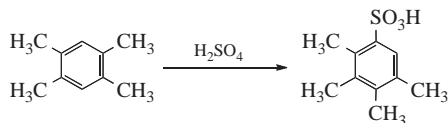


In a similar process, potassium benzoate heated with Cd salts disproportionates to benzene and **74**. The term *Henkel reaction* (named for the company that patented the process) is used for these rearrangements.⁶⁶⁵ An $\text{S}_{\text{E}}1$ mechanism has been suggested.⁶⁶⁶ The terphthalate is the main product because it crystallizes from the reaction mixture, driving the equilibrium in that direction.⁶⁶⁷

For aliphatic decarboxylation, see Reaction **12-40**.

OS **I**, 274, 455, 541; **II**, 100, 214, 217, 341; **III**, 267, 272, 471, 637; **IV**, 590, 628; **V**, 635, 813, 982, 985. Also see, OS **I**, 56.

11-36 The Jacobsen Reaction



When polyalkyl- or polyhalobenzenes are treated with sulfuric acid, the ring is sulfonated, but rearrangement also takes place. The reaction, known as the *Jacobsen reaction*, is limited to benzene rings that have at least four substituents, which can be

⁶⁵⁵ Cohen, T.; Berninger, R.W.; Wood, J.T. *J. Org. Chem.* **1978**, 43, 37.

⁶⁵⁶ See Ibne-Rasa, K.M. *J. Am. Chem. Soc.* **1962**, 84, 4962.

⁶⁵⁷ Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* **1970**, 24, 3353.

⁶⁵⁸ Goößen, L.J.; Linder, C.; Rodríguez, N.; Lange, P.P.; Fromm, A. *Chem. Commun.* **2009**, 7173.

⁶⁵⁹ Farhadi, S.; Zaringhadam, P.; Sahamieh, R.Z. *Tetrahedron Lett.* **2006**, 47, 1965.

⁶⁶⁰ Singh, R.; Just, G. *Synth. Commun.* **1988**, 18, 1327.

⁶⁶¹ See Grovenstein, Jr., E.; Ropp, G.A. *J. Am. Chem. Soc.* **1956**, 78, 2560.

⁶⁶² Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, **1985**, pp. 101–105.

⁶⁶³ Goossen, L.J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L.M. *J. Am. Chem. Soc.* **2007**, 129, 4824.

Goossen, L.J.; Rodríguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, 130, 15248.

⁶⁶⁴ Ogata, Y.; Nakajima, K. *Tetrahedron* **1965**, 21, 2393; Ratusky, J.; Sorm, F. *Chem. Ind. (London)*, **1966**, 1798.

⁶⁶⁵ See Ratusky, J. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, **1979**, pp. 915–944.

⁶⁶⁶ See Ratusky, J. *Collect. Czech. Chem. Commun.* **1973**, 38, 74, 87, and references cited therein.

⁶⁶⁷ Ratusky, J. *Collect. Czech. Chem. Commun.* **1968**, 33, 2346.

any combination of alkyl and halogen groups, where the alkyl groups can be ethyl or methyl and the halogen iodo, chloro, or bromo. When isopropyl or *tert*-butyl groups are on the ring, these groups are cleaved to give alkenes. Since a sulfo group can later be removed (Reaction **11-38**), the Jacobsen reaction can be used as a means of rearranging polyalkylbenzenes. The rearrangement always brings the alkyl or halo groups closer together than they were originally. Side products in the case illustrated above are pentamethylbenzenesulfonic acid, 2,4,5-trimethylbenzenesulfonic acid, and so on, indicating an intermolecular process, at least partially.

The mechanism of the *Jacobsen reaction* is not established,⁶⁶⁸ but there is evidence, at least for polymethylbenzenes, that the rearrangement is intermolecular, and that the species to which the methyl group migrates is a polymethylbenzene, not a sulfonic acid. Sulfonation takes place after the migration.⁶⁶⁹ It has been shown by labeling that ethyl groups migrate without internal rearrangement.⁶⁷⁰

Isomerization of alkyl groups in substituted biphenyls has been observed⁶⁷¹ when the medium is a superacid (see Sec. 5.A.ii).

B. Oxygen Leaving Groups

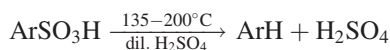
11-37 Deoxygenation



In a few cases, it is possible to remove an oxygen substituent directly from the aromatic ring. Treatment of an aryl mesylate (ArOMs) with a Ni catalyst in DMF, for example, leads to the deoxygenated product, Ar-H.⁶⁷²

C. Sulfur Leaving Groups

11-38 Desulfonation or Hydro-de-sulfonation



The cleavage of sulfo groups from aromatic rings is the reverse of Reaction **11-7**.⁶⁷³ By the principle of microscopic reversibility, the mechanism is also the reverse.⁶⁷⁴ Dilution is generally used, as the reversibility of sulfonation decreases with increasing H₂SO₄ concentration. The reaction permits the sulfo group to be used as a blocking group to direct meta and then to be removed. The sulfo group has also been replaced by nitro and halogen groups. Sulfo groups have also been removed from the ring by heating with an alkaline solution of Raney nickel.⁶⁷⁵ In another catalytic process, aromatic

⁶⁶⁸ See Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* **1977**, 717; Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, **1968**, pp. 214–226; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 22–32, 48–55.

⁶⁶⁹ Cerfontain, H.; Koeberg-Telder, A. *Can. J. Chem.* **1988**, 66, 162.

⁶⁷⁰ Marvell, E.N.; Webb, D. *J. Org. Chem.* **1962**, 27, 4408.

⁶⁷¹ Sherman, S.C.; Iretskii, A.V.; White, M.G.; Gumieny, C.; Tolbert, L.M.; Schiraldi, D.A. *J. Org. Chem.* **2002**, 67, 2034.

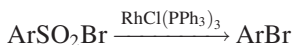
⁶⁷² Sasaki, K.; Kubo, T.; Sakai, M.; Kuroda, Y. *Chem. Lett.* **1997**, 617.

⁶⁷³ See Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, **1968**, pp. 185–214; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 349–355; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, **1965**, pp. 427–442. See also, Krylov, E.N. *J. Org. Chem. USSR* **1988**, 24, 709.

⁶⁷⁴ See Kozlov, V.A.; Bagrovskaya, N.A. *J. Org. Chem. USSR* **1989**, 25, 1152.

⁶⁷⁵ Feigl, F. *Angew. Chem.* **1961**, 73, 113.

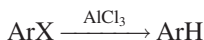
sulfonyl bromides or chlorides are converted to aryl bromides or chlorides, respectively, on heating with an Rh catalyst.⁶⁷⁶ This reaction is similar to the decarbonylation of aromatic acyl halides mentioned in Reaction 14-32.



OS I, 388; II, 97; III, 262; IV, 364. Also see, OS I, 519; II, 128; V, 1070.

D. Halogen Leaving groups

11-39 Dehalogenation or Hydro-de-halogenation



Aryl halides can be dehalogenated by *Friedel–Crafts catalysts*. Iodine is the most easily cleaved. Dechlorination is seldom performed and defluorination apparently never. The reaction is most successful when a reducing agent, say, Br^- or I^- is present to combine with the I^+ or Br^+ coming off.⁶⁷⁷ Except for deiodination, the reaction is seldom used for preparative purposes. Migration of halogen is also found,⁶⁷⁸ both intramolecular⁶⁷⁹ and intermolecular.⁶⁸⁰ The mechanism is probably the reverse of that of Reaction 11-10.⁶⁸¹ Debromination of aromatic rings having two attached amino groups was accomplished by refluxing in aniline containing acetic acid/HBr.⁶⁸²

Rearrangement of polyhalobenzenes can also be catalyzed by very strong bases (e.g., 1,2,4-tribromobenzene) is converted to 1,3,5-tribromobenzene by treatment with PhNHK.⁶⁸³ This reaction, which involves aryl carbanion intermediates ($\text{S}_{\text{E}}1$ mechanism), has been called the *halogen dance*.⁶⁸⁴

Removal of halogen from aromatic rings can also be accomplished by various reducing agents, among them Bu_3SnH ,⁶⁸⁵ catalytic-hydrogenolysis,⁶⁸⁶ catalytic-transfer hydrogenolysis,⁶⁸⁷ Na—Hg in liquid NH_3 ,⁶⁸⁸ LiAlH_4 ,⁶⁸⁹ NaBH_4 and a catalyst,⁶⁹⁰ NaH ,⁶⁹¹ HCO_2H ⁶⁹² or

⁶⁷⁶ Blum, J.; Scharf, G. *J. Org. Chem.* **1970**, 35, 1895.

⁶⁷⁷ Pettit, G.R.; Piatak, D.M. *J. Org. Chem.* **1960**, 25, 721.

⁶⁷⁸ Olah, G.A.; Meidar, D.; Olah, J.A. *Nouv. J. Chim.*, **1979**, 3, 275.

⁶⁷⁹ Jacquesy, J.; Jouannetaud, M. *Tetrahedron Lett.* **1982**, 23, 1673.

⁶⁸⁰ Augustijn, G.J.P.; Kooyma, E.C.; Louw, R. *Recl. Trav. Chim. Pays-Bas* **1963**, 82, 965.

⁶⁸¹ Choguill, H.S.; Ridd, J.H. *J. Chem. Soc.* **1961**, 822; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, p. 1; Ref. 636.

⁶⁸² Choi, H.; Chi, D.Y. *J. Am. Chem. Soc.* **2001**, 123, 9202.

⁶⁸³ Moyer, Jr., C.E.; Bunnett, J.F. *J. Am. Chem. Soc.* **1963**, 85, 1891.

⁶⁸⁴ Bunnett, J.F. *Acc. Chem. Res.* **1972**, 5, 139; Mach, M.H.; Bunnett, J.F. *J. Org. Chem.* **1980**, 45, 4660; Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* **1989**, 771.

⁶⁸⁵ Maitra, U.; Sarma, K.D. *Tetrahedron Lett.* **1994**, 35, 7861.

⁶⁸⁶ See Subba Rao, Y.V.; Mukkanti, K.; Choudary, B.M. *J. Organomet. Chem.* **1989**, 367, C29. See also, Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* **2002**, 43, 7247.

⁶⁸⁷ Anwer, M.K.; Spatola, A.F. *Tetrahedron Lett.* **1985**, 26, 1381.

⁶⁸⁸ Austin, E.; Alonso, R.A.; Rossi, R.A. *J. Chem. Res. (S)* **1990**, 190.

⁶⁸⁹ Brown, H.C.; Chung, S.; Chung, F. *Tetrahedron Lett.* **1979**, 2473. See Chung, F.; Filmore, K.L. *J. Chem. Soc., Chem. Commun.* **1983**, 358; Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* **1983**, 905. See also, Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* **1983**, 907.

⁶⁹⁰ Narisada, M.; Horibe, I.; Watanabe, F.; Takeda, K. *J. Org. Chem.* **1989**, 54, 5308.

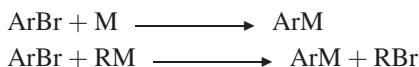
⁶⁹¹ Nelson, R.B.; Gribble, G.W. *J. Org. Chem.* **1974**, 39, 1425.

⁶⁹² Barren, J.P.; Baghel, S.S.; McCloskey, P.J. *Synth. Commun.* **1993**, 23, 1601.

aq HCO_2^- ⁶⁹³ with Pd/C,⁶⁹⁴ ammonium formate in aq isopropyl alcohol with a Pd catalyst,⁶⁹⁵ and Raney nickel in alkaline solution,⁶⁹⁶ the last method being effective for fluorine as well as for the other halogens. Aryl iodides are reduced with DMAP methiodide salt.⁶⁹⁷ Carbon monoxide, with potassium tetracarbonylhydridoferrate $[\text{KHF}(\text{CO})_4]$ as a catalyst, specifically reduces aryl iodides.⁶⁹⁸ Not all of these reagents operate by electrophilic substitution mechanisms. Some are nucleophilic substitutions and some are free radical processes. Photochemical⁶⁹⁹ and electrochemical⁷⁰⁰ reduction are also known. Halogen can also be removed from aromatic rings indirectly by conversion to *Grignard reagents* (Reaction 12-38) followed by hydrolysis (Reaction 11-41).

OS III, 132, 475, 519; V, 149, 346, 998; VI, 82, 821.

11-40 Formation of Organometallic Compounds



These reactions are considered along with their aliphatic counterparts at Reactions 12-38 and 12-39.

E. Metal Leaving Groups

11-41 Hydrolysis of Organometallic Compounds

Hydro-de-metalation or Demetalation



Organometallic compounds can be hydrolyzed by acid treatment. For active metals (e. g., Mg, Li, etc.), water is sufficiently acidic. The most important example of this reaction is hydrolysis of *Grignard reagents*, but M may be many other metals or metalloids. Examples are SiR_3 , HgR , Na, and $\text{B}(\text{OH})_2$. Since aryl *Grignard* and aryllithium compounds are fairly easy to prepare, they are often used to prepare salts of weak acids (e.g., alkynes).



Where the bond between the metal and the ring is covalent, the usual arenium ion mechanism operates.⁷⁰¹ Where the bonding is essentially ionic, this is a simple acid-base reaction. For the aliphatic counterpart of this reaction, see Reaction 12-24.

Other reactions of aryl organometallic compounds are treated with their aliphatic analogues: Reactions 12-25–12-27 and 12-30–12-37.

⁶⁹³ Arcadi, A.; Cerichelli, G.; Chiarini, M.; Vico, R.; Zorzan, D. *Eur. J. Org. Chem.* **2004**, 3404.

⁶⁹⁴ See Monguchi, Y.; Kume, A.; Hattori, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* **2006**, 62, 7926. Also see Chen, J.; Zhang, Y.; Yang, L.; Zhang, X.; Liu, J.; Li, L.; Zhang, H. *Tetrahedron* **2007**, 63, 4266.

⁶⁹⁵ Nakao, R.; Rhee, H.; Uozumi, Y. *Org. Lett.* **2005**, 7, 163.

⁶⁹⁶ de Koning, A.J. *Org. Prep. Proced. Int.* **1975**, 7, 31.

⁶⁹⁷ Garnier, J.; Murphy, J.A.; Zhou, S.-Z.; Turner, A.T. *Synlett* **2008**, 2127.

⁶⁹⁸ Brunet, J.; Taillefer, M. *J. Organomet. Chem.* **1988**, 348, C5.

⁶⁹⁹ See Barltrop, J.A.; Bradbury, D. *J. Am. Chem. Soc.* **1973**, 95, 5085.

⁷⁰⁰ See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, **1989**, pp. 142–143. Also see, Bhuvaneswari, N.; Venkatachalam, C.S.; Balasubramanian, K.K. *Tetrahedron Lett.* **1992**, 33, 1499.

⁷⁰¹ See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 278–303, 324–349.

Aliphatic, Alkenyl, and Alkynyl Substitution, Electrophilic and Organometallic

Chapter 11 pointed out that the most important leaving groups in electrophilic substitution are those that can best exist with an outer shell that is deficient in a pair of electrons. For aromatic systems, the most common leaving group is the proton. The proton is also a leaving group in aliphatic systems, but the reactivity depends on the acidity. Protons in saturated alkanes are very unreactive, but electrophilic substitutions are often easily carried out at more acidic positions [e.g., α to a carbonyl group or at an alkynyl position ($\text{RC}\equiv\text{CH}$)]. Since metallic ions are easily able to bear positive charges, organometallic compounds should be especially susceptible to electrophilic substitution, and this is indeed the case.¹ Another important type of electrophilic substitution, known as *anionic cleavage*, involves the breaking of C—C bonds; in these reactions there are carbon leaving groups (Reactions 12-40–12-46). A number of electrophilic substitutions at a nitrogen atom are treated at the end of the chapter.

Since a carbanion is generated when an atom or group is removed as a positive species from a carbon atom, the subject of carbanion structure and stability (Chapter 5) is inevitably related to the material in this chapter. So is the subject of very weak acids and very strong bases (Chapter 8), because the weakest acids are those in which the hydrogen is bonded to carbon.

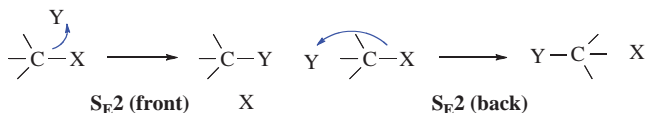
¹ See Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, 5 Vols., Wiley, NY, **1984–1990**; Haiduc, I.; Zuckerman, J.J. *Basic Organometallic Chemistry*, Walter de Gruyter, NY, **1985**; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, **1980**; Aylett, B.J. *Organometallic Compounds*, 4th ed., Vol. 1, pt. 2; Chapman and Hall, NY, **1979**; Maslowsky, Jr., E. *Chem. Soc. Rev.* **1980**, 9, 25, and in Tsutsui, M. *Characterization of Organometallic Compounds*, Wiley, NY, **1969–1971**, the articles by Cartledge, F.K.; Gilman, H. pt. 1, pp. 1–33, and by Reichle, W.T. pt. 2, pp. 653–826.

12.A. MECHANISMS

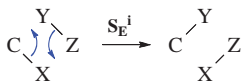
For aliphatic electrophilic substitution, at least four possible major mechanisms can be distinguished:² S_E1 , S_E2 (front), S_E2 (back), and S_Ei . The S_E1 is unimolecular; the other three are bimolecular. Note that the term " S_EAr " has been proposed to represent electrophilic aromatic substitution, so that the term " S_E2 " refers exclusively to electrophilic substitutions where a steric course is possible.³ To describe the steric course of an aliphatic substitution reaction, the suffixes "ret" and "inv" were proposed, referring to retention and inversion of configuration, respectively.

12.A.i. Bimolecular Mechanisms: S_E2 and S_Ei

The bimolecular mechanisms for electrophilic aliphatic substitution are analogous to the S_N2 mechanism in that the new bond forms as the old one breaks. However, in the S_N2 mechanism the incoming group brings with it a pair of electrons, and this orbital can overlap with the central carbon only to the extent that the leaving group takes away its electrons; otherwise the carbon would have more than eight electrons at once in its outer shell. Since electron clouds repel, this also means that the incoming group attacks backside, at a position 180° from the leaving group, resulting in inversion of configuration. When the nucleophilic species attacks (donates electrons to) an electrophile, it brings only a vacant orbital to the substrate. Predicting the direction of the attack is not as straightforward. Two main possibilities can be imagined: delivery of the electrophile to the front, which is S_E2 (front), or delivery of the electrophile to the rear, which is S_E2 (back). The possibilities can be pictured (charges not shown):



Both the S_E2 (front) and S_E2 (back) mechanisms are designated D_EA_E in the IUPAC system. With substrates in which these possibilities may be distinguished, the former mechanism should result in retention of configuration and the latter results in inversion. The reaction of allylsilanes with adamantyl chloride and $TiCl_4$, for example, gives primarily the antiprodukt via a S_E2' reaction.⁴ When the electrophile reacts from the front, there is a third possibility. A portion of the electrophile may assist in the removal of the leaving group, forming a bond with it at the same time that the new $C—Y$ bond is formed:

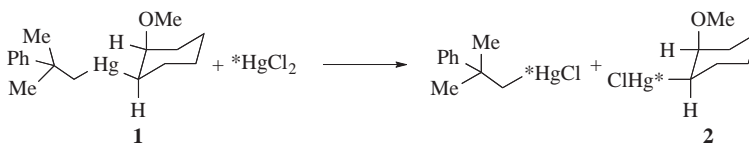


² See Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, **1973**; Reutov, O.A.; Beletskaya, I.P. *Reaction Mechanisms of Organometallic Compounds*, North-Holland Publishing Company, Amsterdam, The Netherlands, **1968**; Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 25–149; Reutov, O.A. *Pure Appl. Chem.* **1978**, *50*, 717; *Tetrahedron* **1978**, *34*, 2827.

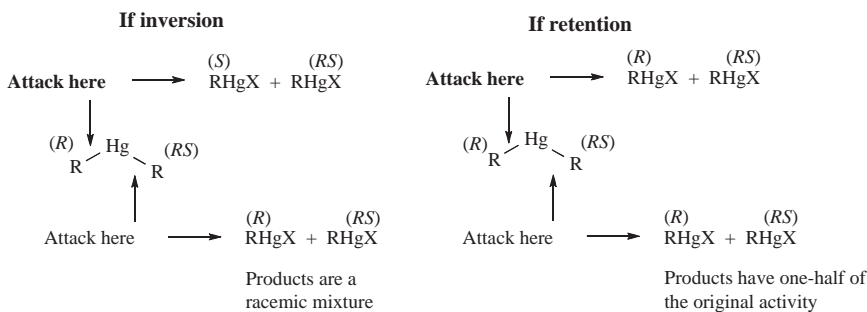
³ Gawley, R.E. *Tetrahedron Lett.* **1999**, *40*, 4297.

⁴ Buckle, M.J.C.; Fleming, I.; Gil, S. *Tetrahedron Lett.* **1992**, *33*, 4479.

This mechanism, which is called the S_{Ei} mechanism⁵ (IUPAC designation: *cyclo-D_EA_ED_nA_n*), also results in retention of configuration.⁶ Plainly, where a second-order mechanism involves this kind of internal assistance, backside attack is impossible.



It is evident that these three mechanisms are not easy to distinguish. All three mechanisms give second-order kinetics, and two mechanisms result in retention of configuration.⁷ In fact, although much work has been done on this question, there are few cases in which one of these three can be unequivocally established to demonstrate that another is not actually taking place. Clearly, a study of the stereochemistry can distinguish between S_{E2} (back) on the one hand and S_{E2} (front) or S_{Ei} on the other. Many such investigations have been made. In the overwhelming majority of second-order electrophilic substitutions, the result has been retention of configuration or some other indication of frontside attack, indicating an S_{E2} (front) or S_{Ei} mechanism. For example, when *cis*-**1** was treated with labeled mercuric chloride, the **2** produced was 100% *cis*. The bond between the mercury and the ring must have been broken (as well as the other Hg—C bond), since each of the products contained about one-half of the labeled mercury.⁸ Another indication of frontside attack is that second-order electrophilic substitutions proceed very easily at *bridgehead* carbons (see Sec. 10.A.i).⁹ Still another indication is the behavior of neopentyl as a substrate. The S_N2 reactions at neopentyl are extremely slow (Sec. 10.G.i), because attack from the rear is blocked and the transition state for the reaction lies very high in energy. The fact that neopentyl systems undergo electrophilic substitution only slightly more slowly than ethyl¹⁰ is further evidence for frontside attack. One final elegant experiment may be noted.



⁵ The names for these mechanisms vary throughout the literature. For example, the S_{Ei} mechanism has also been called the S_{E2} , the S_{E2} (closed), and the S_{E2} (cyclic) mechanism. The original designations, S_{E1} , S_{E2} , and so on, were devised by the Hughes–Ingold school.

⁶ It has been contended that the S_{Ei} mechanism violates the principle of conservation of orbital symmetry (see Reaction 15-60, A), and that the S_{E2} (back) mechanism partially violates it: Slack, D.A.; Baird, M.C. *J. Am. Chem. Soc.* **1976**, 98, 5539.

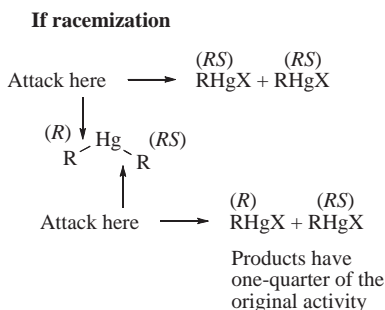
⁷ See Flood, T.C. *Top. Stereochem.* **1981**, 12, 37. See also, Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc.* **1971**, 93, 4048.

⁸ Winstein, S.; Traylor, T.G.; Garner, C.S. *J. Am. Chem. Soc.* **1955**, 77, 3741.

⁹ Schöllkopf, U. *Angew. Chem.* **1960**, 72, 147. See Fort, Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* **1966**, 1, 283, pp. 353–370.

¹⁰ Hughes, E.D.; Volger, H.C. *J. Chem. Soc.* **1961**, 2359.

The compound di-*sec*-butylmercury was prepared with one *sec*-butyl group optically active and the other racemic.¹¹ This compound was prepared by treatment of optically active *sec*-butylmercuric bromide with racemic *sec*-butylmagnesium bromide. The di-*sec*-butyl compound was then treated with mercuric bromide to give 2 molar equivalents of *sec*-butylmercuric bromide. The steric course of the reaction could then be predicted by the following analysis, assuming that the bonds between the mercury and each carbon have a 50% chance of breaking. The original activity referred to is the activity of the optically active *sec*-butylmercuric bromide used to make the dialkyl compound. The actual result was that, under several different sets of conditions, the product had one-half of the original activity, demonstrating retention of configuration.



However, inversion of configuration has been found in certain cases, demonstrating that the S_E2 (back) mechanism can take place. For example, the reaction of optically active *sec*-butyltrineopentyltin with bromine (Reaction 12-40) gives inverted *sec*-butyl bromide.¹² A number of other organometallic compounds have also been shown to give inversion when treated with halogens,¹³ although others do not.¹⁴ So far, no inversion has been found with an organomercury substrate. It may be that still other examples of backside



attack exist¹⁵ but have escaped detection because of the difficulty in preparing compounds with a configurationally stable carbon–metal bond. Compounds that are chiral because of a stereogenic carbon at which a carbon–metal bond is located¹⁶ are often difficult to resolve and once resolved are often easily racemized. The resolution has been accomplished most often with organomercury compounds,¹⁷ and most stereochemical investigations have therefore been made with these substrates. Only a few optically active *Grignard reagents* (see Sec. 12-38) have been prepared¹⁸ (i.e., in which the only stereogenic center is the

¹¹ Jensen, F.R. *J. Am. Chem. Soc.* **1960**, 82, 2469; Ingold, C.K. *Helv. Chim. Acta* **1964**, 47, 1191.

¹² Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc.* **1971**, 93, 4048. See Fukuto, J.M.; Jensen, F.R. *Acc. Chem. Res.* **1983**, 16, 177.

¹³ See Magnuso, R.H.; Halpern, J.; Levitin, I.Ya.; Vol'pin, M.E. *J. Chem. Soc. Chem. Commun.* **1978**, 44.

¹⁴ See Rahm, A.; Pereyre, M. *J. Am. Chem. Soc.* **1977**, 99, 1672; McGahey, L.F.; Jensen, F.R. *J. Am. Chem. Soc.* **1979**, 101, 4397; Olszowy, H.A.; Kitching, W. *Organometallics* **1984**, 3, 1676. Also see Rahm, A.; Grimeau, J.; Pereyre, M. *J. Organomet. Chem.* **1985**, 286, 305.

¹⁵ See Bergbreiter, D.E.; Rainville, D.P. *J. Organomet. Chem.* **1976**, 121, 19.

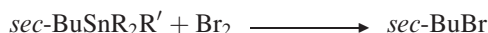
¹⁶ See Sokolov, V.I. *Chirality and Optical Activity in Organometallic Compounds*, Gordon and Breach, NY, **1990**.

¹⁷ See Jensen, F.R.; Whipple, L.D.; Wedegaertner, D.K.; Landgrebe, J.A. *J. Am. Chem. Soc.* **1959**, 81, 1262; Charman, H.B.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* **1959**, 2523, 2530.

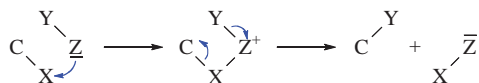
¹⁸ This was done first by Walborsky, H.M.; Young, A.E. *J. Am. Chem. Soc.* **1964**, 86, 3288.

carbon bonded to the magnesium). Because of this, the steric course of electrophilic substitutions at the C—Mg bond has not often been determined. However, in one such case, the reaction of both the exo and endo isomers of the 2-norbornyl *Grignard reagent* with HgBr_2 (to give 2-norbornylmercuric bromide) has been shown to proceed with retention of configuration.¹⁹ It is likely that inversion takes place only when steric hindrance prevents reaction on the frontside and when the electrophile does not carry a Z group (see above).

The $\text{S}_{\text{E}2}$ (back) mechanism can be identified in certain cases (if inversion of configuration is found), but it is plain that stereochemical investigations cannot distinguish between the $\text{S}_{\text{E}2}$ (front) and the $\text{S}_{\text{E}i}$ mechanisms and that, in the many cases where configurationally stable substrates cannot be prepared, such investigations are of no help at all in distinguishing among all three of the second-order mechanisms. Unfortunately, there are not many other methods that lead to unequivocal conclusions. One method that has been used in an attempt to distinguish between the $\text{S}_{\text{E}i}$ mechanism on the one hand and the $\text{S}_{\text{E}2}$ pathways on the other, involves the study of salt effects on the rate. It may be recalled (Sec. 10.G.iv) that reactions in which neutral starting molecules acquire charges in the transition state are aided by an increasing concentration of added ions. Thus the $\text{S}_{\text{E}i}$ mechanism would be less influenced by salt effects than would either of the $\text{S}_{\text{E}2}$ mechanisms. On this basis, Abraham and Johnson²⁰ concluded that the reactions $\text{R}_4\text{Sn} + \text{HgX}_2 \rightarrow \text{RHgX} + \text{R}_3\text{SnX}$ ($\text{X} = \text{Cl}$ or I) take place by $\text{S}_{\text{E}2}$ and not by $\text{S}_{\text{E}i}$ mechanisms. Similar investigations involve changes in solvent polarity²¹ (see also, Sec. 12.C.i). In the case of the reaction (where $\text{R} = \text{R}' = i\text{Pr}$ and $\text{R} = i\text{Pr}$, $\text{R}' = \text{neopentyl}$), the use of polar solvents gave predominant inversion, while nonpolar solvents gave predominant retention.²²



On the basis of evidence from reactivity studies, it has been suggested²³ that a variation of the $\text{S}_{\text{E}i}$ mechanism is possible in which the group Z becomes attached to X before the latter becomes detached:



This process has been called the $\text{S}_{\text{E}}\text{C}^{22}$ or $\text{S}_{\text{E}2}$ (co-ord)²⁴ mechanism (IUPAC designation $\text{A}_n + \text{cyclo-D}_\text{E}\text{A}_\text{E}\text{D}_\text{n}$).

It has been shown that in certain cases (e.g., $\text{Me}_4\text{Sn} + \text{I}_2$) the reactants in an $\text{S}_{\text{E}2}$ reaction, when mixed, give rise to an immediate charge-transfer spectrum (Sec. 3.C.i), showing that an EDA complex has been formed.²⁵ In these cases, it is likely that the EDA complex is an intermediate in the reaction.

¹⁹ Jensen, F.R.; Nakamaye, K.L. *J. Am. Chem. Soc.* **1966**, 88, 3437.

²⁰ Abraham, M.H.; Johnston, G.F. *J. Chem. Soc. A*, **1970**, 188.

²¹ See Abraham, M.H.; Dorrell, F.J. *J. Chem. Soc. Perkin Trans. 2* **1973**, 444.

²² Fukuto, J.M.; Newman, D.A.; Jensen, F.R. *Organometallics* **1987**, 6, 415.

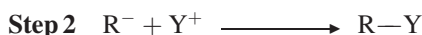
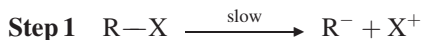
²³ Abraham, M.H.; Hill, J.A. *J. Organomet. Chem.* **1967**, 7, 11.

²⁴ Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12, Elsevier, NY, **1973**, p. 15.

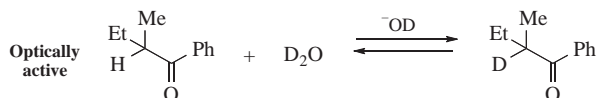
²⁵ Fukuzumi, S.; Kochi, J.K. *J. Am. Chem. Soc.* **1980**, 102, 2141, 7290.

12.A.ii. The S_E1 Mechanism

The S_E1 mechanism is analogous to the S_N1. It involves two steps: A slow ionization and a fast combination.

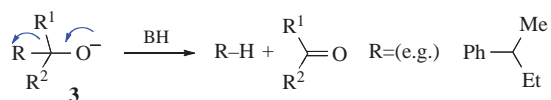


The IUPAC designation is D_E + A_E. First-order kinetics are predicted and many such examples have been found. Other evidence for the S_E1 mechanism was obtained in a study of base-catalyzed tautomerization. In the reaction, the rate of deuterium exchange was the same as the rate of racemization²⁶ and there was an isotope effect.²⁷



It is known that S_N1 reactions do not proceed at strained bridgehead carbons (e.g., in [2.2.1]bicyclic systems, Sec. 10.A.ii) because planar carbocations cannot form at these carbons. However, carbanions not stabilized by resonance are probably not planar, and S_E1 reactions readily occur with this type of substrate. Indeed, the question of carbanion structure is intimately tied into the problem of the stereochemistry of the S_E1 reaction. If a carbanion is planar, racemization should occur. If it is pyramidal and *can hold its structure*, the result should be retention of configuration, or at least partial retention. On the other hand, even a pyramidal carbanion will give racemization if it cannot hold its structure (this means that there is pyramidal inversion as with amines, Sec. 4.C, category 3). Unfortunately, the only carbanions that can be studied easily are those stabilized by resonance, which makes them planar, as expected (Sec. 5.B.i). For simple alkyl carbanions, the main approach to deduce the structure has been to study the stereochemistry of S_E1 reactions rather than the other way around. Racemization is almost always observed, but whether this is caused by planar carbanions or by oscillating pyramidal carbanions is not known. In either case, racemization occurs whenever a carbanion is completely free or is symmetrically solvated.

However, even planar carbanions need not give racemization. Cram found that retention and even inversion can occur in an alkoxide (see **3**) cleavage Reaction (12-41):



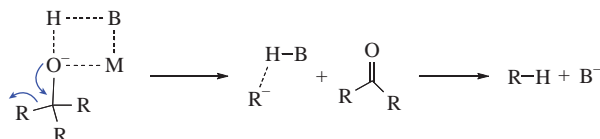
which is a first-order S_E1 reaction involving resonance-stabilized planar carbanions (here designated R⁻).²⁸ By changing the solvent, Cram was able to produce products ranging from 99% retention to 60% inversion and including complete racemization. These results are explained by a carbanion that is not completely free, but is solvated. In nondissociating,

²⁶ Hsu, S.K.; Ingold, C.K.; Wilson, C.L. *J. Chem. Soc.* **1938**, 78.

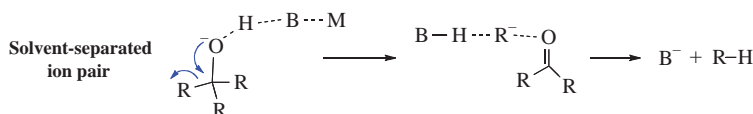
²⁷ Wilson, C.L. *J. Chem. Soc.* **1936**, 1550.

²⁸ See Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc.* **1969**, *91*, 1009. For a discussion, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, **1965**, pp. 138–158.

nonpolar solvents (e.g., benzene or dioxane), the alkoxide ion exists as an ion pair, solvated by the solvent BH:



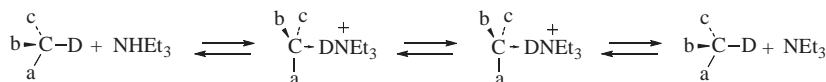
In the course of the cleavage, the proton of the solvent moves in to solvate the newly forming carbanion. This solvation is asymmetrical since the solvent molecule is already on the front side of the carbanion. When the carbanion actually bonds with the proton, the result is retention of the original configuration. In protic solvents (e.g., diethylene glycol), a good deal of inversion is found. In these solvents, the *leaving group* solvates the carbanion, so the solvent can solvate it only from the opposite side:



When C—H bond formation occurs, the result is inversion. Racemization occurs in polar aprotic solvents (e.g., DMSO). In these solvents, the carbanions are relatively long lived (because the solvent has no proton to donate) and is solvated symmetrically.

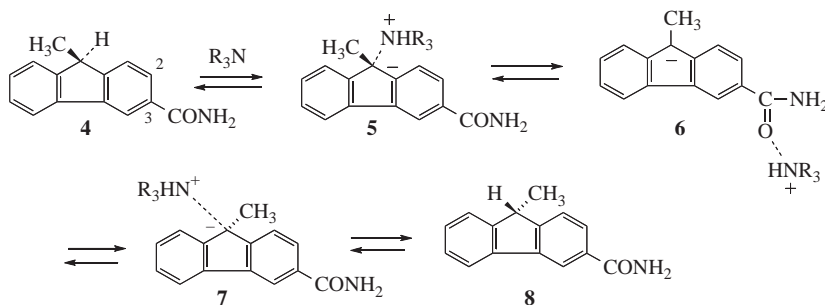


Similar behavior was found for carbanions generated by base-catalyzed hydrogen-exchange (Reaction 12-1).²⁹ In this case, information was obtained from measurement of the ratio of k_e (rate constant for isotopic exchange) to k_a (rate constant for racemization). A k_e/k_a ratio substantially >1 means retention of configuration, since many individual isotopic exchanges are not producing a change in configuration. A k_e/k_a ratio of ~ 1 indicates racemization and a ratio of $\frac{1}{2}$ corresponds to inversion (see Sec. 10.A.i). All three types of steric behavior were found, depending on R, the base, and the solvent. As with the alkoxide cleavage reaction, retention was generally found in solvents of low dielectric constant, racemization in polar aprotic solvents, and inversion in protic solvents. However, in the proton-exchange reactions, a fourth type of behavior was encountered. In aprotic solvents, with aprotic bases like tertiary amines, the k_e/k_a ratio was found to be <0.5 , indicating that racemization took place *faster* than isotopic exchange (this process is known as *isoracemization*). Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton:

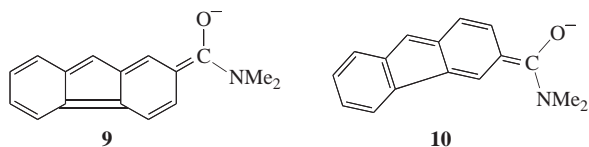


²⁹ See Roitman, J.N.; Cram, D.J. *J. Am. Chem. Soc.* **1971**, 93, 2225, 2231 and references cited therein; Cram, J.M.; Cram, D.J. *Intra-Sci. Chem. Rep.* **1973**, 7(3), 1; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, **1965**, pp. 85–105.

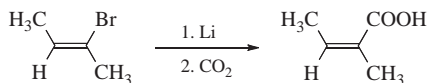
Thus, inversion (and hence racemization, which is produced by repeated acts of inversion) occurs without exchange. A single act of inversion without exchange is called *isoinversion*.



The isoinversion process can take place by a pathway in which a positive species migrates in a stepwise fashion around a molecule from one nucleophilic position to another. For example, in the exchange reaction of 3-carboxamido-9-methylfluorene (**4**) with Pr₃N in *t*-BuOH, it has been proposed that the amine removes a proton from the 9 position of **4** and conducts the proton out to the C=O oxygen (**6**), around the molecule, and back to C-9 on the opposite face of the anion. Collapse of **7** gives the inverted product **8**. Of course, **6** could also go back to **4**, but a molecule that undergoes the total process **4** → **5** → **6** → **7** → **8** has experienced an inversion without an exchange. Evidence for this pathway, called the *conducted tour mechanism*,³⁰ is that the 12-carboxamido isomer of **4** does not give isoracemization. In this case, the negative charge on the oxygen atom in the anion corresponding to **6** is less, because a canonical form in which oxygen acquires a full negative charge (**9**) results in disruption of the aromatic sextet in both benzene rings (cf. **10** where one benzene ring is intact). Whether the isoracemization process takes place by the conducted tour mechanism or a simple nonstructured contact ion-pair mechanism depends on the nature of the substrate (e.g., a proper functional group is necessary for the conducted tour mechanism) and of the base.³¹



It is known that vinylic carbanions *can* maintain configuration, so that S_E1 mechanisms should produce retention, which is the case. For example, *trans*-2-bromo-2-butene was converted to 64–74% angelic acid:³²



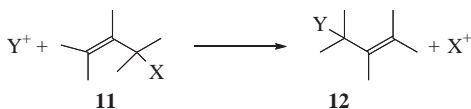
³⁰ Cram, D.J.; Ford, W.T.; Gosser, L. *J. Am. Chem. Soc.* **1968**, *90*, 2598; Ford, W.T.; Cram, D.J. *J. Am. Chem. Soc.* **1968**, *90*, 2606, 2612. See also, Buchholz, S.; Harms, K.; Massa, W.; Boche, G. *Angew. Chem. Int. Ed.* **1989**, *28*, 73.

³¹ Almy, J.; Hoffman, D.H.; Chu, K.C.; Cram, D.J. *J. Am. Chem. Soc.* **1973**, *95*, 1185.

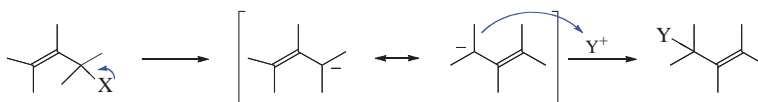
³² Dreiding, A.S.; Pratt, R.J. *J. Am. Chem. Soc.* **1954**, *76*, 1902. See also, Walborsky, H.M.; Turner, L.M. *J. Am. Chem. Soc.* **1972**, *94*, 2273.

Only ~5% of the cis isomer (tiglic acid) was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration (Sec. 5.B.ii) and S_E1 reactions involving them proceed with retention of configuration.

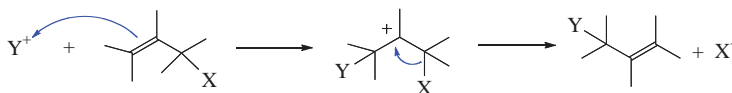
12.A.iii. Electrophilic Substitution Accompanied by Double-Bond Shifts



When electrophilic substitution is carried out at an allylic substrate, the product may be rearranged (**11** \rightarrow **12**). This type of process is analogous to the nucleophilic allylic rearrangements discussed in Section 10.D. There are two principal pathways. The first of these is analogous to the S_E1 mechanism in that the leaving group is first removed, giving a resonance-stabilized allylic carbanion, which then attacks the electrophile Y.

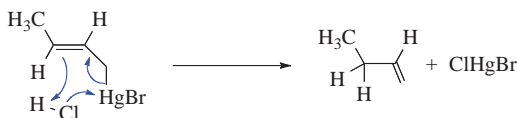


In the other pathway, the Y group is first attacked by the π -bond, giving a carbocation, which then loses X with formation of the alkene unit.

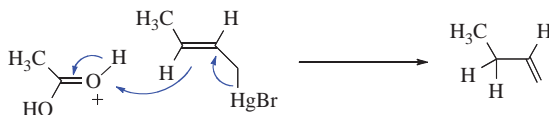


These mechanisms are more fully discussed under Reaction **12-2**.

Most electrophilic allylic rearrangements involve loss of hydrogen, but they have also been observed with metallic leaving groups.³³ Sleezer et al.³⁴ found that crotylmercuric bromide reacted with HCl $\sim 10^7$ times faster than *n*-butylmercuric bromide and the product was >99% 1-butene. These facts point to an $S_{Ei'}$ mechanism (IUPAC designation *cyclo*-1/3/ $D_EA_E D_n A_n$):



The reaction of the same compound with acetic acid–perchloric acid seems to proceed by an $S_{E2'}$ mechanism (IUPAC designation 1/3/ D_EA_E)³⁴:



³³ See Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, 69, 1.

³⁴ Sleezer, P.D.; Winstein, S.; Young, W.G. *J. Am. Chem. Soc.* **1963**, 85, 1890. See also, Kashin, A.N.; Bakunin, V.N.; Khutoryanskii, V.A.; Beletskaya, I.P.; Reutov, O.A. *J. Organomet. Chem.* **1979**, 171, 309.

The geometry of electrophilic allylic rearrangement has not been studied very much (cf. the nucleophilic case, Sec. 10.E), but in most cases the rearrangement takes place with antistereoselectivity,³⁵ although syn stereoselectivity has also been demonstrated.³⁶ In one case, use of the electrophile H^+ and the leaving group $SnMe_3$ gave both syn and anti stereoselectivity, depending on whether the substrate was cis or trans.³⁷

12.A.iv. Other Mechanisms

Addition–elimination (Reaction 12-16) and cyclic mechanisms (Reaction 12-40) are also known.

Much less work has been done on electrophilic aliphatic substitution mechanisms than on nucleophilic substitutions. The exact mechanisms of many of the reactions in this chapter are in doubt. For many of them, not enough work has been done to permit us to decide which of the mechanisms described in this chapter is operating, if indeed any is. There may be other electrophilic substitution mechanisms, and some of the reactions in this chapter may not even be electrophilic substitutions at all.

12.B. REACTIVITY

Only a small amount of work has been done in this area, compared to the vast amount done for aliphatic nucleophilic substitution and aromatic electrophilic substitution. Therefore, only a few conclusions can be drawn, most of them sketchy or tentative.³⁸

1. *Effect of Substrate.* For S_E1 reactions, electron-donating groups decrease rates and electron-withdrawing groups increase them. This is expected for a reaction in which the rate-determining step is analogous to the cleavage of a proton from an acid. For the S_E2 (back) mechanism, Jensen and Davis¹² showed that the reactivity of alkyl groups is similar to that for the S_N2 mechanism (i.e., $Me > Et > Pr > iPr > neopentyl$), as is expected, since both involve backside attack and both are equally affected by steric hindrance. In fact, this pattern of reactivity can be regarded as evidence for the occurrence of the S_E2 (back) mechanism in cases where stereochemical investigation is not feasible.³⁹ For S_E2 reactions that proceed with retention, several studies have been made with varying results, depending on the reaction.⁴⁰ One such study, which examined the reaction $RHgBr + Br_2 \rightarrow RBr$ catalyzed by Br^- , gave the results shown in Table 12.1.⁴¹ This data shows that branching increased the rates, while β branching decreased them. Sayre and Jensen⁴¹

³⁵ Matassa, V.G.; Jenkins, P.R.; Kümin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* **1989**, 29, 321.

³⁶ Young, D.; Kitching, W. *J. Org. Chem.* **1983**, 48, 614; *Tetrahedron Lett.* **1983**, 24, 5793.

³⁷ Kashin, A.N.; Bakunin, V.N.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* **1982**, 18, 1973. See also, Wickham, G.; Young, D.; Kitching, W. *Organometallics* **1988**, 7, 1187.

³⁸ See Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12, Elsevier, NY, **1973**, pp. 211–241.

³⁹ Also see Isaacs, N.S.; Laila, A.H. *Tetrahedron Lett.* **1984**, 25, 2407.

⁴⁰ See Abraham, M.H.; Broadhurst, A.T.; Clark, I.D.; Koenigsberger, R.U.; Dadjour, D.F. *J. Organomet. Chem.* **1981**, 209, 37.

⁴¹ Sayre, L.M.; Jensen, F.R. *J. Am. Chem. Soc.* **1979**, 101, 6001.

TABLE 12.1 Relative Rates of the Reaction of RHgBr with Br₂ and Br^a

R	Relative Rate	R	Relative Rate
Me	1	Et	10.8
Et	10.8	<i>i</i> -Bu	1.24
<i>i</i> Pr	780	Neopentyl	0.173
<i>t</i> -Bu	3370		

Reprinted with permission Sayre, L.M.; Jensen, F.R. *J. Am. Chem. Soc.* 1979, 101, 6001. Copyright © 1979 American Chemical Society.

^aSee Ref. 41.

attributed the decreased rates to steric hindrance, although attack here was definitely frontside, and the increased rates to the electron-donating effect of the alkyl groups, which stabilized the electron-deficient transition state.⁴² Of course, steric hindrance should also be present with the a branched groups, so these workers concluded that if it were not, the rates would be even greater. The Br electrophile is a rather large one and it is likely that smaller steric effects are present with smaller electrophiles. The rates of certain second-order substitutions of organotin compounds have been found to increase with increasing electron withdrawal by substituents. This behavior has been ascribed⁴³ to an S_E2 mechanism involving ion pairs, analogous to S_N2's ion-pair mechanism for nucleophilic substitution (Sec. 10.A.iv). Solvolysis of 2-bromo-1,1,1-trifluoro-2-(*p*-methoxyphenyl)ethane in water proceeds via a free carbocation intermediate, but ion pairing influences the reaction in the presence of bromide ion.⁴⁴

2. *Effect of Leaving Group.* For both S_E1 and second-order mechanisms, the more polar the C—X bond, the easier it is for the electrofuge to cleave. For metallic leaving groups in which the metal has a valence >1, the nature of the other group or groups attached to the metal thus has an effect on the reaction. For example, consider a series of organomercurials (RHgW). Because a more electronegative W decreases the polarity of the C—Hg bond and furthermore results in a less stable HgW⁺, the electrofugal ability of HgW decreases with increasing electronegativity of W. Thus, HgR' (from RHgR') is a better leaving group than HgCl (from RHgCl). Also in accord with this is the leaving-group order Hg—*t*-Bu > Hg—*i*Pr > HgEt > HgMe, reported for acetolysis of R₂Hg,⁴² since the more highly branched alkyl groups better help to spread the positive charge. It might be expected that, when metals are the leaving groups, S_E1 mechanisms would be favored, while with carbon leaving groups, second-order mechanisms would be found. However, the reported results have been just about the reverse of this. For carbon leaving groups the mechanism is usually S_E1, while for metallic leaving groups the mechanism is almost always S_E2 or S_Ei. A number of reports of S_E1 reactions with metallic leaving groups have appeared,⁴⁵ but the mechanism is not easy to prove and many of

⁴² Also see Nugent, W.A.; Kochi, J.K. *J. Am. Chem. Soc.* 1976, 98, 5979.

⁴³ Reutov, O.A. *J. Organomet. Chem.* 1983, 250, 145. See also, Butin, K.P.; Magdesieva, T.V. *J. Organomet. Chem.* 1985, 292, 47.

⁴⁴ Richard, J.P. *J. Org. Chem.* 1992, 57, 625.

⁴⁵ See Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* 1980, 29, 1461. See also, Dembech, P.; Eaborn, C.; Seconi, G. *J. Chem. Soc. Chem. Commun.* 1985, 1289.

these reports have been challenged.⁴⁶ Reutov and co-workers⁴⁵ expressed the view that in such reactions a nucleophile (which may be the solvent) must assist in the removal of the electrofuge and refer to such processes as $S_E1(N)$ reactions.

3. *Effect of Solvent.*⁴⁷ In addition to the solvent effects on certain S_E1 reactions mentioned earlier (Sec. 12.A.ii), solvents can influence the mechanism that is preferred. As with nucleophilic substitution (Sec. 10.G.iv), an increase in solvent polarity increases the possibility of an ionizing mechanism, in this case S_E1 , in comparison with the second-order mechanisms, which do not involve ions. As previously mentioned (Sec. 12.A.ii), the solvent can also exert an influence between the S_E2 (front or back) and S_{Ei} mechanisms in that the rates of S_E2 mechanisms should be increased by an increase in solvent polarity, while S_{Ei} mechanisms are much less affected.

12.C. REACTIONS

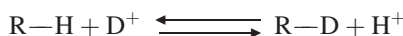
The reactions in this chapter are arranged in order of leaving group: hydrogen, metals, halogen, and carbon. Electrophilic substitutions at a nitrogen atom are treated last.

12.C.i. Hydrogen as Leaving Group

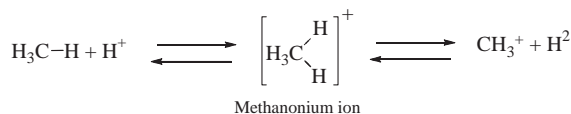
A. Hydrogen as the Electrophile

12-1 Hydrogen Exchange

Deuterio-de-hydrogenation or Deuteriation



Hydrogen exchange can be accomplished by treatment with acids or bases. As with Reaction 11-1, the exchange reaction is mostly used to study mechanistic questions (e.g., relative acidities), but it can be used synthetically to prepare deuterated or tritiated molecules. When ordinary strong acids (e.g., H_2SO_4) are used, only fairly acidic protons on carbon can exchange (e.g., acetylenic and allylic). However, primary, secondary, and tertiary hydrogen atoms of alkanes can be exchanged by treatment with superacids (Sec. 5.A.ii).⁴⁸ The order of hydrogen reactivity is tertiary > secondary > primary. Where C—C bonds are present, they may be cleaved also (Reaction 12-47). The mechanism of the exchange (illustrated for methane) has been formulated as involving attack of H^+ on the C—H bond to give the pentavalent methanonium ion, which loses



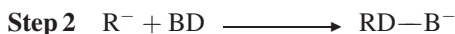
⁴⁶ See Kitching, W. *Rev. Pure Appl. Chem.* **1969**, 19, 1.

⁴⁷ See Petrosyan, V.S. *J. Organomet. Chem.* **1983**, 250, 157.

⁴⁸ See Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids*, Wiley, NY, **1985**, pp. 244–249; Olah, G.A. *Angew. Chem. Int. Ed.* **1973**, 12, 173.

H₂ to give a tervalent carbocation.⁴⁹ The methanonium ion (CH₅⁺) has a three-center, two-electron bond.⁵⁰ It is not known whether the methanonium ion is a transition state or a true intermediate, but an ion (CH₅⁺) has been detected in the mass spectrum.⁵¹ The IR spectrum of the ethanonium ion (C₂H₇⁺) has been measured in the gas phase.⁵² Note that the two electrons in the three-center, two-electron bond can move in three directions, in accord with the threefold symmetry of such a structure. The electrons can move to unite the two hydrogen atoms, leaving the CH₃⁺ free (the forward reaction), or they can unite the CH₃ with either of the two hydrogen atoms, leaving the other hydrogen as a free H⁺ ion (the reverse reaction). Actually, the methyl cation is not stable under these conditions. It can go back to CH₄ by the route shown (leading to H⁺ exchange), or it can react with additional CH₄ molecules (Reaction 12-20) to eventually yield the *tert*-butyl cation, which is stable in these superacid solutions. Hydride ion can also be removed from alkanes (producing tervalent carbocations) by treatment with pure SbF₅ in the absence of any source of H⁺.⁵³ Complete or almost complete perdeuteration of cyclic alkenes has been achieved by treatment with dilute DCl/D₂O in sealed Pyrex tubes at 165–280 °C.⁵⁴

Exchange with bases involves an S_E1 mechanism.



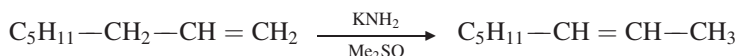
Of course, such exchange is most successful for relatively acidic protons (e.g., those α to a carbonyl group), but even weakly acidic protons can exchange with bases if the bases are strong enough (see Sec. 5.B.i).

Alkanes and cycloalkanes, of both low and high molecular weight, can be fully perdeuterated treatment with D₂ gas and a catalyst (e.g., Rh, Pt, or Pd).⁵⁵

OS VI, 432.

12-2 Migration of Double Bonds

3/Hydro-de-hydrogenation



The double bonds of many unsaturated compounds may be isomerized⁵⁶ upon treatment with strong bases.⁵⁷ In many cases, equilibrium mixtures are obtained and the

⁴⁹ See McMurry, J.E.; Lectka, T. *J. Am. Chem. Soc.* **1990**, *112*, 869; Culmann, J.; Sommer, J. *J. Am. Chem. Soc.* **1990**, *112*, 4057.

⁵⁰ See Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*, Wiley, NY, **1987**.

⁵¹ See Sefcik, M.D.; Henis, J.M.S.; Gaspar, P.P. *J. Chem. Phys.* **1974**, *61*, 4321.

⁵² Yeh, L.I.; Pric, J.M.; Lee, Y.T. *J. Am. Chem. Soc.* **1989**, *111*, 5597.

⁵³ Lukas, J.; Kramer, P.A.; Kouwenhoven, A.P. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 44.

⁵⁴ Werstiuk, N.H.; Timmins, G. *Can. J. Chem.* **1985**, *63*, 530; **1986**, *64*, 1564.

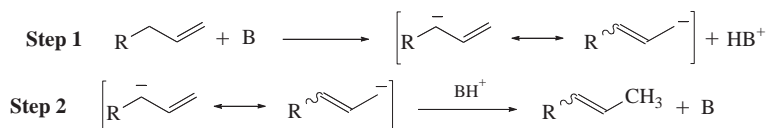
⁵⁵ See Atkinson, J.G.; Luke, M.O.; Stuart, R.S. *Can. J. Chem.* **1967**, *45*, 1511.

⁵⁶ For a list of methods used to shift double and triple bonds, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 220–226, 567–568.

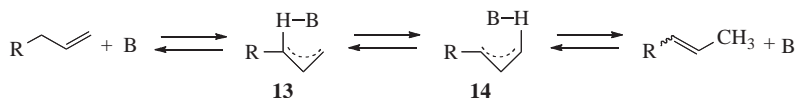
⁵⁷ See Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, **1977**, pp. 25–123; DeWolfe, R.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, pp. 437–449; Hubert, A.J.; Reimlinger, H. **1970**, 405; Mackenzie, K. in *The Chemistry of Alkenes*, Vol. 1, Patai, S., pp. 416–436, Vol. 2, Zabicky, J., pp. 132–148; Wiley, NY, 1964, **1970**; Broaddus, C.D. *Acc. Chem. Res.* **1968**, *1*, 231.

thermodynamically most stable isomer predominates.⁵⁸ If the new double bond can be in conjugation with one already present or with an aromatic ring, the conjugated compound is favored.⁵⁹ If the choice is between an exocyclic and an endocyclic double bond (particularly with six-membered rings), endocyclic is usually preferred. In the absence of such considerations, *Zaitsev's rule* (Sec. 17.B) applies and the double bond goes to the carbon with the fewest hydrogen atoms. All these considerations lead to predictions that terminal alkenes can be isomerized to internal ones, nonconjugated alkenes to conjugated, exo six-membered ring alkenes to endo, and so on, and not the other way around.

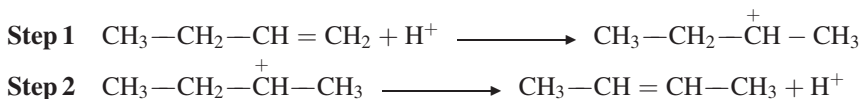
The term *prototropic rearrangement* is sometimes used as an example of electrophilic substitution with accompanying allylic rearrangement. The mechanism involves abstraction by a base to give a resonance-stabilized carbanion, and reaction with a proton is at the position that will give the more stable alkene.⁶⁰



This mechanism is exactly analogous to the allylic-rearrangement mechanism for nucleophilic substitution (Sec. 10.D). Ultraviolet spectra of allylbenzene and 1-propenylbenzene in solutions containing NH_2^+ are identical, showing that the same carbanion is present in both cases, as required by this mechanism.⁶¹ The acid BH^+ protonates the position that will give the more stable product, although the ratio of the two possible products can vary with the identity of BH^+ .⁶² It has been shown that base-catalyzed double-bond shifts are partially intramolecular, at least in some cases.⁶³ The intramolecular nature has been ascribed to a *conducted tour mechanism* (Sec. 12.A.iii) in which the base leads the proton from one carbanionic site to the other (**13** \rightarrow **14**).⁶⁴



Double-bond rearrangements can also take place on treatment with acids. Both proton and Lewis⁶⁵ acids can be used. The mechanism in the case of proton acids is the reverse of the previous one; first a proton is gained, giving a carbocation and then another is lost:



⁵⁸ See Hine, J.; Skoglund, M.J. *J. Org. Chem.* **1982**, *47*, 4766. See also, Hine, J.; Linden, S. *J. Org. Chem.* **1983**, *48*, 584.

⁵⁹ For a review of conversions of β,γ enones to α,β enones, see Pollack, R.M.; Bounds, P.L.; Bevins, C.L. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, **1989**, pp. 559–597.

⁶⁰ See Pollack, R.M.; Mack, J.P.G.; Eldin, S. *J. Am. Chem. Soc.* **1987**, *109*, 5048.

⁶¹ Rabinovich, E.A.; Astaf'ev, I.V.; Shatenshtein, A.I. *J. Gen. Chem. USSR* **1962**, *32*, 746.

⁶² Hünig, S.; Klaunzer, N.; Schlund, R. *Angew. Chem. Int. Ed.* **1987**, *26*, 1281.

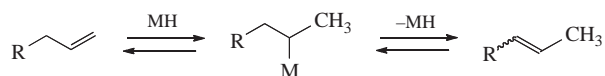
⁶³ See Cram, D.J.; Uyeda, R.T. *J. Am. Chem. Soc.* **1964**, *86*, 5466; Ohlsson, L.; Wold, S.; Bergson, G. *Ark. Kemi.*, **1968**, *29*, 351.

⁶⁴ Hussénius, A.; Matsson, O.; Bergson, G. *J. Chem. Soc. Perkin Trans. 2* **1989**, 851.

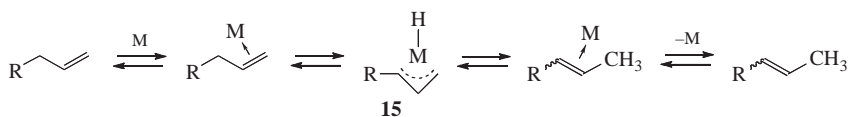
⁶⁵ See Cameron G.S.; Stimson, V.R. *Aust. J. Chem.* **1977**, *30*, 923.

As in the case of the base-catalyzed reaction, the thermodynamically most stable alkene is the one predominantly formed. However, the acid-catalyzed reaction is much less synthetically useful because carbocations give rise to many side products. If the substrate has several possible locations for a double bond, mixtures of all possible isomers are usually obtained. Isomerization of 1-decene, for example, gives a mixture that contains not only 1-decene and *cis*- and *trans*-2-decene, but also the *cis* and *trans* isomers of 3-, 4-, and 5-decene as well as branched alkenes resulting from rearrangement of carbocations. It is true that the most stable alkenes predominate, but many of them have stabilities that are close together.

Double-bond isomerization can take place in other ways. Nucleophilic allylic rearrangements were discussed in Chapter 10 (Sec. 10.E). Electrocyclic and sigmatropic rearrangements are treated at Reactions **18-27** to **18-35**. Double-bond migrations have also been accomplished photochemically,⁶⁶ and by means of metallic ion (most often complex ions containing Pt, Rh, or Ru) or metal carbonyl catalysts.⁶⁷ With metal compounds there are at least two possible mechanisms. One of these, which requires external hydrogen, is called the *metal hydride addition-elimination mechanism*:



The other mechanism, called the *π -allyl complex mechanism*, does not require external hydrogen and proceeds by hydrogen abstraction to form the η^3 - π -allyl complex **15** (see Sec. 3.C.i, category 1 and Reaction **10-60**). Another difference between the two mechanisms is that the former involves 1,2- and the latter 1,3-shifts. The isomerization of 1-butene Rh catalyzed reaction is an example that takes place by the metal hydride mechanism,⁶⁸ while an example of the π -allyl complex mechanism is found in the $\text{Fe}_3(\text{CO})_{12}$ catalyzed isomerization of 3-ethyl-1-pentene.⁶⁹ A Pd catalyst was used to convert alkynones ($\text{RCOC}\equiv\text{CCH}_2\text{CH}_2\text{R}'$) to 2,4-alkadien-1-ones ($\text{RCOCH}=\text{CHCH}=\text{CHCHR}'$).⁷⁰ The reaction of an en-yne with HSiCl_3 and a Pd catalyst generated an allene with moderate enantioselectivity (see Sec. 4.C, category 5 for chiral allenes).⁷¹



The metal-catalysis method has been used for the preparation of simple enols, by isomerization of allylic alcohols, for example.⁷² Some enols are stable enough for isolation

⁶⁶ Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, **1968**, pp. 22–24.

⁶⁷ See Rodriguez, J.; Brun, P.; Waegell, B. *Bull. Soc. Chim. Fr.* **1989**, 799–823; Otsuka, S.; Tani, K. in Morrison, J. D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, **1985**, pp. 171–191 (enantioselective); Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, **1984**, pp. 173–193; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Academic Press, NY, **1974**, pp. 9–37; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, **1974**, pp. 76–82; Jira, R.; Freiesleben, W. *Organomet. React.* **1972**, 3, 1, pp. 133–149.

⁶⁸ Cramer, R. *J. Am. Chem. Soc.* **1966**, 88, 2272.

⁶⁹ Casey, C.P.; Cyr, C.R. *J. Am. Chem. Soc.* **1973**, 95, 2248.

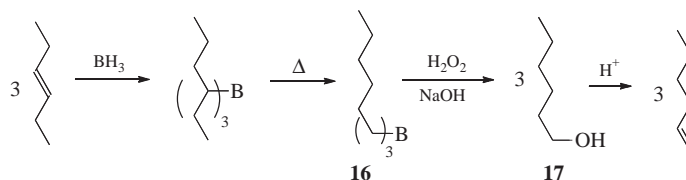
⁷⁰ Trost, B.M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, 110, 2301.

⁷¹ Han, J.W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, 123, 12915.

⁷² Bergens, S.H.; Bosnich, B. *J. Am. Chem. Soc.* **1991**, 113, 958.

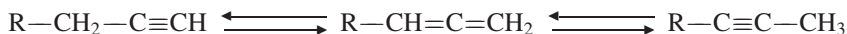
(see Sec. 4.Q.iv), but slowly tautomerize to the aldehyde or ketone, with half-lives ranging from 40 to 50 min to several days.⁷²

No matter which of the electrophilic methods of double-bond shifting is employed, the thermodynamically most stable alkene is usually formed in the largest amount, although a few anomalies are known. An indirect method of double-bond isomerization is known, leading to migration in the other direction. This involves conversion of the alkene to a borane (Reaction **15-16**), rearrangement of the borane (Reaction **18-11**), oxidation and hydrolysis of the newly formed borane to the alcohol (**17**) (see Reaction **12-31**), and dehydration of the alcohol (Reaction **17-1**) to the alkene. The reaction is driven by the fact that with heating the addition of borane is reversible, and the equilibrium favors formation of the less sterically hindered borane, **16** in this case.



Since the migration reaction is always toward the end of a chain, terminal alkenes can be produced from internal ones, so the migration is often opposite to that with the other methods. Alternatively, the rearranged borane can be converted directly to the alkene by heating with an alkene of molecular weight higher than that of the product (Reaction **17-15**). Photochemical isomerization can also lead to the thermodynamically less stable isomer.⁷³

See Reaction **15-1** for related reactions in which double bonds migrate or isomerize.



Triple bonds can also migrate in the presence of bases,⁷⁴ but through an allene intermediate:⁷⁵ In general, strong bases (e.g., NaNH_2) convert internal alkynes to terminal alkynes (a particularly good base for this purpose is potassium 3-aminopropylamide, $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NHHK}$ ⁷⁶), because the equilibrium is shifted by formation of the acetylide ion. With weaker bases (e.g., NaOH), which are not strong enough to remove the acetylenic proton, the internal alkynes are favored because of their greater thermodynamic stability. In some cases, the reaction can be stopped at the allene stage.⁷⁷ The reaction then becomes a method for the preparation of allenes.⁷⁸ The reaction of propargylic alcohols with tosylhydrazine (PPh_3) and DEAD also generates allenes.⁷⁹ In a related reaction, base

⁷³ See Duhaime, R.M.; Lombardo, D.A.; Skinner, I.A.; Weedon, A.C. *J. Org. Chem.* **1985**, *50*, 873.

⁷⁴ See Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, **1977**, pp. 124–204; Théron F.; Verny, M.; Vessière, R. in Patai, S. *The Chemistry of Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, **1978**, pp. 381–445; Bushby, R.J. *Q. Rev. Chem. Soc.* **1970**, *24*, 585; Iwai, I. *Mech. Mol. Migr.* **1969**, *2*, 73.

⁷⁵ See Huntsman, W.D. in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 2, Wiley, NY, **1980**, pp. 521–667.

⁷⁶ Macaulay, S.R. *J. Org. Chem.* **1980**, *45*, 734; Abrams, S.R. *Can. J. Chem.* **1984**, *62*, 1333.

⁷⁷ See Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. *Synlett* **2000**, 493.

⁷⁸ See Cunico, R.F.; Zaporowski, L.F.; Rogers, M. *J. Org. Chem.* **1999**, *64*, 9307.

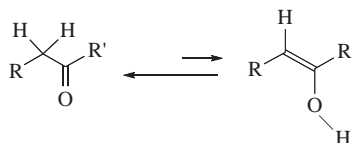
⁷⁹ Myers, A.G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. See Moghaddam, F.M.; Emami, R. *Synth. Commun.* **1997**, *27*, 4073 for the formation of alkoxy allenes from propargyl ethers.

induced isomerization of propargylic alcohols leads to conjugated ketones in some cases.⁸⁰ Acid-catalyzed migration of triple bonds (with allene intermediates) can be accomplished if very strong acids (e.g., $\text{HF}-\text{PF}_5$) are used.⁸¹ If the mechanism is the same as that for double bonds, vinyl cations are intermediates.

OS II, 140; III, 207; IV, 189, 192, 195, 234, 398, 683; VI, 68, 87, 815, 925; VII, 249; VIII, 146, 196, 251, 396, 553; X, 156, 165; 81, 147

12-3 Keto–Enol Tautomerization

3/O-Hydro-de-hydrogenation



The tautomeric equilibrium between enols and ketones or aldehydes (keto–enol tautomerism) is a form of prototropy,⁸² but is not normally a preparative reaction. For some ketones, however, both forms can be prepared (see Sec. 2.N.i, category 3 for a discussion of this and other types of tautomerism). Keto–enol tautomerism occurs in systems containing one or more carbonyl groups linked to sp^3 carbons bearing one or more hydrogen atoms. *The keto is generally more stable than the enol tautomer for neutral systems*, and for most ketones and aldehydes only the keto form is detectable under ordinary conditions. The availability of additional intramolecular stabilization through hydrogen bonding or complete electron delocalization (as in phenol), may cause the enol tautomer to be favored.

Keto–enol tautomerism is usually a slow process, but it can be catalyzed by a trace of acid or base.⁸³ In this equilibrium, the heteroatom is the basic site and the proton is the acidic site. For tautomerism in general (see Sec. 2.N.i),⁸⁴ the presence of an acid or a base is not necessary to initiate the isomerization since each tautomeric substance possesses amphotropic properties.⁸⁴ Polar protic solvents (e.g., water or alcohol) may participate in the proton transfer by forming a cyclic or a linear complex with the tautomers.⁸⁵ Whether the complex formed is cyclic or linear depends on the conformation and configuration of the tautomers. In a strongly polar aprotic solvent and in the presence of an acid or a base,

⁸⁰ Sonye, J.P.; Koide, K. *J. Org. Chem.* **2006**, 71, 6254.

⁸¹ Barry, B.J.; Beale, W.J.; Carr, M.D.; Hei, S.; Reid, I. *J. Chem. Soc. Chem. Commun.* **1973**, 177.

⁸² Patai, S. *The Chemistry of the Carbonyl Group*, Wiley, London, **1966**; Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, **1990**; Rappoport, Z.; Frey, J.; Sigalov, M.; Rochlin, E. *Pure Appl. Chem.* **1997**, 69, 1933; Fontana, A.; De Maria, P.; Siani, G.; Pierini, M.; Cerritelli, S.; Ballini, R. *Eur. J. Org. Chem.* **2000**, 1641; Iglesias, E. *Curr. Org. Chem.* **2004**, 8, 1.

⁸³ See Jones, J.R. *The Ionisation of Carbon Acids*, Academic Press, London, **1973**; Toullec, J. *Adv. Phys. Org. Chem.* **1982**, 18, 1; Chiang, Y.; Kresge, A.J.; Santaballa, J.A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, 110, 5506.

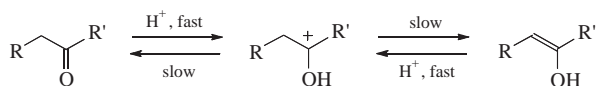
⁸⁴ See Raczyńska, E.D.; Kosinska, W.; Osmialowski, B.; Gawinecki, R. *Chem. Rev.* **2005**, 105, 3561 for a general discussion of tautomerism. Also see Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, **1990**; Zabicky, J. *The Chemistry of Amides*, Wiley, London, **1970**; Boyer, J.H. *The Chemistry of the Nitro and Nitroso Groups*, Interscience Publishers, NY, **1969**; Patai, S. *The Chemistry of Amino, Nitroso, Nitro Compounds and their Derivatives*, Wiley, NY, **1982**; Patai, S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups, Supplement F2*, Wiley, Chichester, **1996**; Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, **1998**.

⁸⁵ Gorb, L.; Leszczynski, J. *J. Am. Chem. Soc.* **1998**, 120, 5024; Guo, J. X.; Ho, J. J. *J. Phys. Chem. A* **1999**, 103, 6433.

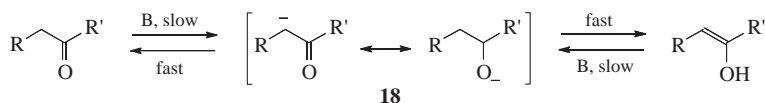
the tautomeric molecule may lose or gain a proton and form the corresponding mesomeric anion or cation, which, in turn, may gain or lose a proton, respectively, and yield a new tautomeric form.⁸⁶ The structural features of the carbonyl compound influences the equilibrium.⁸⁷ Differing conjugative stabilization by CH- π orbital overlap does not directly influence stereoselectivity, and steric effects are generally not large enough to cause the several kilocalorie per mole (kcal mol^{-1}) energy difference seen between transition structures unless there is exceptional crowding.⁸⁸ Note that sterically stabilized enols are known,⁸⁹ including arylacetaldehydes.⁹⁰ Torsional strain involving vicinal bonds does contribute significantly to stereoselectivity in enolate formation.⁸⁸

The acid base catalyzed mechanisms are identical to those in Reaction 12-2.⁹¹

Acid catalyzed



Base catalyzed⁹²



For each catalyst, the mechanism for one direction is the exact reverse of the other, by the principle of *microscopic reversibility*.⁹³ As expected from mechanisms in which the C—H bond is broken in the rate-determining step, substrates of the type RCD_2COR show deuterium isotope effects (of ~ 5) in both the basic-⁹⁴ and the acid-⁹⁵-catalyzed processes. The keto-enol/enolate anion equilibrium has been studied in terms of the influence of β -oxygen⁹⁶ or β -nitrogen⁹⁷ substituents. The stereochemistry of enol protonation can be controlled by varying the proximal group and by changing the acidity of the medium.⁹⁸

⁸⁶ Briegleb, G.; Strohmeier, W. *Angew. Chem.* **1952**, 64, 409; Baddar, F. G.; Iskander, Z. *J. Chem. Soc.* **1954**, 203.

⁸⁷ Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc.* **1998**, 120, 2290.

⁸⁸ Behnam, S.M.; Behnam, S.E.; Ando, K.; Green, N.S.; Houk, K.N. *J. Org. Chem.* **2000**, 65, 8970.

⁸⁹ Miller, A.R. *J. Org. Chem.*, **1976**, 41, 3599.

⁹⁰ Fuson, R.C.; Tan, T.-L. *J. Am. Chem. Soc.* **1948**, 70, 602.

⁹¹ See Keeffe, J.R.; Kresge, A.J. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, **1990**, pp. 399–480; Toullec, J. *Adv. Phys. Org. Chem.* **1982**, 18, 1. Also see Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell Univ. Press, Ithaca, NY, **1973**, pp. 171–181; Shelly, K.P.; Venimadhavan, S.; Nagarajan, K.; Stewart, R. *Can. J. Chem.* **1989**, 67, 1274. Also see Pollack, R.M. *Tetrahedron* **1989**, 45, 4913.

⁹² Another mechanism for base-catalyzed enolization has been reported when the base is a tertiary amine: See Bruce, P.Y. *J. Am. Chem. Soc.* **1990**, 112, 7361 and references cited therein.

⁹³ For a proposed concerted mechanism, see Capon, B.; Siddhanta, A.K.; Zucco, C. *J. Org. Chem.* **1985**, 50, 3580. For evidence against it, see Chiang, Y.; Hojatti, M.; Keeffe, J.R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. **1987**, 109, 4000 and references cited therein.

⁹⁴ Xie, L.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* **1991**, 113, 3123.

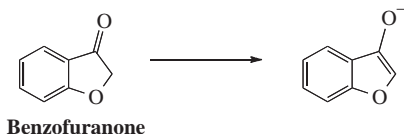
⁹⁵ Lienhard, G.E.; Wang, T. *J. Am. Chem. Soc.* **1969**, 91, 1146. See also, Toullec, J.; Dubois, J.E. *J. Am. Chem. Soc.* **1974**, 96, 3524.

⁹⁶ Chiang, Y.; Kresge, A.J.; Meng, Q.; More O'Ferrall, R.A.; Zhu, Y. *J. Am. Chem. Soc.* **2001**, 123, 11562.

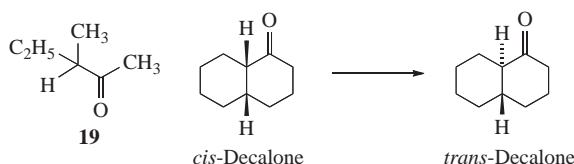
⁹⁷ Chiang, Y.; Griesbeck, A.G.; Heckroth, H.; Hellrung, B.; Kresge, A.J.; Meng, Q.; O'Donoghue, A.C.; Richard, J.P.; Wirz, J. *J. Am. Chem. Soc.* **2001**, 123, 8979.

⁹⁸ Zimmerman, H.E.; Cheng, J. *J. Org. Chem.* **2006**, 71, 873.

The base induced reaction generates an enolate anion rather than an enol, and the formation of and reactions of enolate anions are discussed further in Reactions **10-60**, **10-67**, **16-24**, and **16-34**. Note that ring strain plays no significant role on the rate of base-catalyzed enolization.⁹⁹ In certain cases (e.g., benzofuranones), base-induced enolate anion formation may give a transition state in which aromaticity can play a role. One study showed that aromatic stabilization of the transition state is ahead of proton transfer, and aromaticity appears to lower the intrinsic barrier to this reaction.¹⁰⁰ Enolizable hydrogen atoms can be replaced by deuterium (and ¹⁶O by ¹⁸O) by passage of a sample through a deuterated (or ¹⁸O containing) gas-chromatography column.¹⁰¹



Although the conversion of an aldehyde or a ketone to its enol tautomer is not generally a preparative procedure, the reactions do have their preparative aspects. When enol ethers or esters are hydrolyzed, the initially formed enols immediately tautomerize to the aldehydes or ketones. In addition, the overall processes (forward plus reverse reactions) are often used for equilibration purposes. When an optically active compound in which the chirality is due to a stereogenic carbon α to a carbonyl group (as in **19**) is treated with acid or base, racemization results.¹⁰² If there is another stereogenic center in the molecule, the less stable diastereomer can be converted to the more stable one in this manner. For example, *cis*-decalone can be equilibrated to the *trans* isomer. Isotopic exchange can similarly be accomplished at the α position of an aldehyde or ketone. In cyclic compounds, *cis*- to *trans*- isomerization can occur via the enol.¹⁰³ The role of additives (e.g., ZnCl_2) on the stereogenic enolization reactions using chiral cases has been discussed.¹⁰⁴



If a full equivalent of base per equivalent of ketone is used, the enolate ion (**18**) is formed and can be isolated¹⁰⁵ (see, e.g., the alkylation reaction in Reaction **10-68**).¹⁰⁶

⁹⁹ Cantlin, R.J.; Drake, J.; Nagorski, R.W. *Org. Lett.* **2002**, 4, 2433.

¹⁰⁰ Bernasconi, C.F.; Pérez-Lorenzo, M. *J. Am. Chem. Soc.* **2007**, 129, 2704.

¹⁰¹ Senn, M.; Richter, W.J.; Burlingame, A.L. *J. Am. Chem. Soc.* **1965**, 87, 680; Richter, W.J.; Senn, M.; Burlingame, A.L. *Tetrahedron Lett.* **1965**, 1235.

¹⁰² For an exception, see Guthrie, R.D.; Nicolas, E.C. *J. Am. Chem. Soc.* **1981**, 103, 4637.

¹⁰³ Dechoux, L.; Doris, E. *Tetrahedron Lett.* **1994**, 35, 2017.

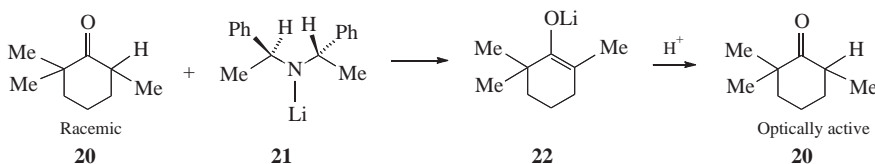
¹⁰⁴ Coggins, P.; Gaur, S.; Simpkins, N.S. *Tetrahedron Lett.* **1995**, 36, 1545.

¹⁰⁵ See Wen, J.Q.; Grutzner, J.B. *J. Org. Chem.* **1986**, 51, 4220.

¹⁰⁶ See d'Angelo, J. *Tetrahedron* **1976**, 32, 2979. Also see Fruchart, J.-S.; Lippens, G.; Kuhn, C.; Gran-Masse, H.; Melnyk, O. *J. Org. Chem.* **2002**, 67, 526.

Enantioselective enolate anion protonation reactions have been studied.¹⁰⁷ Enolate protonation is discussed in section Reaction 16-34. For the acid-catalyzed process, exchange or equilibration is accomplished only if the carbonyl compound is completely converted to the enol and then back, but in the base-catalyzed process exchange or equilibration can take place if only the first step (conversion to the enolate ion) takes place. The difference is usually academic. Aggregation behavior of stereoselective enolizations mediated by Mg and Ca bis(amides) have been studied.¹⁰⁸

In the case of the ketone (**20**), a racemic mixture was converted to an optically active mixture (optical yield 46%) by treatment with the chiral base (**21**).¹⁰⁹ This happened because **21** reacted with one enantiomer of **20** faster than with the other (an example of *kinetic resolution*). The enolate (**22**) must remain coordinated with the chiral amine, and it is the amine that reprotonate **22**, not an added proton donor.



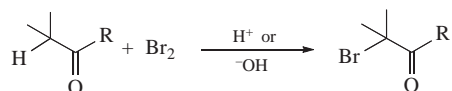
There are many enol–keto interconversions and acidification reactions of enolate ions to the keto forms listed in *Organic Syntheses*. No attempt is made to list them here.

B. Halogen Electrophiles

Halogenation of unactivated hydrocarbons is discussed in Reaction 14-1.

12-4 Halogenation of Aldehydes and Ketones

Halogenation or Halo-de-hydrogenation



Aldehydes and ketones can be halogenated in the α position with bromine, chlorine, or iodine,¹¹⁰ although the reaction is less successful with fluorine.¹¹¹ Sulfuryl chloride,¹¹² $Me_3SiCl-Me_2SO$,¹¹³ and NCS ¹¹⁴ have been used as reagents for chlorination.

¹⁰⁷ Vedejs, E.; Kruger, A.W.; Suna, E. *J. Org. Chem.* **1999**, 64, 7863.

¹⁰⁸ He, X.; Allan, J.F.; Noll, B.C.; Kennedy, A.R.; Henderson, K.W. *J. Am. Chem. Soc.* **2005**, 127, 6920.

¹⁰⁹ Eleveld, M.B.; Hogeveen, H. *Tetrahedron Lett.* **1986**, 27, 631. See also, Cain, C.M.; Cousins, R.P.C.; Coumbarides, G.; Simpkins, N.S. *Tetrahedron* **1990**, 46, 523.

¹¹⁰ See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 459–478; De Kimpe, N.; Verhé, R. *The Chemistry of α -Haloketones, α -Haloaldehydes, and α -Haloimines*, Wiley, NY, 1988. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp.709–719.

¹¹¹ See Rozen, S.; Filler, R. *Tetrahedron* **1985**, 41, 1111; German, L.; Zemskov, S. *New Fluorinating Agents in Organic Chemistry*; Springer, NY, **1989**.

¹¹² Tabushi, I.; Kitaguchi, H. in Pizey, J.S. *Synthetic Reagents*, Vol. 4; Wiley, NY, **1981**, pp. 336–396.

¹¹³ Fraser, R.R.; Kong, F. *Synth. Commun.* **1988**, 18, 1071.

¹¹⁴ See Mei, Y.; Bentley, P.A.; Du, J. *Tetrahedron Lett.* **2008**, 49, 3802. Also see Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron* **2008**, 64, 5191.

α -Chloroaldehydes are formed with Cl_2 and a catalytic amount of tetraethylammonium chloride.¹¹⁵ Bromination methods include NBS (see Reaction 14-3),¹¹⁶ Me_3SiBr —DMSO,¹¹⁷ tetrabutylammonium tribromide,¹¹⁸ *in situ* generated ZnBr_2 in water,¹¹⁹ and bromine•dioxane on silica with microwave irradiation.¹²⁰ α -Chlorination¹²¹ and also bromination¹²² have been reported in ionic liquids. Enantioselective chlorination¹²³ and bromination¹²⁴ methods are known, including methods that use enolate anions as intermediates.¹²⁵ Organocatalyzed asymmetric α -halogenation methods are known that can be applied to incorporation of virtually any halogen.¹²⁶ β -Keto esters and 1,3-diketones are α -brominated using bromodimethylsulfonium bromide.¹²⁷ 1,3-Diketones, β -ketoesters, and malonates are chlorinated using sodium hypochlorite or brominated using sodium hypobromite.¹²⁸

Iodination has been accomplished by the direct reaction of ketones with molecular iodine,¹²⁹ with I_2 -cerium(IV) ammonium nitrate,¹³⁰ NCS/NaI ,¹³¹ $\text{ICl}/\text{NaI}/\text{FeCl}_3$,¹³² and with iodine using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) in methanol.¹³³ Methyl ketones react with NIS and tosic acid with microwave irradiation without solvent to give the α -iodoketone.¹³⁴ An asymmetric iodination of aldehydes used NIS, with a catalytic amount of benzoic acid and a chiral biaryl amine.¹³⁵

Although less prevalent than those noted above, several methods have been reported for the preparation of α -fluoro aldehydes and ketones,¹³⁶ including enantioselective fluorination protocols.¹³⁷ Organocatalytic α -fluorination is known for aldehydes and ketones.¹³⁸

¹¹⁵ Bellesia, F.; DeBuyck, L.; Ghelfi, F.; Pagnoni, U.M.; Parson, A.F.; Pinetti, A. *Synthesis* **2003**, 2173.

¹¹⁶ Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun.* **2004**, 470. See Guha, S.K.; Wu, B.; Kim, B.S.; Baik, W.; Koo, S. *Tetrahedron Lett.* **2006**, 47, 291; Arbu, S.S.; Waghmode, S.B.; Ramaswamy, A.V. *Tetrahedron Lett.* **2007**, 48, 1411. See also Sreedhar, B.; Reddy, P.S.; Madhavi, M. *Synth. Commun.* **2007**, 37, 4149.

¹¹⁷ Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U.M. *J. Chem. Res. (S)* **1986**, 428.

¹¹⁸ Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Fujisaki, S. *Bull. Chem. Soc. Jpn.* **1987**, 60, 1159.

¹¹⁹ Juneja, S.K.; Choudhary, D.; Paul, S.; Gupta, R. *Synth. Commun.* **2006**, 36, 2877.

¹²⁰ Paul, S.; Gupta, V.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2003**, 44, 439.

¹²¹ Lee, J.C.; Park, H.J. *Synth. Commun.* **2006**, 36, 777.

¹²² Pingali, S.R.K.; Madhav, M.; Jursic, B.S. *Tetrahedron Lett.* **2010**, 51, 1383.

¹²³ Brochu, M.P.; Brown, S.P.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2004**, 126, 4108; Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jorgensen, K.A. *J. Am. Chem. Soc.* **2004**, 126, 4790. See Wang, L.; Cai, C.; Curran, D. P.; Zhang, W. *Synlett* **2010**, 433.

¹²⁴ See Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K.A. *Chem. Commun.* **2005**, 4821.

¹²⁵ See France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475.

¹²⁶ See Ueda, M.; Kano, T.; Maruoka, K. *Org. Biomol. Chem.* **2009**, 7, 2005.

¹²⁷ Khan, A.T.; Ali, Md.A.; Goswami, P.; Choudhury, L.H. *J. Org. Chem.* **2006**, 71, 8961.

¹²⁸ Meketa, M.L.; Mahajan, Y.R.; Weinreb, S.M. *Tetrahedron Lett.* **2005**, 46, 4749.

¹²⁹ Rao, M.L.N.; Jadhav, D.N. *Tetrahedron Lett.* **2006**, 47, 6883. Also see Yadav, J.S.; Kondaji, G.; Reddy, M.S.R.; Srihari, P. *Tetrahedron Lett.* **2008**, 49, 3810.

¹³⁰ Horiuchi, C.A.; Kiji, S. *Bull. Chem. Soc. Jpn.* **1997**, 70, 421. For another reagent, see Sket, B.; Zupet, P.; Zupan, M.; Dolenc, D. *Bull. Chem. Soc. Jpn.* **1989**, 62, 3406.

¹³¹ Yamamoto, T.; Toyota, K.; Morita, N. *Tetrahedron Lett.* **2010**, 51, 1364.

¹³² Mohanakrishnan, A.K.; Prakash, C.; Ramesh, N. *Tetrahedron* **2006**, 62, 3242.

¹³³ Jerreb, M.; Stavber, S.; Zupan, M. *Tetrahedron* **2003**, 59, 5935.

¹³⁴ Lee, J.C.; Bae, Y.H. *Synlett* **2003**, 507.

¹³⁵ Kano, T.; Ueda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, 130, 3728.

¹³⁶ Davis, F.A.; Kasu, P.V.N. *Org. Prep. Proceed. Int.* **1999**, 31, 125.

¹³⁷ See Pihko, P.M. *Angew. Chem. Int. Ed.* **2006**, 45, 544.

¹³⁸ Enders, D.; Hüttl, M.R.M. *Synlett* **2005**, 991.

Selectfluor, [F–TEDA–BF₄. 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] has been used for the monofluorination of ketones,¹³⁹ as has a mixture of KI–KIO₃–H₂SO₄.¹⁴⁰ Active compounds (e.g., β -keto esters and β -diketones) have been fluorinated with an *N*-fluoro-*N*-alkylsulfonamide¹⁴¹ (this can result in enantioselective fluorination, if an optically active *N*-fluorosulfonamide is used¹⁴²), with F₂/N₂–HCO₂H,¹⁴³ and with NF₃O/Bu₄NOH.¹⁴⁴ Acetyl hypofluorite fluorinates simple ketones in the form of their lithium enolate anions.¹⁴⁵ Aldehydes have been α -fluorinated using *N*-fluorobenzenesulfonimide as an electrophilic source of fluorine and an imidazolidinone as an organocatalyst.¹⁴⁶ The enantioselective α -fluorination of oxindoles has been reported using *N*-fluorobenzenesulfonimide, a Pd catalyst, and a chiral ligand,¹⁴⁷ and also with an organocatalyst.¹⁴⁸

For unsymmetrical ketones, the preferred position of halogenation is usually the more substituted: a CH group, then a CH₂ group, and then CH₃.¹⁴⁹ However, mixtures are frequent. With aldehydes the aldehydic hydrogen is sometimes replaced, but only when there is no α -hydrogen and the reaction is generally not very useful (see Reaction 14-4). It is also possible to prepare di- and polyhalides. When basic catalysts are used, one α position of a ketone is completely halogenated before the other is attacked, and the reaction cannot be stopped until all the hydrogen atoms of the first carbon have been replaced (see below). If one of the groups is methyl, the haloform reaction (12-44) takes place. With acid catalysts, it is usually possible to stop the reaction after only one halogen has been incorporated, although a second halogen can be introduced by the use of excess reagent. In chlorination, the second halogen generally appears on the same side as the first,¹⁵⁰ while in bromination the α,α' -dibromo product is found.¹⁵¹ Actually, with both halogens it is the α,α -dihalo ketone that is formed first, but in the case of bromination this compound isomerizes under the reaction conditions to the α,α' -isomer.¹⁵⁰ α,α' -Dichloro ketones are formed by reaction of a methyl ketone with an excess of CuCl₂ and LiCl in DMF¹⁵² or with HCl and H₂O₂ in methanol.¹⁵³ Aryl methyl ketones can be dibrominated in high yields with benzyltrimethylammonium tribromide.¹⁵⁴ Active methylene compounds are chlorinated

¹³⁹ See Loghmani-Khouzani, H.; Poorheravi, M.R.; Sadeghi, M.M.M.; Caggiano, L.; Jackson, R.F.W. *Tetrahedron* **2008**, *64*, 7419.

¹⁴⁰ Okamoto, T.; Kakinami, T.; Nishimura, T.; Hermawan, I.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1731.

¹⁴¹ Barnette, W.E. *J. Am. Chem. Soc.* **1984**, *106*, 452; Ma, J.-A. For an example with asymmetric induction, see Cahard, D. *Tetrahedron Asymmetry* **2004**, *15*, 1007.

¹⁴² Differding, E.; Lang, R.W. *Tetrahedron* **1988**, *29*, 6087.

¹⁴³ Chambers, R.D.; Greenhall, M.P.; Hutchinson, J. *J. Chem. Soc. Chem. Commun.* **1995**, 21.

¹⁴⁴ Gupta, O.D.; Shreeve, J.M. *Tetrahedron Lett.* **2003**, *44*, 2799.

¹⁴⁵ Rozen, S.; Brand, M. *Synthesis* **1985**, 665. For another reagent, see Davis, F.A.; Han, W. *Tetrahedron Lett.* **1991**, *32*, 1631.

¹⁴⁶ Beeson, T.D.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.

¹⁴⁷ Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164.

¹⁴⁸ Steiner, D.D.; Mase, N.; Barbas III, C.F. *Angew. Chem. Int. Ed.* **2005**, *44*, 3706.

¹⁴⁹ For chlorination this is reversed if the solvent is methanol: Gallucci, R.R.; Going, R. *J. Org. Chem.* **1981**, *46*, 2532.

¹⁵⁰ Rappe, C. *Ark. Kemi* **1965**, *24*, 321. But see also, Teo, K.E.; Warnhoff, E.W. *J. Am. Chem. Soc.* **1973**, *95*, 2728.

¹⁵¹ Garbisch Jr., E.W. *J. Org. Chem.* **1965**, *30*, 2109.

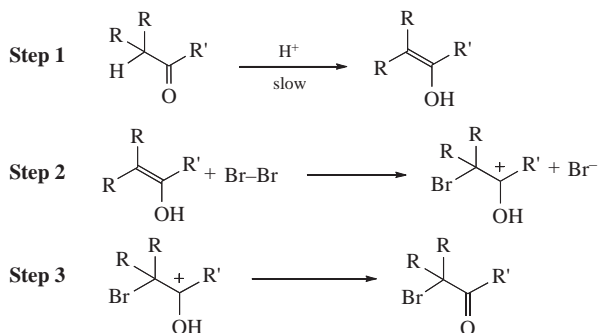
¹⁵² Nobrega, J.A.; Goncalves, S.M.C.; Reppe, C. *Synth. Commun.* **2002**, *32*, 3711.

¹⁵³ Terent'ev, A.O.; Khodykin, S.V.; Troitskii, N.A.; Ogibin, Y.N.; Nikishin, G.I. *Synthesis* **2004**, 2845.

¹⁵⁴ Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2667.

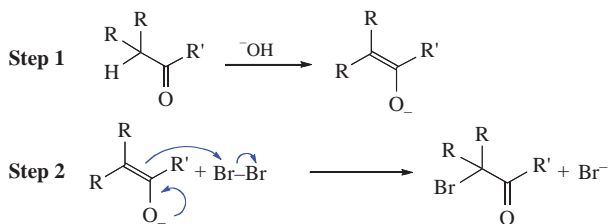
with NCS and $\text{Mg}(\text{ClO}_4)_2$.¹⁵⁵ Similar chlorination in the presence of a chiral copper catalyst led to α -chlorination with modest enantioselectivity.¹⁵⁶

It is not the aldehyde or ketone itself that is halogenated, but the corresponding enol or enolate ion. The purpose of the catalyst is to provide a small amount of enol or enolate (Reaction 12-3). The reaction is often done without addition of acid or base, but traces of acid or base are always present, and these are enough to catalyze formation of the enol or enolate. With acid catalysis the mechanism is



The first step, as seen in Reaction 12-3, actually consists of two steps. The second step is very similar to the first step in electrophilic addition to double bonds (Sec. 15.A.i). There is a great deal of evidence for this mechanism: (1) the rate is first order in substrate; (2) bromine does not appear in the rate expression at all,¹⁵⁷ a fact consistent with a rate-determining first step;¹⁵⁸ (3) the reaction rate is the same for bromination, chlorination, and iodination under the same conditions;¹⁵⁹ (4) the reaction shows an isotope effect; and (5) the rate of the step 2–step 3 sequence has been independently measured (by starting with the enol) and found to be very fast.¹⁶⁰

With basic catalysts the mechanism may be the same as that given above (since bases also catalyze formation of the enol), or the reaction may go directly through the enolate ion without formation of the enol:



It is difficult to distinguish the two possibilities. It was mentioned above that in the base-catalyzed reaction, if the substrate has two or three α halogens on the same side of

¹⁵⁵ Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* **2002**, 67, 7429.

¹⁵⁶ Marigo, M.; Kumaragurubaran, N.; Jørgensen, K.A. *Chem. Eur. J.* **2004**, 10, 2133.

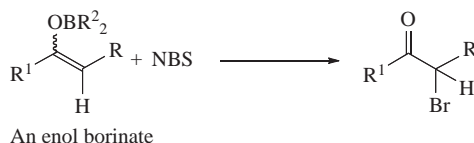
¹⁵⁷ See Tapuhi, E.; Jencks, W.P. *J. Am. Chem. Soc.* **1982**, 104, 5758. Also see Pinkus, A.G.; Gopalan, R. *J. Am. Chem. Soc.* **1984**, 106, 2630; Pinkus, A.G.; Gopalan, R. *Tetrahedron* **1986**, 42, 3411.

¹⁵⁸ See, however, Deno, N.C.; Fishbein, R. *J. Am. Chem. Soc.* **1973**, 95, 7445.

¹⁵⁹ Bell, R.P.; Yates, K. *J. Chem. Soc.* **1962**, 1927.

¹⁶⁰ Hochstrasser, R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. *J. Am. Chem. Soc.* **1988**, 110, 7875.

the C=O group, it is not possible to stop the reaction after just one halogen atom has entered. The reason is that the electron-withdrawing field effect of the first halogen increases the acidity of the remaining hydrogen atoms; that is, a CHX group is more acidic than a CH₂ group, so that the initially formed halo ketone is converted to enolate ion (and hence halogenated) more rapidly than the original substrate. Other halogenating agents can be used in this reaction.



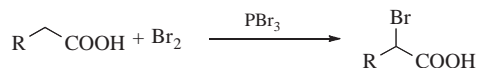
Regioselectivity in the halogenation of unsymmetrical ketones can be attained by treatment of the appropriate enol borinate of the ketone with NBS or NCS.¹⁶¹ The desired halo ketone is formed in high yield. The appropriate lithium enolate can be brominated at a low temperature¹⁶² (see Reaction 10-68, category 4 for the regioselective formation of enolate ions). α -Halo aldehydes have been prepared in good yield by treatment of silyl enol ethers (R₂C=CHOSiMe₃) with Br₂ or Cl₂,¹⁶³ with sulfonyl chloride (SO₂Cl₂),¹⁶⁴ or with I₂ and silver acetate.¹⁶⁵ Silyl enol ethers generate α -chloroketones with good enantioselectivity using ZrCl₄ in conjunction with an α,α -dichloromalonate ester.¹⁶⁶ Silyl enol ethers can also be fluorinated, with XeF₂¹⁶⁷ or with 5% F₂ in N₂ at -78 °C in FCCL₃.¹⁶⁸ Enol acetates have been regioselectively iodinated with I₂ and either Th(I) acetate¹⁶⁹ or Cu(II) acetate.¹⁷⁰

α,β -Unsaturated ketones can be converted to α -halo- α,β -unsaturated ketones by treatment with phenylselenium bromide or chloride,¹⁷¹ and to α -halo- β,γ -unsaturated ketones by two-phase treatment with HOCl.¹⁷² Conjugated ketones were converted to the α -bromo conjugated ketone (a vinyl bromide) using the *Dess-Martin periodinane* (see Reaction 19-3, category 5) and tetraethylammonium bromide.¹⁷³

OS I, 127; II, 87, 88, 244, 480; III, 188, 343, 538; IV, 110, 162, 590; V, 514; VI, 175, 193, 368, 401, 512, 520, 711, 991; VII, 271; VIII, 286. See also, OS VI, 1033; VIII, 192.

12-5 Halogenation of Carboxylic Acids and Acyl Halides

Halogenation or Halo-de-hydrogenation



¹⁶¹ Hooz, J.; Bridson, J.N. *Can. J. Chem.* **1972**, 50, 2387.

¹⁶² Stotter, P.L.; Hill, K.A. *J. Org. Chem.* **1973**, 38, 2576.

¹⁶³ Blanco, L.; Amice, P.; Conia, J.M. *Synthesis* **1976**, 194.

¹⁶⁴ Olah, G.A.; Ohannesian, L.; Arvanaghi, M.; Prakash, G.K.S. *J. Org. Chem.* **1984**, 49, 2032.

¹⁶⁵ Rubottom, G.M.; Mott, R.C. *J. Org. Chem.* **1979**, 44, 1731.

¹⁶⁶ Zhang, Y.; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, 126, 15038.

¹⁶⁷ Tsushima, T.; Kawada, K.; Tsuji, T. *Tetrahedron Lett.* **1982**, 23, 1165.

¹⁶⁸ Purrington, S.T.; Bumgardner, C.L.; Lazaridis, N.V.; Singh, P. *J. Org. Chem.* **1987**, 52, 4307.

¹⁶⁹ Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* **1978**, 126.

¹⁷⁰ Horiuchi, C.A.; Satoh, J.Y. *Synthesis* **1981**, 312.

¹⁷¹ Ley, S.V.; Whittle, A.J. *Tetrahedron Lett.* **1981**, 22, 3301.

¹⁷² Hegde, S.G.; Wolinsky, J. *Tetrahedron Lett.* **1981**, 22, 5019.

¹⁷³ Fache, F.; Piva, O. *Synlett* **2002**, 2035.

The α hydrogen atoms of carboxylic acids are replaced by bromine or chlorine using a phosphorus halide as catalyst.¹⁷⁴ The reaction, known as the *Hell–Volhard–Zelinskii reaction*, is not applicable to iodine or fluorine. When there are two α hydrogen atoms, one or both may be replaced, although it is often hard to stop with just one. The reaction actually takes place on the acyl halide formed initially from the carboxylic acid and the halogenating reagent. This means that each molecule of acid is α halogenated while it is in the acyl halide stage. The acids alone are inactive, except for those with relatively high enol content (e.g., malonic acid). Less than one full molar equivalent of catalyst (per molar equivalent of substrate) is required, because of the exchange reaction between carboxylic acids and acyl halides (see Reaction 16-79). The halogen from the catalyst is *not* transferred to the α position. For example, the use of Cl_2 and PBr_3 results in α -chlorination, not bromination. As expected from the foregoing, acyl halides undergo a halogenation without a catalyst. An enantioselective α -halogenation was reported to give chiral α -haloesters via an alkaloid-catalyzed reaction of acyl halides with perhaloquinone-derived reagents.¹⁷⁵ So do anhydrides and many compounds that enolize easily (e.g., malonic ester and aliphatic nitro compounds). The mechanism is usually regarded as proceeding through the enol as in Reaction 12-4.¹⁷⁶ If chlorosulfuric acid (ClSO_2OH) is used as a catalyst, carboxylic acids can be α -iodinated,¹⁷⁷ as well as chlorinated or brominated.¹⁷⁸ *N*-Bromosuccinimide in a mixture of sulfuric acid–trifluoroacetic acid can monobrominate simple carboxylic acids.¹⁷⁹

A number of other methods exist for the α halogenation of carboxylic acids or their derivatives.¹⁸⁰ Under electrolytic conditions with NaCl , malonates are converted to 2-chloro malonates.¹⁸¹ Acyl halides can be α brominated or chlorinated by use of NBS or NCS and HBr or HCl .¹⁸² The latter is an ionic, not a free radical halogenation (see Reaction 14-3). Direct iodination of carboxylic acids has been achieved with I_2 – Cu(II) acetate in HOAc .¹⁸³ Acyl chlorides can be α iodinated with I_2 and a trace of HI .¹⁸⁴ Carboxylic acids, esters, and amides have been α -fluorinated at -78°C with F_2 diluted in N_2 .¹⁸⁵ Amides have been α -iodinated using iodine and *s*-collidine.¹⁸⁶

OS I, 115, 245; II, 74, 93; III, 347, 381, 495, 523, 623, 705, 848; IV, 254, 348, 398, 608, 616; V, 255; VI, 90, 190, 403; IX, 526. Also see, OS IV, 877; VI, 427.

¹⁷⁴ See Harwood, H.J. *Chem. Rev.* **1962**, 62, 99, pp. 102-103.

¹⁷⁵ Wack, H.; Taggi, A.E.; Hafez, A.M.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* **2001**, 123, 1531. See also, France, S.; Wack, H.; Taggi, A.E.; Hafez, A.M.; Wagerle, Ty.R.; Shah, M.H.; Dusich, C.L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, 126, 4245.

¹⁷⁶ See, however, Kwart, H.; Scalzi, F.V. *J. Am. Chem. Soc.* **1964**, 86, 5496.

¹⁷⁷ Ogata, Y.; Watanabe, S. *J. Org. Chem.* **1979**, 44, 2768; **1980**, 45, 2831.

¹⁷⁸ Ogata, Y.; Adachi, K. *J. Org. Chem.* **1982**, 47, 1182.

¹⁷⁹ Zhang, L.H.; Duan, J.; Xu, Y.; Dolbier, Jr., W.R. *Tetrahedron Lett.* **1998**, 39, 9621.

¹⁸⁰ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 730–738.

¹⁸¹ Okimoto, M.; Takahashi, Y. *Synthesis* **2002**, 2215.

¹⁸² Harpp, D.N.; Bao, L.Q.; Black, C.J.; Gleason, J.G.; Smith, R.A. *J. Org. Chem.* **1975**, 40, 3420.

¹⁸³ Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* **1984**, 1509.

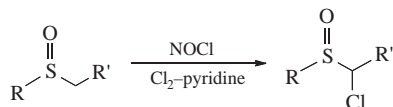
¹⁸⁴ Rathke, M.W.; Lindert, A. *Tetrahedron Lett.* **1971**, 3995.

¹⁸⁵ Purrington, S.T.; Woodard, D.L. *J. Org. Chem.* **1990**, 55, 3423.

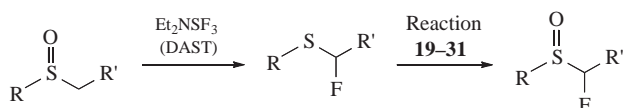
¹⁸⁶ Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, 33, 1299.

12-6 Halogenation of Sulfoxides and Sulfones

Halogenation or Halo-de-hydrogenation



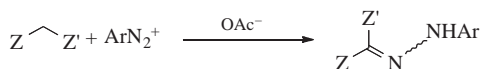
Sulfoxides can be chlorinated in the α position¹⁸⁷ by treatment with Cl_2 ¹⁸⁸ or NCS ,¹⁸⁹ in the presence of pyridine. These methods involve basic conditions. The reaction can also be accomplished in the absence of base with SO_2Cl_2 in CH_2Cl_2 ,¹⁹⁰ or with TsNCl_2 .¹⁹¹ The bromination of sulfoxides with bromine¹⁹² and with NBS -bromine¹⁹³ have also been reported. Sulfones have been chlorinated by treatment of their conjugate bases ($\text{RSO}_2\text{C}^-\text{HR}'$) with various reagents, among them SO_2Cl_2 , CCl_4 ,¹⁹⁴ or NCS .¹⁹⁵ The α -fluorination of sulfoxides was reported via treatment with diethylaminosulfur trifluoride (Et_2NSF_3 , DAST) to give an α -fluoro thioether, usually in high yield. Oxidation of this compound with *m*-chloroperoxybenzoic acid gave the sulfoxide.¹⁹⁶



C. Nitrogen Electrophiles

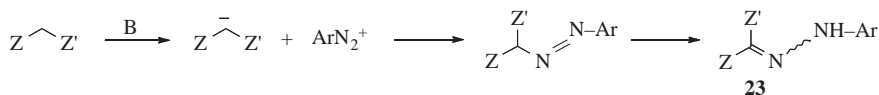
12-7 Aliphatic Diazonium Coupling

Arylhydrazono-de-dihydro-bisubstitution



If a $\text{C}-\text{H}$ unit is acidic enough, that carbon couples with diazonium salts in the presence of a base (via the enolate anion), most often aq sodium acetate.¹⁹⁷ The reaction is commonly carried out on compounds of the form $\text{Z}-\text{CH}_2-\text{Z}'$, where Z and Z' are as defined in Section 16-38 (e.g., β -keto esters, β -keto amides, malonic ester).

The mechanism is probably of the simple $\text{S}_{\text{E}}1$ type:



¹⁸⁷ For a review, see Venier, C.G.; Barager, III, H.J. *Org. Prep. Proced. Int.* **1974**, 6, 77, pp. 81–84.

¹⁸⁸ Tsuchihashi, G.; Iriuchijima, S. *Bull. Chem. Soc. Jpn.* **1970**, 43, 2271.

¹⁸⁹ Ogura, K.; Imaizumi, J.; Iida, H.; Tsuchihashi, G. *Chem. Lett.* **1980**, 1587.

¹⁹⁰ Tin, K.; Durst, T. *Tetrahedron Lett.* **1970**, 4643.

¹⁹¹ Kim, Y.H.; Lim, S.C.; Kim, H.R.; Yoon, D.C. *Chem. Lett.* **1990**, 79.

¹⁹² Cinquini, M.; Colonna, S. *J. Chem. Soc. Perkin Trans. I* **1972**, 1883. See also, Cinquini, M.; Colonna, S. *Synthesis* **1972**, 259.

¹⁹³ Iriuchijima, S.; Tsuchihashi, G. *Synthesis* **1970**, 588.

¹⁹⁴ Regis, R.R.; Dowsyko, A.M. *Tetrahedron Lett.* **1982**, 23, 2539.

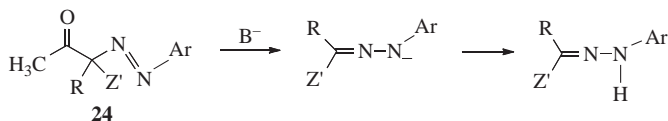
¹⁹⁵ Paquette, L.A.; Houser, R.W. *J. Org. Chem.* **1971**, 36, 1015.

¹⁹⁶ McCarthy, J.R.; Pee, N.P.; LeTourneau, M.E.; Inbasekaran, M. *J. Am. Chem. Soc.* **1985**, 107, 735. See also, Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* **1986**, 59, 3625.

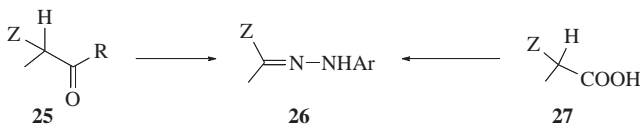
¹⁹⁷ See Parmeter, S.M. *Org. React.* **1959**, 10, 1.

Aliphatic azo compounds in which the carbon containing the azo group is attached to a hydrogen are unstable and tautomerize to the isomeric hydrazones (**23**), which are the products of the reaction.

When the reaction is carried out on a compound of the form $Z-CHR-Z'$, the azo compound does not have a hydrogen that can lead to tautomerism, and at least one Z is acyl or carboxyl, this group usually cleaves:



so the product in this case is also the hydrazone, and not the azo compound. In fact, compounds of the type **24** are seldom isolable from the reaction, although this has been accomplished.¹⁹⁸ The cleavage step shown is an example of Reaction **12-43** and, when a carboxyl group cleaves, of Reaction **12-40**. The overall process in this case is called the *Japp-Klingemann reaction*¹⁹⁹ and involves conversion of a ketone (**25**) or a carboxylic acid (**26**)

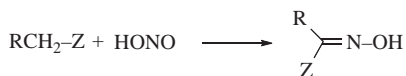


to a hydrazone (**27**). When an acyl and a carboxyl group are both present, the leaving group order has been reported to be $\text{MeCO} > \text{COOH} > \text{PhCO}$.²⁰⁰ When there is no acyl or carboxyl group present, the aliphatic azo compound is stable.

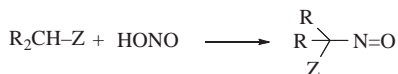
OS **III**, 660; **IV**, 633.

12-8 Nitrosation at a Carbon Bearing an Active Hydrogen

Hydroxyimino-de-dihydro-bisubstitution



Nitrosation or Nitroso-de-hydrogenation



Carbons adjacent to a Z group (as defined in Reaction **10-67**) can be nitrosated with nitrous acid or alkyl nitrites.²⁰¹ The initial product is the C-nitroso compound, but these are stable only when there is no hydrogen that can undergo tautomerism. When there is, the product is the more stable oxime. The situation is analogous to that with azo compounds

¹⁹⁸ See Yao, H.C.; Resnick, P. *J. Am. Chem. Soc.* **1962**, *84*, 3514.

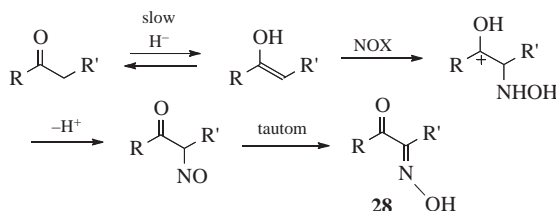
¹⁹⁹ For a review, see Phillips, R.R. *Org. React.* **1959**, *10*, 143.

²⁰⁰ Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *J. Org. Chem. USSR* **1989**, *25*, 2011. This paper also includes a sequence of leaving group ability for other Z groups.

²⁰¹ For a review, see Williams, D.L.H. *Nitrosation*, Cambridge Univ. Press, Cambridge, **1988**, pp. 1–45.

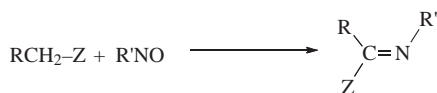
and hydrazones (Reaction 12-7). The mechanism is similar to that in Reaction 12-7:²⁰² $R-H \rightarrow R^- + {}^+N=O \rightarrow R-N=O$. The reactive species is either NO^+ or a carrier of it. When the substrate is a simple ketone, the mechanism goes through the enol (as in halogenation Reaction 12-4):

Evidence is that the reaction, in the presence of X^- (Br^- , Cl^- , or SCN^-) was first order in ketone and in H^+ , but zero order in HNO_2 and X^- .²⁰³ Furthermore, the rate of the nitrosation was about the same as that for enolization of the same ketones. The species NOX is formed by $HONO + X^- + H^+ \rightarrow HOX + H_2O$. In the cases of $F_3CCOCH_2COCF_3$ and malononitrile, the nitrosation went entirely through the enolate ion rather than the enol.²⁰⁴



As in the *Japp-Klingemann reaction*, when Z is an acyl or carboxyl group (in the case of R_2CH-Z), it can be cleaved. Since oximes and nitroso compounds can be reduced to primary amines, this reaction often provides a route to amino acids. As in the case of Reaction 12-4, the silyl enol ether of a ketone can be used instead of the ketone itself.²⁰⁵ Good yields of α -oximinoketones (**28**) can be obtained by treating ketones with *tert*-butyl thionitrate.²⁰⁶

Imines can be prepared in a similar manner by treatment of an active hydrogen compound with a nitroso compound:

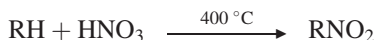


Alkanes can be nitrosated photochemically, by treatment with $NOCl$ and UV light.²⁰⁷ For nitration at an activated carbon, see Reaction 12-9. Trialkyltin enol ethers ($C=C-O-SnR_3$) react with $PhNO$ to give α -(*N*-hydroxylamino)ketones.²⁰⁸

OS II, 202, 204, 223, 363; III, 191, 513; V, 32, 373; VI, 199, 840. Also see, OS V, 650.

12-9 Nitration of Alkanes

Nitration or Nitro-de-hydrogenation



²⁰² For a review, see Williams, D.L.H. *Adv. Phys. Org. Chem.* **1983**, 19, 381. See also, Williams, D.L.H. *Nitrosation*, Cambridge Univ. Press, Cambridge, **1988**.

²⁰³ Leis, J.R.; Peña, M.E.; Williams, D.L.H.; Mawson, S.D. *J. Chem. Soc. Perkin Trans. 2* **1988**, 157.

²⁰⁴ Iglesias, E.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* **1989**, 343; Crookes, M.J.; Roy, P.; Williams, D.L. *H. J. Chem. Soc. Perkin Trans. 2* **1989**, 1015. See also, Graham, A.; Williams, D.L.H. *J. Chem. Soc. Chem. Commun.* **1991**, 407.

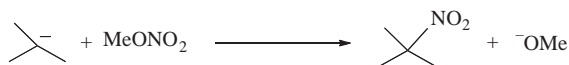
²⁰⁵ Rasmussen, J.K.; Hassner, A. *J. Org. Chem.* **1974**, 39, 2558.

²⁰⁶ Kim, Y.H.; Park, Y.J.; Kim, K. *Tetrahedron Lett.* **1989**, 30, 2833.

²⁰⁷ See Pape, M. *Fortschr. Chem. Forsch.* **1967**, 7, 559.

²⁰⁸ Momiyama, N.; Yamamoto, H. *Org. Lett.* **2002**, 4, 3579.

Nitration of alkanes²⁰⁹ can be carried out in the gas phase at $\sim 400^\circ\text{C}$ or in the liquid phase. The reaction is not practical for the production of pure products for any alkane except methane. For other alkanes, not only does the reaction produce mixtures of the mono-, di-, and polynitrated alkanes at every combination of positions, but extensive chain cleavage occurs.²¹⁰ A free radical mechanism is involved.²¹¹



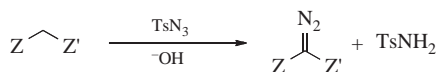
Activated positions (e.g., $\text{ZCH}_2\text{Z}'$ compounds) can be nitrated by fuming nitric acid in acetic acid, by acetyl nitrate and an acid catalyst,²¹² or by alkyl nitrates under alkaline conditions.²¹³ In the latter case, it is the carbanionic form of the substrate that is actually nitrated. The conjugate base of the nitro compound is isolated under these alkaline conditions, but yields are not high. Of course, the mechanism in this case is not of the free radical type, but is electrophilic substitution with respect to the carbon (similar to the mechanisms of Reactions 12-7 and 12-8). Positions activated by only one electron-withdrawing group (e.g., α positions of simple ketones, nitriles, sulfones, or *N,N*-dialkyl amides) can be nitrated with alkyl nitrates if a very strong base (e.g., *t*-BuOK or NaNH_2) is present to convert the substrate to the carbanionic form.²¹⁴

Electrophilic nitration of alkanes has been performed with nitronium salts (e.g., $\text{NO}_2^+ \text{PF}_6^-$ and with $\text{HNO}_3\text{--H}_2\text{SO}_4$ mixtures), but mixtures of nitration and cleavage products are obtained and yields are generally low.²¹⁵ The reaction of alkanes with nitric acid and *N*-hydroxysuccinimide (NHS), however, gave moderate-to-good yields of the corresponding nitroalkane.²¹⁶ Similar nitration was accomplished with NO_2 , NHS and air.²¹⁷ Aliphatic nitro compounds can be nitrated [$\text{R}_2\text{C--NO}_2 \rightarrow \text{R}_2\text{C(NO}_2)_2$] by treatment of their conjugate bases RCNO_2 with NO_2^- and $\text{K}_3\text{Fe(CN)}_6$.²¹⁸

OS I, 390; II, 440, 512.

12-10 Direct Formation of Diazo Compounds

Diazo-de-dihydro-bisubstitution



²⁰⁹ See Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration*, VCH, NY, **1989**, pp. 219–295; Ogata, Y. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, part C, Academic Press, NY, **1978**, pp. 295–342; Ballod, A.P.; Shtern, V.Ya. *Russ. Chem. Rev.* **1976**, *45*, 721.

²¹⁰ See Matasa, C.; Hass, H.B. *Can. J. Chem.* **1971**, *49*, 1284.

²¹¹ Titov, A.I. *Tetrahedron* **1963**, *19*, 557.

²¹² Sifniades, S. *J. Org. Chem.* **1975**, *40*, 3562.

²¹³ See Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, **1969**, pp. 310–316.

²¹⁴ See Feuer, H.; Van Buren, II, W.D.; Grutzner, J.B. *J. Org. Chem.* **1978**, *43*, 4676.

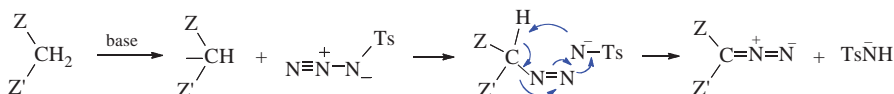
²¹⁵ Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* **1973**, *93*, 1259. See also, Bach, R.D.; Holubka, J.W.; Badger, R.C.; Rajan, S. *J. Am. Chem. Soc.* **1979**, *101*, 4416.

²¹⁶ Isozaki, S.; Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2001**, 1352.

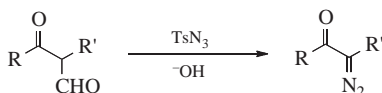
²¹⁷ Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 5663.

²¹⁸ Garver, L.C.; Grakauskas, V.; Baum, K. *J. Org. Chem.* **1985**, *50*, 1699.

Compounds containing a CH_2 bonded to two Z groups (active methylene compounds, with Z as defined in Reaction 10-67) can be converted to diazo compounds on treatment with tosyl azide in the presence of a base.²¹⁹ The use of phase-transfer catalysis increases the convenience of the method.²²⁰ Sulfonyl azides also give the reaction.²²¹ The *diazo-transfer reaction* can also be applied to other reactive positions (e.g., the 5 position of cyclopentadiene).²²² The mechanism is probably as follows:



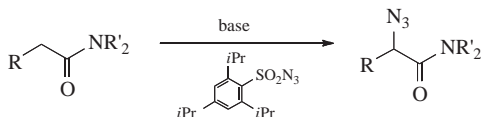
A diazo group can be introduced adjacent to a single carbonyl group indirectly by first converting the ketone to an α -formyl ketone (Reaction 16-85) and then treating it with tosyl azide. As in the similar cases of Reactions 12-7 and 12-8, the formyl group is cleaved during the reaction.²²³



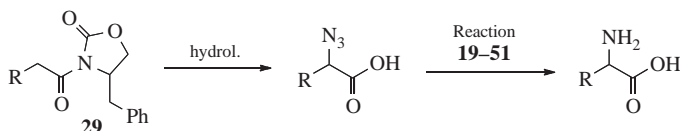
OS V, 179; VI, 389, 414.

12-11 Conversion of Amides to α -Azido Amides

Azidation or Azido-de-hydrogenation



In Reaction 12-10, treatment of $\text{Z}-\text{CH}_2-\text{Z}'$ with tosyl azide gave the α -diazo compound via diazo transfer. When this reaction is performed on a compound with a single Z group (e.g., an amide), formation of the azide becomes a competing process via the enolate anion.²²⁴ Factors favoring azide formation rather than diazo transfer include K^+ as the enolate counterion rather than Na^+ or Li^+ and the use of 2,4,6-triisopropylbenzenesulfonyl azide rather than TsN_3 . When the reaction was applied to amides with a chiral R' (e.g., the oxazolidinone derivative 29), it was highly stereoselective, and the product could be converted to an optically active amino acid.²²⁴



²¹⁹ See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, **1986**, pp. 326–435; Regitz, M. *Synthesis* **1972**, 351. See also, Koskinen, A.M.P.; Muñoz, L. *J. Chem. Soc. Chem. Commun.* **1990**, 652.

²²⁰ Ledon, H. *Synthesis* **1974**, 347, *Org. Synth.* **VI**, 414; Also see Ghosh, S.; Datta, I. *Synth. Commun.* **1991**, 21, 191.

²²¹ Taber, D.F.; Ruckle, Jr., R.E.; Hennessy, M.J. *J. Org. Chem.* **1986**, 51, 4077; Baum, J.S.; Shook, D.A.; Davies, H.M.L.; Smith, H.D. *Synth. Commun.* **1987**, 17, 1709.

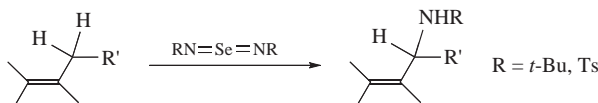
²²² Doering, W. von E.; DePuy, C.H. *J. Am. Chem. Soc.* **1953**, 75, 5955.

²²³ See also Danheiser, R.L.; Miller, R.F.; Brisbois, R.G.; Park, S.Z. *J. Org. Chem.* **1990**, 55, 1959.

²²⁴ Evans, D.A.; Britton, T.C. *J. Am. Chem. Soc.* **1987**, 109, 6881, and references cited therein.

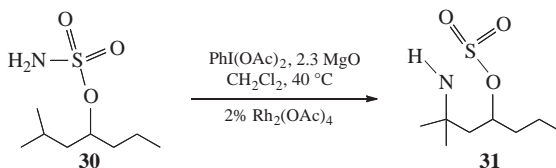
12-12 Direct Amination at an Activated Position

Alkyamino-de-hydrogenation, and so on



Alkenes can be aminated²²⁵ in the allylic position by treatment with solutions of imido selenium compounds ($\text{R}-\text{N}=\text{Se}=\text{N}-\text{R}$).²²⁶ The reaction, which is similar to the allylic oxidation of alkenes with SeO_2 (see Reaction 19-14), has been performed with $\text{R} = t\text{-Bu}$ and $\text{R} = \text{Ts}$. The imido sulfur compound $\text{TsN}=\text{S}=\text{NTs}$ has also been used,²²⁷ as well as $\text{PhNHOH}-\text{FeCl}_2/\text{FeCl}_3$.²²⁸ Benzylic positions can be aminated with $t\text{-BuOOCONHTs}$ in the presence of a catalytic amount of $\text{Cu}(\text{OTf})_2$.²²⁹ Enantioselective allylic amination has been reported using organocatalysts.²³⁰ A Rh catalyzed amination of benzylic positions has also been reported.²³¹

Tertiary alkyl hydrogen can be replaced in some cases via $\text{C}-\text{H}$ nitrogen insertion. The reaction of sulfamate ester (**30**) with $\text{PhI}(\text{OAc})_2$, MgO , and a dinuclear Rh carboxylate catalyst, for example, generated oxathiazinane (**31**).²³² This transformation is a formal oxidation, and primary carbamates have been similarly converted to oxazolidin-2-ones.²³³



Amination of 1,3-dicarbonyl compounds can be done using functionalized dimides and an appropriate catalyst, generating the corresponding hydrazone. Enantioselective amination using this method has been reported, using a chiral guanidine catalyst.²³⁴

See also, Reaction 10-39.

12-13 Insertion by Nitrenes

CH-[Acylimino]-insertion, and so on



²²⁵ See Sheradsky, T. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, **1982**, pp. 395–416.

²²⁶ Sharpless, K.B.; Hori, T.; Truesdale, L.K.; Dietrich, C.O. *J. Am. Chem. Soc.* **1976**, 98, 269; Kresze, G.; Münsterer, H. *J. Org. Chem.* **1983**, 48, 3561. For a review, see Cheikh, R.B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685, pp. 691–696.

²²⁷ Sharpless, K.B.; Hori, T. *J. Org. Chem.* **1979**, 41, 176. For other reagents, see Tsushima, S.; Yamada, Y.; Onami, T.; Oshima, K.; Chaney, M.O.; Jones, N.D.; Swartzendruber, J.K. *Bull. Chem. Soc. Jpn.* **1989**, 62, 1167.

²²⁸ Srivastava, R.S.; Nicholas, K.M. *Tetrahedron Lett.* **1994**, 35, 8739.

²²⁹ Kohmura, Y.; Kawasaki, K.; Katsuki, T. *Synlett*, **1997**, 1456.

²³⁰ Poulsen, T.B.; Alemparte, C.; Jørgensen, K.A. *J. Am. Chem. Soc.* **2005**, 127, 11614.

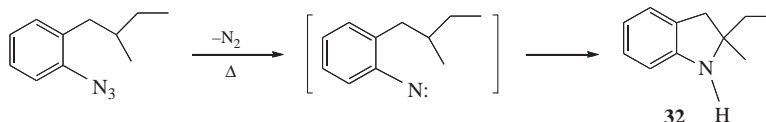
²³¹ Fiori, J.W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, 129, 562.

²³² Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, 123, 6935.

²³³ Espino, C.G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, 40, 598.

²³⁴ Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, 128, 16044.

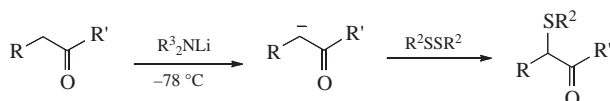
Carbonylnitrenes (:NCOW, W = R', Ar, or OR') are very reactive species (Sec. 5.E) and insert into the C—H bonds of alkanes to give amides (W = R' or Ar) or carbamates (W = OR').²³⁵ The nitrenes are generated as discussed in Section 5.E. The order of reactivity among alkane C—H bonds is tertiary > secondary > primary.²³⁶ Nitrenes are much more selective (and less reactive) in this reaction than carbenes (Reaction 12-17).²³⁷ It is likely that only singlet and not triplet nitrenes insert.²³⁸ Retention of configuration is found at a stereogenic carbon.²³⁹ The mechanism is presumably similar to the simple one-step mechanism for insertion of carbenes (Reaction 12-21). Other nitrenes [e.g., cyanonitrene (NCN)²⁴⁰ and aryl nitrenes (NAr)²⁴¹] can also insert into C—H bonds, but alkyl nitrenes usually undergo rearrangement before they can react with the alkane. The Au(III) catalyzed insertion of nitrenes into aromatic and benzylic C—H groups has been reported.²⁴² *N*-Carbamoyl nitrenes undergo insertion reactions that often lead to mixtures of products, but exceptions are known,²⁴³ chiefly in cyclizations.²⁴⁴ For example, heating of 2-(2-methylbutyl)phenyl azide gave ~60% 2-ethyl-2-methylindoline (32).²³⁹ Enantioselective nitrene insertion reactions are known.²⁴⁵



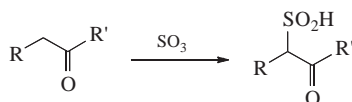
D. Sulfur Electrophiles

12-14 Sulfenylation, Sulfonation, and Selenylation of Ketones and Carboxylic Esters

Alkylthio-de-hydrogenation, and so on



Sulfonation or Sulfo-de-hydrogenation



²³⁵ See Lwowski, W. in Lwowski, W. *Nitrenes*, Wiley, NY, **1970**, pp. 199–207.

²³⁶ See Maslak, P. *J. Am. Chem. Soc.* **1989**, *111*, 8201.

²³⁷ See Alewood, P.F.; Kazmaier, P.M.; Rauk, A. *J. Am. Chem. Soc.* **1973**, *95*, 5466.

²³⁸ See Inagaki, M.; Shingaki, T.; Nagai, T. *Chem. Lett.* **1981**, 1419.

²³⁹ Smolinsky, G.; Feuer, B.I. *J. Am. Chem. Soc.* **1964**, *86*, 3085.

²⁴⁰ See Anastassiou, A.G.; Shepelavy, J.N.; Simmons, H.E.; Marsh, F.D. in Lwowski, W. *Nitrenes*, Wiley, NY, **1970**, pp. 305–344.

²⁴¹ See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, **1984**, pp. 95–204.

²⁴² Li, Z.; Capretto, D.A.; Rahaman, R.O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058.

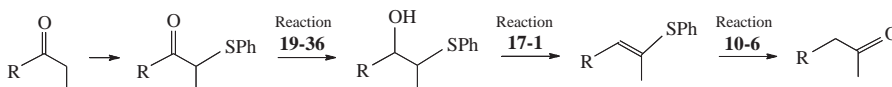
²⁴³ See also, Meinwald, J.; Aue, D.H. *Tetrahedron Lett.* **1967**, 2317.

²⁴⁴ For a list of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1148–1149.

²⁴⁵ See Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

Ketones, carboxylic esters (including lactones),²⁴⁶ and amides (including lactams)²⁴⁷ can be sulfonylated²⁴⁸ in the α position by conversion to the enolate anion (see Sec. 8.F, part 7), and subsequent treatment with a disulfide.²⁴⁹ The reaction, shown above for ketones, involves nucleophilic substitution at sulfur. α -Phenylseleno ketones [RCH(SePh)COR'] and α -phenylseleno esters [RCH(SePh)COOR'] can be similarly prepared²⁵⁰ by treatment of the corresponding enolate anions with PhSeBr,²⁵¹ PhSeSePh,²⁵² or benzeneseleninic anhydride [PhSe(O)OSe(O)Ph].²⁵³ Another method for the introduction of a phenylseleno group into the α position of a ketone involves simple treatment of an ethyl acetate solution of the ketone with PhSeCl (but not PhSeBr) at room temperature.²⁵⁴ This procedure is also successful for aldehydes but not for carboxylic esters. *N*-Phenylselenophthalimide has been used to convert ketones²⁵⁵ and aldehydes²⁵⁶ to the α -PhSe derivative. Silyl enol ethers are converted to α -alkylthio and α -arylthio ketones via a sulfonylation method, driven by aromatization of an added quinone mono-*O,S*-acetal in the presence of Me₃SiOTf.²⁵⁷

The α -seleno and α -sulfonyl carbonyl compounds prepared by this reaction can be converted to α,β -unsaturated carbonyl compounds (Reaction 17-12). The sulfonylation reaction has also been used²⁵⁸ as a key step in a sequence for moving the position of a carbonyl group to an adjacent carbon.²⁵⁹



Aldehydes, ketones, and carboxylic acids containing α hydrogen atoms can be sulfonated with sulfur trioxide.²⁶⁰ The mechanism is presumably similar to that of Reaction 12-4. Sulfonation has also been accomplished at vinylic hydrogen.

OS VI, 23, 109; VIII, 550. OS IV, 846, 862.

²⁴⁶ See Trost, B.M. *Pure Appl. Chem.* **1975**, 43, 563, pp. 572–578; Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, **1979**, pp. 278–282.

²⁴⁷ Gassman, P.G.; Balchunis, R.J. *J. Org. Chem.* **1977**, 42, 3236.

²⁴⁸ See Sandrinelli, F.; Fontaine, G.; Perrio, S.; Beslin, P. *J. Org. Chem.* **2004**, 69, 6916.

²⁴⁹ For another reagent, see Scholz, D. *Synthesis* **1983**, 944.

²⁵⁰ See Back, T.G. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, **1987**, pp. 1–125; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, **1986**, pp. 95–98.

²⁵¹ Brocksom, T.J.; Petragnani, N.; Rodrigues, R. *J. Org. Chem.* **1974**, 39, 2114. See also, Liotta, D. *Acc. Chem. Res.* **1984**, 17, 28.

²⁵² Grieco, P.A.; Miyashita, M. *J. Org. Chem.* **1974**, 39, 120. See Miyoshi, N.; Yamamoto, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1982**, 23, 4813.

²⁵³ Barton, D.H.R.; Morzycki, J.W.; Motherwell, W.B.; Ley, S.V. *J. Chem. Soc. Chem. Commun.* **1981**, 1044.

²⁵⁴ Sharpless, K.B.; Lauer, R.F.; Teranishi, A.Y. *J. Am. Chem. Soc.* **1973**, 95, 6137.

²⁵⁵ Cossy, J.; Furet, N. *Tetrahedron Lett.* **1993**, 34, 7755.

²⁵⁶ Wang, W.; Wang, K.; Li, H. *Org. Lett.* **2004**, 6, 2817.

²⁵⁷ Matsugi, M.; Murata, K.; Gotanda, K.; Nambu, H.; Anilkumar, G.; Matsumoto, K.; Kita, Y. *J. Org. Chem.*, **2001**, 66, 2434.

²⁵⁸ Trost, B.M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc.* **1975**, 97, 438.

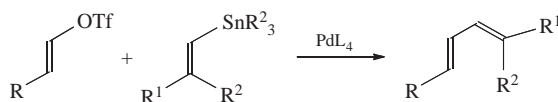
²⁵⁹ See OS VI, 23, 109; 68, 8. See also Morris, D.G. *Chem. Soc. Rev.* **1982**, 11, 397; Kane, V.V.; Singh, V.; Martin, A.; Doyle, D.L. *Tetrahedron* **1983**, 39, 345.

²⁶⁰ See Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, **1965**, pp. 33–61.

E. Carbon Reagents

12-15 Alkylation and Alkenylation of Alkenes

Alkylation or Alkyl-de-oxy-sulfonation (de-halogenation), Arylation or Aryl-de-oxy-sulfonation (de-halogenation), and so on



Vinyl triflates ($\text{C}=\text{C}-\text{OSO}_2\text{CF}_3$) react with vinyl tin derivatives in the presence of Pd catalysts to form dienes, in what is known as *Stille coupling*.²⁶¹ Phosphine or bis (phosphine) ligands are most commonly used with the Pd catalyst,²⁶² but other ligands have been used,²⁶³ including triphenylarsine.²⁶⁴ Vinyl triflates can be prepared from the enolate anion by reaction with *N*-phenyl triflimide.²⁶⁵ Vinyltin compounds are generally prepared by the reaction of an alkyne with an trialkyltin halide (see Reactions **15-17** and **15-21**).²⁶⁶ *Stille cross-coupling* reactions are an important variation of the basic reaction,²⁶⁷ including cross-coupling reactions of unactivated secondary halides and monoorganotin reagents.²⁶⁸ Stille reactions are compatible with many functional groups. Vinyl halides can be used,²⁶⁹ and allenic tin compounds have been used.²⁷⁰ Intramolecular reactions are possible.²⁷¹ *Stille coupling* has been done using microwave irradiation,²⁷² in fluorous solvents,²⁷³ and in supercritical carbon dioxide (see Sec. 9.D.ii).²⁷⁴ *Stille coupling* using alkynes as a substrate are known.²⁷⁵

This reaction is highly stereoselective, and proceeds with a retention of geometry of the $\text{C}=\text{C}$ units, and are usually regiospecific with respect to the newly formed $\text{C}-\text{C}$ σ -bond. Cine substitution is known with this reaction, and its mechanism has been studied.²⁷⁶ Using ArSnCl_3 derivatives, Stille coupling can be done in aq. KOH.²⁷⁷

²⁶¹ Scott, W.J.; Crisp, G.T.; Stille, J.K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. See Roth, G.P.; Farina, V.; Liebeskind, L.S.; Peña-Cabrera, E. *Tetrahedron Lett.* **1995**, *36*, 2191 for an optimized version of this reaction. Also see Echavarren, A.M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3962; Reiser, O. *Angew. Chem. Int. Ed.* **2006**, *45*, 2838.

²⁶² See Zhou, W.-J.; Wang, K.-H.; Wang, J.-X. *J. Org. Chem.* **2009**, *74*, 5599.

²⁶³ Gajare, A.S.; Jensen, R.S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Synlett* **2005**, 144. For a ligand free reaction, see Yabe, Y.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* **2010**, *66*, 8654.

²⁶⁴ Lau, K.C.Y.; Chiu, P. *Tetrahedron Lett.* **2007**, *48*, 1813.

²⁶⁵ McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* **1983**, *24*, 979.

²⁶⁶ See Maleczka Jr., R.E.; Lavis, J.M.; Clark, D.H.; Gallagher, W.P. *Org. Lett.* **2000**, *2*, 3655.

²⁶⁷ Farina, V.; Krishnamurthy, V.; Scott, W.J. *Org. React.* **1997**, *50*, 1; Li, J.-H.; Liang, Y.; Wang, D.-P.; Liu, W.-J.; Xie, Y.-X.; Yin, D.-L. *J. Org. Chem.* **2005**, *70*, 2832.

²⁶⁸ Powell, D.A.; Maki, T.; Fu, G.C. *J. Am. Chem. Soc.* **2005**, *127*, 510.

²⁶⁹ Johnson, C.R.; Adams, J.P.; Braun, M.P.; Senanayake, C.B.W. *Tetrahedron Lett.* **1992**, *33*, 919.

²⁷⁰ Badone, D.; Cardamone, R.; Guzzi, U. *Tetrahedron Lett.* **1994**, *35*, 5477.

²⁷¹ Segorbe, M.M.; Adrio, J.; Carretero, J.C. *Tetrahedron Lett.* **2000**, *41*, 1983.

²⁷² Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D.P. *J. Org. Chem.* **1997**, *62*, 5583.

²⁷³ Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D.P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539.

²⁷⁴ Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475.

²⁷⁵ Shi, Y.; Peterson, S.M.; Haberaecker III, W.W.; Blum, S.A. *J. Am. Chem. Soc.* **2008**, *130*, 2168.

²⁷⁶ Farina, V.; Hossain, M.A. *Tetrahedron Lett.* **1996**, *37*, 6997.

²⁷⁷ Rai, R.; Aubrecht, K.B.; Collum, D.B. *Tetrahedron Lett.* **1995**, *36*, 3111.

Aryl halides,²⁷⁸ heteroaryl halides,²⁷⁹ and heteroaryl triflates²⁸⁰ can be coupled to vinyltin reagents²⁸¹ using a Pd catalyst. A Mo catalyzed variation is known.²⁸² A Cu catalyzed cross coupling variation²⁸³ has been reported in ionic liquids.²⁸⁴ Vinyl halides can be coupled to alkenes to form dienes.²⁸⁵ The reaction of dihydrofurans with vinyl triflates and a Pd catalyst leads to a nonconjugated diene,²⁸⁶ illustrating that the product is formed by an elimination step, as with the *Heck reaction* (**13-10**), and double-bond migration can occur resulting in allylic rearrangement.

The accepted mechanism for the *Stille reaction* involves a catalytic cycle²⁸⁷ in which an oxidative addition²⁸⁸ and a reductive elimination step²⁸⁹ are fast, relative to Sn/Pd transmetalation (the rate-determining step).²⁹⁰ It appears that the greater the coordinating ability of the unsaturated species is important, and a coordinated solvent molecule is likely involved in the electrophilic substitution at tin. Another mechanism has been proposed, in which oxidative addition of the vinyl triflate to the ligated Pd gives a *cis*-Pd complex that isomerizes rapidly to a *trans*-Pd complex, which then reacts with the organotin compound following an S_E2 (cyclic) mechanism, with release of a ligand.²⁹¹ This pathway gives a bridged intermediate, and subsequent elimination of XSnBu₃ yields a three-coordinate species *cis*-Pd complex, which readily gives the coupling product.²⁹¹ Most of the major intermediates have been intercepted, isolated, and characterized using electrospray ionization mass spectrometry.²⁹²

Cyclopropylboronic acids (Reaction **12-28**) couple with vinylic halides²⁹³ or vinyl triflates²⁹⁴ to give vinylcyclopropanes, using a Pd catalyst. Vinyl borates (Reaction **12-28**) were coupled to vinyl triflates using a Pd catalyst.²⁹⁵ Vinyltrifluoroborates can be coupled to allylic chlorides using microwave irradiation²⁹⁶ and vinyl halides react with vinyltrifluoroborates to give dienes with high stereoselectivity.²⁹⁷ Stille coupling to enols has

²⁷⁸ Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* **1999**, 38, 2411.

²⁷⁹ Clapham, B.; Sutherland, A.J. *J. Org. Chem.* **2001**, 66, 9033.

²⁸⁰ Schaus, J.V.; Panek, J.S. *Org. Lett.* **2000**, 2, 469.

²⁸¹ See Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Org. Lett.* **1999**, 1, 701. Also see Minière, S.; Cintrat, J.-C. *J. Org. Chem.* **2001**, 66, 7385.

²⁸² Lindh, J.; Fardost, A.; Almeida, M.; Nilsson, P. *Tetrahedron Lett.* **2010**, 51, 2470; Sävmarker, J.; Lindh, J.; Nilsson, P. *Tetrahedron Lett.* **2010**, 51, 6886.

²⁸³ Mee, S.P.H.; Lee, V.; Baldwin, J.E. *Chemistry: European J.* **2005**, 11, 3294.

²⁸⁴ Li, J.-H.; Tang, B.-X.; Tao, L.-M.; Xie, Y.-X.; Liang, Y.; Zhang, M.-B. *J. Org. Chem.* **2006**, 71, 7488.

²⁸⁵ Voigt, K.; Schick, U.; Meyer, F.E.; de Meijere, A. *Synlett* **1994**, 189.

²⁸⁶ Gilbertson, S.R.; Fu, Z.; Xie, D. *Tetrahedron Lett.* **2001**, 42, 365.

²⁸⁷ Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* **1986**, 108, 3033; Stille, J.K. *Angew. Chem., Int. Ed.* **1986**, 25, 508; Farina, V. in Abel, E.W.; Stone, F.G.A.; Wilkinson, G. *Comprehensive Organometallic Chemistry II*, Vol. 12, Pergamon, Oxford, U.K., **1995**, Chapter 3.4.; Brown, J.M.; Cooley, N.A. *Chem. Rev.* **1988**, 88, 1031.

²⁸⁸ Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, 115, 9531 and references cited therein.

²⁸⁹ Ozawa, F.; Fujimori, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1986**, 5, 2144; Tatsumi, K.; Hoffmann, R.; Moravski, A.; Stille, J.K. *J. Am. Chem. Soc.* **1981**, 103, 4182; Loar, M.K.; Stille, J.K. *J. Am. Chem. Soc.* **1981**, 103, 4174.

²⁹⁰ Deacon, G.B.; Gatehouse, B.M.; Nelson-Reed, K.T. *J. Organomet. Chem.* **1989**, 359, 267.

²⁹¹ Casado, A.L.; Espinet, P.; Gallego, A.M. *J. Am. Chem. Soc.* **2000**, 122, 11771.

²⁹² Santos, L.S.; Rosso, G.B.; Pilli, R.A.; Eberlin, M.N. *J. Org. Chem.* **2007**, 72, 5809.

²⁹³ Zhou, S.-m.; Deng, M.-z. *Tetrahedron Lett.* **2000**, 41, 3951.

²⁹⁴ Yao, M.-L.; Deng, M.-Z. *J. Org. Chem.* **2000**, 65, 5034; Yao, M.-L.; Deng, M.-Z. *Tetrahedron Lett.* **2000**, 41, 9083.

²⁹⁵ Occhiato, E.G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, 66, 2459.

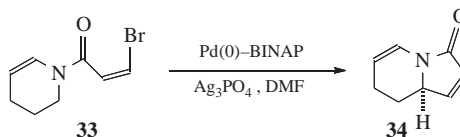
²⁹⁶ Kabalka, G.W.; Dadush, E.; Al-Masum, M. *Tetrahedron Lett.* **2006**, 47, 7459.

²⁹⁷ Molander, G.A.; Felix, L.A. *J. Org. Chem.* **2005**, 70, 3950.

been reported.²⁹⁸ The coupling of vinyl silanes to give the symmetrically conjugated diene using CuCl and air has also been reported.²⁹⁹

Other methods are available to give Stille-like products. 1-Lithioalkynes were coupled to vinyl tellurium compounds ($\text{C}=\text{C}-\text{TeBu}$) using a Ni³⁰⁰ or a Pd catalyst³⁰¹ to give a conjugated en-yne. 2-Alkynes ($\text{R}-\text{C}\equiv\text{C}-\text{Me}$) react with HgCl_2 , *n*-butyllithium, and ZnBr_2 , sequentially, and then with vinyl iodides and a Pd catalyst to give the nonconjugated en-yne.³⁰² Alkynyl groups can be coupled to vinyl groups to give ene-yne, via reaction of silver alkynes ($\text{Ag}-\text{C}\equiv\text{C}-\text{R}$) with vinyl triflates and a Pd catalyst.³⁰³ In the presence of CuI and a Pd catalyst, vinyl triflates³⁰⁴ or vinyl halides³⁰⁵ couple to terminal alkynes. Alkynyl zinc reagents ($\text{R}-\text{C}\equiv\text{C}-\text{ZnBr}$) can be coupled to vinyl halides with a Pd catalyst to give the conjugated en-yne.³⁰⁶

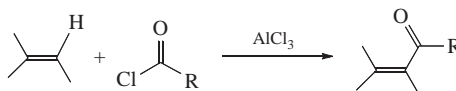
Alkyl groups can be coupled to a vinyl unit to give substituted alkenes. The reaction of vinyl iodides and EtZnBr , with a Pd catalyst, gave the ethylated alkene ($\text{C}=\text{C}-\text{Et}$).³⁰⁷ Aliphatic alkyl bromides reacted with vinyltin compounds to give the alkylated alkene using a Pd catalyst.³⁰⁸ Allylic tosylates were coupled to conjugated alkenes to give a non-conjugated diene using a Pd catalyst.³⁰⁹ An internal coupling reaction was reported in which an alkenyl enamide (**33**) reacted with Ag_3PO_4 and a chiral palladium catalyst to give **34** enantioselectively.³¹⁰



For the related coupling reaction of alkenes and aryl compounds (arylation of alkenes), see Reaction 13-10.

12-16 Acylation at an Aliphatic Carbon

Acylation or Acyl-de-hydrogenation



²⁹⁸ Fu, X.; Zhang, S.; Yin, J.; McAllister, T.L.; Jiang, S.A.; Tann, C.-H.; Thiruvengadam, T.K.; Zhang, F. *Tetrahedron Lett.* **2002**, 43, 573. See Vallin, K.S.A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* **2000**, 65, 4537.

²⁹⁹ Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, 73, 985.

³⁰⁰ Raminelli, C.; Gargalak Jr., J.; Silveira, C.C.; Comasseto, J.V. *Tetrahedron Lett.* **2004**, 45, 4927; Silveira, C.C.; Braga, A.L.; Vieira, A.S.; Zeni, G. *J. Org. Chem.* **2003**, 68, 662.

³⁰¹ Zeni, G.; Comasseto, J.V. *Tetrahedron Lett.* **1999**, 40, 4619.

³⁰² Ma, S.; Zhang, A.; Yu, Y.; Xia, W. *J. Org. Chem.* **2000**, 65, 2287.

³⁰³ Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, 3, 1661. See Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett.* **2001**, 42, 8641; Bertus, P.; Halbes, U.; Pale, P. *Eur. J. Org. Chem.* **2001**, 4391.

³⁰⁴ Braga, A.L.; Emmerich, D.J.; Silveira, C.C.; Martins, T.L.C.; Rodrigues, O.E.D. *Synlett* **2001**, 369.

³⁰⁵ Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett.* **2002**, 4, 1171. Also see Bates, C.G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, 6, 1441.

³⁰⁶ Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, 5, 1597.

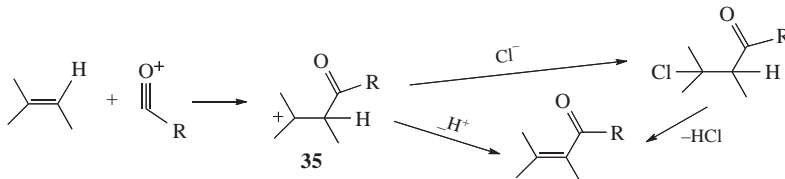
³⁰⁷ Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R.; Duchêne, A. *J. Org. Chem.* **2000**, 65, 7475.

³⁰⁸ Menzel, K.; Fu, G.C. *J. Am. Chem. Soc.* **2003**, 125, 3718.

³⁰⁹ Tsukada, N.; Sato, T.; Inoue, Y. *Chem. Commun.* **2003**, 2404.

³¹⁰ Kiewel, K.; Tallant, M.; Sulikowski, G.A. *Tetrahedron Lett.* **2001**, 42, 6621.

Alkenes can be acylated with an acyl halide and a Lewis acid catalyst in what is essentially a *Friedel–Crafts Reaction* (**11-17**) at an aliphatic carbon.³¹¹ The product can arise by two paths. The initial attack is by the π bond of the alkene unit on the acyl cation (RCO^+ ; or on the acyl halide free or complexed; see Reaction **11-17**) to give a carbocation, (**35**).



Ion **35** can either lose a proton or combine with chloride ion. If it loses a proton, the product is an unsaturated ketone. The mechanism is similar to the *tetrahedral mechanism* in Section 16.A.i, but with the charges reversed. If it combines with chloride, the product is a β -halo ketone, which can be isolated, so that the result is addition to the double bond (see Reaction **15-47**). On the other hand, the β -halo ketone may, under the conditions of the reaction, lose HCl to give the unsaturated ketone, this time by an addition–elimination mechanism. In the case of unsymmetrical alkenes, the more stable alkene is formed (the more highly substituted and/or conjugated alkene, following *Markovnikov's rule*, see Sec. 15.B.ii). Anhydrides and carboxylic acids (the latter with a proton acid e.g., anhydrous HF , H_2SO_4 , or polyphosphoric acid as a catalyst) are sometimes used instead of acyl halides. With some substrates and catalysts, double-bond migrations are occasionally encountered so that, for example, when 1-methylcyclohexene was acylated with acetic anhydride and zinc chloride, the major product was 6-acetyl-1-methylcyclohexene.³¹²

Conjugated dienes can be acylated by treatment with acyl- or alkylcobalt tetracarbonyls, followed by base-catalyzed cleavage of the resulting π -allyl carbonyl derivatives³¹³ (π -allyl metal complexes were discussed in Sec. 3.C.i. The reaction is very general. With unsymmetrical dienes, the acyl group generally substitutes most readily at a *cis* double bond, next at a terminal alkenyl group, and least readily at a *trans* double bond. The most useful bases are strongly basic, hindered amines (e.g., dicyclohexylethylamine). Acylation of vinylic ethers has been accomplished with aromatic acyl chlorides, a base, and a Pd catalyst: $\text{ROCH}=\text{CH}_2 \rightarrow \text{ROCH}=\text{CHCOAr}$.³¹⁴

Formylation of alkenes can be accomplished with *N*-disubstituted formamides and POCl_3 .³¹⁵ This is an aliphatic *Vilsmeier reaction* (see Reaction **11-18**). Vilsmeier formylation can also be performed on the α position of acetals and ketals, so that hydrolysis of the products gives keto aldehydes or dialdehydes:³¹⁶ A variation

³¹¹ See Groves, E.E. *Chem. Soc. Rev.* **1972**, 1, 73; Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 259–266, 270–273; Nenitzescu, C.D.; Balaban, A.T. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 1033–1152.

³¹² Deno, N.C.; Chafetz, H. *J. Am. Chem. Soc.* **1952**, 74, 3940. For other examples, see Grignon-Dubois, M.; Cazaux, M. *Bull. Soc. Chim. Fr.* **1986**, 332.

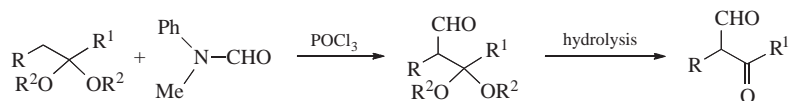
³¹³ See Heck, R.F. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 1, Wiley, NY, **1968**, pp. 388–397.

³¹⁴ Andersson, C.; Hallberg, A. *J. Org. Chem.* **1988**, 53, 4257.

³¹⁵ See Burn, D. *Chem. Ind. (London)* **1973**, 870; Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 281–282.

³¹⁶ Youssefyeh, R.D. *Tetrahedron Lett.* **1964**, 2161.

heated a 1,1-dibromoalkene with a secondary amine in aq DMF to give the corresponding amide.³¹⁷

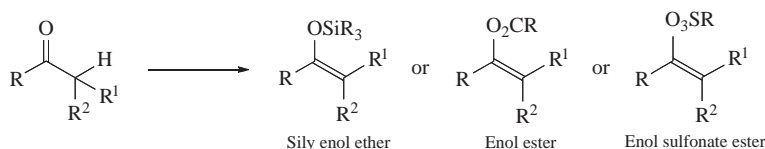


Acetylation of acetals or ketals can be accomplished with acetic anhydride and BF_3 -etherate.³¹⁸ The mechanism with acetals or ketals also involves attack at an alkenyl carbon, since enol ethers are intermediates.³¹⁸ Ketones can be formylated in the α position by treatment with CO and a strong base.³¹⁹

OS IV, 555, 560; VI, 744. Also see, OS VI, 28.

12-17 Conversion of Enolates to Silyl Enol Ethers, Silyl Enol Esters, and Silyl Enol Sulfonate Esters

3/O-Trimethylsilyl-de-hydrogenation



Silyl enol ethers,³²⁰ important reagents with a number of synthetic uses (see, e.g., Reactions **10-68**, **12-4**, **15-24**, **15-64**, and **16-36**), can be prepared by base treatment of a ketone (converting it to its enolate anion) followed by addition of a trialkylchlorosilane. Other silylating agents have also been used.³²¹ Both strong bases (e.g., LDA), and weaker bases (Et_3N) have been used for this purpose.³²² In some cases, the base and the silylating agent can be present at the same time.³²³ Enolate anions prepared in other ways (e.g., as shown in Reaction **10-58**) also give the reaction.³²⁴ The reaction can be applied to aldehydes by the use of the base KH in 1,2-dimethoxyethane.³²⁵ A particularly mild method for conversion of ketones or aldehydes to silyl enol ethers uses Me_3SiI and the base hexamethyldisilazane [$(\text{Me}_3\text{Si})_2\text{NH}$].³²⁶ Cyclic ketones can be converted to silyl enol ethers in the presence of acyclic ketones, by treatment with Me_3SiBr , tetraphenylstibonium

³¹⁷ Shen, W.; Kunzer, A. *Org. Lett.* **2002**, *4*, 1315.

³¹⁸ Youssefeyeh, R.D. *J. Am. Chem. Soc.* **1963**, *85*, 3901.

³¹⁹ See van der Zeeuw, A.J.; Gersmann, H.R. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1535.

³²⁰ See Poirier, J. *Org. Prep. Proced. Int.* **1988**, *20*, 319; Brownbridge, P. *Synthesis* **1983**, *1*, 85; Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, **1988**; Colvin, E.W. in Hartley, C.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, pp. 539–621; Ager, D.J. *Chem. Soc. Rev.* **1982**, *11*, 493.

³²¹ See Mizhiritskii, M.D.; Yuzhelevskii, Yu.A. *Russ. Chem. Rev.* **1987**, *56*, 355. For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1488–1491.

³²² Di-*tert*-butylmagnesium has also been used. See Kerr, W.J.; Watson, A.J.B.; Hayes, D. *Synlett* **2008**, 1386.

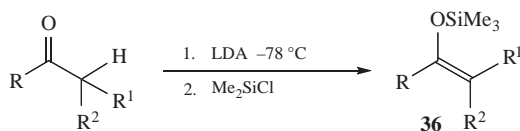
³²³ Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* **1984**, *25*, 495. Also see Lipshutz, B.H.; Wood, M.R.; Lindsley, C.W. *Tetrahedron Lett.* **1995**, *36*, 4385.

³²⁴ See Cahiez, G.; Figadère, B.; Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 6295.

³²⁵ Ladjama, D.; Riehl, J.J. *Synthesis* **1979**, 504. See Orban, J.; Turner, J.V.; Twitchin, B. *Tetrahedron Lett.* **1984**, *25*, 5099.

³²⁶ Miller, R.D.; McKean, D.R. *Synth. Commun.* **1982**, *12*, 319. See also, Ahmad, S.; Khan, M.A.; Iqbal, J. *Synth. Commun.* **1988**, *18*, 1679.

bromide (Ph_4SbBr), and an aziridine.³²⁷ bis(Trimethylsilyl)acetamide is an effective reagent for the conversion of ketones to the silyl enol ether, typically giving the thermodynamic product (see below).³²⁸ Silyl enol ethers have also been prepared by the direct reaction of a ketone and a silane (R_3SiH) with a Pt catalyst.³²⁹



For substituted ketones, (*E*) and (*Z*) isomers are usually formed. For **36**, the enol is (*Z*) when R^1 is the priority group, but (*E*) when R^2 is the priority group. In some cases, it is possible to control the selectivity to favor more of one isomer than the other. Treatment of 2-methyl-3-pentanone with LDA (THF, -78°C), for example, gave a 60:40 mixture of the (*Z*) and (*E*) enolates.³³⁰ The base used to generate an enolate anion, the solvent and temperature, the conjugate acid of the base used, and the nature of the carbonyl substrate will all play a role in the selectivity. In general, equilibrating (thermodynamic) conditions [protic solvents (e.g., ethanol, water, or ammonia), a base generating a conjugate acid stronger than the starting ketone, more ionic counterions (e.g., K or Na), higher temperatures and longer reaction times] are expected to give more of the (*E*)-isomer. Conversely, kinetic conditions [aprotic solvents (e.g., ether or THF), a base generating a conjugate acid weaker than the starting ketone, more covalent counterions (e.g., Li, lower temperatures), and relatively short reaction times] usually give more of the (*Z*)-isomer. It is not always easy to predict the ratio, however. Either isomer is possible from aldehydes using the proper Rh catalyst.³³¹

Magnesium diisopropylamide has been used to prepare kinetic silyl enol ethers in virtual quantitative yield.³³² Reaction with $\text{Me}_3\text{SiCl/KI}$ in DMF gives primarily the thermodynamic silyl enol ether.³³³

An interesting synthesis of silyl enol ethers involves chain extension of an aldehyde. Aldehydes are converted to the silyl enol ether of a ketone upon reaction with lithium (trimethylsilyl)diazomethane and then a dirhodium catalyst.³³⁴ For example, initial reaction of lithium(trimethylsilyl)diazomethane [LTMSD, prepared *in situ* by reaction of butyllithium with (trimethylsilyl)diazomethane] to the aldehyde (e.g., **37**) gave the alkoxide addition product. Protonation and then capture by a transition metal catalyst, and a 1,2-hydride migration gave the silyl enol ether, (**38**). Silyl enol ethers can be prepared from acyloin derivatives (see Reaction **19-78**).³³⁵

³²⁷ Fujiwara, M.; Baba, A.; Matsuda, H. *Chem. Lett.* **1989**, 1247.

³²⁸ Smietana, M.; Mioskowski, C. *Org. Lett.* **2001**, 3, 1037. See also, Tanabe, Y.; Misaki, T.; Kurihara, M.; Iida, A.; Nishii, Y. *Chem. Commun.* **2002**, 1628.

³²⁹ Ozawa, F.; Yamamoto, S.; Kayagishi, S.; Hiraoka, M.; Ideda, S.; Minami, T.; Ito, S.; Yoshifuji, M. *Chem. Lett.* **2001**, 972. See Blackwell, J.M.; Morrison, D.J.; Piers, W.E. *Tetrahedron* **2002**, 58, 8247; Mori, A.; Kato, T. *Synlett* **2002**, 1167.

³³⁰ Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.A.; Sohn, J.E.; Lampe, J. *J. Org. Chem.* **1980**, 45, 1066.

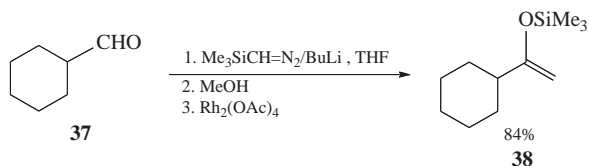
³³¹ Vitale, M.; Lecourt, T.; Sheldon, C.G.; Aggarwal, V.K. *J. Am. Chem. Soc.* **2006**, 128, 2524.

³³² Lessène, G.; Tripoli, R.; Cazeau, P.; Biran, C.; Bordeau, M. *Tetrahedron Lett.* **1999**, 40, 4037. Also see Patonay, T.; Hajdu, C.; Jeko, J.; Lévai, A.; Micskei, K.; Zucchi, C. *Tetrahedron Lett.* **1999**, 40, 1373.

³³³ Lin, J.-M.; Liu, B.-S. *Synth. Commun.* **1997**, 27, 739.

³³⁴ Aggarwal, V.K.; Sheldon, C.G.; Macdonald, G.J.; Martin, W.P. *J. Am. Chem. Soc.* **2002**, 124, 10300.

³³⁵ Robertson, B.D.; Hartel, A.M. *Tetrahedron Lett.* **2008**, 49, 2088.



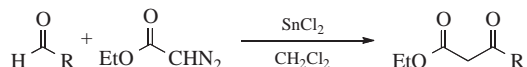
Enol acetates are generally prepared by the reaction of an enolate anion with a suitable acylating reagent.³³⁶ Enolate anions react with acyl halides and with anhydrides to give the acylated product. Both C- and O-acylation are possible, but in general O-acylation predominates.³³⁷ Note that the extent of O- versus C-acylation is very dependent on the local environment and electronic effects within the enolate anion.³³⁸ O-Benzoate enols are formed in good yield from aldehydes or 1,3-diketones in the presence of CuBr and *tert*-butylhydroperoxide.³³⁹ Silyl sulfonate esters can be prepared by similar methods, using sulfonic acid anhydrides rather than carboxylic anhydrides. A polymer-supported triflating agent was used to prepare silyl enol triflate from ketones, in the presence of diisopropylethylamine.³⁴⁰

When a silyl enol ether is the trimethylsilyl derivative ($\text{Me}_3\text{Si}-\text{O}-\text{C}=\text{C}$), treatment with methylolithium will regenerate the lithium enolate anion and the volatile trimethylsilane (Me_3SiH).³⁴¹

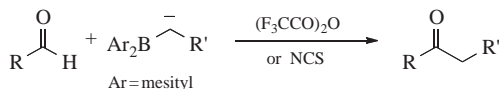
OS VI, 327, 445; VII, 282, 312, 424, 512; VIII, 1, 286, 460; IX, 573. See also, OS VII, 66, 266. For the conversion of ketones to vinylic triflates,³⁴² see OS VIII, 97, 126.

12-18 Conversion of Aldehydes to β -Keto Esters or Ketones

Alkoxyacylalkylation or Alkoxyacylalkyl-de-hydrogenation



β -Keto esters have been prepared in moderate to high yields by treatment of aldehydes with diethyl diazoacetate in the presence of a catalytic amount of a Lewis acid (e.g., SnCl_2 , BF_3 , or GeCl_2).³⁴³ The reaction was successful for both aliphatic and aromatic aldehydes, but the former react more rapidly than the latter, and the difference is great enough to allow selective reactivity. In a similar process, aldehydes react with certain carbanions stabilized by boron, in the presence of $(\text{F}_3\text{CCO})_2\text{O}$ or NCS, to give ketones.³⁴⁴



³³⁶ For the synthesis of enol acetates, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, 1484–1485.

³³⁷ See Krapcho, A.P.; Diamanti, J.; Cayen, C.; Bingham, R. *Org. Synth. Coll. Vol. V* **1973**, 198.

³³⁸ See Honda, T.; Namiki, H.; Kudoh, M.; Watanabe, N.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* **2000**, *41*, 5927.

³³⁹ Yoo, W.-J.; Li, C.-J. *J. Org. Chem.* **2006**, *71*, 6266.

³⁴⁰ Wentworth, A.D.; Wentworth, Jr., P.; Mansoor, U.F.; Janda, K.D. *Org. Lett.* **2000**, *2*, 477.

³⁴¹ House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* **1969**, *34*, 2324.

³⁴² Comins, D.L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

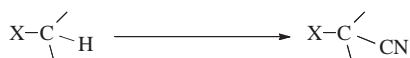
³⁴³ Holmquist, C.R.; Roskamp, E.J. *J. Org. Chem.* **1989**, *54*, 3258.

³⁴⁴ Pelter, A.; Smith, K.; Elgendy, S.; Rowlands, M. *Tetrahedron Lett.* **1989**, *30*, 5643.

Ketones can be prepared from aryl aldehydes (ArCHO) by treatment with a Rh complex $[(\text{Ph}_3\text{P})_2\text{Rh}(\text{CO})\text{Ar}']$, whereby the Ar group is transferred to the aldehyde, producing the ketone (Ar—CO—Ar').³⁴⁵ In another Rh catalyzed reaction, aryl aldehydes (ArCHO) react with $\text{Me}_3\text{SnAr}'$ to give the diaryl ketone (Ar—CO—Ar').³⁴⁶

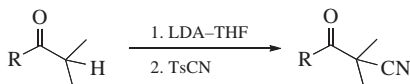
Acylation of aryl halides with aldehydes gives arylketones in the presence of a Pd catalyst.³⁴⁷

12-19 Cyanation or Cyano-de-hydrogenation



There are several reactions in which a C—H unit is replaced by C—CN. In virtually all cases, the hydrogen being replaced is on a carbon α to a heteroatom or functional group. There are several examples.

Introduction of a cyano group α to the carbonyl group of a ketone can be accomplished by prior formation of the enolate anion with LDA in THF and addition of this solution to *p*-TsCN at -78°C .³⁴⁸ The products are formed in moderate to high yields but the reaction is not applicable to methyl ketones. Treatment of $\text{TMSCH}_2\text{N}(\text{Me})\text{C}=\text{N}t\text{-Bu}$ with *sec*-butyllithium and $\text{R}_2\text{C}=\text{O}$, followed by iodomethane and NaOMe leads to the nitrile ($\text{R}_2\text{CH}-\text{CN}$).³⁴⁹



Cyanation has been shown to occur α to a nitrogen, specifically in *N,N*-dimethylaniline derivatives. Treatment with a catalytic amount of RuCl_3 in the presence of oxygen and NaCN leads to the corresponding cyanomethylamine.³⁵⁰ Conversion of tertiary amines to the α -cyanoamine has been reported in the presence of FeCl_2 and *t*-BuOOH.³⁵¹

In a different kind of reaction, nitro compounds are α -cyanated by treatment with CN^- and $\text{K}_3\text{Fe}(\text{CN})_6$.³⁵² The mechanism probably involves ion radicals. In still another reaction, secondary amines are converted to α -cyanoamines by treatment with phenylseleninic anhydride and NaCN or Me_3SiCN .^{353,354}

Another specialized reaction converts the methyl group of arenes (e.g., toluene) into a cyano group: toluene \rightarrow benzonitrile, for example.³⁵⁵

³⁴⁵ Krug, C.; Hartwig, J.F. *J. Am. Chem. Soc.* **2002**, *124*, 1674.

³⁴⁶ Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356.

³⁴⁷ Ruan, J.; Saidi, O.; Iggo, J.A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510.

³⁴⁸ Kahne, D.; Collum, D.B. *Tetrahedron Lett.* **1981**, *22*, 5011.

³⁴⁹ Santiago, B.; Meyers, A.I. *Tetrahedron Lett.* **1993**, *34*, 5839.

³⁵⁰ North, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4126.

³⁵¹ Han, W.; Ofial, A.R. *Chem. Commun.* **2009**, 5024.

³⁵² Kornblum, N.; Singh, N.K.; Kelly, W.J. *J. Org. Chem.* **1983**, *48*, 332.

³⁵³ Barton, D.H.R.; Billion, A.; Boivin, J. *Tetrahedron Lett.* **1985**, *26*, 1229.

³⁵⁴ Lemaire, M.; Doussot, J.; Guy, A. *Chem. Lett.* **1988**, 1581. See also, Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* **1987**, 1811.

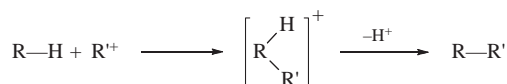
³⁵⁵ Zhou, W.; Zhang, L.; Jiao, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 7094.

12-20 Alkylation of Alkanes

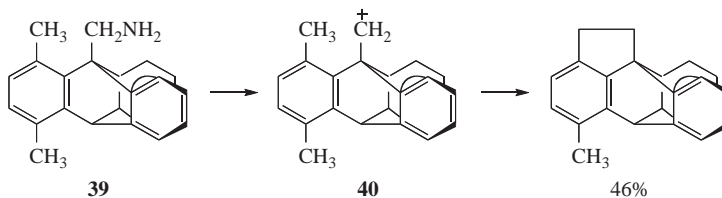
Alkylation or Alkyl-de-hydrogenation



Alkanes can be alkylated by treatment with solutions of stable carbocations³⁵⁶ (Sec. 5.A.ii), but the availability of such carbocations is limited and mixtures are usually obtained. In a typical experiment, the treatment of propane with isopropyl fluoroantimonate ($\text{Me}_2\text{HC}^+ \text{SbF}_6^-$) gave 26% 2,3-dimethylbutane, 28% 2-methylpentane, 14% 3-methylpentane, and 32% *n*-hexane, as well as some butanes, pentanes (formed by Reaction 12-47), and higher alkanes. Mixtures arise in part because intermolecular hydrogen exchange ($\text{RH} + \text{R}'^+ \rightarrow \text{R}^+ + \text{R}'\text{H}$) is much faster than alkylation, so that alkylation products are also derived from the new alkanes and carbocations formed in the exchange reaction. Furthermore, the carbocations present are subject to rearrangement (Chapter 18), giving rise to new carbocations. Products result from all the hydrocarbons and carbocations present in the system. As expected from their relative stabilities, secondary alkyl cations alkylate alkanes more readily than tertiary alkyl cations (the *tert*-butyl cation does not alkylate methane or ethane). Stable primary alkyl cations are not available, but alkylation has been achieved with complexes formed between CH_3F or $\text{C}_2\text{H}_5\text{F}$ and SbF_5 .³⁵⁷ The mechanism of alkylation can be formulated (similar to that shown in hydrogen exchange with superacids, Reaction 12-1) as



It is by means of successive reactions of this sort that simple alkanes like methane and ethane give *tert*-butyl cations in superacid solutions (Sec. 5.A.ii).³⁵⁸



Intramolecular insertion has been reported. The positively charged carbon of the carbocation (**40**), generated from the diazonium salt of the triptycene compound (**39**), reacted with the CH_3 group in close proximity with it.³⁵⁹

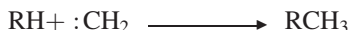
³⁵⁶ Olah, G.A.; Mo, Y.K.; Olah, J.A. *J. Am. Chem. Soc.* **1973**, 95, 4939. See Olah, G.A.; Farooq, O.; Prakash, G.K. S. in Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, **1989**, pp. 27–78; Ref. 48; Fabre, P.; Devynck, J.; Trémillon, B. *Chem. Rev.* **1982**, 82, 591. See also, Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*, Wiley, NY, **1987**.

³⁵⁷ Olah, G.A.; DeMember, J.R.; Shen, J. *J. Am. Chem. Soc.* **1973**, 95, 4952. See also, Sommer, J.; Muller, M.; Laali, K. *Nouv. J. Chem.* **1982**, 6, 3.

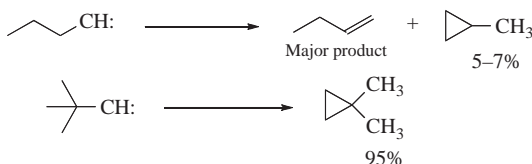
³⁵⁸ For example, see Hogeveen, H.; Roobeek, C.F. *Recl. Trav. Chim. Pays-Bas* **1972**, 91, 137.

³⁵⁹ Yamamoto, G.; Oki, M. *Chem. Lett.* **1987**, 1163.

12-21 Insertion by Carbenes

CH-Methylene-insertion

The highly reactive species methylene (:CH_2) inserts into C—H bonds,³⁶⁰ both aliphatic and aromatic,³⁶¹ although with aromatic compounds subsequent ring expansion is also possible (see Reaction 15-64). This is effectively a homologation reaction.³⁶² The methylene insertion reaction has limited utility because of its nonselectivity (see Sec. 5.D.i). The insertion reaction of carbenes has been used for synthetic purposes.³⁶³



The carbenes can be generated in any of the ways mentioned in Chapter 5 (Sec. 5.D.ii). Alkylcarbenes usually rearrange rather than give insertion (Sec. 5.D.ii, category 4), but, when this is impossible, *intramolecular* insertion³⁶⁴ is found rather than intermolecular.³⁶⁵ Methylene (:CH_2) generated by photolysis of diazomethane (CH_2N_2) in the liquid phase is indiscriminate (totally nonselective) in its reactivity (Sec. 5.D.ii, category 2). Methylene (:CH_2) generated in other ways and monoalkyl and dialkyl carbenes are less reactive and insert in the order tertiary > secondary > primary.³⁶⁶ Carbene insertion with certain allylic systems can proceed with rearrangement of the double bond.³⁶⁷ Carbenes have been generated using ultrasound.³⁶⁸ Halocarbenes (:CCl_2 , :CBr_2 , etc.) insert much less readily, although a number of instances have been reported.³⁶⁹

Insertion at an allylic carbon of alkenes has been reported.³⁷⁰ Dirhodium catalyzed insertion into H—C^{sp^2} bonds is known,³⁷¹ and also H—C^{sp} bonds.³⁷² Note that

³⁶⁰ First reported by Meerwein, H.; Rathjen, H.; Werner, H. *Ber.* **1942**, 75, 1610. See Doyle, M.P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, 110, 704; Bethell, D. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, **1973**, pp. 92–101; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, **1971**, pp. 209–266.

³⁶¹ Terao, T.; Shida, S. *Bull. Chem. Soc. Jpn.* **1964**, 37, 687. See also, Moss, R.A.; Fedé, J.-M.; Yan, S. *J. Am. Chem. Soc.* **2000**, 122, 9878.

³⁶² See Marek, I. *Tetrahedron* **2002**, 58, 9463.

³⁶³ See Paquette, L.A.; Kobayashi, T.; Gallucci, J.C. *J. Am. Chem. Soc.* **1988**, 110, 1305; Doyle, M.P.; Bagheri, V.; Pearson, M.M.; Edwards, J.D. *Tetrahedron Lett.* **1989**, 30, 7001.

³⁶⁴ Friedman, L.; Berger, J.G. *J. Am. Chem. Soc.* **1961**, 83, 492, 500. See Padwa, A.; Krumpe, K.E. *Tetrahedron* **1992**, 48, 5385.

³⁶⁵ See Burke, S.D.; Grieco, P.A. *Org. React.* **1979**, 26, 361.

³⁶⁶ Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* **1961**, 83, 1989.

³⁶⁷ Carter, D.S.; Van Vranken, D.L. *Org. Lett.* **2000**, 2, 1303; Doyle, M.P.; McKervery, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, NY, **1998**.

³⁶⁸ Bertram, A.K.; Liu, M.T.H. *J. Chem. Soc. Chem. Commun.* **1993**, 467.

³⁶⁹ See Steinbeck, K. *Tetrahedron Lett.* **1978**, 1103; Boev, V.I. *J. Org. Chem. USSR* **1981**, 17, 1190.

³⁷⁰ Davies, H.M.L.; Ren, P.; Jin, Q. *Org. Lett.* **2001**, 3, 3587.

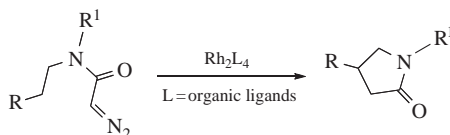
³⁷¹ Gibe, R.; Kerr, M.A. *J. Org. Chem.* **2002**, 67, 6247.

³⁷² Arduengo, III, A.J.; Calabrese, J.C.; Davidson, F.; Dias, H.V.R.; Goerlich, J.R.; Krafczyk, R.; Marshall, W.J.; Tamm, M.; Schmutzler, R. *Helv. Chim. Acta.* **1999**, 82, 2348.

cyclopropanation may compete with C—H insertion with electron-rich highly substituted alkenes.³⁷³ Palladacycles formed by C—H insertion reactions with biphenylene have been intercepted.³⁷⁴ Such species have been implicated in the *Heck reaction* (Reaction **13-10**). Insertion of diazoalkane and diazocarbonyl compounds can be catalyzed by copper compounds³⁷⁵ and silver compounds³⁷⁶ as well. Insertion into the α -C—H bond of an aldehyde gives an α -substituted aldehyde.³⁷⁷ Intramolecular insertion at the α carbon of a ketone by a diazoketone, using TiCl_4 , gives a bicyclic 1,3-diketone.³⁷⁸ The reaction in which aldehydes are converted to methyl ketones, $\text{RCHO} + \text{CH}_2\text{N}_2 \rightarrow \text{RCOCH}_3$, while apparently similar, does not involve a free carbene intermediate and is considered in Reaction **18-9**. Note that aryl ketenes react with $\text{Me}_3\text{SiCHN}_2$ and then silica to give 2-indanone derivatives.³⁷⁹ A three component coupling reaction of vinyl iodides, secondary amines, and diazo(trimethylsilyl)methane gives allylic amines.³⁸⁰ A gold-catalyzed reaction is known that uses alkynes as an α -diazo ketone equivalent.³⁸¹

Insertion into the O—H bond of alcohols, to produce ethers, has been reported using a diazocarbonyl compound and an $\text{In}(\text{OTf})_3$ catalyst.³⁸² The Cu catalyzed insertion of a diazo ester into an oxetane gives the ring-expanded THF derivative.³⁸³ Insertion is also possible with other ethers, including silyl ethers.³⁸⁴ Metal-catalyzed silylene insertion into allylic ethers leads to allylic silanes.³⁸⁵ Similar insertion at the α carbon of an ether leads to cyclic ethers, with high enantioselectivity when a chiral ligand is used with a Rh catalyst.³⁸⁶

The insertion of the diazocarbonyl unit into the C—H bond of an α -diazo amide gives the lactam shown in the reaction.³⁸⁷ Insertion into a 2-pyrrolidinone derivative using $\text{Me}_3\text{SiCH}_2\text{N}_2$ followed by AgCO_2Ph with ultrasound gave the ring-expanded 2-piperidone derivative.³⁸⁸ Intramolecular insertion reactions are well known,³⁸⁹ and tolerate a variety of functional groups.³⁹⁰



³⁷³ Ventura, D.L.; Li, Z.; Coleman, M.G.; Davies, H.M.L. *Tetrahedron* **2009**, 65, 3052.

³⁷⁴ Masselot, D.; Charmant, J.P.H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, 128, 694.

³⁷⁵ See Caballero, A.; Díaz-Requejo, M.M.; Belderrain, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* **2003**, 125, 1446.

³⁷⁶ Dias, H.V.R.; Browning, R.G.; Polach, S.A.; Diyabalanage, H.V.K.; Lovely, C.J. *J. Am. Chem. Soc.* **2003**, 125, 9270.

³⁷⁷ Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, 130, 2434.

³⁷⁸ Wee, A.G.H.; Duncan, S.C. *J. Org. Chem.* **2005**, 70, 8372.

³⁷⁹ Dalton, A.M.; Zhang, Y.; Davie, C.P.; Danheiser, R.L. *Org. Lett.* **2002**, 4, 2465.

³⁸⁰ Devine, S.K.J.; Van Vranken, D.L. *Org. Lett.* **2007**, 9, 2047.

³⁸¹ Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, 132, 3258.

³⁸² Matusamy, S.; Arulananda, S.; Babu, A.; Gunanathan, C. *Tetrahedron Lett.* **2002**, 43, 3133.

³⁸³ Lo, M.M.-C.; Fu, G.C. *Tetrahedron* **2001**, 57, 2621.

³⁸⁴ Davies, H.M.L.; Hedley, S.J.; Brooks, R.; Bohall, B.R. *J. Org. Chem.* **2005**, 70, 10737.

³⁸⁵ Bourque, L.E.; Cleary, P.A.; Woerpel, K.A. *J. Am. Chem. Soc.* **2007**, 129, 12602.

³⁸⁶ Davies, H.M.L.; Grazini, M.V.A.; Aouad, E. *Org. Lett.* **2001**, 3, 1475.

³⁸⁷ Doyle, M.P.; Protopopova, M.N.; Winchester, W.R.; Daniel, K.L. *Tetrahedron Lett.* **1992**, 33, 7819. See also, Clark, J.S.; Hodgson, P.B.; Goldsmith, M.D.; Street, L.J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3312.

³⁸⁸ Coutts, I.G.C.; Saint, R.E.; Saint, S.L.; Chambers-Asman, D.M. *Synthesis* **2001**, 247.

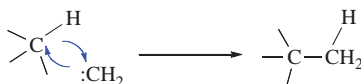
³⁸⁹ See Shi, W.; Zhang, B.; Zhang, J.; Liu, B.; Zhang, S.; Wang, J. *Org. Lett.* **2005**, 7, 3103.

³⁹⁰ See Doyle, M.P.; Kalinin, A.V. *Synlett*, **1995**, 1075; Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1995**, 36, 1491; Maruoka, K.; Concepcion, A.B.; Yamamoto, H. *J. Org. Chem.* **1994**, 59, 4725.

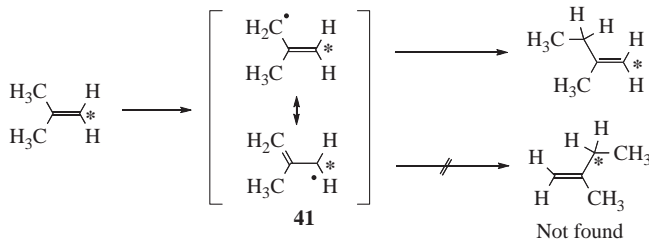
The metal carbene insertion reaction, in contrast to the methylene insertion reaction can be highly selective³⁹¹ and useful in synthesis.³⁹² There are numerous examples, usually requiring a transition metal catalyst.³⁹³ The catalyst typically converts a diazoalkane or diazocarbonyl compound to the metal carbene *in situ*, allowing the subsequent insertion reaction. Intermolecular reactions are known, including diazoalkane insertion reaction with a dirhodium catalyst.³⁹⁴ When chiral ligands are present good enantioselectivity is observed in the insertion product.³⁹⁵

The mechanism³⁹⁶ of the insertion reaction is not known with certainty, but there seem to be at least two possible pathways.

1. A simple one-step process involving a three-center cyclic transition state:

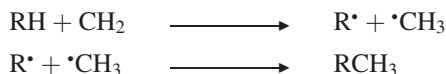


The most convincing evidence for this mechanism is that in the reaction between isobutene-1—¹⁴C and carbene the product 2-methyl-1-butene was labeled only in the 1 position.³⁹⁷ This rules out a free radical or a carbocation or carbanion intermediate. If **41** (or a corresponding ion) were an intermediate, resonance would ensure that some carbene attacked at the 1 position:



Other evidence is that retention of configuration, which is predicted by this mechanism, has been found in a number of instances.³⁹⁸ An ylid intermediate was trapped in the reaction of :CH_2 with allyl alcohol.³⁹⁹

2. A free radical process in which the carbene directly abstracts a hydrogen from the substrate to generate a pair of free radicals:



³⁹¹ See Sulikowski, G.A.; Cha, K.L.; Sulikowski, M.M. *Tetrahedron Asymmetry*, **1998**, 9, 3145.

³⁹² Ye, T.; McKervey, M.A. *Chem. Rev.* **1994**, 94, 1091.

³⁹³ Doyle, M.P. *Pure Appl. Chem.* **1998**, 70, 1123. See Taber, D.F.; Malcolm, S.C. *J. Org. Chem.* **1998**, 63, 3717 for a discussion of transition state geometry in rhodium mediated C—H insertion.

³⁹⁴ Davies, H.M.L.; Jin, Q. *Org. Lett.* **2004**, 6, 1769; Davies, H.M.L.; Loe, J. *Synthesis* **2004**, 2595.

³⁹⁵ See Davies, H.M.L.; Beckwith, R.E.J. *Chem. Rev.* **2003**, 103, 2861. See also Davies, H.M.L.; Nikolai, J. *Org. Biomol. Chem.* **2005**, 3, 4176; Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, 131, 14218.

³⁹⁶ See Bethell, D. *Adv. Phys. Org. Chem.* **1969**, 7, 153, pp. 190–194.

³⁹⁷ Doering, W. von E.; Prinzbach, H. *Tetrahedron* **1959**, 6, 24.

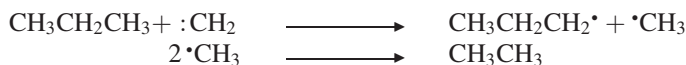
³⁹⁸ See Seyferth, D.; Cheng, Y.M. *J. Am. Chem. Soc.* **1971**, 93, 4072.

³⁹⁹ Sobery, W.; DeLucca, J.P. *Tetrahedron Lett.* **1995**, 36, 3315.

One fact supporting this mechanism is that among the products obtained (beside butane and isobutane) on treatment of propane with CH_2 (generated by photolysis of diazomethane and ketene) were propene and ethane,⁴⁰⁰ which could arise, respectively, by



and



That this mechanism can take place under suitable conditions has been demonstrated by isotopic labeling⁴⁰¹ and by other means.⁴⁰² However, the formation of disproportionation and dimerization products does not always mean that the free radical abstraction process takes place. In some cases, these products arise in a different manner.⁴⁰³ The product of the reaction between a carbene and a molecule may have excess energy (see Sec. 5.D.ii). Therefore it is possible for the substrate and the carbene to react by mechanism 1 (the direct-insertion process) and for the excess energy to cause the compound thus formed to cleave to free radicals. When this pathway is in operation, the free radicals are formed *after* the actual insertion reaction.

The mechanism of cyclopropylcarbene reactions has also been discussed.⁴⁰⁴

It has been suggested⁴⁰⁵ that singlet carbenes insert by the one-step direct-insertion process and triplets (which, being free radicals, are more likely to abstract hydrogen) by the free radical process. In support of this suggestion, CIDNP signals⁴⁰⁶ (Sec. 5.C.i) were observed in the ethylbenzene produced from toluene and triplet CH_2 , but not from the same reaction with singlet CH_2 .⁴⁰⁷ Carbenoids (e.g., compounds of the form R_2CMCl , see Reaction 12-39) can insert into a C—H bond by a different mechanism, similar to pathway 2, but involving abstraction of a hydride ion rather than a hydrogen atom.⁴⁰⁸

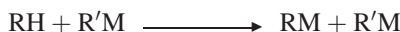
For the similar insertion reaction of nitrenes, see Reaction 12-13.

OS VII, 200.

F. Metal Electrophiles

12-22 Metalation with Organometallic Compounds

Metalation or Metalo-de-hydrogenation



⁴⁰⁰ Frey, H.M. *Proc. Chem. Soc.* **1959**, 318.

⁴⁰¹ McNesby, J.R.; Kelly, R.V. *Int. J. Chem. Kinet.* **1971**, 3, 293.

⁴⁰² Ring, D.F.; Rabinovitch, B.S. *J. Am. Chem. Soc.* **1966**, 88, 4285; *Can J. Chem.* **1968**, 46, 2435.

⁴⁰³ Bell, J.A. *Prog. Phys. Org. Chem.* **1964**, 2, 1, pp. 30–43.

⁴⁰⁴ Cummins, J.M.; Porter, T.A.; Jones, Jr., M. *J. Am. Chem. Soc.* **1998**, 120, 6473.

⁴⁰⁵ Richardson, D.B.; Simmons, M.C.; Dvoretzky, I. *J. Am. Chem. Soc.* **1961**, 83, 1934.

⁴⁰⁶ See Roth, H.D. *Acc. Chem. Res.* **1977**, 10, 85.

⁴⁰⁷ Roth, H.D. *J. Am. Chem. Soc.* **1972**, 94, 1761. See also, Bethell, D.; McDonald, K. *J. Chem. Soc. Perkin Trans. 2* **1977**, 671.

⁴⁰⁸ See Oku, A.; Yamaura, Y.; Harada, T. *J. Org. Chem.* **1986**, 51, 3730; Ritter, R.H.; Cohen, T. *J. Am. Chem. Soc.* **1986**, 108, 3718.

Many organic compounds can be metalated by treatment with an organometallic compound.⁴⁰⁹ Since the reaction involves a proton transfer, the equilibrium lies on the side of the weaker acid.⁴¹⁰ For example, fluorene reacts with *n*-butyllithium to give butane and 9-fluorenyllithium. Since aromatic hydrocarbons are usually stronger acids than aliphatic ones, R is most often aryl. The most common reagent is probably butyllithium.⁴¹¹ Reductive lithiation is an important method for the preparation of organolithium reagents.⁴¹² Normally, only active aromatic rings react with butyllithium. Benzene itself reacts very slowly and in low yield, although benzene can be metalated by butyllithium either in the presence of *tert*-BuOK⁴¹³ or by *n*-butyllithium that is coordinated with various diamines.⁴¹⁴ Metalation of aliphatic RH is most successful when the carbanions are stabilized by resonance (allylic, benzylic, propargylic,⁴¹⁵ etc.) or when the negative charge is at an *sp* carbon (at triple bonds). Trimethylsilylmethyl potassium (Me₃SiCH₂K)⁴¹⁶ and also a combination of an organolithium compound with a bulky alkoxide (LICKOR superbases)⁴¹⁷ are very good reagents for allylic metalation. The former is also useful for benzylic positions. A combination of BuLi, *t*-BuOK, and tetramethylethylenediamine has been used to convert ethylene to vinylpotassium.⁴¹⁸ The reaction can be used to determine relative acidities of very weak acids by allowing two R—H compounds to compete for the same R'M and to determine which proton in a molecule is the most acidic.⁴¹⁹

Note that organolithium compounds are aggregated species and can form hetero-aggregates containing different organic groups.⁴²⁰ *N*-Lithio-*N*-(trialkylsilyl)allylamines are deprotonated in ether solvents at the *cis*-vinyl position to give 3,*N*-dilithio-*N*-(trialkylsilyl)allylamines.⁴²¹

In general, the reaction can be performed only with organometallics of active metals (e.g., Li, Na, and K), but *Grignard reagents* abstract protons from a sufficiently acidic C—H bond, as in $R-C\equiv C-H \rightarrow R-C\equiv C-MgX$. This is the best method for the

⁴⁰⁹ See Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, **1988**, pp. 44–107; Wardell, J.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, pp. 1–157, pp. 27–71; Narasimhan, M.S.; Mali, R.S. *Synthesis* **1983**, 957; Biellmann, J.F.; Ducep, J. *Org. React.* **1982**, 27, 1; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* **1979**, 26, 1; Mallan, J.M.; Bebb, R.L. *Chem. Rev.* **1969**, 69, 693.

⁴¹⁰ See Saá, J.M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996**, 61, 5194.

⁴¹¹ See Durst, T. in Buncl, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, **1984**, pp. 239–291, pp. 265–279. For an article on the safe handling of RLi compounds, see Anderson, R. *Chem. Ind. (London)* **1984**, 205.

⁴¹² Ivanov, R.; Marek, I.; Cohen, T. *Tetrahedron Lett.* **2010**, 51, 174.

⁴¹³ Schlosser, M. *J. Organomet. Chem.* **1967**, 8, 9. See also, Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett*, **1990**, 747.

⁴¹⁴ Rausch, M.D.; Ciappenelli, D.J. *J. Organomet. Chem.* **1967**, 10, 127.

⁴¹⁵ See Klein, J. *Tetrahedron* **1983**, 39, 2733; Klein, J. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, **1978**, pp. 343–379.

⁴¹⁶ Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* **1976**, 59, 453.

⁴¹⁷ Schlosser, M. *Pure Appl. Chem.* **1988**, 60, 1627. For sodium analogues, see Schlosser, M.; Hartmann, J.; Stähle, M.; Kramar, J.; Walde, A.; Mordini, A. *Chimia*, **1986**, 40, 306.

⁴¹⁸ Brandsma, L.; Verkruijsse, H.D.; Schade, C.; Schleyer, P.v.R. *J. Chem. Soc. Chem. Commun.* **1986**, 260.

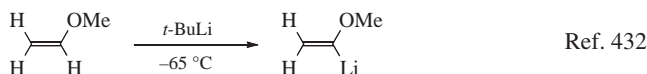
⁴¹⁹ See Shirley, D.A.; Hendrix, J.P. *J. Organomet. Chem.* **1968**, 11, 217.

⁴²⁰ Gossage, R.A.; Jastrzebski, J.T.B.H.; van Koten, G. *Angew. Chem. Int. Ed.* **2005**, 44, 1448.

⁴²¹ Jacobson, M.A.; Keresztes, I.; Williard, P.G. *J. Am. Chem. Soc.* **2005**, 127, 4965. For a computational study of mixed aggregates of chloromethylolithium and lithium dialkylamides, see Pratt, L.M.; Lê, L.T.; Truong, T.N. *J. Org. Chem.* **2005**, 70, 8298. Also see Gupta, L.; Hoepker, A.C.; Singh, K.J.; Collum, D.B. *J. Org. Chem.* **2009**, 74, 2231 for a LiCl catalyzed reaction.

preparation of alkynyl *Grignard reagents*.⁴²² Lewis acids have been used to promote α -lithiation of amines.⁴²³ Triethylgallium has been used to generate enolate anions from ketones.⁴²⁴

When a heteroatom (e.g., N, O, S,⁴²⁵ or a halogen),⁴²⁶ is present in a molecule containing an aromatic ring or a double bond, lithiation is usually quite regioselective.⁴²⁷ It has been shown that fluorine is more effective for stabilization of carbanions when compared to the heavier halogens.⁴²⁸ In such compounds, the lithium usually bonds with the sp^2 carbon closest to the heteroatom, probably because the attacking species coordinates with the heteroatom.⁴²⁹ This type of reaction with compounds such as anisole are often called directed metalations.⁴³⁰ In the case of aromatic rings, this means attack at the ortho position,⁴³¹ but this is considered in Reaction 13-17.



In the case of γ,δ -unsaturated disubstituted amides (**42**), the lithium does not go to the closest position, but in this case too the regiochemistry is controlled by coordination to the oxygen.⁴³³ Cyclopropyllithium reagents are rather stable.⁴³⁴



The mechanism involves an attack by R'^- (or a polar R') on the *hydrogen*⁴³⁵ (an acid–base reaction) Evidence is that resonance effects of substituents in R seem to make little difference. When R is aryl, OMe and CF_3 *both* direct ortho, while isopropyl directs meta

⁴²² See Blagoev, B.; Ivanov, D. *Synthesis* **1970**, 615.

⁴²³ Kessar, S.V.; Singh, P.; Singh, K.N.; Venugopalan, P.; Kaur, A.; Bharatam, P.V.; Sharma, A.K. *J. Am. Chem. Soc.* **2007**, *129*, 4506.

⁴²⁴ Nishimura, Y.; Miyake, Y.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* **2006**, *8*, 5077.

⁴²⁵ See Figuly, G.D.; Loop, C.K.; Martin, J.C. *J. Am. Chem. Soc.* **1989**, *111*, 654; Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.* **1989**, *111*, 658; Smith, K.; Lindsay, C.M.; Pritchard, G.J. *J. Am. Chem. Soc.* **1989**, *111*, 665.

⁴²⁶ See Gilday, J.P.; Negri, J.T.; Widdowson, D.A. *Tetrahedron* **1989**, *45*, 4605.

⁴²⁷ See Katritzky, A.R.; Lam, J.N.; Sengupta, S. *Prog. Heterocycl. Chem.* **1989**, *1*, 1.

⁴²⁸ Bickelhaupt, F.M.; Hermann, H.L.; Boche, G. *Angew. Chem. Int. Ed.* **2006**, *45*, 823.

⁴²⁹ See Beak, P.; Meyers, A.I. *Acc. Chem. Res.* **1986**, *19*, 356; Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306; Narasimhan, N.S.; Mali, R.S. *Top. Curr. Chem.* **1987**, *138*, 63; Reuman, M.; Meyers, A.I. *Tetrahedron* **1985**, *41*, 837.

⁴³⁰ Slocum, D.W.; Coffey, D.S.; Siegel, A.; Grimes, P. *Tetrahedron Lett.* **1994**, *35*, 389.

⁴³¹ See Snieckus, V. *Chem. Rev.* **1990**, *90*, 879; *Pure Appl. Chem.* **1990**, *62*, 2047. For a discussion of the mechanism, see Bauer, W.; Schleyer, P. v.R. *J. Am. Chem. Soc.* **1989**, *111*, 7191.

⁴³² Baldwin, J.E.; Höfle, G.A.; Lever Jr., O.W. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

⁴³³ Beak, P.; Hunter, J.E.; Jun, Y.M.; Wallin, A.P. *J. Am. Chem. Soc.* **1987**, *109*, 5403. See also, Stork, G.; Polt, R. L.; Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* **1988**, *110*, 8360; Barluenga, J.; Foubelo, F.; Fañanas, F.J.; Yus, M. *J. Chem. Res. (S)* **1989**, 200.

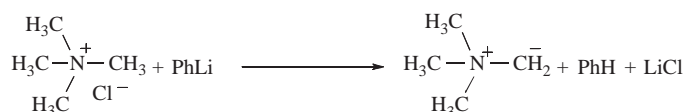
⁴³⁴ Peñafiel, I.; Pastor, I.M.; Yus, M. *Tetrahedron* **2010**, *66*, 2928.

⁴³⁵ Benkeser, R.A.; Trevillyan, E.A.; Hooz, J. *J. Am. Chem. Soc.* **1962**, *84*, 4971.

and para (mostly meta).⁴³⁶ These results are exactly what would be expected from pure field effects, with no contribution from resonance effects, which implies that attack occurs at the hydrogen and not at R. Other evidence for the involvement of H in the rate-determining step is that there are large isotope effects.⁴³⁷ The nature of R' also has an effect on the rate. In the reaction between triphenylmethane and R'Li, the rate decreased in the order R' = allyl > Bu > Ph > vinyl > Me, although this order changed with changing concentration of R'Li, because of varying degrees of aggregation of the R'Li.⁴³⁸ With respect to the reagent, this reaction is a special case of Reaction 12-24.

Enantioselective reactions are known. The preparation of chlorodeuteriomethylithium proceeds with inversion from the corresponding enantiopure stannyl derivative.⁴³⁹ Although highly reactive chemically, it is configurationally stable at temperatures up to -78°C . Enantioselective catalytic deprotonation with chiral ligands has been used for the deprotonation of *N*-Boc amines to give chiral α -trimethylsilyl derivatives.⁴⁴⁰ A barrier to enantiomerization has been observed for unstabilized, chelated, and dipole-stabilized organolithium compounds. Studies of lithiopyrrolidines show free energies for enantiomerization in the range of $19\text{--}22\text{ kcal mol}^{-1}$ ($79.5\text{--}92.1\text{ kJ mol}^{-1}$) at 0°C .⁴⁴¹

A closely related reaction is formation of nitrogen ylids⁴⁴² from quaternary ammonium salts (see Reaction 17-8):



Phosphonium salts undergo a similar reaction (see Reaction 16-44).

OS II, 198; III, 413, 757; IV, 792; V, 751; VI, 436, 478, 737, 979; VII, 172, 334, 456, 524; VIII, 19, 391, 396, 606.

12-23 Metalation with Metals and Strong Bases

Metalation or Metalo-de-hydrogenation



Organic compounds can be metalated at suitably acidic positions by active metals and by strong bases.⁴⁴³ The reaction has been used to study the acidities of very weak acids (see Sec. 5.B.i). The conversion of terminal alkynes to acetylide ions is one important

⁴³⁶ Bryce-Smith, D. *J. Chem. Soc.* **1963**, 5983; Benkeser, R.A.; Hooz, J.; Liston, T.V.; Trevillyan, E.A. *J. Am. Chem. Soc.* **1963**, 85, 3984.

⁴³⁷ Pocker, Y.; Exner, J.H. *J. Am. Chem. Soc.* **1968**, 90, 6764.

⁴³⁸ West, P.; Waack, R.; Purmort, J.I. *J. Am. Chem. Soc.* **1970**, 92, 840.

⁴³⁹ Kapeller, D.C.; Hammerschmidt, F. *J. Am. Chem. Soc.* **2008**, 130, 2329.

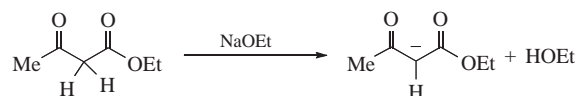
⁴⁴⁰ McGrath, M.J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, 127, 16378.

⁴⁴¹ Ashweek, J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R.E.; Häffner, F.; Klein, R.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, 127, 449.

⁴⁴² Zugravescu, I.; Petrovanu, M. *Nitrogen-Ylid Chemistry*, McGraw Hill, NY, **1976**, pp. 251–283; Wittig, G.; Rieber, M. *Ann.* **1949**, 562, 177; Wittig, G.; Polster, R. *Ann.* **1956**, 599, 1.

⁴⁴³ See Durst, T. in Buncl, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, **1984**, pp. 239–291; Wardell, J.L. Ref. 388; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, **1988**, pp. 32–44.

application.⁴⁴⁴ A gold-catalyst conversion of trimethylsilyl substituted esters and carbonates to the corresponding enolate anion has been reported⁴⁴⁵. Synthetically, an important use of the method is to convert aldehydes and ketones,⁴⁴⁶ carboxylic esters, and similar compounds to their enolate forms,⁴⁴⁷ for example,



for use in nucleophilic substitutions (Reactions **10-67**, **10-68**, and **13-14**) and in additions to multiple bonds (Reactions **15-24** and **16-53**). Note that the reaction of carbonyl compounds with lithium dialkylamides leads to the corresponding enolate anion. This reaction was discussed in Reaction **10-68**, in connection with the alkylation reaction of enolate anions.

OS I, 70, 161, 490; IV, 473; VI, 468, 542, 611, 683, 709; VII, 229, 339. Conversions of ketones or esters to enolates are not listed.

12.C.ii. Metals as Leaving Groups

A. Hydrogen as the Electrophile

12-24 Replacement of Metals by Hydrogen

Hydro-de-metalation or Demetalation



Organometallic compounds, including enolate anions, react with acids in reactions that replace the metal with hydrogen.⁴⁴⁸ The R group may be aryl (see Reaction **11-41**). The reaction is often used to introduce deuterium or tritium into susceptible positions. For *Grignard reagents*, water is usually a strong enough acid, but stronger acids are also used. An important method for the reduction of alkyl halides consists of the process $\text{RX} \rightarrow \text{RMgX} \rightarrow \text{RH}$.

The organometallic compounds that are hydrolyzed by water are the ones high in the electromotive series: Na, K, Li, Zn, and so on. Enantioselective protonation of lithium enolates⁴⁴⁹ and cyclopropyllithium compounds⁴⁵⁰ have been reported. When the metal is less active, stronger acids are required. For example, R_2Zn compounds react explosively with water, R_2Cd slowly, and R_2Hg not at all, although the latter can be cleaved with

⁴⁴⁴ See Ziegenbein, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 170–185. For an improved method, see Fisch, A.; Coisne, J.M.; Figeys, H.P. *Synthesis* **1982**, 211.

⁴⁴⁵ Wang, S.; Zhang, L. *Org. Lett.* **2006**, 8, 4585.

⁴⁴⁶ Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc.* **1998**, 120, 2290.

⁴⁴⁷ See Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, **1979**, pp. 95–145, 284–291.

⁴⁴⁸ See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 25–149, pp. 105–136; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, **1973**, pp. 107–134; Schlosser, M. *Angew. Chem. Int. Ed.* **1964**, 3, 287, 362; *Newer Methods Prep. Org. Chem.* **1968**, 5, 238.

⁴⁴⁹ Mitsuhashi, K.; Ito, R.; Arai, T.; Yanagisawa, A. *Org. Lett.* **2006**, 8, 1721.

⁴⁵⁰ Walborsky, H.M.; Ollman, J.; Hamdouchi, C.; Topolski, M. *Tetrahedron Lett.* **1992**, 33, 761.

concentrated HCl. However, this general statement has many exceptions, some hard to explain. For example, BR_3 compounds are completely inert to water, and GaR_3 at room temperature cleave just one R group, but AlR_3 reacts violently with water. However, BR_3 can be converted to RH with carboxylic acids.⁴⁵¹ For less active metals, it is often possible to cleave just one R group from a multivalent metal. For example,



Organometallic compounds of less active metals and metalloids (e.g., Si,⁴⁵² Sb, and Bi), are quite inert to water. Organomercury compounds (RHgX or R_2Hg) can be reduced to RH by H_2 , NaBH_4 , or other reducing agents.⁴⁵³ The reduction with NaBH_4 takes place by a free radical mechanism.⁴⁵⁴ Alkyl-Si bonds are cleaved by H_2SO_4 [e.g., $\text{HOOCCH}_2\text{CH}_2\text{SiMe}_3 \rightarrow 2\text{CH}_2 + (\text{HOOCCH}_2\text{CH}_2\text{SiMe}_3)_2\text{O}$].⁴⁵⁵

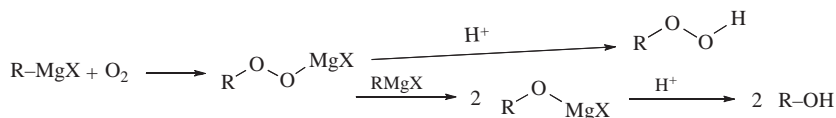
When the hydrogen of the HA is attached to carbon, this reaction is the same as **12-22**.

This section does not list the many hydrolyses of Na or K enolates, and so on found in *Organic Syntheses*. The hydrolysis of a *Grignard reagent* to give an alkane is found at **OS II**, 478; the reduction of a vinylic tin compound at **OS VIII**, 381; and the reduction of an alkynylsilane at **OS VIII**, 281.

B. Oxygen Electrophiles

12-25 The Reaction between Organometallic Reagents and Oxygen⁴⁵⁶

Hydroperoxy-de-metalation; Hydroxy-de-metalation



Oxygen reacts with *Grignard reagents* to give either hydroperoxides⁴⁵⁷ or alcohols. The reaction can be used to convert alkyl halides to alcohols without side reactions. With aryl *Grignard reagents*, yields are lower and only phenols are obtained, not hydroperoxides. Because of this reaction, oxygen should be excluded when *Grignard reagents* are prepared and used in various reactions.

Most other organometallic compounds also react with oxygen. Trialkylboranes and alkylchloroboranes (RBCl_2) can be conveniently converted to hydroperoxides by treatment with oxygen followed by hydrolysis.⁴⁵⁸ Dilithiated carboxylic acids (see Reaction **10-70**) react with oxygen to give (after hydrolysis) α -hydroxy carboxylic

⁴⁵¹ Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, see pp. 242–244.

⁴⁵² See Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, 37, 57, pp. 89–97, 194–243.

⁴⁵³ See Makarova, L.G. *Organomet. React.* **1970**, 1, 119, see pp. 251–270, 275–300.

⁴⁵⁴ See Barluenga, J.; Yus, M. *Chem. Rev.* **1988**, 88, 487.

⁴⁵⁵ Sommer, L.H.; Marans, N.S.; Goldberg, G.M.; Rockett, J.; Pioch, R.P. *J. Am. Chem. Soc.* **1951**, 73, 882. See also, Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, p. 117.

⁴⁵⁶ See Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton, FL, **1969**; Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, **1985**, see pp. 219–338, pp. 311–316.

⁴⁵⁷ See Harada, T.; Kutsuwa, E. *J. Org. Chem.* **2003**, 68, 6716.

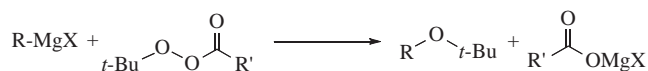
⁴⁵⁸ Brown, H.C.; Midland, M.M. *Tetrahedron* **1987**, 43, 4059.

acids.⁴⁵⁹ There is evidence that the reaction between *Grignard reagents* and oxygen involves a free radical mechanism.⁴⁶⁰

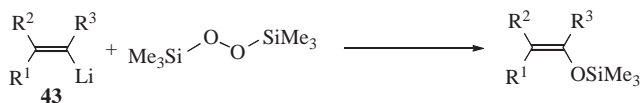
OS V, 918. See also, OS VIII, 315.

12-26 Reaction between Organometallic Reagents and Peroxides

tert-Butoxy-de-metalation



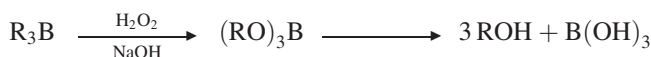
A convenient method of preparation of *tert*-butyl ethers consists of treating *Grignard reagents* with *tert*-butyl acyl peroxides.⁴⁶¹ Both alkyl and aryl *Grignard reagents* can be used. The application of this reaction to *Grignard reagents* prepared from cyclopropyl halides permits cyclopropyl halides to be converted to *tert*-butyl ethers of cyclopropanols,⁴⁶² which can then be easily hydrolyzed to the cyclopropanols. The direct conversion of cyclopropyl halides to cyclopropanols by Reaction 10-1 is not generally feasible, because cyclopropyl halides do not generally undergo nucleophilic substitutions without ring opening.



Vinyl lithium reagents (**43**) react with silyl peroxides to give high yields of silyl enol ethers with retention of configuration.⁴⁶³ Since the preparation of **43** from vinylic halides (Reaction 12-39) also proceeds with retention, the overall procedure is a method for the stereospecific conversion of a vinylic halide to a silyl enol ether. Dialky ethers have been prepared from organotrifluoroborates and acetals.⁴⁶⁴

OS V, 642, 924.

12-27 Oxidation of Trialkylboranes to Borates



The reaction of alkenes with borane, monoalkyl, and dialkylboranes leads to a new organoborane (see Reaction 15-16). Treatment of organoboranes with alkaline H₂O₂ oxidizes trialkylboranes to esters of boric acid.⁴⁶⁵ This reaction does not affect double

⁴⁵⁹ Adam, W.; Cueto, O. *J. Org. Chem.* **1977**, 42, 38.

⁴⁶⁰ Garst, J.F.; Smith, C.D.; Farrar, A.C. *J. Am. Chem. Soc.* **1972**, 94, 7707. See Davies, A.G. *J. Organomet. Chem.* **1980**, 200, 87.

⁴⁶¹ Lawesson, S.; Frisell, C.; Denney, D.B.; Denney, D.Z. *Tetrahedron* **1963**, 19, 1229. See Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton, FL, **1969**; Razuvaev, G.A.; Shushunov, V.A.; Dodonov, V.A.; Brilkina, T.G. in Swern, D. *Organic Peroxides*, Vol. 3, Wiley, NY, **1972**, pp. 141–270.

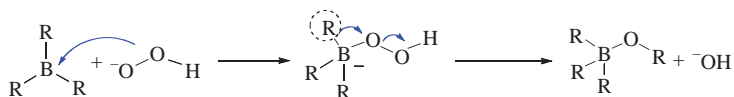
⁴⁶² Longone, D.T.; Miller, A.H. *Tetrahedron Lett.* **1967**, 4941.

⁴⁶³ Davis, F.A.; Lal, G.S.; Wei, J. *Tetrahedron Lett.* **1988**, 29, 4269.

⁴⁶⁴ Mitchell, T.A.; Bode, J.W. *J. Am. Chem. Soc.* **2009**, 131, 18057.

⁴⁶⁵ See Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, pp. 244–249; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**, pp. 321–325. See also, Brown, H.C.; Snyder, C.; Subba Rao, B.C.; Zweifel, G. *Tetrahedron* **1986**, 42, 5505.

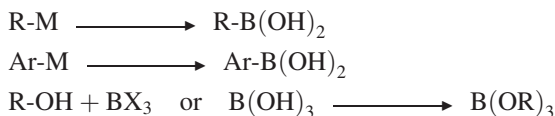
or triple bonds, aldehydes, ketones, halides, or nitriles that may be present elsewhere in the molecule. There is no rearrangement of the R group itself, and this reaction is a step in the hydroboration method of converting alkenes to alcohols (Reaction 15-16). The mechanism has been formulated as involving initial formation of an ate complex when the hydroperoxide anion attacks the electrophilic boron atom. Subsequent rearrangement from boron to oxygen,⁴⁶⁵ as shown, leads to the B—O—R unit.



Similar migration of the other two R groups and hydrolysis of the B—O bonds leads to the alcohol and boric acid. Retention of configuration is observed in R. Boranes can also be oxidized to borates in good yields with oxygen,⁴⁶⁶ with sodium perborate (NaBO_3)⁴⁶⁷ and with trimethylamine oxide, either anhydrous⁴⁶⁸ or in the form of the dihydrate.⁴⁶⁹ The reaction with oxygen is free radical in nature.⁴⁷⁰

OS V, 918; VI, 719, 852, 919.

12-28 Preparation of Borates and Boronic Acids



Alkylboronic and arylboronic acids [RB(OH)_2 , and ArB(OH)_2], respectively, are increasingly important in organic chemistry. The Pd catalyzed coupling reaction of aryl halides and aryl triflates with arylboronic acids (the *Suzuki–Miyaura reaction*, 13-12) is probably the most notable example. A simple synthesis involves the reaction of a *Grignard reagent* (e.g., phenylmagnesium bromide) with an alkyl borate to give phenylboronic acid.⁴⁷¹ Alkylboronic acids are similarly prepared.⁴⁷² Note that boronic acids are subject to cyclic trimerization with loss of water to form boroxines. Tetrahydroxydiboron has been used to prepare allylboronic acids, as well as potassium trifluoro(allyl)borates.⁴⁷³

Trimethylborate [B(OMe)_3] can be used in place of tri-*n*-butyl borate.⁴⁷⁴ Newer methods involve the Pd mediated borylation of alcohols with bis(pinacolato)diboron⁴⁷⁵ or pinacolborane,⁴⁷⁶ but deprotection of the boronate esters can be a problem. Diolboranes (e.g., catecholborane 44)⁴⁷⁷ are prepared by the reaction of a diol with borane.

⁴⁶⁶ Brown, H.C.; Midland, M.M.; Kabalka, G.W. *Tetrahedron* **1986**, 42, 5523.

⁴⁶⁷ Kabalka, G.W.; Shoup, T.M.; Goudgaon, N.M. *J. Org. Chem.* **1989**, 54, 5930.

⁴⁶⁸ Köster, R.; Arora, S.; Binger, P. *Angew. Chem. Int. Ed.* **1969**, 8, 205.

⁴⁶⁹ Kabalka, G.W.; Slayden, S.W. *J. Organomet. Chem.* **1977**, 125, 273.

⁴⁷⁰ Midland, M.M.; Brown, H.C. *J. Am. Chem. Soc.* **1971**, 93, 1506.

⁴⁷¹ Bean, F.R.; Johnson, J.R. *J. Am. Chem. Soc.* **1932**, 54, 4415; Lappert, M.F. *Chem. Rev.* **1956**, 56, 959.

⁴⁷² Khotinsky, E.; Melamed, M. *Chem. Ber.* **1909**, 42, 3090.

⁴⁷³ Sebelius, S.; Olsson, V.J.; Szabó, K.J. *J. Am. Chem. Soc.* **2005**, 127, 10478.

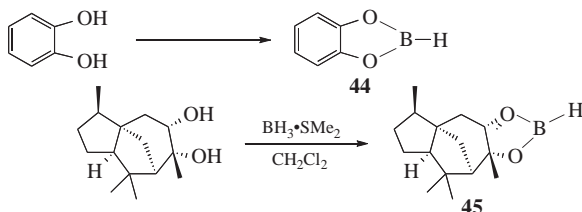
⁴⁷⁴ Soloway, A.H. *J. Am. Chem. Soc.* **1959**, 81, 3017.

⁴⁷⁵ Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, 60, 7508.

⁴⁷⁶ Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, 65, 164; Song, Y.L. *Synlett* **2000**, 1210.

⁴⁷⁷ Kanth, J.V.B.; Periasamy, M.; Brown, H.C. *Org. Process Res. Dev.* **2000**, 4, 550.

Cedranediolborane (**45**, prepared from the cedrane-8,9-diol⁴⁷⁸ by treatment with borane•dimethyl sulfide) can be coupled to aryl iodides with a palladium catalyst, and generates the free boronic acid by treatment with diethanolamine and then aq acid.⁴⁷⁹ Boronate esters are often prepared as a means to purify the organoboron species, but some of these esters are hydrolytically unstable and difficult to deal with upon completion of the reaction.⁴⁸⁰



Alkeneboronic esters and acids are also readily available, as in the addition of vinylmagnesium chloride⁴⁸¹ to trimethyl borate below -50°C , followed by hydrolysis.⁴⁸² A nonaqueous workup procedure has been reported for the preparation of arylboronic esters $[\text{ArB}(\text{OR}')_2]$.⁴⁸³ Uncontrollable polymerization or oxidation of much of the boronic acid occurred during the final stages of the isolation procedure, but could be avoided by *in situ* conversion to the dibutyl ester by adding the crude product to 1-butanol. The Sm(III) catalyzed hydroboration of olefins with catecholborane is a good synthesis of boronate esters.⁴⁸⁴

Trialkyl borates (sometimes called orthoborates) can be prepared by heating the appropriate alcohol with boron trichloride in a sealed tube, but the procedure works well only for relatively simple alkyl groups.⁴⁸⁵ Heating alcohols with boron trioxide (B_2O_3) in an autoclave at $110\text{--}170^{\circ}\text{C}$ give the trialkyl borate.⁴⁸⁶ Boric acid can be used for the preparation of orthoborates⁴⁸⁷ by heating with alcohols in the presence of either hydrogen chloride or concentrated sulfuric acid. Removal of water as an azeotrope with excess alcohol improves the yield,⁴⁸⁸ and good yields can be obtained for trialkyl borates⁴⁸⁹ and even for triphenyl borate.⁴⁹⁰ This method is unsuccessful for those borates whose parent alcohols do not form azeotropes with water and for the tertiary alkyl borates,⁴⁸⁹ impure samples are usually obtained.⁴⁹¹

⁴⁷⁸ Song, Y.; Ding, Z.; Wang, Q.; Tao, F. *Synth. Commun.* **1998**, 28, 3757.

⁴⁷⁹ Song, Y.-L.; Morin, C. *Synlett* **2001**, 266.

⁴⁸⁰ Lightfoot, A.P.; Maw, G.; Thirsk, C.; Twiddle, S.J.R.; Whiting, A. *Tetrahedron Lett.* **2003**, 44, 7645.

⁴⁸¹ Ramsden, H.E.; Leebrick, J.R.; Rosenberg, S.D.; Miller, E.H.; Walburn, J.J.; Balint, A.E.; Cserr, R. *J. Org. Chem.*, **1957**, 22, 1602.

⁴⁸² Matteson, D.S. *Acc. Chem. Res.* **1970**, 3, 186; Matteson, D.S. *Progr. Boron Chem.* **1970**, 3, 117.

⁴⁸³ Wong, K.-T.; Chien, Y.-Y.; Liao, Y.-L.; Lin, C.-C.; Chou, M.-Y.; Leung, M.-K. *J. Org. Chem.* **2002**, 67, 1041.

⁴⁸⁴ Evans, D.A.; Muci, A.R.; Stuermer, R. *J. Org. Chem.*, **1993**, 58, 5307.

⁴⁸⁵ Counciler, C. *Ber.* **1876**, 9, 485; **1877**, 10, 1655; **1878**, 11, 1106.

⁴⁸⁶ Schiff, H. *Ann. Suppl.* **1867**, 6, 158; Counciler, C. *J. Prakt. Chem.* **1871**, 16, 371.

⁴⁸⁷ Cohn, G. *Pharm. Zentr.* **1911**, 62, 479.

⁴⁸⁸ Bannister, W.J. U.S. Patent 1,668,797 (*Chem. Abstr.* **1928**, 22:2172).

⁴⁸⁹ Haider, S.Z.; Khundhar, M.H.; Siddiquah, Md. *J. Appl. Chem.* **1954**, 4, 93.

⁴⁹⁰ Colclough, T.; Gerrard, W.; Lappert, M.F. *J. Chem. Soc.* **1955**, 907.

⁴⁹¹ Ahmad, T.; Khundkar, M.H. *Chem. Ind.* **1954**, 248.

Potassium organotrifluoroborates (RBF_3K) are readily prepared by the addition of inexpensive KHF_2 to a variety of organoboron intermediates.⁴⁹² They are monomeric, crystalline solids that are readily isolated and indefinitely stable in the air. These reagents can be used in several of the applications where boronic acids or esters are used (Reactions 13-10–13-13).⁴⁹³ Note that vinylboronic acid and even vinylboronate esters are unstable to polymerization,⁴⁹⁴ whereas the analogous vinyltrifluoroborate is readily synthesized and completely stable.⁴⁹⁵

OS 13, 16; 81, 134.

12-29 Oxygenation of Organometallic Reagents and Other Substrates to O-Esters and Related Compounds

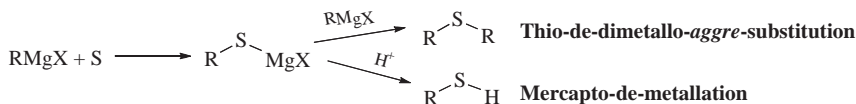


In some cases, it is possible to oxygenate a nonaromatic carbon atom using various reagents, where the product is an *O*- ester rather than an alcohol. In one example, a vinyl iodonium salt was heated with DMF to produce the corresponding formate ester.⁴⁹⁶

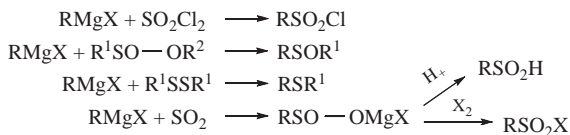


C. Sulfur Electrophiles

12-30 Conversion of Organometallic Reagents to Sulfur Compounds



Thiols and sulfides are occasionally prepared by treatment of *Grignard reagents* with sulfur.⁴⁹⁷ Analogous reactions are known for selenium and tellurium compounds. *Grignard reagents* and other



⁴⁹² Vedejs, E.; Fields, S.C.; Hayashi, R.; Hitchcock, S.R.; Powell, D.R.; Schrimpf, M.R. *J. Am. Chem. Soc.* **1999**, *121*, 2460.

⁴⁹³ Molander, G.A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302; Molander, G.A.; Yun, C.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534; Molander, G.A.; Ribagorda, M. *J. Am. Chem. Soc.* **2003**, *125*, 11148.

⁴⁹⁴ Matteson, D. S. *J. Am. Chem. Soc.* **1960**, *82*, 4228.

⁴⁹⁵ Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950.

⁴⁹⁶ Ochiai, M.; Yamamoto, S.; Sato, K. *Chem. Commun.* **1999**, 1363.

⁴⁹⁷ See Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, **1985**, pp. 316–323; Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, **1974**, pp. 211–215; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, **1988**, pp. 135–142.

organometallic compounds⁴⁹⁸ react with sulfonyl chloride to give sulfonyl chlorides,⁴⁹⁹ with esters of sulfinic acids to give (stereospecifically) sulfoxides,⁵⁰⁰ with disulfides to give sulfides,⁵⁰¹ and with SO₂ to give sulfinic acid salts,⁵⁰² which can be hydrolyzed to sulfinic acids or treated with halogens to give sulfonyl halides.⁵⁰³

OS **III**, 771; **IV**, 667; **VI**, 533, 979.

D. Halogen Electrophiles

12-31 Halo-de-metalation



Grignard reagents react with halogens to give alkyl halides. The reaction is useful for the preparation of iodo compounds from the corresponding chloro or bromo compounds. The reaction is not useful for preparing chlorides, since the reagents RMgBr and RMgI react with Cl₂ to give mostly RBr and RI, respectively.⁵⁰⁴

Most organometallic compounds, both alkyl and aryl, also react with halogens to give alkyl or aryl halides.⁵⁰⁵ The reaction can be used to convert acetylide ions to 1-haloalkynes.⁵⁰⁶ Vinylodonium tetrafluoroborates were converted to vinyl fluorides by heating.⁵⁰⁷ Similarly, vinyl trifluoroborates were converted to the vinyl iodide with NaI and chloramine-T in aq THF.⁵⁰⁸ The reaction of an alkene with CuO·BF₄, iodine and triethylsilane gave the 2-iodoalkane.⁵⁰⁹ Vinylzirconate reagents react with I₂ to give the corresponding vinyl iodide.⁵¹⁰

Enolate anions can be converted to the corresponding vinyl phosphate, and subsequent reaction with triphenylphosphine dihalide leads to the vinyl halide.⁵¹¹

Trialkylboranes react rapidly with I₂⁵¹² or Br₂⁵¹³ in the presence of NaOMe in methanol, or with FeCl₃ or other reagents⁵¹⁴ to give alkyl iodides, bromides, or chlorides,

⁴⁹⁸ Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, **1985**, pp. 210–216.

⁴⁹⁹ Bhattacharya, S.N.; Eaborn, C.; Walton, D.R.M. *J. Chem. Soc. C* **1968**, 1265. For similar reactions with organolithiums, see Hamada, T.; Yonemitsu, O. *Synthesis* **1986**, 852.

⁵⁰⁰ Harpp, D.N.; Vines, S.M.; Montillier, J.P.; Chan, T.H. *J. Org. Chem.* **1976**, *41*, 3987.

⁵⁰¹ See Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, **1980**, pp. 243–247.

⁵⁰² See Kitching, W.; Fong, C.W. *Organomet. Chem. Rev. Sect. A* **1970**, *5*, 281.

⁵⁰³ Asinger, F.; Laue, P.; Fell, B.; Gubelt, C. *Chem. Ber.* **1967**, *100*, 1696.

⁵⁰⁴ Zakharkin, L.I.; Gavrilenko, V.V.; Paley, B.A. *J. Organomet. Chem.* **1970**, *21*, 269.

⁵⁰⁵ See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 72–105; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, **1985**, pp. 158–178; Makarova, L.G. *Organomet. React.* **1970**, *1*, 119, pp. 325–348.

⁵⁰⁶ See Delavarenne, S.Y.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 665–688. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 655–656. For an improved procedure, see Brandsma, L.; Verkruijsse, H.D. *Synthesis* **1990**, 984.

⁵⁰⁷ Okuyama, T.; Fujita, M.; Gronheid, R.; Lodder, G. *Tetrahedron Lett.* **2000**, *41*, 5125.

⁵⁰⁸ Kabalka, G.W.; Mereddy, A.R. *Tetrahedron Lett.* **2004**, *45*, 1417.

⁵⁰⁹ Campos, P.J.; García, B.; Rodríguez, M.A. *Tetrahedron Lett.* **2002**, *43*, 6111.

⁵¹⁰ Zhang, D.; Ready, J.M. *J. Am. Chem. Soc.* **2007**, *129*, 12088.

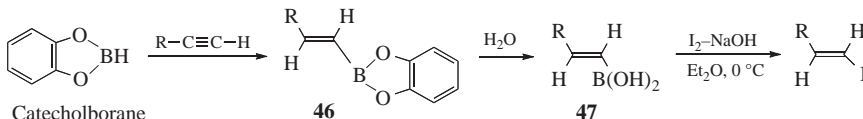
⁵¹¹ Kamei, K.; Maeda, N.; Tatsuoka, T. *Tetrahedron Lett.* **2005**, *46*, 229.

⁵¹² Brown, H.C.; Rathke, M.W.; Rogic, M.M.; De Lue, N.R. *Tetrahedron* **1988**, *44*, 2751.

⁵¹³ Brown, H.C.; Lane, C.F. *Tetrahedron* **1988**, *44*, 2763; Brown, H.C.; Lane, C.F.; De Lue, N.R. *Tetrahedron* **1988**, *44*, 2273. Also see Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* **1989**, *54*, 340.

⁵¹⁴ Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* **1988**, *53*, 5664. For other reagents, see Jigajinni, V.B.; Brown, H.C.; De Lue, N.R. *Tetrahedron* **1988**, *44*, 2785.

respectively. Combined with the hydroboration reaction (Reaction **15-16**), this is an indirect way of adding HBr, HI, or HCl to a double bond to give products with an *anti-Markovnikov* orientation (see Reaction **15-1**). Trialkylboranes can also be converted to alkyl iodides by treatment with allyl iodide and air in a free radical process.⁵¹⁵ *trans*-1-Alkenylboronic acids (**47**), prepared by hydroboration of terminal alkynes with catecholborane to give **46**⁵¹⁶ (Reaction **15-16**), followed by hydrolysis, react with I₂ in the presence of NaOH at 0 °C in ethereal solvents to give *trans*-vinylic iodides.⁵¹⁷



Treatment with ICl also gives the vinyl iodide.⁵¹⁸ This is an indirect way of accomplishing the *anti-Markovnikov* addition of HI to a terminal triple bond. The reaction cannot be applied to alkenylboronic acids prepared from internal alkynes. However, alkenylboronic acids prepared from both internal and terminal alkynes react with Br₂ (2 molar equivalents of Br₂ must be used) followed by base to give the corresponding vinylic bromide, but in this case with *inversion* of configuration; so the product is the *cis*-vinylic bromide.⁵¹⁹ Alkenylboronic acids also give vinylic bromides and iodides when treated with a mild oxidizing agent and NaBr or NaI, respectively.⁵²⁰ Treatment of **47** (prepared from terminal alkynes) with Cl₂ gave vinylic chlorides with inversion.⁵²¹ Vinylic boranes can be converted to the corresponding vinylic halide by treatment with NCS or NBS.⁵²² Vinylic halides can also be prepared from vinylic silanes⁵²³ and from vinylic copper reagents. The latter react with I₂ to give iodides,⁵²⁴ and with NCS or NBS at -45 °C to give chlorides or bromides.⁵²⁵ The reaction of an aryl alkyne with HInCl₂/BEt₃ and then iodine leads to a (*Z*)-vinyl iodide with respect to the aryl group and the iodine atom.⁵²⁶ Boronic acids can be fluorinated in a reaction mediated by Ag(I) triflate.⁵²⁷

For the reaction of lithium enolate anions of esters with I_2 or CX_4 , see Reaction **12-5**.

The conversion of terminal alkynes to 1-iodo-1-alkynes was reported using NaI under electrochemical conditions.⁵²⁸ 1-Bromo-1-alkynes were converted to the 1-iodo-1-alkyne

⁵¹⁵ Suzuki, A.; Nozawa, S.; Harada, M.; Itoh, M.; Brown, H.C.; Midland, M.M. *J. Am. Chem. Soc.* **1971**, 93, 1508; Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed.* **1972**, 11, 692, pp. 699–700; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, **1972**, pp. 442–446.

⁵¹⁶ See Kabalka, G.W. *Org. Prep. Proced. Int.* **1977**, 9, 131.

⁵¹⁷ Brown, H.C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N.G. *J. Org. Chem.* **1989**, *54*, 6075. See also, Kabalka, G.W.; Gooch, E.E.; Hsu, H.C. *Synth. Commun.* **1981**, *11*, 247.

⁵¹⁸ Stewart, S.K.; Whiting, A. *Tetrahedron Lett.* **1995**, 36, 3929.

⁵¹⁹ Brown, H.C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, 95, 6456. See also, Brown, H.C.; Bhat, N.G. *Tetrahedron Lett.* **1988**, 29, 21.

⁵²⁰ See Kabalka, G.W.; Sastry, K.A.R.; Knapp, F.F.; Srivastava, P.C. *Synth. Commun.* **1983**, *13*, 1027.

⁵²¹ Kunda, S.A.; Smith, T.L.; Hylarides, M.D.; Kabalka, G.W. *Tetrahedron Lett.* **1985**, 26, 279.

⁵²² Hoshi, M.; Shirakawa, K. *Tetrahedron Lett.* **2000**, 41, 2595.

⁵²³ See Chou, S.P.; Kuo, H.; Wang, C.; Tsai, C.; Sun, C. *J. Org. Chem.* **1989**, *54*, 868.

⁵²⁴ Normant, J.F.; Chaiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* **1974**, 77, 269; *Synthesis* **1974**, 803.

⁵²⁵ Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1977**, 96, 168; Levy, A.B.; Talley, P.; Dunford, J.A. *Tetrahedron Lett.* **1977**, 3545.

⁵²⁶ Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, 4, 2993.

⁵²⁷ Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860.

⁵²⁸ Nishiguchi, I.; Kanbe, O.; Itoh, K.; Maekawa, H. *Synlett* **2000**, 89.

with CuI.⁵²⁹ 1-Trialkyldisilylalkynes were converted to the corresponding 1-bromoalkyne via reaction with NBS and AgF.⁵³⁰ Terminal alkynes react with (diacetoxyiodo)benzene, KI, and CuI to give 1-iodo-alkynes.⁵³¹ Trichloroisocyanuric acid has been used to convert terminal alkynes to 1-chloroalkynes.⁵³²

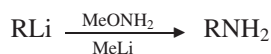
It is unlikely that a single mechanism suffices to cover all conversions of organometallic compounds to alkyl halides.⁵³³ In a number of cases, the reaction has been shown to involve inversion of configuration (see Sec. 12.A.i), indicating an S_E2 (back) mechanism, while in other cases retention of configuration has been shown,⁵³⁴ implicating an S_E2 (front) or S_Ei mechanism. In still other cases, complete loss of configuration as well as other evidence demonstrated the presence of a free radical mechanism.^{534,535}

OS I, 125, 325, 326; III, 774, 813; V, 921; VI, 709; VII, 290; VIII, 586; IX, 573. Also see, OS II, 150.

E. Nitrogen Electrophiles

12-32 The Conversion of Organometallic Compounds to Amines

Amino-de-metalation



There are several methods for conversion of alkyl- or aryllithium compounds to primary amines.⁵³⁶ The two most important are treatment with hydroxylamine derivatives and with certain azides.⁵³⁷ In the first of these methods, treatment of RLi with methoxyamine and MeLi in ether at -78°C gives RNH₂.⁵³⁸ Grignard reagents from aliphatic halides give lower yields. The reaction can be extended to give secondary amines by the use of *N*-substituted methoxyamines (CH₃ONHR').⁵³⁹ There is evidence⁵⁴⁰ that the mechanism involves the direct displacement of OCH₃ by R on an intermediate CH₂ONR' (CH₂ONR' Li⁺ + RLi → CH₃OLi + RNR' Li⁺). Tosyl azide (TsN₃) is a highly useful azide.⁵⁴¹ The initial product is usually RN₃, but this is easily reduced to the amine (Reaction 19-51). With some azides (e.g., azidomethyl phenyl sulfide, PhSCH₂N₃), the group attached to the N₃ is a poor leaving group, so the initial

⁵²⁹ Abe, H.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1999**, 72, 787.

⁵³⁰ Lee, T.; Kang, H.R.; Kim, S.; Kim, S. *Tetrahedron* **2006**, 62, 4081.

⁵³¹ Yan, J.; Li, J.; Cheng, D. *Synlett* **2007**, 2442.

⁵³² Vilhelmsen, M.H.; Andersson, A.S.; Nielsen, M.B. *Synthesis* **2009**, 1469.

⁵³³ See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon-Metal Bond*, Vol. 2, Wiley, NY, p. 72; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, **1973**, pp. 135–177; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, **1968**, pp. 75–97.

⁵³⁴ See Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* **1960**, 82, 148.

⁵³⁵ See de Ryck, P.H.; Verdonck, L.; Van der Kelen, G.P. *Bull. Soc. Chim. Belg.*, **1985**, 94, 621.

⁵³⁶ See Erdik, E.; Ay, M. *Chem. Rev.* **1989**, 89, 1947.

⁵³⁷ See Genet, J.P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* **1991**, 32, 2359.

⁵³⁸ Beak, P.; Kokko, B.J. *J. Org. Chem.* **1982**, 47, 2822; Colvin, E.W.; Kirby, G.W.; Wilson, A.C. *Tetrahedron Lett.* **1982**, 23, 3835; Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* **1982**, 23, 5399; Boche, G.; Schrott, W. *Tetrahedron Lett.* **1982**, 23, 5403.

⁵³⁹ Kokko, B.J.; Beak, P. *Tetrahedron Lett.* **1983**, 24, 561.

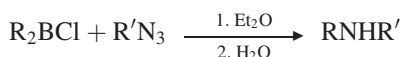
⁵⁴⁰ Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, 108, 6016.

⁵⁴¹ Spagnolo, P.; Zanirato, P.; Gronowitz, S. *J. Org. Chem.* **1982**, 47, 3177; Reed, J.N.; Snieckus, V. *Tetrahedron Lett.* **1983**, 24, 3795; Mori, S.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1984**, 25, 429.

product is a triazene (in this case $\text{ArNHN}=\text{NCH}_2\text{SPh}$ from ArMgX), which can be hydrolyzed to the amine.⁵⁴²



Organoboranes react with a mixture of aq NH_3 and NaOCl to produce primary amines.⁵⁴³ It is likely that the actual reagent is chloramine (NH_2Cl). Chloramine itself,⁵⁴⁴ hydroxylamine-*O*-sulfonic acid in diglyme,⁵⁴⁵ and trimethylsilyl azide⁵⁴⁶ also give the reaction. Since the boranes can be prepared by the hydroboration of alkenes (Reaction 15-16), this is an indirect method for the addition of NH_3 to a double bond with *anti*-Markovnikov orientation. Secondary amines can be prepared⁵⁴⁷ by the treatment of alkyl- or aryl dichloroboranes or dialkylchloroboranes with alkyl or aryl azides.



The use of an optically active R^*BCl_2 gave secondary amines of essentially 100% optical purity.⁵⁴⁸ Aryllead triacetates $[\text{ArPb}(\text{OAc})_3]$ give secondary amines (ArNHR') when treated with primary aromatic amines $\text{Ar}'\text{NH}_2$ and $\text{Cu}(\text{OAc})_2$.⁵⁴⁹

Secondary amines have been converted to tertiary amines by treatment with lithium dialkylcuprate reagents: $\text{R}_2\text{CuLi} + \text{NHR} \rightarrow \text{RNR}'_2$.⁵⁵⁰ The reaction was also used to convert primary amines to secondary, but yields were lower.⁵⁵¹

Terminal alkynes reacted with chlorodiphenylphosphine (Ph_3PCl) and a Ni catalyst to give the 1-diphenylphosphino alkyne ($\text{R}-\text{C}\equiv\text{C}-\text{PPh}_2$).⁵⁵² Alkynyl halides can be used for a similar reaction. Treatment of methyl carbamates with KHMDS and CuI , followed by 2 equiv of 1-bromophenylacetylene gave the *N*-substituted alkyne, $\text{Ph}-\text{C}\equiv\text{C}-\text{N}(\text{CO}_2\text{Me})\text{R}$.⁵⁵³

Metal-catalyzed amination reactions are increasingly important in organic methodology. In a typical reaction, an amine is coupled to an alkyl, vinyl, or aryl halide (or with a different leaving group) in the presence of a transition metal, usually Pd. Presumably, the amination occurs via reaction with a transient organometallic species. Amination of aromatic compounds via this approach is discussed in section Reaction 13-5. Aliphatic

⁵⁴² Trost, B.M.; Pearson, W.H. *J. Am. Chem. Soc.* **1981**, 103, 2483; **1983**, 105, 1054.

⁵⁴³ Kabalka, G.W.; Wang, Z.; Goudgaon, N.M. *Synth. Commun.* **1989**, 19, 2409. See Kabalka, G.W.; Wang, Z. *Organometallics* **1989**, 8, 1093; *Synth. Commun.* **1990**, 20, 231.

⁵⁴⁴ Brown, H.C.; Heydkamp, W.R.; Breuer, E.; Murphy, W.S. *J. Am. Chem. Soc.* **1964**, 86, 3565.

⁵⁴⁵ Brown, H.C.; Kim, K.; Srebnik, M.; Singaram, B. *Tetrahedron* **1987**, 43, 4071. See Brown, H.C.; Kim, K.; Cole, T.E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, 106, 6761.

⁵⁴⁶ Kabalka, G.W.; Goudgaon, N.M.; Liang, Y. *Synth. Commun.* **1988**, 18, 1363.

⁵⁴⁷ Carboni, B.; Vaultier, M.; Courgeon, T.; Carrié, R. *Bull. Soc. Chim. Fr.* **1989**, 844.

⁵⁴⁸ Brown, H.C.; Salunkhe, A.M.; Singaram, B. *J. Org. Chem.* **1991**, 56, 1170.

⁵⁴⁹ Barton, D.H.R.; Donnelly, D.M.X.; Finet, J.; Guiry, P.J. *Tetrahedron Lett.* **1989**, 30, 1377.

⁵⁵⁰ Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, 45, 2739.

⁵⁵¹ Merkushev, E.B. *Synthesis* **1988**, 923.

⁵⁵² Beletskaya, I.P.; Affanasiev, V.V.; Kazankova, M.A.; Efimova, I.V. *Org. Lett.* **2003**, 5, 4309.

⁵⁵³ Dunetz, J.R.; Danheiser, R.L. *Org. Lett.* **2003**, 5, 4011.

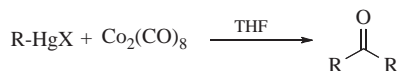
and vinyl substrates are treated here. In one example, a vinyl triflate is converted to an enamine via reaction with pyrrole in the presence of a Pd catalyst.⁵⁵⁴

OS VI, 943.

F. Carbon Electrophiles

12-33 The Conversion of Organometallic Compounds to Ketones, Aldehydes, Carboxylic Esters, or Amides

Acyl-de-metalation, and so on



Symmetrical ketones⁵⁵⁵ can be prepared in good yields by the reaction of organomercuric halides⁵⁵⁶ with dicobalt octacarbonyl in THF,⁵⁵⁷ or with nickel carbonyl in DMF or certain other solvents.⁵⁵⁸ The R group may be aryl or alkyl. However, when R is alkyl, rearrangements may intervene in the $\text{Co}_2(\text{CO})_8$ reaction, although the $\text{Ni}(\text{CO})_4$ reaction seems to be free from such rearrangements.⁵⁵⁹ Divinylic ketones (useful in the *Nazarov cyclization*, **15-20**) have been prepared in high yields by treatment of vinylic mercuric halides with CO and a Rh catalyst.⁵⁵⁹ In a more general synthesis of unsymmetrical ketones, tetraalkyltin compounds (R_4Sn) are treated with a halide $\text{R}'\text{X}$ ($\text{R}' = \text{aryl, vinylic, benzylic}$), CO, and a Pd complex catalyst.⁵⁶⁰ Similar reactions use *Grignard reagents*, $\text{Fe}(\text{CO})_5$, and an alkyl halide.⁵⁶¹

Grignard reagents react with formic acid to give good yields of aldehydes. Two molar equivalents of RMgX are used; the first converts HCO_2H to HCOO^- , which reacts with the second equivalent to give RCHO .⁵⁶² Alkyl lithium reagents and Grignard reagents react with CO to give symmetrical ketones.⁵⁶³ An interesting variation reacts CO_2 with an organolithium, which is then treated with a different organolithium reagent to give the unsymmetrical ketone.⁵⁶⁴ α,β -Unsaturated aldehydes can be prepared by treatment of vinylic silanes with dichloromethyl methyl ether and TiCl_4 at -90°C .⁵⁶⁵

α,β -Unsaturated esters can be prepared by treating boronic esters (**27**) with CO, PdCl_2 , and NaOAc in MeOH.⁵⁶⁶ The synthesis of α,β -unsaturated esters has also been

⁵⁵⁴ Movassaghi, M.; Ondrus, A.E. *J. Org. Chem.* **2005**, *70*, 8638.

⁵⁵⁵ See Narayana, C.; Periasamy, M. *Synthesis* **1985**, 253; Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* **1988**, *57*, 299.

⁵⁵⁶ See Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, **1985**; Larock, R.C. *Tetrahedron* **1982**, *38*, 1713; *Angew. Chem. Int. Ed.* **1978**, *17*, 27.

⁵⁵⁷ Seyferth, D.; Spohn, R.J. *J. Am. Chem. Soc.* **1969**, *91*, 3037.

⁵⁵⁸ Ryu, I.; Ryang, M.; Rhee, I.; Omura, H.; Murai, S.; Sonoda, N. *Synth. Commun.* **1984**, *14*, 1175 and references cited therein. For another method, see Hatanaka, Y.; Hiyama, T. *Chem. Lett.* **1989**, 2049.

⁵⁵⁹ Larock, R.C.; Hersherberger, S.S. *J. Org. Chem.* **1980**, *45*, 3840.

⁵⁶⁰ Tanaka, M. *Tetrahedron Lett.* **1979**, 2601.

⁵⁶¹ Yamashita, M.; Suemitsu, R. *Tetrahedron Lett.* **1978**, 761. See also, Vitale, A.A.; Doctorovich, F.; Nudelman, N.S. *J. Organomet. Chem.* **1987**, *332*, 9.

⁵⁶² Sato, F.; Oguro, K.; Watanabe, H.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2869. See Amaratunga, W.; Fréchet, J. M.J. *Tetrahedron Lett.* **1983**, *24*, 1143.

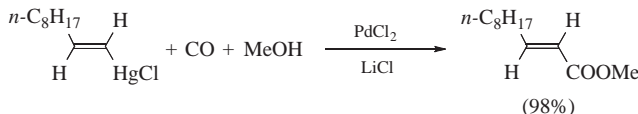
⁵⁶³ Trzupek, L.S.; Newirth, T.L.; Kelly, E.G.; Sbarbati, N.E.; Whitesides, G.M. *J. Am. Chem. Soc.* **1973**, *95*, 8118.

⁵⁶⁴ Zadel, G.; Breitmaier, E. *Angew. Chem. Int. Ed.* **1992**, *31*, 1035.

⁵⁶⁵ Yamamoto, K.; Yohitake, J.; Qui, N.T.; Tsuji, J. *Chem. Lett.* **1978**, 859.

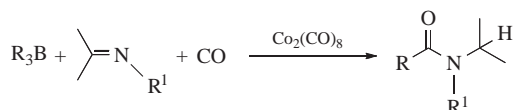
⁵⁶⁶ Miyaura, N.; Suzuki, A. *Chem. Lett.* **1981**, 879. See also, Yamashina, N.; Hyuga, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1989**, *30*, 6555.

accomplished by treatment of vinylic mercuric chlorides with CO at atmospheric pressure and a Pd catalyst in an alcohol as solvent, for example,⁵⁶⁷



Alkyl and aryl *Grignard reagents* can be converted to carboxylic esters with $\text{Fe}(\text{CO})_5$ instead of CO.⁵⁶⁸

Amides have been prepared by the treatment of trialkyl or triarylboranes with CO and an imine, in the presence of catalytic amounts of cobalt carbonyl⁵⁶⁹:



In another method for the conversion $\text{RM} \rightarrow \text{RCONR}$, *Grignard reagents* and organolithium compounds are treated with a formamide (HCONR'_2) to give the intermediate $\text{RCH}(\text{OM})\text{NR}'_2$, which is not isolated, but treated with PhCHO or Ph_2CO to give the product RCONR'_2 .⁵⁷⁰

Direct conversion of a hydrocarbon to an aldehyde ($\text{R}-\text{H} \rightarrow \text{R}-\text{CHO}$) was reported by treatment of the hydrocarbon with GaCl_3 and CO.⁵⁷¹

For carbonylation reactions of aryl halides, see Reaction 13-15.

See also, Reactions 10-76, 15-32, and 18-23-18-24.

OS VIII, 97.

12-34 Cyano-de-metalation



Vinylic copper reagents react with LiCN to give vinyl cyanides, although BrCN and ICN give the vinylic halide instead.⁵⁷² Vinylic cyanides have also been prepared by the reaction between vinylic lithium compounds and phenyl cyanate (PhOCN).⁵⁷³ Alkyl nitriles (RCN) have been prepared, in varying yields, by treatment of sodium trialkylcyanoborates with NaCN and lead tetraacetate.⁵⁷⁴ Vinyl bromides reacted with KCN , in the presence of a Ni complex and Zn metal to give the vinyl nitrile.⁵⁷⁵ Vinyl triflates react with LiCN , in the presence of a Pd catalyst, to give the vinyl nitrile.⁵⁷⁶

⁵⁶⁷ Larock, R.C. *J. Org. Chem.* **1975**, 40, 3237.

⁵⁶⁸ Yamashita, M.; Suemitsu, R. *Tetrahedron Lett.* **1978**, 1477.

⁵⁶⁹ Alper, H.; Amaratunga, S. *J. Org. Chem.* **1982**, 47, 3593.

⁵⁷⁰ Screttas, C.G.; Steele, B.R. *J. Org. Chem.* **1988**, 53, 5151.

⁵⁷¹ Oshita, M.; Chatani, N. *Org. Lett.* **2004**, 6, 4323.

⁵⁷² Westmijze, H.; Vermeer, P. *Synthesis* **1977**, 784.

⁵⁷³ Murray, R.E.; Zweifel, G. *Synthesis* **1980**, 150.

⁵⁷⁴ Masuda, Y.; Hoshi, M.; Yamada, T.; Arase, A. *J. Chem. Soc. Chem. Commun.* **1984**, 398.

⁵⁷⁵ Sakakibara, Y.; Enami, H.; Ogawa, H.; Fujimoto, S.; Kato, H.; Kunitake, K.; Sasaki, K.; Sakai, M. *Bull. Chem. Soc. Jpn.* **1995**, 68, 3137.

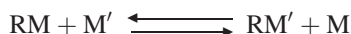
⁵⁷⁶ Piers, E.; Fleming, F.F. *Can. J. Chem.* **1993**, 71, 1867.

For other electrophilic substitutions of the type $RM \rightarrow RC$, which are discussed under nucleophilic substitutions in Chapter 10, see also, Reactions **16-81–16-85** and **16-99**. OS IX, 548

G. Metal Electrophiles

12-35 Transmetalation with a Metal

Metallo-de-metalation

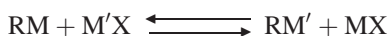


Many organometallic compounds are best prepared by this reaction, which involves replacement of a metal in an organometallic compound by another metal. The RM' compound can be successfully prepared only when M' is above M in the electromotive series, unless some other way is found to shift the equilibrium. That is, RM is usually an unreactive compound and M' is a metal more active than M . Most often, RM is R_2Hg , since mercury alkyls⁵⁷⁶ are easy to prepare and mercury is far down in the electromotive series.⁵⁷⁷ Alkyls of Li, Na, K, Be, Mg, Al, Ga, Zn, Cd, Te, Sn, and so on, have been prepared this way. An important advantage of this method over Reaction **12-38** is that it ensures that the organometallic compound will be prepared free of any possible halide. This method can be used for the isolation of solid sodium and potassium alkyls.⁵⁷⁸ If the metals lie too close together in the series, it may not be possible to shift the equilibrium. For example, alkylbismuth compounds cannot be prepared in this way from alkylmercury compounds.

OS V, 1116.

12-36 Transmetalation with a Metal Halide

Metallo-de-metalation



In contrast to Reaction **12-35**, the reaction between an organometallic compound and a metal *halide* is successful only when M' is *below* M in the electromotive series.⁵⁷⁹ The two reactions considered together therefore constitute a powerful tool for preparing all kinds of organometallic compounds. In this reaction, the most common substrates are *Grignard reagents* and organolithium compounds.⁵⁸⁰

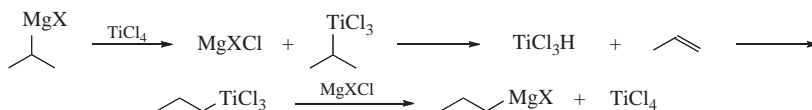
⁵⁷⁷ See Makarova, L.G. *Organomet. React.* **1970**, *1*, 119, pp. 190–226; Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, **1988**, pp. 31–44.

⁵⁷⁸ See Pi, R.; Bauer, W.; Brix, B.; Schade, C.; Schleyer, P.v.R. *J. Organomet. Chem.* **1986**, *306*, C1.

⁵⁷⁹ See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 2, Wiley, NY, pp. 25–149; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, **1973**, pp. 39–106; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, **1968**, pp. 100–192. Also see, Schlosser, M. *Angew. Chem. Int. Ed.* **1964**, *3*, 287, 362; *Newer Methods Prep. Org. Chem.* **1968**, *5*, 238.

⁵⁸⁰ See Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, **1988**; Wakefield, B.J. *The Chemistry of Organolithium Compounds*, Pergamon, Elmsford, NY, **1974**.

The MgX of *Grignard reagents*⁵⁸¹ can migrate to terminal positions in the presence of small amounts of TiCl_4 .⁵⁸² The proposed mechanism consists of metal exchange (Reaction 12-36), elimination–addition, and metal exchange:



The addition step is similar to Reactions 15-16 or 15-17 and follows *Markovnikov's* rule, so the positive titanium goes to the terminal carbon.

Among others, alkyls of Be, Zn,⁵⁸³ Cd, Hg, Al, Sn, Pb, Co, Pt, and Au have been prepared by treatment of *Grignard reagents* with the appropriate halide.⁵⁸⁴ The reaction has been used to prepare alkyls of almost all nontransition metals and even of some transition metals. Alkyls of metalloids and of nonmetals, including Si, B,⁵⁸⁵ Ge, P, As, Sb, and Bi, can also be prepared in this manner.⁵⁸⁶ Except for alkali-metal alkyls and *Grignard reagents*, the reaction between RM and M'X is the most common method for the preparation of organometallic compounds.⁵⁸⁷ In the presence of Ir,⁵⁸⁸ or Pd catalysts,⁵⁸⁹ aromatic compounds react with boranes to give the corresponding arylborane.

Lithium dialkylcopper reagents are prepared from 2 molar equivalents of RLi with 1 molar equivalent of a cuprous halide in ether at low temperatures:⁵⁹⁰ The formation of organocuprates of this type are discussed in more detail in Reaction 10-58, in connection with the coupling reaction of organocuprates with alkyl halides.



Another way is to dissolve an alkylcopper compound in an alkyllithium solution. Higher order cuprates can also be prepared, as well as “non-ate” copper reagents.⁵⁹¹

Metallocenes (48, see Sec. 2.I.ii) are usually made by this method. Among others, metallocenes of Sc, Ti, V, Cr, Mn, Fe, Co, and Ni have been prepared in this manner.⁵⁹²

⁵⁸¹ See Hill, E.A. *Adv. Organomet. Chem.* **1977**, 16, 131; *J. Organomet. Chem.* **1975**, 91, 123.

⁵⁸² Fell, B.; Asinger, F.; Sulzbach, R.A. *Chem. Ber.* **1970**, 103, 3830. See also, Ashby, E.C.; Ainslie, R.D. *J. Organomet. Chem.* **1983**, 250, 1.

⁵⁸³ See Erdik, E. *Tetrahedron* **1987**, 43, 2203.

⁵⁸⁴ See Noltes, J.G. *Bull. Soc. Chim. Fr.* **1972**, 2151.

⁵⁸⁵ See Brown, H.C.; Racherla, U.S. *Tetrahedron Lett.* **1985**, 26, 4311.

⁵⁸⁶ See Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, **1988**, pp. 149–158; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 1306–1345.

⁵⁸⁷ See Mole, T. *Organomet. React.* **1970**, 1, 1, pp. 31–43; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, **1985**, pp. 9–26; Makarova, L.G. *Organomet. React.* **1970**, 1, 119, pp. 129–178, 227–240; van Koten, G. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, **1988**, pp. 219–232; Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, **1988**, pp. 248–270.

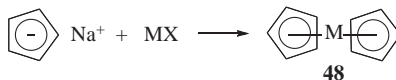
⁵⁸⁸ Chotana, G.A.; Rak, M.A.; Smith III, M.R. *J. Am. Chem. Soc.* **2005**, 127, 10539; Harrisson, P.; Morris, J.; Marder, T.B.; Steel, P.G. *Org. Lett.* **2009**, 11, 3586.

⁵⁸⁹ Billingsley, K.L.; Buchwald, S.L. *J. Org. Chem.* **2008**, 73, 5589.

⁵⁹⁰ House, H.O.; Chu, C.; Wilkins, J.M.; Umen, M.J. *J. Org. Chem.* **1975**, 40, 1460. But see also, Lipshutz, B.H.; Whitney, S.; Kozlowski, J.A.; Breneman, C.M. *Tetrahedron Lett.* **1986**, 27, 4273; Bertz, S.H.; Dabbagh, G. *Tetrahedron* **1989**, 45, 425.

⁵⁹¹ Stack, D.E.; Klein, W.R.; Rieke, R.D. *Tetrahedron Lett.* **1993**, 34, 3063.

⁵⁹² See Bublitz, D.E.; Rinehart Jr., K.L. *Org. React.* **1969**, 17, 1; Birmingham, J.M. *Adv. Organomet. Chem.* **1965**, 2, 365, pp. 375.

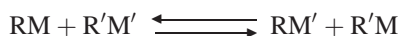


In a related reaction, sulfurated boranes ($\text{R}_2\text{B}-\text{SSiR}'_2$) react with *Grignard reagents* (e.g., methylmagnesium bromide) to give the β -alkyl borane (e.g., $\text{R}_2\text{B}-\text{Me}$) upon heating *in vacuo*.⁵⁹³

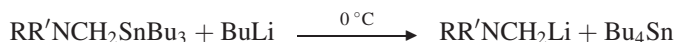
OS **I**, 231, 550; **III**, 601; **IV**, 258, 473, 881; **V**, 211, 496, 727, 918, 1001; **VI**, 776, 875, 1033; **VII**, 236, 290, 524; **VIII**, 23, 57, 268, 474, 586, 606, 609. Also see, OS **IV**, 476

12-37 Transmetalation with an Organometallic Compound

Metallo-de-metalation

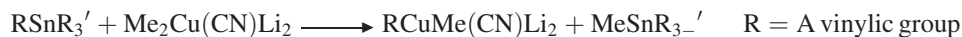


This type of metallic exchange is used much less often than Reactions **12-35** and **12-36**. It is an equilibrium reaction and is useful only if the equilibrium lies in the desired direction. Usually the goal is to prepare a lithium compound that is not prepared easily in other ways,⁵⁹⁴ for example, a vinylic or an allylic lithium, most commonly from an organotin substrate. Examples are the preparation of vinyl lithium from phenyllithium and tetravinyltin and the formation of α -dialkylamino organolithium compounds from the corresponding organotin compounds⁵⁹⁵



The reaction has also been used to prepare 1,3-dilithiopropanes⁵⁹⁶ and 1,1-dilithiomethylenecyclohexane⁵⁹⁷ from the corresponding mercury compounds. In general, the equilibrium lies in the direction in which the more electropositive metal is bonded to that alkyl or aryl group that is the more stable carbanion (Sec. 5.B.i). The reaction proceeds with retention of configuration,⁵⁹⁸ an S_{Ei} mechanism is likely.⁵⁹⁹

“Higher order” cuprates⁶⁰⁰ (see Reaction **10-58**) have been produced by this reaction starting with a vinylic tin compound:⁶⁰¹



⁵⁹³ Soderquist, J.A.; DePomar, J.C.J. *Tetrahedron Lett.* **2000**, 41, 3537.

⁵⁹⁴ See Wardell, J.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon-Metal Bond*, Vol. 4, Wiley, NY, pp. 1-157, see pp. 81-89; Kauffmann, T. *Top. Curr. Chem.* **1980**, 92, 109, pp. 130.

⁵⁹⁵ Pearson, W.H.; Lindbeck, A.C. *J. Org. Chem.* **1989**, 54, 5651.

⁵⁹⁶ Seetz, J.W.F.L.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1982**, 104, 6848.

⁵⁹⁷ Maercker, A.; Dujardin, R. *Angew. Chem. Int. Ed.* **1984**, 23, 224.

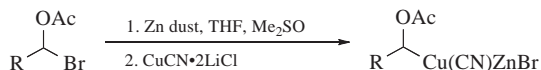
⁵⁹⁸ Sawyer, J.S.; Kucero, A.; Macdonald, T.L.; McGarvey, G.J. *J. Am. Chem. Soc.* **1988**, 110, 842.

⁵⁹⁹ Dessy, R.E.; Kaplan, F.; Coe, G.R.; Salinger, R.M. *J. Am. Chem. Soc.* **1963**, 85, 1191.

⁶⁰⁰ See Lipshutz, B.H. *Synlett*, **1990**, 119. See also, Bertz, S.H. *J. Am. Chem. Soc.* **1990**, 112, 4031; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* **1990**, 112, 4032.

⁶⁰¹ Behling, J.R.; Babiak, K.A.; Ng, J.S.; Campbell, A.L.; Moretti, R.; Koerner, M.; Lipshutz, B.H. *J. Am. Chem. Soc.* **1988**, 110, 2641.

These compounds are not isolated, but used directly *in situ* for conjugate addition reactions (Reaction 15-25). Another method for the preparation of such reagents (but with Zn instead of Li) allows them to be made from α -acetoxy halides:⁶⁰²



OS V, 452; VI, 815; VIII, 97.

12.C.iii. Halogen as Leaving Group

The reduction of alkyl halides can proceed by an electrophilic substitution mechanism, but it is considered in Chapter 19 (Reaction 19-53).

12-38 Metallo-de-halogenation



Alkyl halides react directly with certain metals to give organometallic compounds.⁶⁰³ The most common metal is Mg, and of course this is by far the most common method for the preparation of *Grignard reagents*.⁶⁰⁴ The *Grignard reaction* with aldehydes or ketones is discussed in Reaction 16-24. The order of halide activity is $\text{I} > \text{Br} > \text{Cl}$. This reaction can be applied to many alkyl halides primary, secondary, and tertiary and to aryl halides, although aryl *chlorides* require the use of THF or another higher-boiling solvent instead of the usual ether, or special entrainment methods.⁶⁰⁵ Aryl iodides and bromides can be treated in the usual manner. Allylic *Grignard reagents* can also be prepared in the usual manner (or in THF),⁶⁰⁶ although in the presence of excess halide these may give *Wurtz-type coupling* products (see Reaction 10-56).⁶⁰⁷ Like aryl chlorides, vinylic halides require higher-boiling solvents (see OS IV, 258). A good procedure for benzylic and allylic halides is to use magnesium anthracene (prepared from Mg and anthracene in THF)⁶⁰⁸ instead of ordinary magnesium,⁶⁰⁹ although activated magnesium turnings have also been used.⁶¹⁰ Alkynyl *Grignard reagents* are generally prepared by the method in Reaction 12-22.

Dihalides⁶¹¹ can be converted to *Grignard reagents* if the halogens are different and are at least three carbons apart. If the halogens are the same, it is possible to obtain

⁶⁰² Chou, T.; Knochel, P. *J. Org. Chem.* **1990**, 55, 4791.

⁶⁰³ See Massey, A.G.; Humphries, R.E. *Aldrichimica Acta* **1989**, 22, 31; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, **1980**, pp. 30–37.

⁶⁰⁴ See Raston, C.L.; Salem, G. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 159–306, 162–175; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 5–91.

⁶⁰⁵ Pearson, D.E.; Cowan, D.; Beckler, J.D. *J. Org. Chem.* **1959**, 24, 504.

⁶⁰⁶ See Benkeser, R.A. *Synthesis* **1971**, 347.

⁶⁰⁷ See Oppolzer, W.; Schneider, P. *Tetrahedron Lett.* **1984**, 25, 3305.

⁶⁰⁸ Bogdanovic, B.; Janke, N.; Kinzelmann, H. *Chem. Ber.* **1990**, 123, 1507, and other papers in this series.

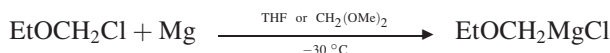
⁶⁰⁹ Gallagher, M.J.; Harvey, S.; Raston, C.L.; Sue, R.E. *J. Chem. Soc. Chem. Commun.* **1988**, 289.

⁶¹⁰ Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem.* **1991**, 56, 698. See Lai, Y. *Synthesis* **1981**, 585.

⁶¹¹ See Raston, C.L.; Salem, G. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 187–193; Heaney, H. *Organomet. Chem. Rev.* **1966**, 1, 27. For a review of di-Grignard reagents, see Bickelhaupt, F. *Angew. Chem. Int. Ed.* **1987**, 26, 990.

dimagnesium compounds [e.g., $\text{BrMg}(\text{CH}_2)_4\text{MgBr}$].⁶¹² 1,2-Dihalides give elimination⁶¹³ rather than *Grignard reagent* formation (Reaction 17-22), and the reaction is seldom successful with 1,1-dihalides, although the preparation of *gem*-disubstituted compounds [e.g., $\text{CH}_2(\text{MgBr})_2$], has been accomplished with these substrates.⁶¹⁴ α -Halo Grignard reagents and α -halolithium reagents can be prepared by the method given in Reaction 12-39.⁶¹⁵ Alkylmagnesium fluorides can be prepared by refluxing alkyl fluorides with Mg in the presence of appropriate catalysts (e.g., I_2 or EtBr) in THF for several days.⁶¹⁶ Nitrogen-containing *Grignard reagents* have been prepared.⁶¹⁷

The presence of other functional groups in the halide usually affects the preparation of the *Grignard reagent*. Groups that contain active hydrogen (defined as any hydrogen that will react with a *Grignard reagent*, e.g., OH, NH_2 , and CO_2H), can be present in the molecule, but only if they are converted to the salt form (O^- , NH^- , COO^- , respectively). Groups that react with *Grignard reagents* (e.g., $\text{C}=\text{O}$, $\text{C}\equiv\text{N}$, NO_2 , CO_2R) inhibit *Grignard* formation entirely. In general, the only functional groups that may be present in the halide molecule without any interference at all are double and triple bonds (except terminal triple bonds) and OR and NR_2 groups. However, β -halo ethers generally give β elimination when treated with Mg (see Reaction 17-24), and *Grignard reagents* from α -halo ethers⁶¹⁸ can only be formed in THF or dimethoxymethane at a low temperature, for example,⁶¹⁹



because such reagents immediately undergo α elimination (see Reaction 12-39) at room temperature in ether solution.

Because *Grignard reagents* react with water (Reaction 12-24) and with oxygen (Reaction 12-25), it is generally best to prepare them in an anhydrous nitrogen atmosphere. *Grignard reagents* are generally neither isolated nor stored; solutions of *Grignard reagents* are used directly for the required synthesis. *Grignard reagents* can also be prepared in benzene or toluene, if a tertiary amine is added to complex with the RMgX .⁶²⁰ This method eliminates the need for an ether solvent. With certain primary alkyl halides it is even possible to prepare alkylmagnesium compounds in hydrocarbon solvents in the absence of an organic base.⁶²¹ It is also possible to obtain *Grignard reagents* in powdered form, by complexing them with the chelating agent tris(3,6-dioxaheptyl)amine [$\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3)_3$].⁶²²

⁶¹² See Seetz, J.W.F.L.; Hartog, F.A.; Böhm, H.P.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Tetrahedron Lett.* **1982**, 23, 1497.

⁶¹³ See van Eikkema Hommes, N.J.R.; Bickelhaupt, F.; Klumpp, G.W. *Angew. Chem. Int. Ed.* **1988**, 27, 1083.

⁶¹⁴ See Bruin, J.W.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Organomet. Chem.* **1985**, 288, 13.

⁶¹⁵ See Chivers, T. *Organomet. Chem. Rev. Sect. A* **1970**, 6, 1.

⁶¹⁶ Yu, S.H.; Ashby, E.C. *J. Org. Chem.* **1971**, 36, 2123.

⁶¹⁷ Sugimoto, O.; Yamada, S.; Tanji, K. *J. Org. Chem.* **2003**, 68, 2054.

⁶¹⁸ See Peterson, D.J. *Organomet. Chem. Rev. Sect. A* **1972**, 7, 295.

⁶¹⁹ See Castro, B. *Bull. Soc. Chim. Fr.* **1967**, 1533, 1540, 1547.

⁶²⁰ Gitlitz, M.H.; Considine, W.J. *J. Organomet. Chem.* **1970**, 23, 291.

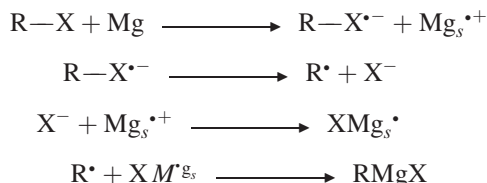
⁶²¹ Smith, Jr., W.N. *J. Organomet. Chem.* **1974**, 64, 25.

⁶²² Boudin, A.; Cerveau, G.; Chuit, C.; Corriu, R.J.P.; Reye, C. *Tetrahedron* **1989**, 45, 171.

Next to the formation of *Grignard reagents*, the most important application of this reaction is the conversion of alkyl and aryl halides to organolithium compounds,⁶²³ but it has also been carried out with many other metals (e.g., Na, Be, Zn, Hg, As, Sb, and Sn). With Na, the *Wurtz Reaction* (**10-56**) is an important side reaction. In some cases, where the reaction between a halide and a metal is too slow, an alloy of the metal with K or Na can be used instead. The most important example is the preparation of tetraethyl-lead from ethyl bromide and a Pb—Na alloy.

The efficiency of the reaction can often be improved by use of the metal in its powdered⁶²⁴ or vapor⁶²⁵ form. These techniques have permitted the preparation of some organometallic compounds that cannot be prepared by the standard procedures. Among the metals produced in an activated form are Mg,⁶²⁶ Ca,⁶²⁷ Zn,⁶²⁸ Al, Sn, Cd,⁶²⁹ Ni, Fe, Ti, Cu,⁶³⁰ Pd, and Pt.⁶³¹

The mechanism of *Grignard reagent* formation involves free radicals,⁶³² and there is much evidence for this, from CIDNP⁶³³ (Sec. 5.C.i) and from stereochemical, rate, and product studies.⁶³⁴ Further evidence is that free radicals have been trapped,⁶³⁵ and that experiments that studied the intrinsic reactivity of MeBr on a magnesium single-crystal surface showed that *Grignard reagent* formation does not take place by a single-step insertion mechanism.⁶³⁶ The following SET mechanism has been proposed:⁶³³



⁶²³ See Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, **1988**, pp. 21–32; Wardell, J.L. in Hartley, F.R.; Patai, S. Vol. 4, pp. 1–157, 5–27; Newcomb, M.E. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, **1988**, pp. 3–14. For a study of halogen–lithium exchange in hydrocarbon solvents, see Slocum, D.W.; Kusmic, D.; Raber, J.C.; Reinscheld, T.K.; Whitley, P.E. *Tetrahedron Lett.* **2010**, *51*, 4793.

⁶²⁴ See Rieke, R.D. *Science* **1989**, *246*, 1260.

⁶²⁵ See Klabunde, K.J. *React. Intermed. (Plenum)* **1980**, *1*, 37; *Acc. Chem. Res.* **1975**, *8*, 393; Skell, P.S. Havel, J.J.; McGlinchey, M.J. *Acc. Chem. Res.* **1973**, *6*, 97.

⁶²⁶ Ebert, G.W.; Rieke, R.D. *J. Org. Chem.* **1988**, *53*, 4482. See also, Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698.

⁶²⁷ Wu, T.; Xiong, H.; Rieke, R.D. *J. Org. Chem.* **1990**, *55*, 5045.

⁶²⁸ Rieke, R.D.; Li, P.T.; Burns, T.P.; Uhm, S.T. *J. Org. Chem.* **1981**, *46*, 4323. See also, Zhu, L.; Wehmeyer, R.M.; Rieke, R.D. *J. Org. Chem.* **1991**, *56*, 1445.

⁶²⁹ Burkhardt, E.R.; Rieke, R.D. *J. Org. Chem.* **1985**, *50*, 416.

⁶³⁰ Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* **1991**, *113*, 4672, and references cited therein.

⁶³¹ See Lai, Y. *Synthesis* **1981**, 585; Rieke, R.D. *Acc. Chem. Res.* **1977**, *10*, 301.

⁶³² See Blomberg, C. *Bull. Soc. Chim. Fr.* **1972**, 2143.

⁶³³ Bodewitz, H.W.H.J.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron* **1975**, *31*, 1053. See also, Schaart, B.J.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Can. J. Chem.* **1980**, *58*, 932.

⁶³⁴ See Rogers, H.R.; Hill, C.L.; Fujiwara, Y.; Rogers, R.J.; Mitchell, H.L.; Whitesides, G.M. *J. Am. Chem. Soc.* **1980**, *102*, 217; Barber, J.J.; Whitesides, G.M. *J. Am. Chem. Soc.* **1980**, *102*, 239.

⁶³⁵ Root, K.S.; Hill, C.L.; Lawrence, L.M.; Whitesides, G.M. *J. Am. Chem. Soc.* **1989**, *111*, 5405.

⁶³⁶ Nuzzo, R.G.; Dubois, L.H. *J. Am. Chem. Soc.* **1986**, *108*, 2881.

Other evidence has been offered to support a SET initiated radical process for the second step of this mechanism.⁶³⁷ The species $R-X^{\bullet-}$ and $Mg^{\bullet+}$ are radical ions.⁶³⁸ The subscript “s” is meant to indicate that the species so marked are bound to the surface of the magnesium. It is known that this is a surface reaction.⁶³⁹ It has been suggested that some of the R^{\bullet} radicals diffuse from the magnesium surface into the solution and then return to the surface to react with the XMg^{\bullet} . There is evidence both for⁶⁴⁰ and against⁶⁴¹ this suggestion. Another proposal is that the fourth step is not the one shown here, but that the R^{\bullet} is reduced by Mg^+ to the carbanion R^- , which combines with MgX^+ to give $RMgX$.⁶⁴²

There are too many preparations of *Grignard reagents* in *Organic Syntheses* for us to list here. Chiral *Grignard reagents* are rare, since they are configurationally unstable in most cases. However, a few chiral *Grignard reagents* are known.⁶⁴³ Use of the reaction to prepare other organometallic compounds can be found in OS **I**, 228; **II**, 184, 517, 607; **III**, 413, 757; **VI**, 240; **VII**, 346; **VIII**, 505. The preparation of unsolvated butylmagnesium bromide is described at OS **V**, 1141. The preparation of highly reactive (powdered) magnesium is given at OS **VI**, 845.

12-39 Replacement of a Halogen by a Metal from an Organometallic Compound

Metallo-de-halogenation



The exchange reaction between halides and organometallic compounds occurs most readily when M is Li and X is Br or I,⁶⁴⁴ although it has been shown to occur with Mg.⁶⁴⁵ The R' group is usually, although not always, alkyl, and often butyl; R is usually aromatic.⁶⁴⁶ Alkyl halides are generally not reactive enough, while allylic and benzylic halides usually give *Wurtz coupling*. Of course, the R that becomes bonded to the halogen is the one for which RH is the weaker acid. Despite the preponderance of reactions with bromides and iodides, it is noted that the reaction of 1-fluorooctane with 4–10 equiv of Li powder and 2–4 equiv of DTBB (4,4'-di-*tert*-butylbiphenyl) in THP (THP=tetrahydropyran) at 0 °C for 5 min, was shown to give a solution of the corresponding 1-octyllithium.⁶⁴⁷ Vinylic halides

⁶³⁷ Hoffmann, R.W.; Brönstrup, M.; Müller, M. *Org. Lett.* **2003**, 5, 313.

⁶³⁸ See Sergeev, G.B.; Zagorsky, V.V.; Badaev, F.Z. *J. Organomet. Chem.* **1983**, 243, 123. See, however, de Souza-Barboza, J.C.; Luche, J.; Pétrier, C. *Tetrahedron Lett.* **1987**, 28, 2013.

⁶³⁹ Walborsky, H.M.; Topolski, M. *J. Am. Chem. Soc.* **1992**, 114, 3455; Walborsky, H.M.; Zimmermann, C. *J. Am. Chem. Soc.* **1992**, 114, 4996; Walborsky, H.M. *Accs. Chem. Res.* **1990**, 23, 286.

⁶⁴⁰ Garst, J.F. *Acc. Chem. Res.* **1991**, 24, 95; Garst, J.F.; Ungváry, F.; Batlaw, R.; Lawrence, K.E. *J. Am. Chem. Soc.* **1991**, 113, 5392.

⁶⁴¹ Walborsky, H.M. *Acc. Chem. Res.* **1990**, 23, 286.

⁶⁴² de Boer, H.J.R.; Akkerman, O.S.; Bickelhaupt, F. *Angew. Chem. Int. Ed.* **1988**, 27, 687.

⁶⁴³ See Hölzer, B.; Hoffmann, R.W. *Chem. Commun.* **2003**, 732; Dakternieks, D.; Dunn, K.; Henry, D.J.; Schiesser, C.H.; Tiekink, E.R. *Organometallics* **1999**, 18, 3342.

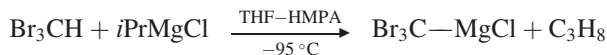
⁶⁴⁴ See Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, **1988**, pp. 107–129; Parham, W.E.; Bradsher, C.K. *Acc. Chem. Res.* **1982**, 15, 300.

⁶⁴⁵ See Tamborski, C.; Moore, G.J. *J. Organomet. Chem.* **1971**, 26, 153.

⁶⁴⁶ See Bailey, W.F.; Punzalan, E.R. *J. Org. Chem.* **1990**, 55, 5404; Negishi, E.; Swanson, D.R.; Rousset, C.J. *J. Org. Chem.* **1990**, 55, 5406.

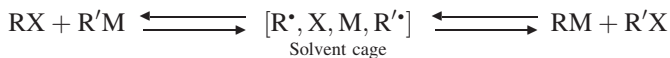
⁶⁴⁷ Yus, M.; Herrera, R.P.; Guijarro, A. *Tetrahedron Lett.*, **2003**, 44, 5025.

react with retention of configuration.⁶⁴⁸ The reaction can be used to prepare α -halo organolithium and α -halo organomagnesium compounds.⁶⁴⁹ Carbon tetrachloride reacts with butyllithium to give lithiotrichloromethane ($\text{Cl}_3\text{C}-\text{Li}$), for example.⁶⁵⁰ Such compounds can also be prepared by hydrogen-metal exchange, for example,⁶⁵¹



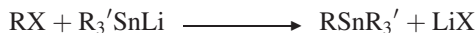
This is an example of Reaction 12-22. However, these α -halo organometallic compounds are stable (and configurationally stable as well⁶⁵²) only at low temperatures (ca. $-100\text{ }^\circ\text{C}$) and only in THF or mixtures of THF and other solvents (e.g., HMPA). At ordinary temperatures, they lose MX (α elimination) to give carbenes, which then react further, or carbenoid reactions. The α -chloro- α -magnesium sulfones $[\text{ArSO}_2\text{CH}(\text{Cl})\text{MgBr}]$ are exceptions, being stable in solution at room temperature and even under reflux.⁶⁵³ Compounds in which a halogen and a transition metal are on the same carbon can be more stable than the ones with lithium.⁶⁵⁴

There is evidence that the mechanism⁶⁵⁵ of the reaction of alkyllithium compounds with alkyl and aryl iodides involves free radicals.⁶⁵⁶



Among the evidence is the fact that coupling and disproportionation products are obtained from R^\bullet and R'^\bullet and the observation of CIDNP.^{656,657} However, in the degenerate exchange between PhI and PhLi the ate complex $\text{Ph}_2\text{I}^- \text{Li}^+$ has been shown to be an intermediate,⁶⁵⁸ and there is other evidence that radicals are not involved in all instances of this reaction.⁶⁵⁹

In a completely different kind of process, alkyl halides can be converted to certain organometallic compounds by treatment with organometalate ions, for example,



⁶⁴⁸ For examples of exchange, R = vinylic, see Miller, R.B.; McGarvey, G. *Synth. Commun.* **1979**, 9, 831; Sugita, T.; Sakabe, Y.; Sasahara, T.; Tsukuda, M.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* **1984**, 57, 2319.

⁶⁴⁹ See Siegel, H. *Top. Curr. Chem.* **1982**, 106, 55; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, **1980**, pp. 136–151; Köbrich, G. *Angew. Chem. Int. Ed.* **1972**, 11, 473. Also see Krief, A. *Tetrahedron* **1980**, 36, 2531; Normant, H. J. *Organomet. Chem.* **1975**, 100, 189.

⁶⁵⁰ Hoeg, D.F.; Lusk, D.L.; Crumbliss, A.L. *J. Am. Chem. Soc.* **1965**, 87, 4147. See also, Villieras, J.; Tarhouni, R.; Kirschleger, B.; Rambaud, M. *Bull. Soc. Chim. Fr.* **1985**, 825.

⁶⁵¹ Villieras, J. *Bull. Soc. Chim. Fr.* **1967**, 1520.

⁶⁵² Schmidt, A.; Köbrich, G.; Hoffmann, R.W. *Chem. Ber.* **1991**, 124, 1253; Hoffmann, R.W.; Bewersdorf, M. *Chem. Ber.* **1991**, 124, 1259.

⁶⁵³ Stetter, H.; Steinbeck, K. *Liebigs Ann. Chem.* **1972**, 766, 89.

⁶⁵⁴ Kauffmann, T.; Fobker, R.; Wensing, M. *Angew. Chem. Int. Ed.* **1988**, 27, 943.

⁶⁵⁵ For reviews of the mechanism, see Bailey, W.F.; Patricia, J.J. *J. Organomet. Chem.* **1988**, 352, 1; Beletskaya, I. P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* **1976**, 45, 330.

⁶⁵⁶ Ashby, E.C.; Pham, T.N. *J. Org. Chem.* **1987**, 52, 1291. See also, Bailey, W.F.; Patricia, J.J.; Nurmi, T.T.; Wang, W. *Tetrahedron Lett.* **1986**, 27, 1861.

⁶⁵⁷ Ward, H.R.; Lawler, R.G.; Loken, H.Y. *J. Am. Chem. Soc.* **1968**, 90, 7359.

⁶⁵⁸ See Reich, H.J.; Green, D.P.; Phillips, N.H. *J. Am. Chem. Soc.* **1989**, 111, 3444.

⁶⁵⁹ Beak, P.; Allen, D.J.; Lee, W.K. *J. Am. Chem. Soc.* **1990**, 112, 1629.

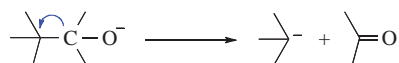
Most of the evidence is in accord with a free radical mechanism involving electron transfer, although an S_N2 mechanism can compete under some conditions.⁶⁶⁰ Electrochemically generated zinc has been used to prepare organozinc bomide from the corresponding alkyl halide.⁶⁶¹

OS VI, 82; VII, 271, 326, 495; VIII, 430. See also, OS VII, 512; VIII, 479.

12.C.iv. Carbon Leaving Groups

In these reactions (12-40–12-48), a carbon–carbon bond cleaves. The substrate is the side that retains the electron pair; hence the reactions are considered electrophilic substitutions. The incoming group is hydrogen in all but one (Reaction 12-42) of the cases. The reactions in groups A and B are sometimes called *anionic cleavages*,⁶⁶² although they do not always occur by mechanisms involving free carbanions (S_E1). When they do, the reactions are facilitated by increasing stability of the carbanion.

A. Carbonyl-Forming Cleavages These reactions follow the pattern:



The leaving group is stabilized because the electron deficiency at its carbon is satisfied by a pair of electrons from the oxygen. With respect to the leaving group the reaction is elimination to form a C=O bond. Retrograde aldol reactions (16-34) and cleavage of cyanohydrins (16-52) belong to this classification but are treated in Chapter 16 under their more important reverse reactions. Other eliminations to form C=O bonds are discussed in Reaction 17-32.

12-40 Decarboxylation of Aliphatic Acids

Hydro-de-carboxylation



Many carboxylic acids can be successfully decarboxylated, either as the free acid or in the salt form, but not simple aliphatic acids.⁶⁶³ An exception is acetic acid, which as the acetate, heated with base, gives good yields of methane. Malonic acid derivatives are the most common substrates for decarboxylation, giving the corresponding mono-carboxylic acid. Decarboxylation of 2-substituted malonic acids has been reported using microwave irradiation.⁶⁶⁴ Aliphatic acids that do undergo successful decarboxylation have certain functional groups or double or triple bonds in the α or β position. Some of these are shown in Table 12.2.

⁶⁶⁰ See Ashby, E.C.; Su, W.; Pham, T.N. *Organometallics* **1985**, 4, 1493; Alnajjar, M.S.; Kuivila, H.G. *J. Am. Chem. Soc.* **1985**, 107, 416.

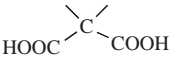
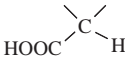
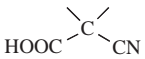
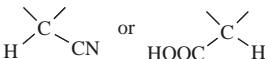
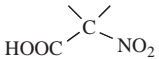
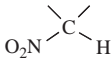
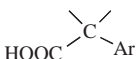

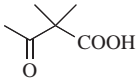

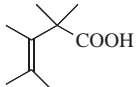

⁶⁶¹ Kurono, N.; Inoue, T.; Tokuda, M. *Tetrahedron* **2005**, 61, 11125.

⁶⁶² See Artamkina, G.A.; Beletskaya, I.P. *Russ. Chem. Rev.* **1987**, 56, 983.

⁶⁶³ March, J. *J. Chem. Educ.* **1963**, 40, 212.

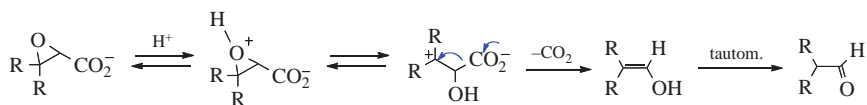
⁶⁶⁴ Zara, C.L.; Jin, T.; Giguere, R.J. *Synth. Commun.* **2000**, 30, 2099.

TABLE 12.2 Some Acids That Undergo Decarboxylation Fairly Readily^a

Acid Type	Decarboxylation Product
	
	
	
	
$X_3C-COOH$	X_3C-H
	
	

^aOthers are described in the text.

For decarboxylation of aromatic acids, see Reaction 11-35. Decarboxylation of an α -cyano acid can give a nitrile or a carboxylic acid, since the cyano group may or may not be hydrolyzed in the course of the reaction. In addition to the compounds listed in Table 12.2, decarboxylation can be carried out on α,β -unsaturated⁶⁶⁵ and α,β -acetylenic acids. Glycidic acids give aldehydes on decarboxylation. The following mechanism has been suggested:⁶⁶⁶

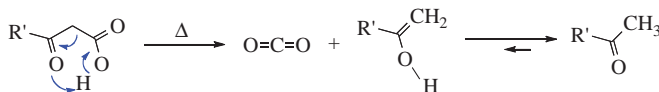


The direct product is an enol that tautomerizes to the aldehyde.⁶⁶⁷ This is the usual last step in the *Darzens Reaction* (16-40).

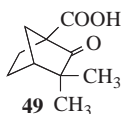
Decarboxylations can be regarded as reversal of the addition of carbanions to carbon dioxide (Reaction 16-82), but free carbanions are not always involved.⁶⁶⁸ When the carboxylate *ion* is decarboxylated, the mechanism can be either S_E1 or S_E2 . In the case of the S_E1 mechanism, the reaction is of course aided by the presence of electron-withdrawing

⁶⁶⁵ See Roy, S.C.; Guin, C.; Maiti, G. *Tetrahedron Lett.* **2001**, 42, 9253.⁶⁶⁶ Singh, S.P.; Kagan, J. J. *Org. Chem.* **1970**, 35, 2203.⁶⁶⁷ Shiner, Jr., V.J.; Martin, B. *J. Am. Chem. Soc.* **1962**, 84, 4824.⁶⁶⁸ See Richardson, W.H.; O'Neal, H.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5, Elsevier, NY, **1972**, pp. 447-482; Clark, L.W. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, **1969**, pp. 589-622. See Dunn, G.E. *Isot. Org. Chem.* **1977**, 3, 1.

groups, which stabilize the carbanion.⁶⁶⁹ Decarboxylation of carboxylate ions can be accelerated by the addition of a suitable crown ether, which in effect removes the metallic ion.⁶⁷⁰ The reaction without the metallic ion has also been performed in the gas phase.⁶⁷¹ Some acids can also be decarboxylated directly and, in most of these cases, there is a cyclic, six-center mechanism:



Here too there is an enol that tautomerizes to the product. The mechanism is illustrated for the case of β -keto acids,⁶⁷² but it is likely that malonic, α -cyano, α -nitro, and β,γ -unsaturated acids⁶⁷³ behave similarly, since similar six-membered transition states can be written for them. Some α,β -unsaturated acids



are also decarboxylated by this mechanism by isomerizing to the β,γ -isomers before they actually decarboxylate.⁶⁷⁴ Evidence is that **49** and similar bicyclic β -keto acids resist decarboxylation.⁶⁷⁵ In such compounds, the six-membered cyclic transition state cannot form for steric reasons,⁶⁷⁶ and if it could, formation of the intermediate enol would violate *Bredt's rule* (Sec. 4.Q.iii).

Some carboxylic acids that cannot form a six-membered transition state can still be decarboxylated, and these presumably react through an S_E1 or S_E2 mechanism.⁶⁷⁷ Further evidence for the cyclic mechanism is that the reaction rate varies very little with a change from a nonpolar to a polar solvent (even from benzene to water⁶⁷⁸), and is not subject to acid catalysis.⁶⁷⁹ The rate of decarboxylation of a β,γ -unsaturated acid was increased $\sim 10^5$ – 10^6 times by introduction of a β -methoxy group, indicating that the cyclic transition state has dipolar character.⁶⁸⁰ Rate constants for decarboxylation reactions have been calculated using no barrier theory.⁶⁸¹

⁶⁶⁹ See Buncel, E.; Venkatachalam, T.K.; Menon, B.C. *J. Org. Chem.* **1984**, *49*, 413.

⁶⁷⁰ Hunter, D.H.; Patel, V.; Perry, R.A. *Can. J. Chem.* **1980**, *58*, 2271, and references cited therein.

⁶⁷¹ Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* **1988**, *110*, 607.

⁶⁷² See Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, **1969**, pp. 116–120.

⁶⁷³ Bigley, D.B.; Clarke, M.J. *J. Chem. Soc. Perkin Trans. 2* **1982**, *1*, and references cited therein. For a review, see Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* **1971**, *8*, 75, pp. 150–153.

⁶⁷⁴ Bigley, D.B. *J. Chem. Soc.* **1964**, 3897.

⁶⁷⁵ Wasserman, H.H. in *Newman Steric Effects in Organic Chemistry*, Wiley, NY, **1956**, p. 352. See also, Buchanan, G.L.; Kean, N.B.; Taylor, R. *Tetrahedron* **1975**, *31*, 1583.

⁶⁷⁶ Sterically hindered β -keto acids decarboxylate more slowly: Meier, H.; Wengenroth, H.; Lauer, W.; Krause, V. *Tetrahedron Lett.* **1989**, *30*, 5253.

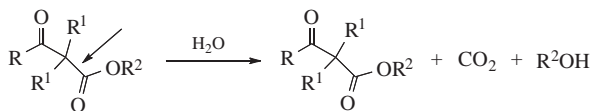
⁶⁷⁷ See Ferris, J.P.; Miller, N.C. *J. Am. Chem. Soc.* **1966**, *88*, 3522.

⁶⁷⁸ Swain, C.G.; Bader, R.F.W.; Esteve Jr., R.M.; Griffin, R.N. *J. Am. Chem. Soc.* **1961**, *83*, 1951.

⁶⁷⁹ Noyce, D.S.; Metesich, M.A. *J. Org. Chem.* **1967**, *32*, 3243.

⁶⁸⁰ Bigley, D.B.; Al-Borno, A. *J. Chem. Soc. Perkin Trans. 2* **1982**, *15*.

⁶⁸¹ Guthrie, J.P.; Peiris, S.; Simkin, M.; Wang, Y. *Can. J. Chem.* **2010**, *88*, 79.



β -Keto acids⁶⁸² are easily decarboxylated, but such acids are usually prepared from β -keto esters, and the esters are easily decarboxylated themselves on hydrolysis without isolation of the acids.⁶⁸³ This decarboxylation of β -keto esters involving cleavage on the carboxyl side of the substituted methylene group (arrow) is carried out under acidic, neutral, or slightly basic conditions to yield a ketone. When strongly basic conditions are used, cleavage occurs on the other side of the CR_2 group (Reaction **12-43**). β -Keto esters can be decarbalkoxylated without passing through the free-acid stage by treatment with boric anhydride (B_2O_3) at 150°C .⁶⁸⁴ The alkyl portion of the ester (R') is converted to an alkene or, if it lacks a β hydrogen, to an ether ($\text{R}'\text{OR}'$). Another method for the decarbalkoxylation of β -keto esters, malonic esters, and α -cyano esters consists of heating the substrate in wet DMSO containing NaCl , Na_3PO_4 , or some other simple salt.⁶⁸⁵ In this method too, the free acid is probably not an intermediate, but here the alkyl portion of the substrate is converted to the corresponding alcohol. α -Amino acids have been decarboxylated by treatment with a catalytic amount of 2-cyclohexenone.⁶⁸⁶ Amino acids are decarboxylated by sequential treatment with NBS at pH 5 followed by NaBH_4 and NiCl_2 .⁶⁸⁷ Certain decarboxylations can also be accomplished photochemically.⁶⁸⁸ See also, the decarbonylation of acyl halides, mentioned in Reaction **14-32**. In some cases, decarboxylations can give organometallic compounds: $\text{RCOOM} \rightarrow \text{RM} + \text{CO}_2$.⁶⁸⁹ The Cu catalyzed decarboxylation of 2-alkynoic acids to terminal alkynes has been reported.⁶⁹⁰

Decarboxylative alkylation and arylation reactions are known. In the presence of a Ru catalyst and a B-phenyl borinate, decarboxylation of proline esters leads to 2-phenylpyrrolidine derivatives.⁶⁹¹ In the presence of a Pd catalyst, esters undergo decarboxylation with coupling between the alkyl groups on the carbonyl and the ester oxygen to give the corresponding hydrocarbon fragment.⁶⁹²

Some of the decarboxylations listed in *Organic Syntheses* are performed with concomitant ester or nitrile hydrolysis and others are simple decarboxylations.

With ester or nitrile hydrolysis: OS **I**, 290, 451, 523; **II**, 200, 391; **III**, 281, 286, 313, 326, 510, 513, 591; **IV**, 55, 93, 176, 441, 664, 708, 790, 804; **V**, 76, 288, 572, 687, 989; **VI**, 615, 781, 873, 932; **VII**, 50, 210, 319; **VIII**, 263.

Simple decarboxylations: OS **I**, 351, 401, 440, 473, 475; **II**, 21, 61, 93, 229, 302, 333, 368, 416, 474, 512, 523; **III**, 213, 425, 495, 705, 733, 783; **IV**, 234, 254, 278, 337, 555, 560,

⁶⁸² See Oshry, L.; Rosenfeld, S.M. *Org. Prep. Proced. Int.* **1982**, 14, 249.

⁶⁸³ For a list of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1542–1543. See Yu, Y.; Zhang, Y. *Synth. Commun.* **1999**, 29, 243.

⁶⁸⁴ Lalancette, J.M.; Lachance, A. *Tetrahedron Lett.* **1970**, 3903.

⁶⁸⁵ See Krapcho, A.P. *Synthesis* **1982**, 805, 893. For other methods, see Dehmlow, E.V.; Kunesch, E. *Synthesis* **1985**, 320; Taber, D.F.; Amedio, Jr., J.C.; Gulino, F. *J. Org. Chem.* **1989**, 54, 3474.

⁶⁸⁶ Hashimoto, M.; Eda, Y.; Osanai, Y.; Iwai, T.; Aoki, S. *Chem. Lett.* **1986**, 893.

⁶⁸⁷ Laval, G.; Golding, B.T. *Synlett* **2003**, 542.

⁶⁸⁸ See Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett.* **1989**, 30, 6733.

⁶⁸⁹ See Deacon, G.B. *Organomet. Chem. Rev. A* **1970**, 355; Deacon, G.B.; Faulks, S.J.; Pain, G.N. *Adv. Organomet. Chem.* **1986**, 25, 237.

⁶⁹⁰ Kolarovi, A.; Fberov, Z. *J. Org. Chem.* **2009**, 74, 7199.

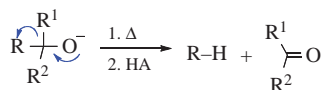
⁶⁹¹ Gribkov, D.V.; Pastine, S.J.; Schnürch, M.; Sames, D. *J. Am. Chem. Soc.* **2007**, 129, 11750.

⁶⁹² Waetzig, S.R.; Tunge, J.A. *J. Am. Chem. Soc.* **2007**, 129, 14860.

597, 630, 731, 857; **V**, 251, 585; **VI**, 271, 965; **VII**, 249, 359; **VIII**, 235, 444, 536; **75**, 195. Also see, OS **IV**, 633.

12-41 Cleavage of Alkoxides

Hydro-de-(α -oxidoalkyl)-substitution



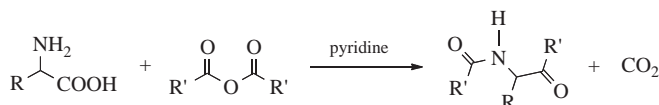
Alkoxides of tertiary alcohols can be cleaved in a reaction that is essentially the reverse of addition of carbanions to ketones (Reaction **16-24**).⁶⁹³ The reaction is unsuccessful when the R groups are simple unbranched alkyl groups (e.g., the alkoxide of triethylcarbinol). Cleavage is accomplished with branched alkoxides (e.g., the alkoxides of diisopropylneopentylcarbinol or tri-*tert*-butylcarbinol).⁶⁹⁴ Allylic,⁶⁹⁵ benzylic,⁶⁹⁶ and aryl groups also cleave (e.g., the alkoxide of triphenylcarbinol gives benzene and benzophenone). Studies in the gas phase show that the cleavage is a simple one, giving the carbanion and ketone directly in one step.⁶⁹⁷ However, with some substrates in solution, substantial amounts of dimer R—R have been found, indicating a radical pathway.⁶⁹⁸ Hindered alcohols (not the alkoxides) also lose one R group by cleavage, also by a radical pathway.⁶⁹⁹ The so-called retro-aldol (see Reaction **16-34**) is another example.

The reaction has been used for extensive mechanistic studies (see Sec. 12.A.ii).

OS **VI**, 268.

12-42 Replacement of a Carboxyl Group by an Acyl Group

Acyl-de-carboxylation



When an α -amino acid is treated with an anhydride in the presence of pyridine, the carboxyl group is replaced by an acyl group and the NH_2 becomes acylated. This is called the *Dakin–West reaction*.⁷⁰⁰ The mechanism involves formation of an oxazolone.⁷⁰¹ The reaction sometimes takes place on carboxylic acids even when an amino group is not present. A number of *N*-substituted amino acids [$\text{RCH}(\text{NHR}')\text{COOH}$] give the corresponding *N*-alkylated products.

OS **IV**, 5; **V**, 27.

⁶⁹³ Benkeser, R.A.; Siklosi, M.P.; Mozdzen, E.C. *J. Am. Chem. Soc.* **1978**, 100, 2134.

⁶⁹⁴ Arnett, E.M.; Small, L.E.; McIver Jr., R.T.; Miller, J.S. *J. Org. Chem.* **1978**, 43, 815. See also, Lomas, J.S.; Dubois, J.E. *J. Org. Chem.* **1984**, 49, 2067.

⁶⁹⁵ See Snowden, R.L.; Linder, S.M.; Muller, B.L.; Schulte-Elte, K.H. *Helv. Chim. Acta* **1987**, 70, 1858, 1879.

⁶⁹⁶ Partington, S.M.; Watt, C.I.F. *J. Chem. Soc. Perkin Trans. 2* **1988**, 983.

⁶⁹⁷ Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* **1988**, 110, 2714; Ibrahim, S.; Watt, C.I.F.; Wilson, J.M.; Moore, C. *J. Chem. Soc. Chem. Commun.* **1989**, 161.

⁶⁹⁸ Paquette, L.A.; Gilday, J.P.; Maynard, G.D. *J. Org. Chem.* **1989**, 54, 5044; Paquette, L.A.; Maynard, G.D. *J. Org. Chem.* **1989**, 54, 5054.

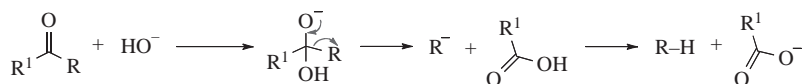
⁶⁹⁹ See Lomas, J.S.; Fain, D.; Briand, S. *J. Org. Chem.* **1990**, 55, 1052, and references cited therein.

⁷⁰⁰ See Buchanan, G.L. *Chem. Soc. Rev.* **1988**, 17, 91.

⁷⁰¹ Allinger, N.L.; Wang, G.L.; Dewhurst, B.B. *J. Org. Chem.* **1974**, 39, 1730.

B. Acyl Cleavages

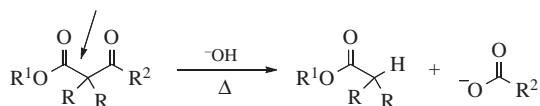
In these reactions (**12-43–2-46**), a carbonyl group is attacked by a hydroxide ion (or an amide ion), giving an intermediate that undergoes cleavage to a carboxylic acid (or an amide). With respect to the leaving group, this is nucleophilic substitution at a carbonyl group and the mechanism is the tetrahedral one discussed in Section 16.A.i.



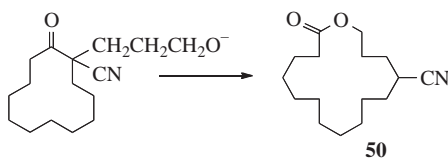
With respect to R this is of course electrophilic substitution. The mechanism is usually $\text{S}_{\text{E}}1$.

12-43 Basic Cleavage of β -Keto Esters and β -Diketones

Hydro-de-acylation



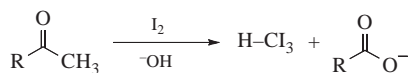
When β -keto esters are treated with concentrated base, cleavage occurs, but on the keto side of the CR_2 group (arrow) in contrast to the acid cleavage mentioned in Reaction **12-40**. The products are a carboxylic ester and the salt of an acid. However, the utility of the reaction is somewhat limited by the fact that decarboxylation is a side reaction, even under basic conditions. β -Diketones behave similarly to give a ketone and the salt of a carboxylic acid. With both β -keto esters and β -diketones, OEt^- can be used instead of OH^- , in which case the ethyl esters of the corresponding acids are obtained instead of the salts. In the case of β -keto esters, this is the reverse of *Claisen condensation* (Reaction **16-85**). The related cleavage of cyclic α -cyano ketones, in an intramolecular fashion, has been used in a synthesis of macrocyclic lactones (e.g., **50**).⁷⁰²



Activated F^- (from KF and a crown ether) has been used as the base to cleave an α -cyano ketone.⁷⁰³ Treatment with ceric ammonium nitrate led to cleavage of β -diketones to give a carboxylic acid.⁷⁰⁴

OS II, 266, 531; III, 379; IV, 415, 957; V, 179, 187, 277, 533, 747, 767.

12-44 Haloform Reaction

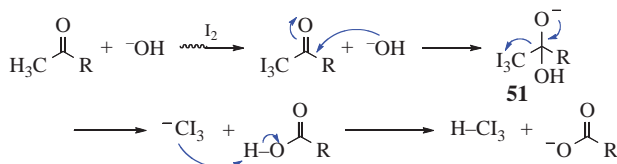


⁷⁰² Milenkov, B.; Hesse, M. *Helv. Chim. Acta* **1987**, 70, 308. For a similar preparation of lactams, see Wälichli, R.; Bienz, S.; Hesse, M. *Helv. Chim. Acta* **1985**, 68, 484.

⁷⁰³ Beletskaya, I.P.; Gulyukina, N.S.; Borodkin, V.S.; Solov'yanov, A.A.; Reutov, O.A. *Doklad. Chem.* **1984**, 276, 202. See also, Mignani, G.; Morel, D.; Grass, F. *Tetrahedron Lett.* **1987**, 28, 5505.

⁷⁰⁴ Zhang, Y.; Jiao, J.; Flowers II, R.A. *J. Org. Chem.* **2006**, 71, 4516.

In the *haloform reaction*, methyl ketones (and the only methyl aldehyde, acetaldehyde) are cleaved with halogen and a base.⁷⁰⁵ The halogen can be bromine, chlorine, or iodine. What takes place is actually a combination of two reactions. The first is an example of Reaction 12-4, in which, under the basic conditions employed, the methyl group is trihalogenated. Then the resulting trihalo ketone is attacked by hydroxide ion to give tetrahedral intermediate (51).⁷⁰⁶ The X_3C^- group is a sufficiently good leaving group (not HX_2C^- or H_2XC^-) that a carboxylic acid is formed, which quickly reacts with the carbanion to give the final products. Primary or secondary methylcarbinols also give the reaction, because they are oxidized to the carbonyl compounds under the conditions employed.

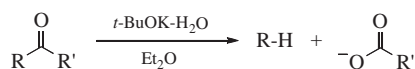


As with Reaction 12-4, the rate-determining step is the preliminary enolization of the methyl ketone.⁷⁰⁷ A side reaction is α halogenation of the non-methyl R group. Sometimes these groups are also cleaved.⁷⁰⁸ The reaction cannot be applied to F_2 , but ketones of the form RCOCF_3 (R = alkyl or aryl) give fluoroform and RCOO^- when treated with base.⁷⁰⁹ Rate constants for cleavage of X_3CCOPh (X = F, Cl, Br) were found to be in the ratio $1 : 5.3 \times 10^{10} : 2.2 \times 10^{13}$, showing that an F_3C^- group cleaves much more slowly than the others.⁷¹⁰ In the past, the haloform reaction was used as a test for methylcarbinols and methyl ketones. Iodine was most often used as the test reagent, since iodoform (HClI_3) is an easily identifiable yellow solid. The reaction can be used for synthetic purposes. Methyl ketones (RCOCH_3) can be converted directly to methyl esters (RCO_2CH_3) by an electrochemical reaction.⁷¹¹ Trifluoromethyl ketones have been converted to ethyl esters via treatment with NaH in aq DMF followed by reaction with bromoethane.⁷¹²

OS I, 526; II, 428; III, 302; IV, 345; V, 8. Also see, OS VI, 618.

12-45 Cleavage of Nonenolizable Ketones

Hydro-de-acylation



Ordinary ketones are generally much more difficult to cleave than trihalo ketones or β -diketones. However, nonenolizable ketones can be cleaved by treatment with a 10:3 mixture of $t\text{-BuOK-H}_2\text{O}$ in an aprotic solvent [e.g., ether, DMSO, 1,2-dimethoxyethane

⁷⁰⁵ See Chakrabartty, S.K. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, **1978**, pp. 343–370.

⁷⁰⁶ See Guthrie, J.P.; Cossar, J. *Can. J. Chem.* **1986**, *64*, 1250; Zucco, C.; Lima, C.F.; Rezende, M.C.; Vianna, J.F.; Nome, F. *J. Org. Chem.* **1987**, *52*, 5356.

⁷⁰⁷ Pocker, Y. *Chem. Ind. (London)* **1959**, 1383.

⁷⁰⁸ Levine, R.; Stephens, J.R. *J. Am. Chem. Soc.* **1950**, *72*, 1642.

⁷⁰⁹ See Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, **1976**, pp. 276–278.

⁷¹⁰ Guthrie, J.P.; Cossar, J. *Can. J. Chem.* **1990**, *68*, 1640.

⁷¹¹ Nikishin, G.I.; Elinson, M.N.; Makhova, I.V. *Tetrahedron* **1991**, *47*, 895.

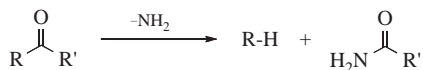
⁷¹² Delgado, A.; Clardy, J. *Tetrahedron Lett.* **1992**, *33*, 2789.

(glyme),⁷¹³ or with solid *t*-BuOK in the absence of a solvent].⁷¹⁴ When the reaction is applied to monosubstituted diaryl ketones, that aryl group preferentially cleaves that comes off as the more stable carbanion, except that aryl groups substituted in the ortho position are more readily cleaved than otherwise because of the steric effect (relief of strain).^{714,715} In certain cases, cyclic ketones can be cleaved by base treatment, even if they are enolizable.⁷¹⁶

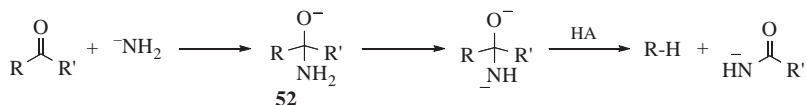
OS VI, 625. See also, OS VII, 297.

12-46 The Haller–Bauer Reaction

Hydro-de-acylation



Cleavage of ketones with sodium amide is called the *Haller–Bauer reaction*.⁷¹⁷ As with Reaction 12-45, which is exactly analogous, the reaction is usually applied only to non-enolizable ketones, most often to ketones of the form ArCOCR₃, where the products R₃CCONH₂ (after hydrolysis) are not easily attainable by other methods. However, many other ketones have been used, although benzophenone is virtually unaffected. It has been shown that the configuration of optically active alkyl groups (R) is retained.⁷¹⁸ The NH₂ loses its proton from the tetrahedral intermediate (**52**) before the R group is cleaved.⁷¹⁹



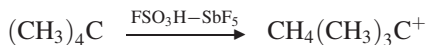
An extension of this cleavage process involves the reaction of α-nitro ketones (O=C—CHRNO₂) with a primary amine, neat, to give the corresponding amide, O=C—NHR'.⁷²⁰

OS V, 384, 1074.

C. Other Cleavages

12-47 The Cleavage of Alkanes

Hydro-de- *tert*- butylation, and so on



The C—C bonds of alkanes can be cleaved by treatment with superacids (Sec. 5.A.ii). For example, neopentane in FSO₃H—SbF₅ can cleave to give methane and the *tert*-butyl cation. The C—H cleavage (see Reaction 12-1) is a competing reaction and, for example,

⁷¹³ Gassman, P.G.; Lumb, J.T.; Zalar, F.V. *J. Am. Chem. Soc.* **1967**, 89, 946.

⁷¹⁴ March, J.; Plankl, W. *J. Chem. Soc. Perkin Trans. 1* **1977**, 460.

⁷¹⁵ Davies, D.G.; Derenberg, M.; Hodge, P. *J. Chem. Soc. C* **1971**, 455.

⁷¹⁶ See Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc.* **1969**, 91, 1009.

⁷¹⁷ See Gilday, J.P.; Paquette, L.A. *Org. Prep. Proced. Int.* **1990**, 22, 167.

⁷¹⁸ Paquette, L.A.; Gilday, J.P. *J. Org. Chem.* **1988**, 53, 4972; Paquette, L.A.; Ra, C.S. *J. Org. Chem.* **1988**, 53, 4978.

⁷¹⁹ Bunnett, J.F.; Hrutfiord, B.F. *J. Org. Chem.* **1962**, 27, 4152.

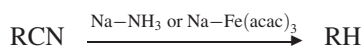
⁷²⁰ Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron* **2003**, 59, 1143.

neopentane can give H_2 and the *tert*-pentyl carbocation (formed by rearrangement of the initially formed neopentyl cation) by this pathway. In general, the order of reactivity is tertiary $C-H > C-C > \text{secondary } C-H \gg \text{primary } C-H$, although steric factors cause a shift in favor of $C-C$ cleavage in such a hindered compound as tri-*tert*-butylmethane. The mechanism is similar to that shown in Reactions 12-1 and 12-20 and involves attack by H^+ on the $C-C$ bond to give a pentavalent cation.

Catalytic hydrogenation seldom breaks unactivated $C-C$ bonds (i.e., $R-R' + H_2 \rightarrow RH + R'H$), but methyl and ethyl groups have been cleaved from substituted adamantanes by hydrogenation with a $Ni-Al_2O_3$ catalyst at $\sim 250^\circ C$.⁷²¹ Certain $C-C$ bonds have been cleaved by alkali metals.⁷²²

The $C-C$ bond of 2-allyl-2-arylmalonate derivatives was cleaved, with loss of the allylic group to give the 2-arylmalonate, by treatment with a Ni catalyst.⁷²³

12-48 Decyanation or Hydro-de-cyanation



The cyano group of alkyl nitriles can be removed⁷²⁴ by treatment with metallic Na , either in liquid ammonia,⁷²⁵ or together with tris(acetylacetonato)iron(III) $[Fe(acac)_3]$ ⁷²⁶ or, with lower yields, titanocene. The two procedures are complementary. Although both can be used to decyanate many kinds of nitriles, the $Na-NH_3$ method gives high yields with R groups (e.g., trityl, benzyl, phenyl, and tertiary alkyl), but lower yields ($\sim 35-50\%$) when R = primary or secondary alkyl. On the other hand, primary and secondary alkyl nitriles are decyanated in high yields by the $Na-Fe(acac)_3$ procedure. Sodium in liquid ammonia is known to be a source of solvated electrons, and the reaction may proceed through the free radical R^\bullet that would then be reduced to the carbanion R^- , which by abstraction of a proton from the solvent, would give RH . The mechanism with $Fe(acac)_3$ is presumably different. Another procedure,⁷²⁷ which is successful for R = primary, secondary, or tertiary, involves the use of potassium metal and the crown ether dicyclohexano-18-crown-6 in toluene.⁷²⁸

α -Amino and α -amido nitriles $RCH(CN)NR'_2$ and $RCH(CN)NHCOR'$ can be decyanated in high yield by treatment with $NaBH_4$.⁷²⁹

⁷²¹ Grubmüller, P.; Schleyer, P.v.R.; McKervey, M.A. *Tetrahedron Lett.* **1979**, 181.

⁷²² See Grovenstein Jr., E.; Bhatti, A.M.; Quest, D.E.; Sengupta, D.; VanDerveer, D. *J. Am. Chem. Soc.* **1983**, 105, 6290.

⁷²³ Necas, D.; Tursky, M.; Kotorá, M. *J. Am. Chem. Soc.* **2004**, 126, 10222.

⁷²⁴ For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, p. 75.

⁷²⁵ Birch, A.J.; Hutchinson, E.G. *J. Chem. Soc. Perkin Trans. 1* **1972**, 1546; Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1976**, 61.

⁷²⁶ Van Tamelen, E.E.; Rudler, H.; Bjorklund, C. *J. Am. Chem. Soc.* **1971**, 93, 7113.

⁷²⁷ See Berkoff, C.E.; Rivard, D.E.; Kirkpatrick, D.; Ives, J.L. *Synth. Commun.* **1980**, 10, 939; Savoia, D.; Tagliavini, E.; Trombini, C.; Umami-Ronchi, A. *J. Org. Chem.* **1980**, 45, 3227; Ozawa, F.; Iri, K.; Yamamoto, A. *Chem. Lett.* **1982**, 1707.

⁷²⁸ Ohsawa, T.; Kobayashi, T.; Mizuguchi, Y.; Saitoh, T.; Oishi, T. *Tetrahedron Lett.* **1985**, 26, 6103.

⁷²⁹ Fabre, C.; Hadj Ali Salem, M.; Welvert, Z. *Bull. Soc. Chim. Fr.* **1975**, 178. See also, Ogura, K.; Shimamura, Y.; Fujita, M. *J. Org. Chem.* **1991**, 56, 2920.

12.C.v. Electrophilic Substitution at Nitrogen

In most of the reactions in this section, an electrophile bonds with the unshared pair of a nitrogen atom. The electrophile may be a free positive ion or a positive species attached to a carrier that breaks off in the course of the attack or shortly after:



Further reaction of **53** depends on the nature of Y and of the other groups attached to the nitrogen.

12-49 The Conversion of Hydrazines to Azides

Hydrazine-azide transformation

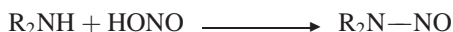


Monosubstituted hydrazines treated with nitrous acid give azides in a reaction exactly analogous to the formation of aliphatic diazo compounds mentioned in Reaction **13-19**. Among other reagents used for this conversion have been N_2O_4 ⁷³⁰ and nitrosyl tetrafluoroborate (NOBF_4).⁷³¹

OS **III**, 710; **IV**, 819; **V**, 157.

12-50 N-Nitrosation

N-Nitroso-de-hydrogenation



When secondary amines are treated with nitrous acid (typically formed from sodium nitrite and a mineral acid),⁷³² *N*-nitroso compounds (also called nitrosamines) are formed.⁷³³ The reaction can be accomplished with dialkyl-, diaryl-, or alkylarylamines, and even with mono-*N*-substituted amides: $\text{RCONHR}' + \text{HONO} \rightarrow \text{RCON}(\text{NO})\text{R}'$.⁷³⁴ Tertiary amines have also been *N*-nitrosated, but in these cases one group cleaves, so that the product is the nitroso derivative of a secondary amine.⁷³⁵ The group that cleaves appears as an aldehyde or ketone product. Other reagents have also been used (e.g., NOCl), which is useful for amines or amides that are not soluble in an acidic aqueous solution or where the *N*-nitroso compounds are highly reactive. *N*-Nitroso compounds can be prepared in basic solution by treatment of secondary amines with gaseous N_2O_3 , N_2O_4 ,⁷³⁶ or alkyl

⁷³⁰ Kim, Y.H.; Kim, K.; Shim, S.B. *Tetrahedron Lett.* **1986**, 27, 4749.

⁷³¹ Pozsgay, V.; Jennings, H.J. *Tetrahedron Lett.* **1987**, 28, 5091.

⁷³² See Zolfigol, M.A. *Synth. Commun.* **1999**, 29, 905; Zolfigol, M.A.; Ghaemi, E.; Madrikian, E.; Kiany-Burazjani, M. *Synth. Commun.* **2000**, 30, 2057.

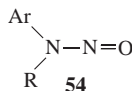
⁷³³ See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, **1988**, pp. 95–109; Kostyukovskii, Ya.L.; Melamed, D.B. *Russ. Chem. Rev.* **1988**, 57, 350; Saavedra, J.E. *Org. Prep. Proced. Int.* **1987**, 19, 83; Challis, B.C.; Challis, J.A. in Patai, S.; Rappoport, Z. *The Chemistry of the Functional Groups Supplement F*, pt. 2, Wiley, NY, **1982**, pp. 1151–1223. Also see Zyranov, G.V.; Rudkevich, D.M. *Org. Lett.* **2003**, 5, 1253.

⁷³⁴ Castro, A.; Iglesias, E.; Leis, J.R.; Peña, M.E.; Tato, J.V. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1725.

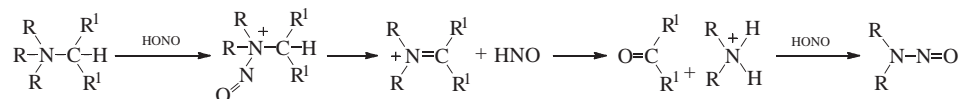
⁷³⁵ Hein, G.E. *J. Chem. Educ.* **1963**, 40, 181. See also, Verardo, G.; Giumanini, A.G.; Strazzolini, P. *Tetrahedron* **1990**, 46, 4303.

⁷³⁶ Challis, B.C.; Kyrtopoulos, S.A. *J. Chem. Soc. Perkin Trans. 1* **1979**, 299.

nitrites,⁷³⁷ and, in aqueous or organic solvents, by treatment with BrCH_2NO_2 .⁷³⁸ Secondary amines are converted to the *N*-nitroso compound with H_5IO_6 on wet silica.⁷³⁹



The mechanism of nitrosation is essentially the same as in Reaction **13-19** up to the point where **54** is formed. Since this species cannot lose a proton, it is stable and the reaction ends there. The attacking entity can be any of those mentioned in Reaction **13-19**. The following has been suggested as the mechanism for the reaction with tertiary amines:⁷⁴⁰

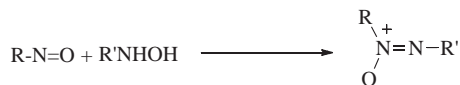


The evidence for this mechanism includes the facts that nitrous oxide is a product (formed by $2\text{HNO} \rightarrow \text{H}_2\text{O} + \text{N}_2\text{O}$) and that quinuclidine, where the nitrogen is at a bridgehead and cannot give elimination, does not react. Tertiary amines have also been converted to nitrosamines with nitric acid in Ac_2O ⁷⁴¹ and with N_2O_4 .⁷⁴²

Amines and amides can be *N*-nitrated⁷⁴³ with nitric acid,⁷⁴⁴ or NO_2^+ ,⁷⁴⁵ and aromatic amines can be converted to triazenes with diazonium salts. Aliphatic primary amines can also be converted to triazenes if the diazonium salts contain electron-withdrawing groups.⁷⁴⁶ *C*-Nitrosation is discussed at Reactions **11-3** and **12-8**.

OS **I**, 177, 399, 417; **II**, 163, 211, 290, 460, 461, 462, 464 (Also see, **V**, 842); **III**, 106, 244; **IV**, 718, 780, 943; **V**, 336, 650, 797, 839, 962; **VI**, 542, 981. Also see, OS **III**, 711.

12-51 Conversion of Nitroso Compounds to Azoxy Compounds



In a reaction similar to **13-24**, azoxy compounds can be prepared by the condensation of a nitroso compound with a hydroxylamine.⁷⁴⁷ The position of the oxygen in the final product is

⁷³⁷ Casado, J.; Castro, A.; Lorenzo, F.M.; Meijide, F. *Monatsh. Chem.* **1986**, 117, 335.

⁷³⁸ Challis, B.C.; Yousaf, T.I. *J. Chem. Soc. Chem. Commun.* **1990**, 1598.

⁷³⁹ Zolfigol, M.A.; Choghamarani, A.G.; Shivini, F.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* **2001**, 31, 359. See Zolfigol, M.A.; Bagherzadeh, M.; Choghamarani, A.G.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* **2001**, 31, 1161.

⁷⁴⁰ Gowenlock, B.G.; Hutchison, R.J.; Little, J.; Pfab, J. *J. Chem. Soc. Perkin Trans. 2* **1979**, 1110. See also, Loeppky, R.N.; Outram, J.R.; Tomasik, W.; Faulconer, J.M. *Tetrahedron Lett.* **1983**, 24, 4271.

⁷⁴¹ Boyer, J.H.; Pillai, T.P.; Ramakrishnan, V.T. *Synthesis* **1985**, 677.

⁷⁴² Boyer, J.H.; Kumar, G.; Pillai, T.P. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1751.

⁷⁴³ See Bottaro, J.C.; Schmitt, R.J.; Bedford, C.D. *J. Org. Chem.* **1987**, 52, 2292; Suri, S.C.; Chapman, R.D. *Synthesis* **1988**, 743; Carvalho, E.; Iley, J.; Norberto, F.; Rosa, E. *J. Chem. Res. (S)* **1989**, 260.

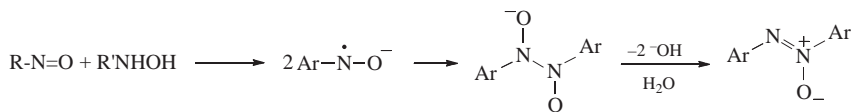
⁷⁴⁴ Cherednichenko, L.V.; Dmitrieva, L.G.; Kuznetsov, L.L.; Gidaspov, B.V. *J. Org. Chem. USSR* **1976**, 12, 2101, 2105.

⁷⁴⁵ Andreev, S.A.; Lededev, B.A.; Tselinskii, I.V. *J. Org. Chem. USSR* **1980**, 16, 1166, 1170, 1175, 1179.

⁷⁴⁶ See Vaughan, K.; Stevens, M.F.G. *Chem. Soc. Rev.* **1978**, 7, 377.

⁷⁴⁷ Boyer, J.H. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, **1969**, pp. 278–283.

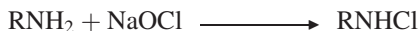
determined by the nature of the R groups, not by which R groups came from which starting compound. Both R and R' can be alkyl or aryl, but when two different aryl groups are involved, mixtures of azoxy compounds (ArNONAr, ArNONAr', and Ar'NONAr') are obtained⁷⁴⁸ and the unsymmetrical product (ArNONAr') is likely to be formed in the smallest amount. This behavior is probably caused by an equilibration between the starting compounds prior to the actual reaction ($\text{ArNO} + \text{Ar}'\text{NHOH} \rightarrow \text{Ar}'\text{NO} + \text{ArNHOH}$).⁷⁴⁹ The mechanism⁷⁵⁰ has been investigated in the presence of base. Under these conditions both reactants are converted to radical anions, which couple:



These radical anions have been detected by ESR.⁷⁵¹ This mechanism is consistent with the following result: When nitrosobenzene and phenylhydroxylamine are coupled, ¹⁸O and ¹⁵N labeling show that the two nitrogen atoms and the two oxygen atoms become equivalent.⁷⁵² Unsymmetrical azoxy compounds can be prepared⁷⁵³ by combination of a nitroso compound with an *N,N*-dibromoamine. Symmetrical and unsymmetrical azo and azoxy compounds are produced when aromatic nitro compounds react with aryliminodimagnesium reagents $[\text{ArN}(\text{MgBr})_2]$.⁷⁵⁴

12-52 N-Halogenation

N-Halo-de-hydrogenation



Treatment with sodium hypochlorite or hypobromite converts primary amines into *N*-halo- or *N,N*-dihaloamines. Secondary amines can be converted to *N*-halo secondary amines. Similar reactions can be carried out on unsubstituted and *N*-substituted amides and on sulfonamides. With unsubstituted amides the *N*-halogen product is seldom isolated but usually rearranges (see Reaction 18-13); however, *N*-halo-*N*-alkyl amides and *N*-halo imides are quite stable. The important reagents NBS and NCS are made in this manner. *N*-Halogenation has also been accomplished with other reagents (e.g., sodium bromite, NaBrO_2),⁷⁵⁵ benzyltrimethylammonium tribromide ($\text{PhCH}_2\text{NMe}_3^+\text{Br}_3^-$),⁷⁵⁶ NaCl with Oxone,⁷⁵⁷ and NCS.⁷⁵⁸ Sodium hypohalite in the presence of *tert*-butanol and acetic acid is

⁷⁴⁸ See Ogata, Y.; Tsuchida, M.; Takagi, Y. *J. Am. Chem. Soc.* **1957**, 79, 3397.

⁷⁴⁹ Knight, G.T.; Saville, B. *J. Chem. Soc. Perkin Trans. 2* **1973**, 1550.

⁷⁵⁰ For discussions of the mechanism in the absence of base, see Becker, A.R.; Sternson, L.A. *J. Org. Chem.* **1980**, 45, 1708. See also, Pizzolatti, M.G.; Yunes, R.A. *J. Chem. Soc. Perkin Trans. 1* **1990**, 759.

⁷⁵¹ Russell, G.A.; Geels, E.J.; Smentowski, F.J.; Chang, K.; Reynolds, J.; Kaupp, G. *J. Am. Chem. Soc.* **1967**, 89, 3821.

⁷⁵² Oae, S.; Fukumoto, T.; Yamagami, M. *Bull. Chem. Soc. Jpn.* **1963**, 36, 728.

⁷⁵³ Zawalski, R.C.; Kovacic, P. *J. Org. Chem.* **1979**, 44, 2130. Also see Moriarty, R.M.; Hopkins, T.E.; Prakash, I.; Vaid, B.K.; Vaid, R.K. *Synth. Commun.* **1990**, 20, 2353.

⁷⁵⁴ Okubo, M.; Matsuo, K.; Yamauchi, A. *Bull. Chem. Soc. Jpn.* **1989**, 62, 915, and other papers in this series.

⁷⁵⁵ Kajigaeshi, S.; Nakagawa, T.; Fujisaki, S. *Chem. Lett.* **1984**, 2045.

⁷⁵⁶ Kajigaeshi, S.; Murakawa, K.; Asano, K.; Fujisaki, S.; Kakinami, T. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1702.

⁷⁵⁷ Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O.; Tsadjout, A. *Synlett* **2000**, 813.

⁷⁵⁸ See Guillemin, J.; Denis, J.N. *Synthesis* **1985**, 1131.

an efficient method for the preparation of *N*-haloamines.⁷⁵⁹ Amides are *N*-chlorinated with trichloroisocyanuric acid.⁷⁶⁰ The mechanisms of these reactions⁷⁶¹ involve attack by a positive halogen and are probably similar to those of Reactions **13-19** and **12-50**.⁷⁶² *N*-Fluorination can be accomplished by direct treatment of amines⁷⁶³ or amides⁷⁶⁴ with F₂. Fluorination of *N*-alkyl-*N*-fluoroamides [RRN(F)COR'] results in cleavage to *N,N*-difluoroamines (RNF₂).^{764,765} Trichloroisocyanuric acid converts primary amines to the *N,N*-dichloroamine.⁷⁶⁶

OS **III**, 159; **IV**, 104, 157; **V**, 208, 663, 909; **VI**, 968; **VII**, 223; **VIII**, 167, 427.

12-53 The Reaction of Amines With Carbon Monoxide or Carbon Dioxide

***N*-Formylation** or ***N*-Formyl-de-hydrogenation**, and so on



Three types of product can be obtained from the reaction of amines with CO, depending on the catalyst. (1) Both primary and secondary amines react with CO in the presence of various catalysts [e.g., Cu(CN)₂, Me₃N-H₂Se, and Rh or Ru complexes] to give *N*-substituted and *N,N*-disubstituted formamides, respectively.⁷⁶⁷ Primary aromatic amines react with ammonium formate to give the formamide.⁷⁶⁸ Tertiary amines react with CO and a Pd catalyst to give an amide.⁷⁶⁹ (2) Symmetrically substituted ureas can be prepared by treatment of a primary amine (or ammonia) with CO⁷⁷⁰ in the presence of Se⁷⁷¹ or S.⁷⁷² The R source can be alkyl or aryl. The same thing can be done with secondary amines, using Pd(OAc)₂—I₂—K₂CO₃.⁷⁷³ Primary aromatic amines react with β-keto esters and a Mo—ZrO₂ catalyst to give the symmetrical urea.⁷⁷⁴ Treatment of a secondary amine with nitrobenzene, selenium and carbon monoxide leads to the unsymmetrical urea.⁷⁷⁵ (3) When PdCl₂ is the catalyst, primary amines yield isocyanates.⁷⁷⁶ Isocyanates can also be obtained by treatment of CO with azides: RN₃ + CO → RNCO,⁷⁷⁷ or with an aromatic

⁷⁵⁹ Zhong, Y.-L.; Zhou, H.; Gauthier, D.R.; Lee, J.; Askin, D.; Dolling, U.H.; Volante, R.P. *Tetrahedron Lett.* **2005**, 46, 1099.

⁷⁶⁰ De Luca, L.; Giacomelli, G.; Nieddu, G. *Synlett* **2005**, 223.

⁷⁶¹ See Matte, D.; Solasiouk, B.; Merlin, A.; Deglise, X. *Can. J. Chem.* **1989**, 67, 786.

⁷⁶² See Thomm, E.W.C.W.; Wayman, M. *Can. J. Chem.* **1969**, 47, 3289; Higuchi, T.; Hussain, A.; Pitman, I.H. *J. Chem. Soc. B*, **1969**, 626.

⁷⁶³ Sharts, C.M. *J. Org. Chem.* **1968**, 33, 1008.

⁷⁶⁴ Grakauskas, V.; Baum, K. *J. Org. Chem.* **1969**, 34, 2840; **1970**, 35, 1545.

⁷⁶⁵ See Barton, D.H.R.; Hesse, R.H.; Klose, T.R.; Pechet, M.M. *J. Chem. Soc. Chem. Commun.* **1975**, 97.

⁷⁶⁶ DeLuca, L.; Giacomelli, G. *Synlett* **2004**, 2180.

⁷⁶⁷ See Bitsi, G.; Jenner, G. *J. Organomet. Chem.* **1987**, 330, 429.

⁷⁶⁸ Reddy, P.G.; Kumar, D.K.; Baskaran, S. *Tetrahedron Lett.* **2000**, 41, 9149.

⁷⁶⁹ Troisi, L.; Granito, C.; Rosato, F.; Videtta, V. *Tetrahedron Lett.* **2010**, 51, 371; Wu, X.-F.; Neumann, H.; Beller, M. *Chemistry: Eur. J.* **2010**, 16, 9750.

⁷⁷⁰ See Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, 69, 4741.

⁷⁷¹ Sonoda, N.; Yasuhara, T.; Kondo, K.; Ikeda, T.; Tsutsumi, S. *J. Am. Chem. Soc.* **1971**, 93, 6344.

⁷⁷² Franz, R.A.; Applegath, F.; Morriss, F.V.; Baiocchi, F.; Bolze, C. *J. Org. Chem.* **1961**, 26, 3309.

⁷⁷³ Pri-Bar, I.; Alper, H. *Can. J. Chem.* **1990**, 68, 1544.

⁷⁷⁴ Reddy, B.M.; Reddy, V.R. *Synth. Commun.* **1999**, 29, 2789.

⁷⁷⁵ Yang, Y.; Lu, S. *Tetrahedron Lett.* **1999**, 40, 4845.

⁷⁷⁶ Stern, E.W.; Spector, M.L. *J. Org. Chem.* **1966**, 31, 596.

⁷⁷⁷ Bennett, R.P.; Hardy, W.B. *J. Am. Chem. Soc.* **1968**, 90, 3295.

nitroso or nitro compound and a Rh complex catalyst.⁷⁷⁸ Primary amines react with di-*tert*-butyltricarboxylate to give the isocyanate.⁷⁷⁹

Lactams are converted to the corresponding *N*-chloro lactam with $\text{Ca}(\text{OCl})_2$ with moist alumina in dichloromethane.⁷⁸⁰ Ring-expanded lactams are obtained from cyclic amines via a similar reaction⁷⁸¹ (see also, Reaction 16-22). Intramolecular carbonylation of amines also leads to lactams.⁷⁸²

A fourth type of product, a carbamate ($\text{RNHCOOR}'$), can be obtained from primary or secondary amines, if these are treated with CO , O_2 , and an alcohol ($\text{R}'\text{OH}$) in the presence of a catalyst.⁷⁸³ Primary amines react with dimethyl carbonate in supercritical CO_2 (see Sec. 9.D.ii) to give a carbamate.⁷⁸⁴ Carbamates can also be obtained from nitroso compounds, by treatment with CO , $\text{R}'\text{OH}$, $\text{Pd}(\text{OAc})_2$, and $\text{Cu}(\text{OAc})_2$,⁷⁸⁵ and from nitro compounds.⁷⁸⁶ When allylic amines ($\text{R}_2\text{C}=\text{CHRCHNR}'_2$) are treated with CO and a Pd-phosphine catalyst, the CO inserts to produce the β,γ -unsaturated amides ($\text{R}_2\text{C}=\text{CHRCHRCONR}'_2$) in good yields.⁷⁸⁷ Silyloxy carbamates ($\text{RNHCO}_2\text{SiR}'_3$) can be prepared by the reaction of a primary amine with carbon dioxide and triethylamine, followed by reaction with triisopropylsilyl triflate and tetrabutylammonium fluoride.⁷⁸⁸

Carbon dioxide reacts with amines (ArNH_2) and alkyl halides, under electrolysis conditions, to give the corresponding carbamate (ArNHCO_2Et).⁷⁸⁹ Secondary amines react with all halides and an onium salt in supercritical CO_2 (see Sec. 9.D.ii) to give the carbamate.⁷⁹⁰ *N*-Phenylthioamines react with CO and a palladium catalyst to give a thiocarbamate ($\text{ArSCO}_2\text{NR}'_2$).⁷⁹¹ Urea derivatives were obtained from amines, CO_2 , and an antimony catalyst.⁷⁹²

Aziridines can be converted to cyclic carbamates (oxazolidinones) by heating with carbon dioxide and a chromium–salen catalyst.⁷⁹³ The reaction of aziridines with LiI , and then CO_2 also generates oxazolidinones.⁷⁹⁴

⁷⁷⁸ Unverferth, K.; Tietz, H.; Schwetlick, K. *J. Prakt. Chem.* **1985**, 327, 932. See also, Kunin, A.J.; Noiro, M.D.; Gladfelter, W.L. *J. Am. Chem. Soc.* **1989**, 111, 2739.

⁷⁷⁹ Peerlings, H.W.I.; Meijer, E.W. *Tetrahedron Lett.* **1999**, 40, 1021.

⁷⁸⁰ Larionov, O.V.; Kozhushkov, S.I.; de Meijere, A. *Synthesis* **2003**, 1916.

⁷⁸¹ Wang, M.D.; Alper, H. *J. Am. Chem. Soc.* **1992**, 114, 7018.

⁷⁸² Lu, S.-M.; Alper, H. *J. Am. Chem. Soc.* **2005**, 127, 14776.

⁷⁸³ Feroci, M.; Inesi, A.; Rossi, L. *Tetrahedron Lett.* **2000**, 41, 963.

⁷⁸⁴ Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* **2002**, 43, 1217. Also see Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* **2005**, 70, 2771.

⁷⁸⁵ Alper, H.; Vasapollo, G. *Tetrahedron Lett.* **1987**, 28, 6411.

⁷⁸⁶ Cenini, S.; Crotti, C.; Pizzotti, M.; Porta, F. *J. Org. Chem.* **1988**, 53, 1243; Reddy, N.P.; Masdeu, A.M.; El Ali, B.; Alper, H. *J. Chem. Soc. Chem. Commun.* **1994**, 863.

⁷⁸⁷ Murahashi, S.; Imada, Y.; Nishimura, K. *J. Chem. Soc. Chem. Commun.* **1988**, 1578.

⁷⁸⁸ Lipshutz, B.H.; Papa, P.; Keith, J.M. *J. Org. Chem.* **1999**, 64, 3792.

⁷⁸⁹ Feroci, M.; Casadei, M.A.; Orsini, M.; Palombi, L.; Inesi, A. *J. Org. Chem.* **2003**, 68, 1548.

⁷⁹⁰ Yoshida, M.; Hara, N.; Okuyama, S. *Chem. Commun.* **2000**, 151.

⁷⁹¹ Kuniyasu, H.; Hiraike, H.; Morita, M.; Tanaka, A.; Sugoh, K.; Kurosawa, H. *J. Org. Chem.* **1999**, 64, 7305.

⁷⁹² Nomura, R.; Hasegawa, Y.; Ishimoto, M.; Toyosaki, T.; Matsuda, H. *J. Org. Chem.* **1992**, 57, 7339.

⁷⁹³ Miller, A.W.; Nguyen, S.T. *Org. Lett.* **2004**, 6, 2301.

⁷⁹⁴ Hancock, M.T.; Pinhas, A.R. *Tetrahedron Lett.* **2003**, 44, 5457.

Aromatic Substitution: Nucleophilic and Organometallic

In Section 10.G, category 2, it was pointed out that nucleophilic substitutions proceed so slowly at an aromatic carbon that the reactions of Chapter 10 are not feasible for aromatic substrates. There are, however, exceptions to this statement, and these exceptions form the subject of this chapter.¹ Reactions that *are* successful at an aromatic substrate are largely of five kinds: (1) reactions activated by electron-withdrawing groups ortho and para to the leaving group; (2) reactions catalyzed by very strong bases and proceeding through aryne intermediates; (3) reactions initiated by electron donors; (4) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile; and (5) coupling reactions catalyzed by transition metals, primarily Pd,² Cu, Ni, and so on. Note that solvent effects can be important.³ The transition metal catalyzed coupling reactions are included because they involve replacement of a leaving group on an aromatic ring.

13.A. MECHANISMS

There are four principal mechanisms for aromatic nucleophilic substitution.⁴ Each of the four is similar to one of the aliphatic nucleophilic substitution mechanisms discussed in Chapter 10.

13.A.i. The S_NAr Mechanism⁵

By far the most important mechanism for nucleophilic aromatic substitution consists of two steps, attack of the nucleophilic species at the ipso carbon of the aromatic ring

¹ See Zoltewicz, J.A. *Top. Curr. Chem.* **1975**, 59, 33.

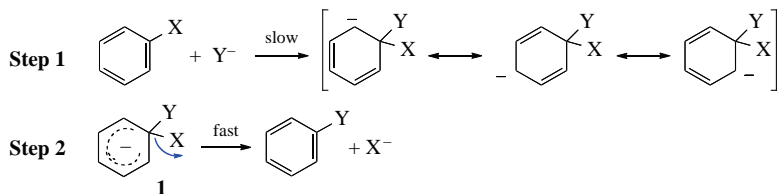
² See Fairlamb, I.J.S. *Tetrahedron* **2005**, 61, 9661.

³ Acevedo, O.; Jorgensen, W.L. *Org. Lett.* **2004**, 6, 2881.

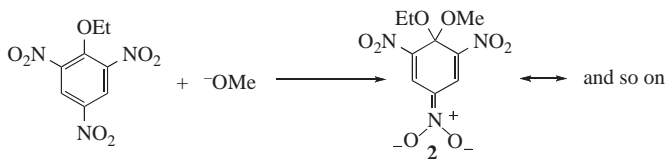
⁴ See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, **1968**. For reviews, see Bernasconi, C.F. *Chimia* **1980**, 34, 1; *Acc. Chem. Res.* **1978**, 11, 147; Bunnett, J.F. *J. Chem. Educ.* **1974**, 51, 312; Ross, S.D. in Bamford, C. H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 407–431; Buck, P. *Angew. Chem, Int. Ed.* **1969**, 8, 120; Bunce, E.; Norris, A.R.; Russell, K.E. *Q. Rev. Chem. Soc.* **1968**, 22, 123; Bunnett, J. F. *Tetrahedron* **1993**, 49, 4477; Zoltewicz, J.A. *Top. Curr. Chem.* **1975**, 59, 33.

⁵ See Barrett, I.C.; Kerr, M.A. *Tetrahedron Lett.* **1999**, 40, 2439.

(the carbon bearing the leaving group in this case), followed by elimination of the leaving group and regeneration of the aromatic ring.



The first step is usually, but not always, rate determining. It can be seen that this mechanism greatly resembles the tetrahedral mechanism discussed in Chapter 16 and, in another way, the arenium ion mechanism of electrophilic aromatic substitution discussed in Chapter 11. In all three cases, the attacking species forms a bond with the substrate, giving an intermediate (e.g., **1**) and then the leaving group departs. This mechanism is the S_NAr mechanism.⁶ The IUPAC designation is $A_N + D_N$ (the same as for the tetrahedral mechanism; cf. the designation $A_E + D_E$ for the arenium ion mechanism). This mechanism is generally found where activating groups are present on the ring (see Sec. 13.B.i).



There is a great deal of evidence for the mechanism.⁴ Probably the most convincing evidence was the isolation, as long ago as 1902, of the intermediate **2** in the reaction between 2,4,6-trinitrophenetole and methoxide ion.⁷ Intermediates of this type are stable salts, called *Meisenheimer* or *Meisenheimer–Jackson salts*,⁸ and many more have been isolated.⁹ The structures of several of these intermediates have been proved by NMR¹⁰ and by X-ray crystallography.¹¹ Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the S_N1 or S_N2 mechanisms described in Chapter 10, the Ar–X bond would be broken in the rate-determining step. In the S_NAr mechanism, this bond is not broken until after the rate-determining step (i.e., if step 1 is rate

⁶ Also see Wu, Z.; Glaser, R. *J. Am. Chem. Soc.* **2004**, *126*, 10632; Terrier, F.; Mokhtari, M.; Goumont, T.; Hallé, J.-C.; Buncel, E. *Org. Biomol. Chem.* **2003**, *1*, 1757.

⁷ Meisenheimer, J. *Liebigs Ann. Chem.* **1902**, 323, 205; Jackson, C.L.; see Jackson, C.L.; Gazzolo, F.H. *Am. Chem. J.* **1900**, *23*, 376; Jackson, C.L.; Earle, R.B. *Am. Chem. J.*, **1903**, *29*, 89.

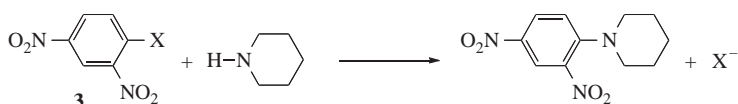
⁸ For heteroatom nucleophiles see Gallardo, I.; Guirado, G.; Marquet, J. *J. Org. Chem.* **2002**, *67*, 2548.

⁹ See Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, **1984**; Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* **1983**, *34*, 305; Terrier, F. *Chem. Rev.* **1982**, *82*, 77; Strauss, M.J. *Acc. Chem. Res.* **1974**, *7*, 181; Hall, T.N.; Poranski, Jr., C.F. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, **1970**, pp. 329–384; Foster, R.; Fyfe, C.A. *Rev. Pure Appl. Chem.* **1966**, *16*, 61.

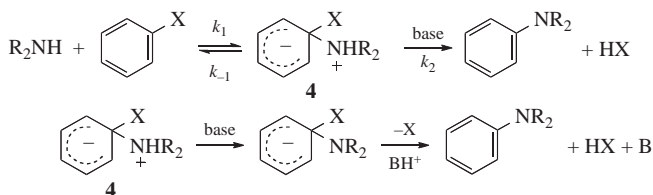
¹⁰ Crampton, M.R.; Gold, V.J. *Chem. Soc. B* **1966**, 893. See Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, **1984**, pp. 15–133.

¹¹ Destro, R.; Gramaccioli, C.M.; Simonetta, M. *Acta Crystallogr.* **1968**, *24*, 1369; Ueda, H.; Sakabe, M.; Tanaka, J.; Furusaki, A. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2866; Messmer, G.G.; Palenik, G.J. *Chem. Commun.* **1969**, 470.

determining). There is some evidence that electron transfer may be operative during this process.¹² If the S_NAr mechanism is operating, a change in leaving group should not have much effect on the reaction rate. In the reaction of dinitro compound **3** with piperidine, when X was Cl, Br, I, SPh, SO₂Ph, or *p*-nitrophenoxy, the rates differed only by a factor of ~ 5 .¹³ This behavior would not be expected in a reaction in which the Ar—X bond is broken in the rate-determining step. The rates are not expected to be *identical*, because the nature of X affects the rate at which Y attacks.¹⁴ An increase in the electronegativity of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile. Thus, in the reaction just mentioned, when X = F, the relative rate was 3300 (compared with I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the S_N1 and the S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens. This is an example of the element effect (Sec. 10.F).



The pattern of base catalysis of reactions with amine nucleophiles provides additional evidence. Bases only catalyze these reactions when a relatively poor leaving group (e.g., OR) is present (not Cl or Br) and only when relatively bulky amines are nucleophiles.¹⁵ Bases could not catalyze step 1, but if amines are nucleophiles, bases can catalyze step 2. Base catalysis is found precisely in those cases where the amine moiety cleaves easily, but X does not, so that k_1 is large and step 2 is rate determining. This is evidence for the S_NAr mechanism because it implies two steps. Furthermore, in cases where bases *are* catalysts, they catalyze only at low-base concentrations: A plot of the rate against the base concentration shows that small increments of base rapidly increase the rate until a certain concentration of base is reached, after which further base addition no longer greatly affects the rate. This behavior, based on a partitioning effect (see Sec. 11.A.i), is also evidence for the S_NAr mechanism. At low-base concentration, each increment of base, by increasing the rate of step 2, increases the fraction of intermediate that goes to product rather than reverting to reactants. At high-base concentration, the process is virtually complete: There is very little reversion to reactants and the rate becomes dependent on step 1. Just how bases catalyze step 2 has been investigated. For protic solvents, two proposals have been presented. One is that step 2 consists of two steps: rate-determining deprotonation of **4** followed by



¹² Grossi, L. *Tetrahedron Lett.* **1992**, 33, 5645.

¹³ Bunnett, J.F.; Garbisch, Jr., E.W.; Pruitt, K.M. *J. Am. Chem. Soc.* **1957**, 79, 385. See Gandler, J.R.; Setiarahardjo, I.U.; Tufon, C.; Chen, C. *J. Org. Chem.* **1992**, 57, 4169.

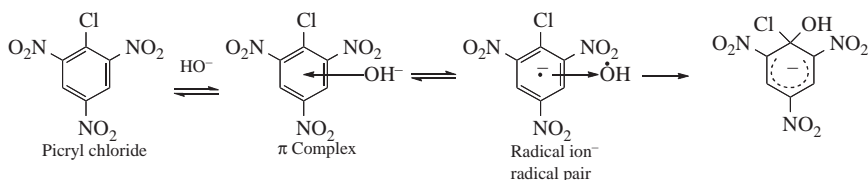
¹⁴ See Fernndez, I.; Frenking, G.; Uggerud, E. *J. Org. Chem.* **2010**, 75, 2971.

¹⁵ Chiacchiera, S.M.; Singh, J.O.; Anunziata, J.D.; Silber, J.J. *J. Chem. Soc. Perkin Trans. 2* **1987**, 987.

rapid loss of X, and that bases catalyze the reaction by increasing the rate of the deprotonation step.¹⁶ According to the other proposal, loss of X assisted by BH^+ is rate determining.¹⁷ Two mechanisms, both based on kinetic evidence, have been proposed for aprotic solvents (e.g., benzene). In both proposals, the ordinary $\text{S}_{\text{N}}\text{Ar}$ mechanism operates, but in one the attacking species involves two molecules of the amine (the *dimer mechanism*),¹⁸ while in the other there is a cyclic transition state.¹⁹ Further evidence for the $\text{S}_{\text{N}}\text{Ar}$ mechanism has been obtained from $^{18}\text{O}/^{16}\text{O}$ and $^{15}\text{N}/^{14}\text{N}$ isotope effects.²⁰

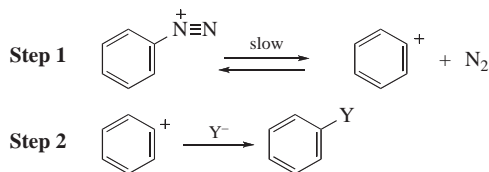
Step 1 of the $\text{S}_{\text{N}}\text{Ar}$ mechanism has been studied for the reaction between picryl chloride (as well as other substrates) and OH^- ions (Reaction **13-1**), and spectral evidence has been reported²¹ for two intermediates, one a π complex (Sec. 11.A.i), and the other a radical ion–radical pair.

As with the tetrahedral mechanism at an acyl carbon, nucleophilic catalysis (Sec. 16.A.i) has been demonstrated with an aryl substrate, in certain cases.²² There is also evidence of an interaction of anions with the π -cloud of aromatic compounds.²³



13.A.ii. The $\text{S}_{\text{N}}1$ Mechanism

For aryl halides and sulfonates, even active ones, a unimolecular $\text{S}_{\text{N}}1$ mechanism (IUPAC: $\text{D}_{\text{N}} + \text{A}_{\text{N}}$) is very rare; it has only been observed for aryl triflates in which both ortho positions contain bulky groups (*tert*-butyl or SiR_3).²⁴ It is in reactions with diazonium salts²⁵ that this mechanism is important²⁶:



¹⁶ Bernasconi, C.F.; de Rossi, R.H.; Schmid, P. *J. Am. Chem. Soc.* **1977**, 99, 4090.

¹⁷ Bunnett, J.F.; Sekiguchi, S.; Smith, L.A. *J. Am. Chem. Soc.* **1981**, 103, 4865.

¹⁸ See Nudelman, N.S. *J. Phys. Org. Chem.* **1989**, 2, 1. See also, Nudelman, N.S.; Montserrat, J.M. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1073.

¹⁹ Jain, A.K.; Gupta, V.K.; Kumar, A. *J. Chem. Soc. Perkin Trans. 2* **1990**, 11.

²⁰ Ayrey, G.; Wylie, W.A. *J. Chem. Soc. B* **1970**, 738.

²¹ Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Dorwin, E.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* **1991**, 113, 238; Crampton, M.R.; Davis, A.B.; Greenhalgh, C.; Stevens, J.A. *J. Chem. Soc. Perkin Trans. 2* **1989**, 675.

²² See Muscio, Jr., O.J.; Rutherford, D.R. *J. Org. Chem.* **1987**, 52, 5194.

²³ Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà, P.M. *Angew. Chem. Int. Ed.* **2002**, 41, 3389.

²⁴ Himeshima, Y.; Kobayashi, H.; Sonoda, T. *J. Am. Chem. Soc.* **1985**, 107, 5286.

²⁵ See Glaser, R.; Horan, C.J.; Nelson, E.D.; Hall, M.K. *J. Org. Chem.* **1992**, 57, 215.

²⁶ Aryl iodonium salts Ar_2I^+ also undergo substitutions by this mechanism (and by a free radical mechanism).

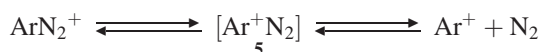
Among the evidence for the S_N1 mechanism²⁷ with aryl cations as intermediates,^{28,29} is the following:³⁰

1. The reaction rate is first order in diazonium salt and independent of the concentration of Y.
2. When high concentrations of halide salts are added, the product is an aryl halide, but the rate is independent of the concentration of the added salts.
3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage.³¹
4. When reactions were run with substrate deuterated in the ortho position, isotope effects of ~ 1.22 were obtained.³² It is difficult to account for such high secondary isotope effects in any other way except that an incipient phenyl cation is stabilized by hyperconjugation (see Sec. 2.M),³³ which is diminished when hydrogen is replaced by deuterium.



5. That the first step is reversible cleavage³⁴ was demonstrated by the observation that when $\text{Ar}^{15}\text{N}^+ \equiv \text{N}$ was the reaction species, recovered starting material contained not only $\text{Ar}^{15}\text{N}^+ \equiv \text{N}$, but also $\text{Ar}^{15}\text{N}^+ \equiv \text{N}$.^{35,36} This could arise only if the nitrogen breaks away from the ring and then returns. Additional evidence was obtained by treating $\text{PhN}^+ \equiv \text{N}^{15}\text{N}$ with unlabeled N_2 at various pressures. At 300 atm, the recovered product had lost $\sim 3\%$ of the labeled nitrogen, indicating that PhN_2^+ was exchanging with atmospheric N_2 .³⁶

There is kinetic and other evidence³⁷ that step 1 is more complicated and involves two steps, both reversible:



²⁷ Also see Lorand, J.P. *Tetrahedron Lett.* **1989**, 30, 7337.

²⁸ See Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* **1979**, 8, 353.

²⁹ Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979. See Hanack, M. *Pure Appl. Chem.* **1984**, 56, 1819; Rappoport, Z. *Reactiv. Intermed. (Plenum)* **1983**, 3, 427; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* **1979**, 8, 353. See also, Charton, M. *Mol. Struct. Energ.* **1987**, 4, 271; Glaser, R.; Horan, C.J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* **1999**, 64, 902.

³⁰ See Zollinger, H. *Angew. Chem, Int. Ed.* **1978**, 17, 141; Swain, C.G.; Sheats, J.E.; Harbison, K.G. *J. Am. Chem. Soc.* **1975**, 97, 783, 796; Burri, P.; Wahl, Jr., G.H.; Zollinger, H. *Helv. Chim. Acta* **1974**, 57, 2099; Richey, Jr., H.G.; Richey, J.M. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, pp. 922–931; Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, **1968**, pp. 29–40.

³¹ Lewis, E.S.; Miller, E.B. *J. Am. Chem. Soc.* **1953**, 75, 429.

³² Swain, C.G.; Sheats, J.E.; Gorenstein, D.G.; Harbison, K.G. *J. Am. Chem. Soc.* **1975**, 97, 791.

³³ See Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.* **1985**, 107, 5285.

³⁴ See Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* Vol. 5, Elsevier, Amsterdam, The Netherlands, **1980**, pp. 147, 212; Zollinger, H. *Pure Appl. Chem.* **1983**, 55, 401.

³⁵ Lewis, E.S.; Kotcher, P.G. *Tetrahedron* **1969**, 25, 4873; Lewis, E.S.; Holliday, R.E. *J. Am. Chem. Soc.* **1969**, 91, 426; Tröndlin, F.; Medina, R.; Rüchardt, C. *Chem. Ber.* **1979**, 112, 1835.

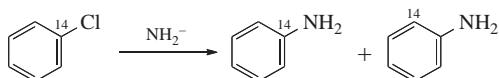
³⁶ Bergstrom, R.G.; Landell, R.G.M.; Wahl, Jr., G.H.; Zollinger, H. *J. Am. Chem. Soc.* **1976**, 98, 3301.

³⁷ Szele, I.; Zollinger, H. *Helv. Chim. Acta* **1981**, 64, 2728.

Intermediate **5**, which is probably some kind of a tight ion–molecule pair, has been trapped with carbon monoxide.³⁸

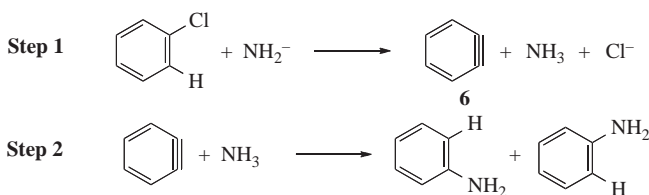
13.A.iii. The Benzyne Mechanism³⁹

Some aromatic nucleophilic substitutions are clearly different in character from those that occur by the S_NAr mechanism (or the S_N1 mechanism). These substitutions occur with aryl halides that have no activating groups; stronger bases are required than those normally used; and the incoming group does not always take the position vacated by the leaving group. The validity of the latter statement was elegantly demonstrated by the reaction of 1-¹⁴C-chlorobenzene with potassium amide:



The product consisted of almost equal amounts of aniline labeled in the 1 and 2 positions.⁴⁰

A mechanism that can explain all these facts involves elimination followed by addition. In step 1, a suitable base removes the ortho hydrogen, with subsequent (or concomitant) loss of the chlorine (leaving group) to



generate symmetrical intermediate **6**⁴¹ called benzyne⁴² (see below).⁴³ In step 2, benzyne is attacked by the NH_3 at either of two positions, which explains why about one-half of the aniline produced from the radioactive chlorobenzene was labeled at the 2 position. The fact that the 1 and 2 positions were not labeled equally is the result of a small isotope effect. Other evidence for this mechanism follows:

1. If the aryl halide contains two ortho substituents, the reaction should not be able to occur. This is indeed the case.³⁸

³⁸ Ravenscroft, M.D.; Skrabal, P.; Weiss, B.; Zollinger, H. *Helv. Chim. Acta* **1988**, 71, 515.

³⁹ See Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, **1967**; Gilchrist, T.L. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, **1983**, pp. 383–419; Bryce, M.R.; Vernon, J.M. *Adv. Heterocycl. Chem.* **1981**, 28, 183; Levin, R.H. *React. Intermed. (Wiley)* **1985**, 3, 1; Fields, E.K. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, **1973**, pp. 449–508.

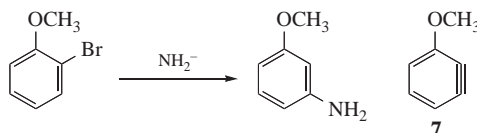
⁴⁰ Roberts, J.D.; Semenow, D.A.; Simmons, H.E.; Carlsmith, L.A. *J. Am. Chem. Soc.* **1965**, 78, 601.

⁴¹ See Hess, Jr., B.A. *Eur. J. Org. Chem.* **2001**, 2185.

⁴² Wentrup, C. *Austr. J. Chem.* **2010**, 63, 979.

⁴³ See Kitamura, T.; Meng, Z.; Fujiwara, Y. *Tetrahedron Lett.* **2000**, 41, 6611; Kawabata, H.; Nishino, T.; Nishiyama, Y.; Sonoda, N. *Tetrahedron Lett.* **2002**, 43, 4911. Microwave spectroscopy can be used to detect benzyne: see Godfrey, P.D. *Austr. J. Chem.* **2010**, 63, 1061.

2. It had been known many years earlier that aromatic nucleophilic substitution occasionally results in substitution at a different position. This is called *cine substitution*⁴⁴ and can be illustrated by the conversion of *o*-bromoanisole to *m*-aminoanisole.⁴⁵ In this particular case, only the meta isomer is formed. The reason a 1:1 mixture is not formed is that the intermediate **7** is not symmetrical and the methoxy group directs the incoming group meta, but not ortho (see Sec. 13.B.i). However, not all cine substitutions proceed by this kind of mechanism (see Reaction **13-30**). A study of the influence of structure on the formation of substituted benzyne, along with rate studies, has been reported.⁴⁶



3. The fact that the order of halide reactivity is Br > I > Cl > F (when the reaction is performed with KNH₂ in liquid NH₃) shows that the S_NAr mechanism is not operating here.⁴⁰

In the conversion of the substrate to **7**, either proton removal or subsequent loss of halide ion can be rate determining. In fact, the unusual leaving-group order just mentioned (Br > I > Cl) stems from a change in the rate-determining step. When the leaving group is Br or I, proton removal is rate determining and the rate order for this step is F > Cl > Br > I. When Cl or F is the leaving group, cleavage of the C—X bond is rate determining and the order for this step is I > Br > Cl > F. Confirmation of the latter order was found in a direct competitive study. *meta*-Dihalobenzenes in which the two halogens are different were treated with ⁻NH₂.⁴⁷ In such compounds, the most acidic hydrogen is the one between the two halogens; when it leaves, the remaining anion can lose either halogen. Therefore a study of which halogen is preferentially lost provides a direct measure of leaving-group ability. The order was found to be I > Br > Cl.^{47,48}

Species, such as **6** and **7**, are called *benzyne*s (sometimes *dehydrobenzenes*), or more generally, *arynes*.⁴⁹ The mechanism in which such species are intermediates is known as the *benzyne mechanism*. Benzyne are very reactive, and neither benzyne nor any other arynes has yet been isolated under ordinary conditions,⁵⁰ but benzyne has been isolated in an Ar matrix at 8 K,⁵¹ and its IR spectrum is observed. In addition, benzyne can be trapped (e.g., they undergo the *Diels–Alder reaction*, See Reaction **15-60**). Note that the extra pair of electrons does not affect the aromaticity. However, evaluation by a series of aromaticity indicators, including magnetic susceptibility anisotropies and exaltations,

⁴⁴ See Suwinski, J.; Swierczek, K. *Tetrahedron* **2001**, 57, 1639.

⁴⁵ See Gilman, H.; Avakian, S. *J. Am. Chem. Soc.* **1945**, 67, 349. For a table of many such examples, see Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* **1951**, 49, 273, p. 385.

⁴⁶ Riggs, J.C.; Ramirez, A.; Cremeens, M.E.; Bashore, C.G.; Candler, J.; Wirtz, M.C.; Coe, J.C.; Collum, D.B. *J. Am. Chem. Soc.* **2008**, 130, 3406.

⁴⁷ Bunnett, J.F.; Kearley, Jr., F.J. *J. Org. Chem.* **1971**, 36, 184.

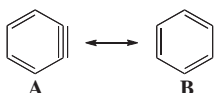
⁴⁸ See Kalendra, D.M.; Sickles, B.R. *J. Org. Chem.* **2003**, 68, 1594.

⁴⁹ See Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, 59, 701.

⁵⁰ See Gaviña, F.; Luis, S.V.; Costero, A.M.; Gil, P. *Tetrahedron* **1986**, 42, 155.

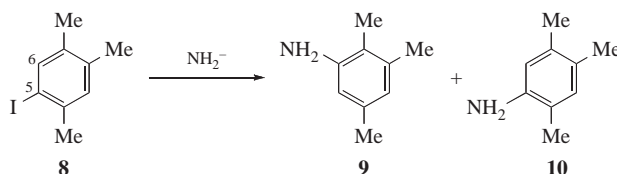
⁵¹ Chapman, O.L.; Mattes, K.; McIntosh, C.L.; Pacansky, J.; Calder, G.V.; Orr, G. *J. Am. Chem. Soc.* **1973**, 95, 6134. For the IR spectrum of pyridyne trapped in a matrix, see Nam, H.; Leroi, G.E. *J. Am. Chem. Soc.* **1988**, 110, 4096. See Brown, R.D.; Godfrey, P.D.; Rodler, M. *J. Am. Chem. Soc.* **1986**, 108, 1296.

nucleus-independent chemical shifts (NICS), aromatic stabilization energies, and valence bond Pauling resonance energies point to the *o*-benzyne > *m*-benzyne > *p*-benzyne aromaticity order.⁵² The relative order with respect to benzene depends on the aromaticity criterion.⁴⁸ Note that tunable reactivity for *m*-benzynes has been demonstrated.⁵³ The aromatic sextet from the aromatic precursor functions as a closed ring, and the two additional electrons are merely located in a π orbital that covers only two carbons. Benzyne does not have a formal triple bond, since two canonical forms (**A** and **B**) contribute to the hybrid. The Ir spectrum, mentioned above, indicates that **A** contributes more than **B**. Not only benzene rings, but also other aromatic rings⁵⁴ and even non-aromatic rings (Sec. 10.F) can react through this kind of intermediate. Of course, the non-aromatic rings do have a formal triple bond. When a benzyne unit is fused to a small ring, strain induced regioselectivity was observed in its reactions.⁵⁵

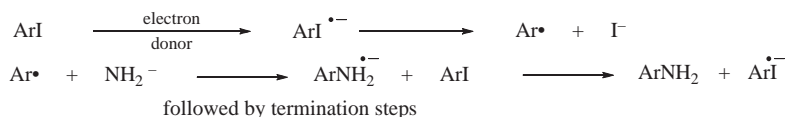


13.A.iv. The $S_{RN}1$ Mechanism

When 5-iodo-1,2,4-trimethylbenzene (**8**) was treated with KNH_2 in NH_3 , **9** and **10** were formed in the ratio 0.63:1. The presence of an unactivated substrate, a strong base, and the occurrence of cine substitution along with normal substitution are strong indications of a benzyne mechanism. Yet if that were so, the 6-iodo isomer of **8** should have given **9** and **10** in the same ratio (because the same aryne intermediate would be formed in both cases), but in this case the ratio of **9** to **10** was 5.9:1 (the chloro and bromo analogues did give the same ratio (1.46:1), showing that the benzyne mechanism may be taking place there).



To explain the iodo result, it has been proposed⁵⁶ that in addition to the benzyne mechanism, a free radical mechanism is also operating here:



⁵² DeProft, F.; Schleyer, P.v.R.; van Lenthe, J.H.; Stahl, F.; Geerlings, P. *Chem. Eur. J.* **2002**, 8, 3402.

⁵³ Nash, J.J.; Nizzi, K.E.; Adeuya, A.; Yurkovich, M.J.; Cramer, C.J.; Kenttämaa, H.I. *J. Am. Chem. Soc.* **2005**, 127, 5760.

⁵⁴ For reviews of *hetarynes*, see van der Plas, H.C.; Roeterdink, F. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, **1983**, pp. 421–511; Reinecke, M.G. *Tetrahedron* **1982**, 38, 427; den Hertog, H.J.; van der Plas, H.C. *Adv. Heterocycl. Chem.* **1971**, 40, 121; Kauffmann, T.; Wirthwein, R. *Angew. Chem, Int. Ed.* **1971**, 10, 20.

⁵⁵ Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* **2003**, 5, 3551.

⁵⁶ Kim, J.K.; Bunnett, J.F. *J. Am. Chem. Soc.* **1970**, 92, 7463, 7464.

This is called the $S_{RN}1$ mechanism,⁵⁷ and many other examples are known (see Reactions **13-3**, **13-4**, **13-6**, and **13-14**). The IUPAC designation is $T + D_N + A_N$.⁵⁸ Note that the last step of the mechanism produces $ArI^{\bullet-}$ radical ions, so the process is a chain mechanism⁵⁹ (see Sec. 14.A.i). An electron donor is required to initiate the reaction. In the case above, it was solvated electrons from KNH_2 in NH_3 . Evidence was that the addition of potassium metal (a good producer of solvated electrons in ammonia) completely suppressed the cine substitution. Further evidence for the $S_{RN}1$ mechanism was that addition of radical scavengers, which would suppress a free radical mechanism, led to **9:10** ratios much closer to 1.46:1. Numerous other observations of $S_{RN}1$ mechanisms that were stimulated by solvated electrons and inhibited by radical scavengers have also been recorded.⁶⁰ Further evidence for the $S_{RN}1$ mechanism in the case above was that some 1,2,4-trimethylbenzene was found among the products. This could easily be formed by abstraction by Ar^{\bullet} of H from the solvent NH_3 . Besides initiation by solvated electrons,⁶¹ $S_{RN}1$ reactions have been initiated photochemically,⁶² electrochemically,⁶³ and even thermally.⁶⁴

The $S_{RN}1$ reactions have a fairly wide scope. The efficiency of the reaction has been traced to the energy level of the radical anion of the substitution product.⁶⁵ There is no requirement for activating groups or strong bases, but in DMSO haloarenes are less reactive as the stability of the anion increases.⁶⁶ The reaction has also been done in liquid ammonia, promoted by ultrasound (Sec. 7.B),⁶⁷ and ferrous ion has been used as a catalyst.⁶⁸ Alkyl, alkoxy, aryl, and COO^- groups do not interfere, although Me_2N , O^- , and NO_2 groups do interfere. Cine substitution is not found.

13.A.v. Other Mechanisms

There is no clear-cut proof that a one-step S_N2 mechanism, so important at a saturated carbon, ever actually occurs with an aromatic substrate. The hypothetical aromatic S_N2 process is sometimes called the *one-stage* mechanism to distinguish it from the *two-stage* S_NAr mechanism. A "clean" example of a $S_{RN}2$ reaction has been reported, the

⁵⁷ See Rossi, R.A.; de Rossi, R.H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*, American Chemical Society, Washington, **1983**; Savéant, J. *Adv. Phys. Org. Chem.* **1990**, 26, 1; Norris, R.K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, **1983**, pp. 681–701; Chanon, M.; Tobe, M.L. *Angew. Chem., Int. Ed.* **1982**, 21, 1; Rossi, R.A. *Acc. Chem. Res.* **1982**, 15, 164. Also see Rossi, R.A.; Pierini, A.B.; Palacios, S.M. *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, 1, 193; Costentin, C.; Hapiot, P.; Médebielle, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1999**, 121, 4451.

⁵⁸ The symbol T is used for electron transfer.

⁵⁹ See Amatore, C.; Pinson, J.; Savéant, J.; Thiébaud, A. *J. Am. Chem. Soc.* **1981**, 103, 6930.

⁶⁰ Bunnett, J.F. *Acc. Chem. Res.* **1978**, 11, 413.

⁶¹ Savéant, J.-M. *Tetrahedron* **1994**, 50, 10117.

⁶² See Cornelisse, J.; de Gunst, G.P.; Havinga, E. *Adv. Phys. Org. Chem.* **1975**, 11, 225; Cornelisse, J. *Pure Appl. Chem.* **1975**, 41, 433; Pietra, F. *Q. Rev. Chem. Soc.* **1969**, 23, 504, p. 519.

⁶³ See Savéant, J. *Acc. Chem. Res.* **1980**, 13, 323. See also, Alam, N.; Amatore, C.; Combella, C.; Thiébaud, A.; Verpeaux, J.N. *J. Org. Chem.* **1990**, 55, 6347.

⁶⁴ Swartz, J.E.; Bunnett, J.F. *J. Org. Chem.* **1979**, 44, 340, and references cited therein.

⁶⁵ Galli, C.; Gentili, P.; Guarnieri, A. *Gazz. Chim. Ital.*, **1995**, 125, 409.

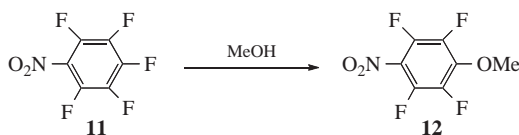
⁶⁶ Borosky, G.L.; Pierini, A.B.; Rossi, R.A. *J. Org. Chem.* **1992**, 57, 247.

⁶⁷ Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* **1994**, 35, 677.

⁶⁸ Galli, C.; Gentili, P. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1135.

conversion of **11** to **12** in methanol.⁶⁹ Both $S_{RN}1$ and $S_{RN}2$ reactions have been reviewed.⁷⁰

Some of the reactions in this chapter operate by still other mechanisms, among them an addition–elimination mechanism (see Reaction **13-17**). A new mechanism has been reported in aromatic chemistry, a reductively activated “polar” nucleophilic aromatic substitution.⁷¹ The reaction of phenoxide with *p*-dinitrobenzene in DMF shows radical features that cannot be attributed to a radical anion, and it is not $S_{RN}2$. The new designation was proposed to account for these results.



13.B. REACTIVITY

13.B.i. The Effect of Substrate Structure

In the discussion of electrophilic aromatic substitution (Chapter 11), equal attention was paid to the effect of substrate structure on reactivity (activation or deactivation) and on orientation. The question of orientation was important because in a typical substitution there are four or five hydrogen atoms that could serve as leaving groups. This type of question is much less important for aromatic nucleophilic substitution, since in most cases there is only one potential leaving group in a molecule. Therefore attention is largely focused on the reactivity of one molecule compared with another and not on the comparison of the reactivity of different positions within the same molecule.

S_NAr Mechanism. These substitutions are accelerated by electron-withdrawing groups, especially in positions ortho and para to the leaving group⁷² and hindered by electron-attracting groups. This is, of course, opposite to the effects of these groups on electrophilic substitutions, and the reasons are similar to those discussed in Section 11.A.i. When attached to a benzene ring, the rate of reaction depends on the substituent.⁷³ Activating groups include 2-nitro,^{74,75} N_2^+ , NO, or C=N units with strong nucleophiles and when a nitro group is attached to SO_2Me , NMe_3 , CF_3 , CN, CHO, COR, CO_2H , SO_3 , halogen, H, Me, or OMe activate.⁷³ Table 13.1 contains a list of groups arranged approximately in order of activating or deactivating ability.^{73–76} Nitrogen

⁶⁹ Marquet, J.; Jiang, Z.; Gallardo, I.; Batlle, A.; Cayón, E. *Tetrahedron Lett.* **1993**, 34, 2801. Also see, Keegstra, M.A. *Tetrahedron* **1992**, 48, 2681.

⁷⁰ Rossi, R.A.; Palacios, S.M. *Tetrahedron* **1993**, 49, 4485.

⁷¹ Marquet, J.; Casado, F.; Cervera, M.; Espín, M.; Gallardo, I.; Mir, M.; Niat, M. *Pure Appl. Chem.* **1995**, 67, 703.

⁷² With meta substituents, electron-withdrawing groups also increase the rate: See Nurgatin, V.V.; Sharnin, G.P.; Ginzburg, B.M. *J. Org. Chem., USSR* **1983**, 19, 343.

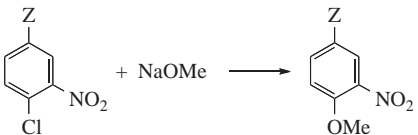
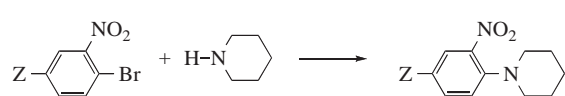


⁷³ See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, **1968**, pp. 61–136.

⁷⁴ For reviews of reactivity of nitrogen-containing heterocycles, see Illuminati, G. *Adv. Heterocycl. Chem.* **1964**, 3, 285; Shepherd, R.G.; Fedrick, J.L. *Adv. Heterocycl. Chem.* **1965**, 4, 145.

⁷⁵ See Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, **1991**, pp. 142–180; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, **1971**, pp. 258–319, 550–553.

⁷⁶ Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* **1951**, 49, 273, pp. 308.

TABLE 13.1 Groups Listed in Approximate Descending Order of Activating Ability in the S_NAr Mechanism⁷³

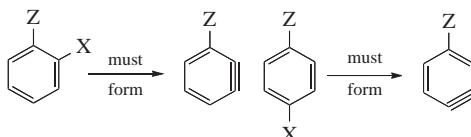
		at 0 °C ⁷⁴ (a) ^a	
		at 25 °C ⁷⁵ (b) ^b	
Comments ^b	Group Z	Relative Rate of Reaction (a) H = 1 ⁷³ (b) NH ₂ = 1 ⁷⁸	
Activates halide exchange at room temperature	N ₂ ⁺		
Activates reaction with strong nucleophiles at room temperature	 (heterocyclic)		
Activate reactions with strong nucleophiles at 80–100 °C	NO	5.22 × 10 ⁶	Very fast
	NO ₂	6.73 × 10 ⁵	
	 (heterocyclic)		
With nitro also present, activate reactions with strong nucleophiles at room temperature	SO ₂ Me	3.81 × 10 ⁴ 2.02 × 10 ⁴	
	NMe ₃ ⁺		
	CF ₃		
	CN		
	CHO		
	COR		
	COOH		
	SO ₃ [−]		
	Br	6.31 × 10 ⁴	
	Cl	4.50 × 10 ⁴	
	I	4.36 × 10 ⁴	
	COO [−]	2.02 × 10 ⁴	
	H	8.06 × 10 ³	
	F	2.10 × 10 ³	
	CMe ₃	1.37 × 10 ³	
	Me	1.17 × 10 ³	
	OMe	145	
	NMe ₂	9.77	
	OH	4.70	
	NH ₂	1	

^aFor reaction (a) the rates are relative to **H**; for (b) they are relative to NH₂.^bThe comments on the left are from Bunnett and Zahler.⁷⁶

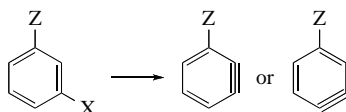
atoms are also strongly activating (especially to the α and γ positions) and are even more so when quaternized.⁷⁷ Both 2- and 4-chloropyridine, for example, are often used as substrates. Heteroaromatic amine *N*-oxides are readily attacked by nucleophiles in the 2 and 4 positions, but the oxygen is generally lost in these reactions.⁷⁸ The most highly activating group (N_2^+) is seldom deliberately used to activate a reaction, but it sometimes happens that in the diazotization of a compound (e.g., *p*-nitroaniline or *p*-chloroaniline), the group para to the diazonium group is replaced by OH from the solvent or by X from $\text{ArN}_2^+ \text{X}^-$ untouched. By far, the most common activating group is the nitro group and the most common substrates are 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides (also called picryl halides).⁷⁹ Polyfluorobenzenes⁸⁰ (see **11**) also undergo aromatic nucleophilic substitution quite well.⁸¹ Benzene rings that lack activating substituents are generally not useful substrates for the $\text{S}_{\text{N}}\text{Ar}$ mechanism, because the two extra electrons in **1** are in an antibonding orbital (Sec. 2.A). Activating groups, by withdrawing electron density, are able to stabilize the intermediates and the transition states leading to them. Reactions taking place by the $\text{S}_{\text{N}}\text{Ar}$ mechanism are also accelerated when the aromatic ring is coordinated with a transition metal.⁸²

Just as electrophilic aromatic substitutions were found more or less to follow the *Hammett relationship* (with σ^+ instead of σ ; see Sec. 9.C) so do nucleophilic substitutions, with σ^- instead of σ for electron-withdrawing groups.⁸³

Benzynes Mechanism. Two factors affect the position of the incoming group, the first being the direction in which the aryne forms.⁸⁴ When there are groups ortho or para to the leaving group, there is no choice:



but when a meta group is present, the aryne can form in two different ways:



⁷⁷ Miller, J.; Parker, A.J. *Aust. J. Chem.* **1958**, *11*, 302.

⁷⁸ Berliner, E.; Monack, L.C. *J. Am. Chem. Soc.* **1952**, *74*, 1574.

⁷⁹ See de Boer, T.J.; Dirkx, I.P. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, **1970**, pp. 487–612.

⁸⁰ Fluorine significantly activates ortho and meta positions, and slightly deactivates para positions (see Table 13.1): See Chambers, R.D.; Seabury, N.J.; Williams, D.L.H.; Hughes, N. *J. Chem. Soc. Perkin Trans. 1* **1988**, 255.

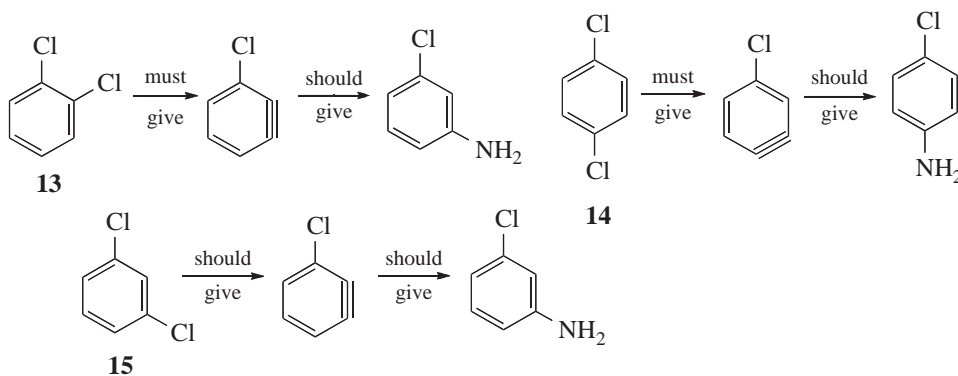
⁸¹ See Yakobson, G.G.; Vlasov, V.M. *Synthesis* **1976**, 652; Kobrina, L.S. *Fluorine Chem. Rev.* **1974**, *7*, 1.

⁸² See Balas, L.; Jhurry, D.; Latxague, L.; Grelrier, S.; Morel, Y.; Hamdani, M.; Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1990**, 401.

⁸³ See Bartoli, G.; Todesco, P.E. *Acc. Chem. Res.* **1977**, *10*, 125; a list of σ^- values in Table 9.4.

⁸⁴ From Roberts, J.D.; Vaughan, C.W.; Carlsmith, L.A.; Semenow, D.A. *J. Am. Chem. Soc.* **1956**, *78*, 611. See Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, **1973**, pp. 134–150.

In such cases, the more acidic hydrogen is removed. Since acidity is related to the field effect of Z, it can be stated that an electron-attracting Z favors removal of the ortho hydrogen while an electron-donating Z favors removal of the para hydrogen. The second factor is that the aryne, once formed, can be attacked at two positions. The favored position for nucleophilic attack is the one that leads to the more stable carbanion intermediate. This in turn also depends on the field effect of Z. For *-I* groups, the more stable carbanion is the one in which the negative charge is closer to the substituent. These principles are illustrated by the reaction of the three dichlorobenzenes (**13-15**) with alkali metal amides to give the predicted products shown. In each case, the predicted product was the one chiefly formed.⁸⁵ The observation that *m*-aminoanisole is obtained, mentioned in Section 13.A.iii, is also in accord with these predictions.



13.B.ii. The Effect of the Leaving Group⁸⁶

The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+ , etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2 , OR, OAr, SO_2R ⁸⁷, and SR, which are not generally lost in aliphatic systems, *are* leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group.⁸⁸ An approximate order of leaving-group ability is⁸⁹ $\text{F} > \text{NO}_2 > \text{OTs} > \text{SOPh} > \text{Cl}, \text{Br}, \text{I} > \text{N}_3 > \text{NR}_3^+ > \text{OAr}, \text{OR}, \text{SR}, \text{NH}_2$. However, this depends greatly on the nature of the nucleophile, as illustrated by the fact that $\text{C}_6\text{Cl}_5\text{OCH}_3$ treated with NH_2^- gives mostly $\text{C}_6\text{Cl}_5\text{NH}_2$; that is, one methoxy group is replaced in preference to five chlorines.⁹⁰ As usual, OH can be a leaving group if it is converted to an

⁸⁵ Wotiz, J.H.; Huba, F. *J. Org. Chem.* **1959**, 24, 595. See also, Biehl, E.R.; Razzuk, A.; Jovanovic, M.V.; Khanapure, S.P. *J. Org. Chem.* **1986**, 51, 5157.

⁸⁶ See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, **1968**, pp. 137–179.

⁸⁷ See Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1839.

⁸⁸ See Beck, J.R. *Tetrahedron* **1978**, 34, 2057. See also, Effenberger, F.; Koch, M.; Streicher, W. *Chem. Ber.* **1991**, 24, 163.

⁸⁹ Loudon, J.D.; Shulman, N. *J. Chem. Soc.* **1941**, 772; Suhr, H. *Chem. Ber.* **1963**, 97, 3268.

⁹⁰ Kobrina, L.S.; Yakobson, G.G. *J. Gen. Chem. USSR* **1963**, 33, 3238.

inorganic ester. Among the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually $\text{Cl} > \text{Br} > \text{I}$, but not always.⁹¹ The leaving-group order is quite different from that for the $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanisms. The most likely explanation is that the first step of the $\text{S}_{\text{N}}\text{Ar}$ mechanism is usually rate determining, and this step is promoted by groups with strong $-I$ effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. Fluoro is the poorest leaving group of the halogens when the second step of the $\text{S}_{\text{N}}\text{Ar}$ mechanism is rate determining or when the benzyne mechanism is operating. The four halogens, as well as SPh , NMe_3^+ , and $\text{OPO}(\text{OEt})_2$, have been shown to be leaving groups in the $\text{S}_{\text{RN}}1$ mechanism.⁶⁰ The only important leaving group in the $\text{S}_{\text{N}}1$ mechanism is N_2^+ .

13.B.iii. The Effect of the Attacking Nucleophile⁹²

It is not possible to construct an invariant nucleophilicity order because different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $^-\text{NH}_2 > \text{Ph}_3\text{C}^- > \text{PhNH}^-$ (aryne mechanism) $> \text{ArS}^- > \text{RO}^- > \text{R}_2\text{NH} > \text{ArO}^- > ^-\text{OH} > \text{ArNH}_2 > \text{NH}_3 > \text{I}^- > \text{Br}^- > \text{Cl}^- > \text{H}_2\text{O} > \text{ROH}$.⁹³ As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions (e.g., ^-OH), a stronger base than ArO^- , is a poorer nucleophile.⁹⁴ In a series of similar nucleophiles (e.g., substituted anilines), nucleophilicity *is* correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts and in the *von Richter* (13-30) and *Rosenmund-von Braun* (13-8) reactions, which are special cases. Studies on the nature of the nucleophile continue. Indeed, the second-order rate constants for vicarious nucleophilic substitution reactions of some carbanions were measured to define electrophilicity parameters for electron-deficient heteroarenes.⁹⁵

13.C. REACTIONS

In the first part of this section, reactions are classified according to attacking species, with all leaving groups considered together, except for hydrogen and N_2^+ , which are treated subsequently. Finally, a few rearrangement reactions are discussed.

⁹¹ Reinheimer, J.D.; Taylor, R.C.; Rohrbaugh, P.E. *J. Am. Chem. Soc.* **1961**, 83, 835; Ross, S.D. *J. Am. Chem. Soc.* **1959**, 81, 2113; Litvinenko, L.M.; Shpan'ko, L.V.; Korostylev, A.P. *Doklad. Chem.* **1982**, 266, 309.

⁹² See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, **1968**, pp. 180–233.

⁹³ From Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* **1951**, 49, 273, p. 340; Sauer, J.; Huisgen, R. *Angew. Chem.* **1960**, 72, 294, p. 311; Bunnett, J.F. *Annu. Rev. Phys. Chem.* **1963**, 14, 271.

⁹⁴ See Amatore, C.; Combéllas, C.; Robveille, S.; Savéant, J.; Thiébaud, A. *J. Am. Chem. Soc.* **1986**, 108, 4754, and references cited therein.

⁹⁵ Seeliger, F.; Błażej, S.; Bernhardt, S.; Mąkosza, M.; Mayr, H. *Chemistry: European J.* **2008**, 14, 6108.

13.C.i. All Leaving Groups Except Hydrogen and N₂⁺

A. Oxygen Nucleophiles

13-1 Hydroxylation of Aromatic Compounds

Hydroxy-de-halogenation



Direct hydroxylation of aryl halides to give phenols generally requires the presence of activating groups or exceedingly strenuous reaction conditions.⁹⁶ When the reaction is carried out at high temperatures, cine substitution is observed, indicating a benzyne mechanism.⁹⁷ However, phenols are prepared from aryl halides using KOH and a Pd catalyst at 100 °C.⁹⁸ Formation of phenols is possible using AgNO₃ with microwave irradiation,⁹⁹ or CuI.¹⁰⁰ There is a hydrogen peroxide promoted hydroxylation of aryl halides with metal hydroxide salts.¹⁰¹ Other microwave-promoted phenol-forming reactions are known.¹⁰²

A slightly related reaction involves the amino group of naphthylamines where can be replaced by a hydroxyl group after treatment with aq bisulfite.¹⁰³ The scope is greatly limited; the amino group, with very few exceptions may be NH₂ or NHR and must be on a naphthalene ring. The reaction is reversible (see **13-6**), and both the forward and reverse reactions are called the *Bucherer reaction*.



An indirect method for conversion of an aryl halide to a phenol involves initial conversion to an organometallic, followed by oxidation to the phenol. For the conversion of aryl *Grignard reagents* to phenols, a good procedure is the use of trimethyl borate followed by oxidation with H₂O₂ in acetic acid¹⁰⁴ (see Reaction **12-31**). Phenols have been obtained from unactivated aryl halides by treatment with borane and a metal (e.g., lithium), followed by oxidation with alkaline H₂O₂.¹⁰⁵ Arylboronic acids [ArB(OH)₂] are oxidized by aq H₂O₂ to give the corresponding phenol.¹⁰⁶ The reaction of an aromatic compound

⁹⁶ See Fyfe, C.A. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, pp. 83–124.

⁹⁷ This benzyne mechanism is also supported by ¹⁴C labeling experiments: Bottini, A.T.; Roberts, J.D. *J. Am. Chem. Soc.* **1957**, 79, 1458; Dalman, G.W.; Neumann, F.W. *J. Am. Chem. Soc.* **1968**, 90, 1601.

⁹⁸ Anderson, K.W.; Ikawa, T.; Tundel, R.E.; Buchwald, S.L. *J. Am. Chem. Soc.* **2006**, 128, 10694. Also see Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, 48, 918; Sergeev, A.G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, 48, 7595.

⁹⁹ Hashemi, M.M.; Akhbari, M. *Synth. Commun.* **2004**, 34, 2783.

¹⁰⁰ Maurer, S.; Liu, W.; Zhang, X.; Jiang, Y.; Ma, D. *Synlett* **2010**, 976. See also Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Zhou, X. *Chem. Commun.* **2010**, 4767.

¹⁰¹ Cantrell, Jr., W.R.; Bauta, W.E.; Engles, T. *Tetrahedron Lett.* **2006**, 47, 4249.

¹⁰² Kormos, C.M.; Leadbeater, N.E. *Tetrahedron* **2006**, 62, 4728.

¹⁰³ See Seeboth, H. *Angew. Chem. Int. Ed.* **1967**, 6, 307; Gilbert, E.E. *Sulfonation and Related Reactions*; Wiley, NY, **1965**, pp. 166–169.

¹⁰⁴ Hawthorne, M.F. *J. Org. Chem.* **1957**, 22, 1001. For other procedures, see Lewis, N.J.; Gabhe, S.Y. *Aust. J. Chem.* **1978**, 31, 2091; Hoffmann, R.W.; Dittrich, K. *Synthesis* **1983**, 107.

¹⁰⁵ Pickles, G.M.; Thorpe, F.G. *J. Organomet. Chem.* **1974**, 76, C23.

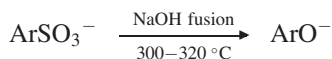
¹⁰⁶ Simon, J.; Salzbrunn, S.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *J. Org. Chem.* **2001**, 66, 633. Also see Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. *Org. Lett.* **2010**, 12, 1964.

with a borane in the presence of an Ir catalyst, followed by oxidation with aq Oxone, gave the corresponding phenol.¹⁰⁷ Aryllithium reagents have been converted to phenols by treatment with oxygen.¹⁰⁸ In a related indirect method, arylthallium bis(trifluoroacetates) (prepared by Reaction 12-23) can be converted to phenols by treatment with lead tetraacetate followed by triphenylphosphine, and then dilute NaOH.¹⁰⁹ Diarylthallium trifluoroacetates undergo the same reaction.¹¹⁰

OS I, 455; II, 451; V, 632. Also see, OS V, 918.

13-2 Alkali Fusion of Sulfonate Salts

Oxido-de-sulfonato-substitution



Aryl sulfonic acids can be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups that are attacked by alkali at the fusion temperatures. Milder conditions can be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is not clear, but a benzyne intermediate has been ruled out by the finding that cine substitution does not occur.¹¹¹

OS I, 175; III, 288.

13-3 Replacement by OR or OAr

Alkoxy-de-halogenation



This reaction is similar to 13-1 and, like that one, generally requires activated substrates.^{96,112} With unactivated substrates, side reactions predominate, although aryl methyl ethers have been prepared from unactivated chlorides by treatment with MeO^- in HMPA.¹¹³ This reaction gives better yields than 13-1 and is used more often. A good solvent is liquid ammonia. Aryl chlorides react with phenol and KOH with microwave irradiation to give the diaryl ether.¹¹⁴ Potassium phenoxide reacts with iodobenzene in an ionic solvent at 100 °C with CuCl .¹¹⁵ Sodium methoxide reacted with *o*- and *p*-fluoronitrobenzenes $\sim 10^9$ times faster in NH_3 at $-70\text{ }^\circ\text{C}$ than in MeOH .¹¹⁶ Phase-transfer catalysis

¹⁰⁷ Maleczka, Jr., R.E.; Shi, F.; Holmes, D.; Smith III, M.R. *J. Am. Chem. Soc.* **2003**, 125, 7792.

¹⁰⁸ Parker, K.A.; Koziski, K.A. *J. Org. Chem.* **1987**, 52, 674. See Taddei, M.; Ricci, A. *Synthesis* **1986**, 633; Einhorn, J.; Luche, J.; Demerseman, P. *J. Chem. Soc. Chem. Commun.* **1988**, 1350.

¹⁰⁹ Taylor, E.C.; Altland, H.W.; Danforth, R.H.; McGillivray, G.; McKillop, A. *J. Am. Chem. Soc.* **1970**, 92, 3520.

¹¹⁰ Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* **1975**, 40, 2351.

¹¹¹ Buzbee, L.R. *J. Org. Chem.* **1966**, 31, 3289; Oae, S.; Furukawa, N.; Kise, M.; Kawanishi, M. *Bull. Chem. Soc. Jpn.* **1966**, 39, 1212.

¹¹² See Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, 31, 2865.

¹¹³ Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Tetrahedron* **1983**, 39, 193.

¹¹⁴ Rebeiro, G.L.; Khadilkar, B.M. *Synth. Commun.* **2003**, 33, 1405.

¹¹⁵ Chauhan, S.M.S.; Jain, N.; Kumar, A.; Srinivas, K.A. *Synth. Commun.* **2003**, 33, 3607.

¹¹⁶ Kizner, T.A.; Shteingarts, V.D. *J. Org. Chem. USSR* **1984**, 20, 991.

has also been used.¹¹⁷ Phenols reacted with aryl fluorides¹¹⁸ or aryl chlorides¹¹⁹ to give the diaryl ether. Intramolecular versions are known that produce benzofurans.¹²⁰ Heating aryl iodides and phenols in an ionic liquid forms ethers.¹²¹ In addition to halides, leaving groups can be other OR, or even OH.¹²²

For aroxide nucleophiles, the reaction is promoted by Cu salts,¹²³ and activating groups need not be present. This method of preparation of diaryl ethers is called the *Ullmann ether synthesis*¹²⁴ and should not be confused with the *Ullmann biaryl synthesis* (13-11). The reactivity order is typical of nucleophilic substitutions, despite the presence of the Cu salts.¹²⁵ Copper-catalyzed coupling is known using ligand and additive-free conditions.¹²⁶ Because aryloxycopper(I) reagents (ArOCu) react with aryl halides to give ethers, it has been suggested that they are intermediates in the Ullmann ether synthesis.¹²⁷ Indeed, high yields of ethers can be obtained by reaction of ROCu or ArOCu with aryl halides.¹²⁸ Aryl halides are converted to aryl ethers with aliphatic alcohols in the presence of suitable Cu salts.¹²⁹

An increasingly important variation of this reaction couples an alkoxide and an aryl halide to give aryl ethers in the presence of a Pd catalyst and a suitable ligand.¹³⁰ Ligand effects are important in such reactions.¹³¹ A Pd catalyzed, intramolecular displacement of an aryl halide with a pendant alkoxide unit leads to dihydrobenzofurans.¹³² Nickel catalysts have also been used.¹³³ Aryl iodides react with phenols in the presence of K₂CO₃, CuI, and Raney nickel alloy.¹³⁴ An Fe catalyzed etherification reaction is known.¹³⁵

¹¹⁷ Artamanova, N.N.; Seregina, V.F.; Shner, V.F.; Salov, B.V.; Kokhlova, V.M.; Zhdamarova, V.N. *J. Org. Chem. USSR* **1989**, 25, 554.

¹¹⁸ See Agejas, J.; Bueno, A.B. *Tetrahedron Lett.* **2006**, 47, 5661.

¹¹⁹ Chaouchi, M.; Loupy, A.; Marque, S.; Petit, A. *Eur. J. Org. Chem.* **2002**, 1278.

¹²⁰ Chen, C.-y.; Dormer, P.G. *J. Org. Chem.* **2005**, 70, 6964.

¹²¹ Luo, Y.; Wu, J.X.; Ren, R.X. *Synlett* **2003**, 1734.

¹²² Oae, S.; Kiritani, R. *Bull. Chem. Soc. Jpn.* **1964**, 37, 770; **1966**, 39, 611.

¹²³ See Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Alikarami, M. *Synlett* **2005**, 1101.

¹²⁴ Naidu, A.B.; Raghunath, O.R.; Prasad, D.J.C.; Sekar, G. *Tetrahedron Lett.* **2008**, 49, 1057; Naidu, A.B.; Sekar, G. *Tetrahedron Lett.* **2008**, 49, 3147. See Moroz, A.A.; Shvartsberg, M.S. *Russ. Chem. Rev.* **1974**, 43, 679; Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

¹²⁵ Weingarten, H. *J. Org. Chem.* **1964**, 29, 977, 3624. See Cai, Q.; Zou, B.; Ma, D. *Angew. Chem. Int. Ed.* **2006**, 45, 1276.

¹²⁶ Chang, J.W.W.; Chee, S.; Mak, S.; Buranaprasertsuk, P.; Chavasiri, W.; Chan, P.W.H. *Tetrahedron Lett.* **2008**, 49, 2018.

¹²⁷ Kawaki, T.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1972**, 45, 1499.

¹²⁸ Whitesides, G.M.; Sadowski, J.S.; Lilburn, J. *J. Am. Chem. Soc.* **1974**, 96, 2829.

¹²⁹ Lipshutz, B.H.; Unger, J.B.; Taft, B.R. *Org. Lett.* **2007**, 9, 1089; Maiti, D.; Buchwald, S.L. *J. Org. Chem.* **2010**, 75, 1791; Maiti, D.; Buchwald, S.L. *J. Am. Chem. Soc.* **2009**, 131, 17423; Tlili, A.; Monnier, F.; Taillefer, M. *Chemistry: Eur. J.* **2010**, 16, 12299; Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. *Angew. Chem. Int. Ed.* **2009**, 48, 8729.

¹³⁰ Parrish, C.A.; Buchwald, S.L. *J. Org. Chem.* **2001**, 66, 2498; Torraca, K.E.; Huang, X.; Parrish, C.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2001**, 123, 10770.

¹³¹ Burgos, C.H.; Barder, T.E.; Huang, X.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2006**, 45, 4321.

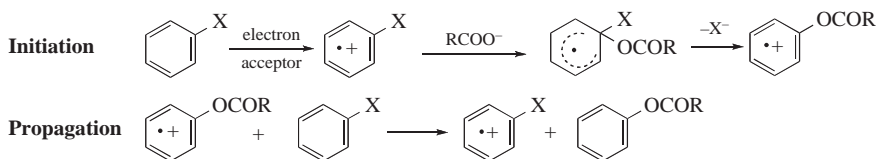
¹³² Kuwabe, S.-i.; Torraca, K.E.; Buchwald, S.L. *J. Am. Chem. Soc.* **2001**, 123, 12202.

¹³³ Manolikakes, G.; Dastbaravardeh, N.; Knochel, P. *Synlett* **2007**, 2077.

¹³⁴ Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Hu, X.-X. *Synlett* **2003**, 2071.

¹³⁵ Bistri, O.; Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, 47, 586.

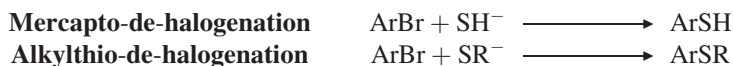
In a related reaction, acid salts (RCOO^-) are sometimes used as nucleophiles.¹³⁶ Unactivated substrates have been converted to carboxylic esters in low-to-moderate yields under oxidizing conditions.¹³⁷ The following chain mechanism, called the $\text{S}_{\text{ON}}2$ mechanism,¹³⁸ has been suggested¹³⁸:



OS I, 219; II, 445; III, 293, 566; V, 926; VI, 150; X, 418.

B. Sulfur Nucleophiles

13-4 Replacement by SH or SR



Aryl thiols and thioethers can be prepared by reactions that are similar to **13-1** and **13-3**.¹³⁹ Activated aryl halides generally give good results, but side reactions are occasionally important. Some reagents give the thiol directly. 4-Bromonitrobenzene reacts with Na_3SPO_3 , in refluxing methanol, to give 4-nitrothiophenol, for example.¹⁴⁰

Diaryl sulfides can be prepared by the use of ^-SAr .¹⁴¹ Even unactivated aryl halides react with ^-SAr if polar aprotic solvents (e.g., DMF,¹⁴² DMSO¹⁴³ 1-methyl-2-pyrrolidinone,¹⁴⁴ or HMPA)¹⁴⁵ are used, though the mechanisms are still mostly or entirely nucleophilic substitution. 2-Iodothiophene reacts directly with thiophenol to give 2-(phenylthio)thiophene.¹⁴⁶

Metal-catalyzed reactions of aryl halides and thiols lead to thioethers. Perhaps the most common metal used nowadays is Pd.¹⁴⁷ Copper catalysts have been used,¹⁴⁸ including

¹³⁶ See Desai, L.V.; Stowers, K.J.; Sanford, M.S. *J. Am. Chem. Soc.* **2008**, *130*, 13285.

¹³⁷ Jönsson, L.; Wistrand, L. *J. Org. Chem.* **1984**, *49*, 3340.

¹³⁸ First proposed by Alder, R.W. *J. Chem. Soc. Chem. Commun.* **1980**, 1184.

¹³⁹ See Peach, M.E. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, **1974**, pp. 735–744.

¹⁴⁰ Bieniarz, C.; Cornwell, M.J. *Tetrahedron Lett.* **1993**, *34*, 939.

¹⁴¹ See Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283.

¹⁴² Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* **1983**, 751. See Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *J. Org. Chem.* **1983**, *48*, 4289.

¹⁴³ Bradshaw, J.S.; South, J.A.; Hales, R.H. *J. Org. Chem.* **1972**, *37*, 2381.

¹⁴⁴ Caruso, A.J.; Colley, A.M.; Bryant, G.L. *J. Org. Chem.* **1991**, *56*, 862; Shaw, J.E. *J. Org. Chem.* **1991**, *56*, 3728.

¹⁴⁵ Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1979**, *44*, 2642. See also, Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* **1980**, *21*, 3099; Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* **1980**, 1363.

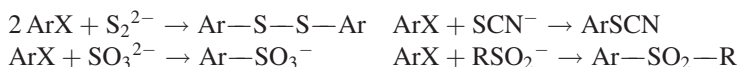
¹⁴⁶ Lee, S.B.; Hong, J.-I. *Tetrahedron Lett.* **1995**, *36*, 8439.

¹⁴⁷ Fernández-Rodríguez, M.A.; Shen, Q.; Hartwig, J.F. *J. Am. Chem. Soc.* **2006**, *128*, 2180.

¹⁴⁸ Sperotto, E.; van Klink, G.P.M.; de Vries, J.G.; van Koten, G. *J. Org. Chem.* **2008**, *73*, 5625; Zhu, D.; Xu, L.; Wu, F.; Wan, B. *Tetrahedron Lett.* **2006**, *47*, 5781; Feng, Y.-S.; Li, Y.-Y.; Tang, L.; Wu, W.; Xu, H.-J. *Tetrahedron Lett.* **2010**, *51*, 2489; Feng, Y.; Wang, H.; Sun, F.; Li, Y.; Fu, X.; Jin, K. *Tetrahedron* **2009**, *65*, 9737.

catalysis in aqueous media,¹⁴⁹ and also Ni¹⁵⁰ or In¹⁵¹ catalysts. Copper-catalyzed coupling is known using ligand- and additive-free conditions.¹⁵² Aryl iodides react with dialkyl disulfides and a nickel catalyst to give aryl alkyl sulfides.¹⁵³ Diaryl sulfides can also be prepared (in high yields) by treatment of unactivated aryl iodides with ArS[−] in liquid ammonia under irradiation.¹⁵⁴ The mechanism in this case is probably S_{RN}1. The reaction (with unactivated halides) has also been carried out electrolytically, with a Ni catalyst.¹⁵⁵ In the presence of a Pd catalyst, thiophenols react with diaryliodonium salts (Ar₂I⁺BF₄[−]) to give the unsymmetrical diaryl sulfide.¹⁵⁶

Other sulfur nucleophiles also react with activated aryl halides:



Arylboronic acids [ArB(OH)₂] react with thiols and copper(II) acetate to give the corresponding alkyl aryl sulfide.¹⁵⁷ Arylboronic acids also react with *N*-methylthiosuccinimide, with a Cu catalyst, to give the aryl methyl sulfide.¹⁵⁸

Aryl sulfones have been prepared from sulfinic acid salts, aryl iodides, and CuI.¹⁵⁹ A Pd catalyzed arylation of sulfenate anions leads to aryl sulfoxides.¹⁶⁰ The copper-catalyzed reaction of NaO₂SMe and aryl iodides give the aryl methyl sulfone,¹⁶¹ and aryl sulfones have been prepared from arylboronic acids using a Cu catalyst.¹⁶² A similar synthesis of diaryl sulfones has been reported using a Pd catalyst.¹⁶³

Aryl selenides (ArSeAr and ArSeAr') can be prepared by similar methodology. Symmetrical diaryl selenides were prepared by the reaction of iodobenzene with diphenyl diselenide (PhSeSePh), in the presence of Mg and a Cu catalyst.¹⁶⁴ Aryl halides react with tin selenides (ArSeSnR₃), with a Cu catalyst, to give the diaryl selenide,¹⁶⁵ and a CuS—Fe catalyst was also used.¹⁶⁶

Thiocyanates have been generated from unactivated aryl halides using charcoal supported copper(I) thiocyanate.¹⁶⁷

¹⁴⁹ Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2008**, 640.

¹⁵⁰ Gómez-Benítez, V.; Baldovino-Pantaleón, O.; Herrera-Álvarez, C.; Toscano, R.A.; Morales-Morales, D. *Tetrahedron Lett.* **2006**, 47, 5059; Yoon, H.-J.; Choi, J.-W.; Kang, H.; Kang, T.; Lee, S.-M.; Jun, B.-H.; Lee, Y.-S. *Synlett* **2010**, 2518.

¹⁵¹ Reddy, V.P.; Swapna, K.; Kumar, A.V.; Rama Rao, K. *J. Org. Chem.* **2009**, 74, 3189.

¹⁵² Buranaprasertsuk, P.; Chang, J.W.W.; Chavasiri, W.; Chan, P.W.H. *Tetrahedron Lett.* **2008**, 49, 2023.

¹⁵³ Tankguchi, N. *J. Org. Chem.* **204**, 69, 6904.

¹⁵⁴ Bunnett, J.F.; Creary, X. *J. Org. Chem.* **1974**, 39, 3173, 3611.

¹⁵⁵ Meyer, G.; Troupel, M. *J. Organomet. Chem.* **1988**, 354, 249.

¹⁵⁶ Wang, L.; Chen, Z.-C. *Synth. Commun.* **2001**, 31, 1227.

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¹⁵⁸ Savarin, C.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* **2002**, 4, 4309.

¹⁵⁹ Suzuki, H.; Abe, H. *Tetrahedron Lett.* **1995**, 36, 6239.

¹⁶⁰ Maitro, G.; Vogel, S.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2006**, 8, 5951.

¹⁶¹ Baskin, J.M.; Wang, Z. *Org. Lett.* **2002**, 4, 4423.

¹⁶² Kar, A.; Sayyed, I.A.; Lo, W.F.; Kaiser, H.M.; Beller, M.; Tse, M.K. *Org. Lett.* **2007**, 9, 3405.

¹⁶³ Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L.M.; Bernini, R. *J. Org. Chem.* **2004**, 69, 5608.

¹⁶⁴ Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, 69, 915; Taniguchi, N.; Onami, T. *Synlett* **2003**, 829.

¹⁶⁵ Beletskaya, I.P.; Sigeev, A.S.; Peregudov, A.S.; Petrovskii, P.V. *Tetrahedron Lett.* **2003**, 44, 7039.

¹⁶⁶ Li, Y.; Wang, H.; Li, X.; Chen, T.; Zhao, D. *Tetrahedron* **2010**, 66, 8583.

¹⁶⁷ Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Soc. Chem. Commun.* **1989**, 81. See also, Yadav, J.S.; Reddy, B.V.S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* **2004**, 45, 2951.

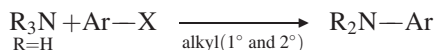
OS I, 220; **III**, 86, 239, 667; **V**, 107, 474; **VI**, 558, 824. Also see, OS **V**, 977.

C. Nitrogen Nucleophiles

13-5 Replacement of Halogen by NH₂, NHR, or NR₂

Amino-de-halogenation

Amido-de-halogenation



Activated aryl halides react with ammonia and primary and secondary amines to give the corresponding arylamines. Primary and secondary amines usually give better results than ammonia, with piperidine especially reactive. Picryl chloride (2,4,6-trinitrochlorobenzene) is often used to form amine derivatives. 2-Chloronitrobenzene also reacts with aniline derivatives directly with microwave irradiation.¹⁶⁸ Other leaving groups in this reaction may be NO₂,¹⁶⁹ N₃, OSO₂R, OR, SR, N=NAr (where Ar contains electron-withdrawing groups)¹⁷⁰ and even NR₂.¹⁷¹ Aryl triflates react directly with secondary amines in *N*-methylpyrrolidine solvent using microwave irradiation.¹⁷² Aniline derivatives react with activated aromatic rings, in the presence of tetrabutylammonium fluoride and under photolysis conditions, to give a *N,N*-diarylamine.¹⁷³ Arylation of amines with aryl halides has also been done in ionic liquids¹⁷⁴ and in supercritical CO₂.¹⁷⁵ Flow reactor technology has been used for the direct, uncatalyzed amination of 2-chloropyridine.¹⁷⁶

Aryl halides can be converted to amines by the use of NaNH₂, NaNHR, or NaNR₂.¹⁷⁷ Lithium dialkylamides also react with aryl halides to give the *N*-arylamine.¹⁷⁸ With amide base reagents, the benzyne mechanism generally operates, so *cine* substitution (Sec. 13.A.iii, category 2) is often found. The amide base is usually generated by reaction of the amine with an organolithium reagent, but other bases may be used. The reaction of an amine, an aryl halide, and potassium *tert*-butoxide generates the *N*-aryl amine.¹⁷⁹ Triarylamines have been prepared in a similar manner from ArI and Ar'₂NLi, even with unactivated ArI.¹⁸⁰

Aryl fluorides react in the presence of KF–alumina and 18-crown-6 in DMSO.¹⁸¹ Aryl fluorides react with amines in the presence of potassium carbonate/DMSO and ultrasound,¹⁸² and aryl chlorides react on basic alumina with microwave irradiation.¹⁸³

¹⁶⁸ Xu, Z.-B.; Lu, Y.; Guo, Z.-R. *Synlett* **2003**, 564. See Li, W.; Yun, L.; Wang, H. *Synth. Commun.* **2002**, 32, 2657.

¹⁶⁹ See Yang, T.; Cho, B.P. *Tetrahedron Lett.* **2003**, 44, 7549.

¹⁷⁰ Kazankov, M.V.; Ginodman, L.G. *J. Org. Chem., USSR* **1975**, 11, 451.

¹⁷¹ Sekiguchi, S.; Horie, T.; Suzuki, T. *J. Chem. Soc. Chem. Commun.* **1988**, 698.

¹⁷² Xu, G.; Wang, Y.-G. *Org. Lett.* **2004**, 6, 985.

¹⁷³ Hertas, I.; Gallardo, I.; Marquet, J. *Tetrahedron Lett.* **2000**, 41, 279.

¹⁷⁴ Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Narsaiah, A.V. *Tetrahedron Lett.* **2003**, 44, 2217.

¹⁷⁵ Smith, C.J.; Tsang, M.W.S.; Holmes, A.B.; Danheiser, R.L.; Tester, J.W. *Org. Biomol. Chem.* **2005**, 3, 3767.

¹⁷⁶ Hamper, B.C.; Tesfu, E. *Synlett* **2007**, 2257.

¹⁷⁷ See Heaney, H. *Chem. Rev.* **1962**, 62, 81, see p. 83.

¹⁷⁸ Tripathy, S.; Le Blanc, R.; Durst, T. *Org. Lett.* **1999**, 1, 1973. See Kanth, J.V.B.; Periasamy, M. *J. Org. Chem.* **1993**, 58, 3156.

¹⁷⁹ Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, 5, 3515.

¹⁸⁰ Neunhoeffer, O.; Heitmann, P. *Chem. Ber.* **1961**, 94, 2511.

¹⁸¹ Smith III, W.J.; Sawyer, J.S. *Tetrahedron Lett.* **1996**, 37, 299.

¹⁸² Magdolen, P.; Meciárová, M.; Toma, S. *Tetrahedron* **2001**, 57, 4781.

¹⁸³ Kidwai, M.; Sapra, P.; Dave, B. *Synth. Commun.* **2000**, 30, 4479.

2-Fluoropyridine reacts with R_2NBH_3Li to give the 2-aminoalkylpyridine.¹⁸⁴ 2,4-Dinitrofluorobenzene, known as *Sanger's reagent*, is used to tag the amino end of a peptide or protein chain.¹⁸⁵

The reaction of amines with aryl halides can be done under milder conditions using a catalyst to initiate or mediate the reaction. Both amines (aliphatic and aniline derivatives)¹⁸⁶ and amide bases¹⁸⁷ have been coupled to aryl halides using Pd catalysts and an appropriate ligand.¹⁸⁸ A considerable amount of work¹⁸⁹ has been done to vary the nature of the ligand and the Pd catalyst, as well as the base.¹⁹⁰ Work to discern the mechanism of this reaction has also received considerable attention.¹⁹¹ This amination has come to be called the *Buchwald–Hartwig Cross-Coupling Reaction*.

Polymer-supported Pd catalysts,¹⁹² polymer-bound phosphine ligands used in conjunction with a Pd catalyst,¹⁹³ and polymer-bound amines¹⁹⁴ have been used for *N*-arylation. These reactions have been done in ionic liquids using a Pd catalyst.¹⁹⁵ Palladium-catalyzed amination of aryl halides has been reported using microwave irradiation.¹⁹⁶ Catalysts are available for the amination of aryl halides in aqueous media.¹⁹⁷ The Pd-catalyzed amination of aryl substrates is not limited to halides, and the reaction with mesylates lead to arylamines.¹⁹⁸ Arylamines with chiral substituents on nitrogen can be prepared using a Pd-catalyst with optically active ligands.¹⁹⁹

Aniline derivatives have been prepared by the reaction of aryl chlorides with silylamines (Ph_3SiNH_2) using lithium hexamethyldisilazide and a Pd catalyst.²⁰⁰ Amines react with

¹⁸⁴ Thomas, S.; Roberts, S.; Pasumansky, J.L.; Gamsey, S.; Singaram, B. *Org. Lett.* **2003**, *5*, 3867.

¹⁸⁵ Sanger, F. *The Biochem. J.* **1945**, *39*, 507.

¹⁸⁶ Ali, M.H.; Buchwald, S.L. *J. Org. Chem.* **2001**, *66*, 2560; Kuwano, R.; Utsunomiya, M.; Hartwig, J.F. *J. Org. Chem.* **2002**, *67*, 6479; Reddy, Ch.V.; Kingston, J.V.; Verkade, J.G. *J. Org. Chem.* **2008**, *73*, 3047; Shen, Q.; Hartwig, J.F. *Org. Lett.* **2008**, *10*, 4109.

¹⁸⁷ Harris, M.C.; Huang, X.; Buchwald, S.L. *Org. Lett.* **2003**, *4*, 2885. See Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923; Shen, Q.; Hartwig, J.F. *J. Am. Chem. Soc.* **2006**, *128*, 10028. For a discussion about the influence of water on this reaction, see Dallas, A.S.; Gothelf, K.V. *J. Org. Chem.* **2005**, *70*, 3321.

¹⁸⁸ See Anderson, K.W.; Tundel, R.E.; Ikawa, T.; Altman, R.A.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6523.

¹⁸⁹ Gajare, A.S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *J. Org. Chem.* **2004**, *69*, 6504; Huang, X.; Anderson, K.W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2004**, *125*, 6653; Singer, R.A.; Tom, N.J.; Frost, H.N.; Simon, W.M. *Tetrahedron Lett.* **2004**, *45*, 4715; Smith, C.J.; Early, T.R.; Holmes, A.B.; Shute, R.E. *Chem. Commun.* **2004**, 1976.

¹⁹⁰ See Singh, U.K.; Strieter, E.R.; Blackmond, D.G.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, *124*, 14104. For a study of rate enhancement by the added base, see Meyers, C.; Maes, B.U.W.; Loones, K.T.J.; Bal, G.; Lemièrre, G.L.F.; Dommissie, R.A. *J. Org. Chem.* **2004**, *69*, 6010.

¹⁹¹ See Strieter, E.R.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2006**, *45*, 925; Fors, B.P.; Davis, N.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2009**, *131*, 5766.

¹⁹² Guinó, M.; Hii, K.K. *Tetrahedron Lett.* **2005**, *46*, 7363. See Inasaki, T.; Ueno, M.; Miyamoto, S.; Kobayashi, S. *Synlett* **2007**, 3209.

¹⁹³ Parrish, C.A.; Buchwald, S.L. *J. Org. Chem.* **2001**, *66*, 3820.

¹⁹⁴ Weigand, K.; Pelka, S. *Org. Lett.* **2002**, *4*, 4689.

¹⁹⁵ See Grasa, G.A.; Viciu, M.S.; Huang, J.; Nolan, S.P. *J. Org. Chem.* **2001**, *66*, 7729.

¹⁹⁶ Jensen, T.A.; Liang, X.; Tanner, D.; Skjaerbaek, N. *J. Org. Chem.* **2004**, *69*, 4936; Loones, K.T.J.; Maes, B.U.W.; Rombouts, G.; Hostyn, S.; Diels, G. *Tetrahedron* **2005**, *61*, 10338.

¹⁹⁷ Xu, C.; Gong, J.-F.; Wu, Y.-J. *Tetrahedron Lett.* **2007**, *48*, 1619.

¹⁹⁸ So, C.M.; Zhou, Z.; Lau, C.P.; Kwong, F.Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 6402.

¹⁹⁹ Tagashira, J.; Imao, D.; Yamamoto, T.; Ohta, T.; Furukawa, I.; Ito, Y. *Tetrahedron Asymmetry* **2005**, *16*, 230.

²⁰⁰ Huang, X.; Buchwald, S.L. *Org. Lett.* **2001**, *3*, 3417.

$\text{Ph}_2\text{I}^+\text{BF}_4^-$, in the presence of Pd catalysts,²⁰¹ or a CuI catalyst²⁰² to give the *N*-phenyl amine. Aminoalkylation of heteroaromatic rings is possible, as in the reaction of 3-bromothiophene with a primary amine and a Pd catalyst.²⁰³ 2-Halopyridines react to give the 2-aminoalkyl pyridine.²⁰⁴

Copper catalysts have been used for the reaction of amines or aniline derivatives with aryl halides.²⁰⁵ The selectivity of *O*- versus *N*-arylation for reactions of amino alcohols has been discussed.²⁰⁶ Copper-catalyzed amination reactions can be done in aqueous media using 2-dimethylaminoethanol as a ligand.²⁰⁷ Ammonium salts serve as a nitrogen source in some cases.²⁰⁸ In the *Goldberg reaction*, an aryl bromide reacts with an acetanilide in the presence of K_2CO_3 and CuI to give an *N*-acetyldiarylamine, which can be hydrolyzed to a diarylamine: $\text{ArBr} + \text{Ar}'\text{NHAc} \rightarrow \text{ArAr}'\text{NAc}$.²⁰⁹

Nickel catalysts have been used in the reaction of aryl halides with *N*-alkyl aniline derivatives²¹⁰ and also with aliphatic amines.²¹¹ *N*-Arylation was also accomplished with butyllithium and a secondary amine using Ni/C-diphenylphosphinoferrocene (dppf).²¹² An intramolecular reaction of a pendant aminoalkyl unit with an aryl chloride moiety, catalyzed by Ni(0) gave a dihydroindole.²¹³ An arylbismuth reagent reacts with aliphatic amines, in the presence of copper(II) acetate, to give an *N*-arylamine.²¹⁴ Diarylzinc reagents give the *N*-aryl amine in the presence of a Cu^{215} or a Ni catalyst²¹⁶. Aryl halides also react with $\text{Zn}(\text{NTMS}_2)_2$ in the presence of a Pd catalyst to give arylamines.²¹⁷ Iron-catalyzed arylation reactions are known.²¹⁸ A $\text{Mo}(\text{CO})_6$ mediated, Pd catalyzed reaction is known for allylamines and aryl halides.²¹⁹

²⁰¹ Kang, S.-K.; Lee, H.-W.; Choi, W.-K.; Hong, R.-K.; Kim, J.-S. *Synth. Commun.* **1996**, 26, 4219. See Carroll, M.A.; Wood, R.A. *Tetrahedron* **2007**, 63, 11349.

²⁰² Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* **2000**, 1022.

²⁰³ Ogawa, K.; Radke, K.R.; Rothstein, S.D.; Rasmussen, S.C. *J. Org. Chem.* **2001**, 66, 9067.

²⁰⁴ Juncckers, T.H.M.; Maes, B.U.W.; Lemi re, G.L.F.; Dommissie, R. *Tetrahedron* **2001**, 57, 7027; Basu, B.; Jha, S.; Mridha, N.K.; Bhuiyan, Md.M.H. *Tetrahedron Lett.* **2002**, 43, 7967.

²⁰⁵ Choudary, B.M.; Sridhar, C.; Kantam, M.L.; Venkanna, G.T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, 127, 9948; Shafir, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2006**, 128, 8742; Wolf, C.; Liu, S.; Mei, X.; August, A.T.; Casimir, M.D. *J. Org. Chem.* **2006**, 71, 3270; Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, 72, 672; Wang, H.; Li, Y.; Sun, F.; Feng, Y.; Jin, K.; Wang, X. *J. Org. Chem.* **2008**, 73, 8639; Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496. For a ligand-free reaction, see Yong, F.F.; Teo, Y.-C. *Synlett* **2010**, 3068.

²⁰⁶ Shafir, A.; Lichtor, P.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2007**, 129, 3490. For an amination using aq ammonia, see Meng, F.; Zhu, X.; Li, Y.; Xie, J.; Wang, B.; Yao, J.; Wan, Y. *Eur. J. Org. Chem.* **2010**, 6149.

²⁰⁷ Lu, Z.; Twieg, R.J. *Tetrahedron Lett.* **2005**, 46, 2997.

²⁰⁸ Kim, J.; Chang, S. *Chem. Commun.* **2008**, 3052.

²⁰⁹ See Renger, B. *Synthesis* **1985**, 856.

²¹⁰ Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1997**, 119, 6054; Lipshutz, B.H.; Ueda, H. *Angew. Chem. Int. Ed.* **2000**, 39, 4492.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **2002**, 58, 6913; Chen, C.; Yang, L.-M. *J. Org. Chem.* **2007**, 72, 6324.

²¹¹ Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, 73, 1429; Gao, C.-Y.; Cao, X.; Yang, L.-M. *Org. Biomol. Chem.* **2009**, 7, 3922.

²¹² Tasler, S.; Lipshutz, B.H. *J. Org. Chem.* **2003**, 68, 1190.

²¹³ Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, 5, 2311.

²¹⁴ Fedorov, A.Yu.; Finet, J.-P. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3775.

²¹⁵ Berman, A.M.; Johnson, J.S. *J. Am. Chem. Soc.* **2004**, 126, 5680.

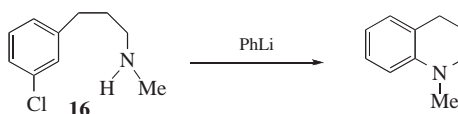
²¹⁶ Berman, A.M.; Johnson, J.S. *Synlett* **2005**, 1799.

²¹⁷ Lee, D.-Y.; Hartwig, J.F. *Org. Lett.* **2005**, 7, 1169.

²¹⁸ Guo, D.; Huang, H.; Xu, J.; Jiang, H.; Liu, H. *Org. Lett.* **2008**, 10, 4513; Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* **2007**, 46, 8862; Correa, A.; Carril, M.; Bolm, C. *Chemistry: European J.* **2008**, 14, 10919.

²¹⁹ Appukkuttan, P.; Axelsson, L.; Van der Eycken, E.; Larhed, M. *Tetrahedron Lett.* **2008**, 49, 5625.

Intramolecular versions of this reaction generate bicyclic or polycyclic amines.²²⁰ An example is the conversion of **16** to the tetrahydroquinoline.²²¹ Larger ring amines can be prepared using this approach: 8- and even 12-membered.



Arylboronic acids react with aliphatic amines²²² or aq ammonia²²³ in the presence of a Cu catalyst. *N*-Aryl imides have been prepared by similar methodology, from arylboronic acids.²²⁴ Trifluoroarylboronates react with copper(II) acetate and then an aliphatic amine to give the *N*-phenylamine.²²⁵ Primary aromatic amines (ArNH₂) were converted to diaryl amines (ArNHPh) by treatment with Ph₃Bi(OAc)₂²²⁶ and a Cu powder catalyst.²²⁷

The metal-catalyzed reaction with ammonia or amines likely proceeds by the S_NAr mechanism.²²⁸ This reaction, with phase-transfer catalysis, has been used to synthesize triarylamines.²²⁹ In certain cases, the S_{RN}1 mechanism has been found (Reaction 10-26). When the substrate is a heterocyclic aromatic nitrogen compound, still a different mechanism [the S_N(ANRORC) mechanism], involving opening and reclosing of the aromatic ring, has been shown to take place.²³⁰

There are a number of indirect approaches for the preparation of aryl amines. Activated aromatic compounds can be directly converted to the *N*-aryl amine in high yield with hydroxylamine in the presence of strong bases.²³¹ Aryl halides can be converted to the corresponding *Grignard reagent* (Reaction 12-38). Subsequent reaction with allyl azide followed by hydrolysis leads to the corresponding aniline derivative.²³² Aryl *Grignard reagents* react with nitroaryl compounds to give, after reduction with FeCl₃/NaBH₄, a diaryl amine.²³³ Aryl halides can be converted to the aryllithium via halogen–lithium exchange or hydrogen–lithium exchange (Reactions 12-38 and 12-39).

The use of transition metal catalysts allows aryl halides to react with the nitrogen of amides or carbamates to give the corresponding *N*-aryl amide or *N*-aryl carbamate.

²²⁰ See Jordan-Hore, J.A.; Johansson, C.C.C.; Gulias, M.; Beck, E.M.; Gaunt, M.J. *J. Am. Chem. Soc.* **2008**, *130*, 16184; Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2005**, *70*, 413.

²²¹ See Bunnett, J.F.; Hrutford, B.F. *J. Am. Chem. Soc.* **1961**, *83*, 1691. Also see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, **1973**, pp. 150–164.

²²² Chiang, G.C.H.; Olsson, T. *Org. Lett.* **2004**, *6*, 3079; Lan, J.-B.; Zhang, G.-L.; Yu, X.-Q.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G. *Synlett* **2004**, 1095.

²²³ Jiang, Z.; Wu, Z.; Wang, L.; Wu, D.; Zhou, X. *Can. J. Chem.* **2010**, *88*, 964.

²²⁴ Chernick, E.T.; Ahrens, M.J.; Scheidt, K.A.; Wasielewski, M.R. *J. Org. Chem.* **2005**, *70*, 1486.

²²⁵ Quach, T.D.; Batey, R.A. *Org. Lett.* **2003**, *5*, 4397.

²²⁶ See Finet, J. *Chem. Rev.* **1989**, *89*, 1487.

²²⁷ See Barton, D.H.R.; Yadav-Bhatnagar, N.; Finet, J.; Khamsi, J. *Tetrahedron Lett.* **1987**, *28*, 3111.

²²⁸ See Bethell, D.; Jenkins, I.L.; Quan, P.M. *J. Chem. Soc. Perkin Trans. 1* **1985**, 1789; Paine, A.J. *J. Am. Chem. Soc.* **1987**, *109*, 1496.

²²⁹ Gauthier, S.; Fréchet, J.M.J. *Synthesis* **1987**, 383.

²³⁰ See van der Plas, H.C. *Tetrahedron* **1985**, *41*, 237; *Acc. Chem. Res.* **1978**, *11*, 462.

²³¹ See Chupakhin, O.N.; Postovskii, I.Ya. *Russ. Chem. Rev.* **1976**, *45*, 454, p. 456.

²³² Kabalka, G.W.; Li, G. *Tetrahedron Lett.* **1997**, *38*, 5777.

²³³ Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390.

Amides react with aryl halides in the presence of a Pd²³⁴ or a Cu catalyst.²³⁵ *N*-Aryl lactams are prepared by the reaction of a lactam with an aryl halide in the presence of a Pd catalyst.²³⁶ β -Lactams also react.²³⁷ The reaction of 2-oxazolidinones with aryl halides in the presence of a Pd catalyst gave the *N*-aryl-2-oxazolidinone.²³⁸ *N*-Aryl amides are prepared from amides using PhSi(OMe)₃/Cu(OAc)₂/Bu₄NF.²³⁹ *N*-Boc hydrazine derivatives (BocNHNH₂) gave the *N*-phenyl derivative [BocN(Ph)NH₂] when reacted with iodobenzene and a catalytic amount of CuI and 10% of 1,10-phenanthroline.²⁴⁰ 3-Bromothiophene was converted to the 3-amido derivative with an amide and CuI-dimethylethylenediamine.²⁴¹ *N*-(2-Thiophene)-2-pyrrolidinone was similarly prepared from 2-iodothiophene, the lactam, and a copper catalyst.²⁴² *N*-Arylation of urea is possible using a Cu catalyst.²⁴³

The transition metal catalyzed couplings of primary or secondary phosphines with aryl halides or sulfonate esters to give arylphosphines is known.²⁴⁴ The Pd catalyzed conversion of aryl halides to aryl phosphines using (trimethylsilyl)diphenylphosphine tolerates many functional groups (not those that are easily reducible, e.g., aldehydes, because Zn metal²⁴⁵ is often used as a coreagent), but it is mainly limited to aryl iodides.²⁴⁶ Diphenylphosphine reacts with aryl iodides and a copper catalyst to give the triarylphosphine.²⁴⁷ Aryl iodides also react with a secondary phosphine and 5% Pd/C to give the *P*-arylphosphine.²⁴⁸ Tertiary phosphines can be used via aryl-aryl exchange, as in the reaction of an aryl triflate and triphenylphosphine and a Pd catalyst, for example, gave the arylphosphonium salt (ArPPh₃).²⁴⁹ Aryl iodides can also be used.²⁵⁰

OS I, 544; II, 15, 221, 228; III, 53, 307, 573; IV, 336, 364; V, 816, 1067; VII, 15. OS III, 664. OS X, 423.

²³⁴ Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676; Fors, B.P.; Dooleweerd, K.; Zeng, Q.; Buchwald, S.L. *Tetrahedron* **2009**, *65*, 6576. For an intramolecular reaction, see Yang, B.H.; Buchwald, S.L. *Org. Lett.* **1999**, *1*, 35.

²³⁵ Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Mehdinejad, H. *Synlett* **2004**, 1517.

²³⁶ Browning, R.G.; Badarinarayana, V.; Mahmud, H.; Lovely, C.J. *Tetrahedron* **2004**, *60*, 359; Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2004**, *45*, 2311. Also see Klapars, A.; Huang, X.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, *124*, 7421; Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759.

²³⁷ Also see Klapars, A.; Parris, S.; Anderson, K.W.; Buchwald, S.L. *J. Am. Chem. Soc.* **2004**, *126*, 3529.

²³⁸ Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539.

²³⁹ Lam, P.Y.S.; Deudon, S.; Hauptman, E.; Clark, C.G. *Tetrahedron Lett.* **2001**, *42*, 2427.

²⁴⁰ Wolter, M.; Klapars, A.; Buchwald, S.L. *Org. Lett.* **2001**, *3*, 3803.

²⁴¹ Padwa, A.; Crawford, K.R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609.

²⁴² Kang, S.-K.; Kim, D.-H.; Park, J.-N. *Synlett* **2002**, 427.

²⁴³ Nandakumar, M.V. *Tetrahedron Lett.* **2004**, *45*, 1989.

²⁴⁴ Gelpke, A.E.S.; Kooijman, H.; Spek, A.L.; Hiemstra, H. *Chem. Eur. J.* **1999**, *5*, 2472; Ding, K.; Wang, Y.; Yun, H.; Liu, J.; Wu, Y.; Terada, M.; Okubo, Y.; Mikami, K. *Chem. Eur. J.* **1999**, *5*, 1734; Vyskocil, S.; Smrcina, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7738; Martorell, G.; Garcias, X.; Janura, M.; Saá, J. M. *J. Org. Chem.* **1998**, *63*, 3463; Lipshutz, B.H.; Buzard, D.H.; Yun, C.S. *Tetrahedron Lett.* **1999**, *40*, 201.

²⁴⁵ Ager, D.J.; Laneman, S. *Chem. Commun.* **1997**, 2359.

²⁴⁶ Tunney, B.H.; Stille, J.K. *J. Org. Chem.* **1987**, *52*, 748.

²⁴⁷ Van Allen, D.; Venkataraman, D. *J. Org. Chem.* **2003**, *68*, 4590.

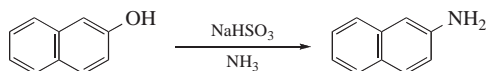
²⁴⁸ Stadler, A.; Kappe, C.O. *Org. Lett.* **2002**, *4*, 3541.

²⁴⁹ Kwong, F.Y.; Lai, C.W.; Chan, K.S. *Tetrahedron Lett.* **2002**, *43*, 3537.

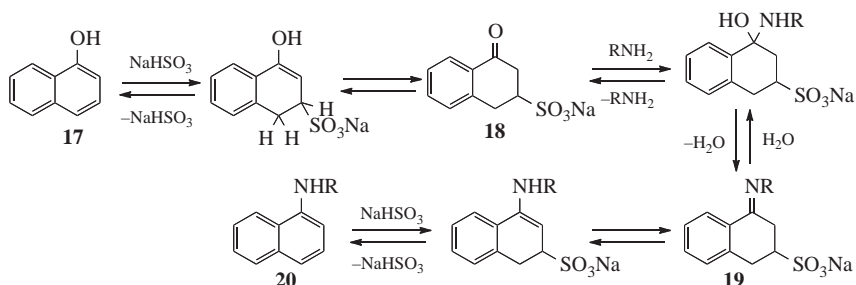
²⁵⁰ Marcoux, D.; Charette, A.B. *J. Org. Chem.* **2008**, *73*, 590.

13-6 Replacement of a Hydroxy Group by an Amino Group

Amino-de-hydroxylation



The reaction of naphthols with ammonia and sodium bisulfite is called the *Bucherer reaction*. Primary amines can be used instead of ammonia, in which case *N*-substituted naphthylamines are obtained. In addition, primary naphthylamines can be converted to secondary ($\text{ArNH}_2 + \text{RNH}_2 + \text{NaSO}_3 \rightarrow \text{ArNHR}$), by a transamination reaction. The mechanism of the *Bucherer reaction* amounts to a kind of overall addition–elimination, via **18** and **19**.²⁵¹



The first step in either direction consists of addition of NaHSO₃ to one of the double bonds of the ring, which gives an enol from **17** (or enamine from **20**) that tautomerizes to the keto form **18** (or imine form, **19**). The conversion of **18** to **19** (or vice versa) is an example of Reaction 16-13 (or 16-2). Evidence for this mechanism was the isolation of **18**²⁵² and the demonstration that for β-naphthol treated with ammonia and HSO₃[−], the rate of the reaction depends only on the substrate and on HSO₃[−], indicating that ammonia is not involved in the rate-determining step.²⁵³ If the starting compound is a β-naphthol, the intermediate is a 2-keto-4-sulfonic acid compound, so the sulfur of the bisulfite in either case attacks meta to the OH or NH₂.²⁵⁴

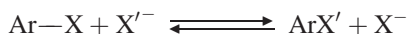
Hydroxy groups on benzene rings can be replaced by NH₂ groups if they are first converted to aryl diethyl phosphates. Treatment of these with KNH₂ and potassium metal in liquid ammonia gives the corresponding primary aromatic amines.²⁵⁵ The mechanism of the second step is S_{RN}1.²⁵⁶

OS III, 78.

D. Halogen Nucleophiles

13-7 The Introduction of Halogens

Halo-de-halogenation, and so on



²⁵¹ Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* **1960**, 638, 66.

²⁵² Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* **1960**, 638, 43, 57.

²⁵³ Kozlov, V.V.; Veselovskaia, I.K. *J. Gen. Chem. USSR* **1958**, 28, 3359.

²⁵⁴ Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* **1960**, 638, 76.

²⁵⁵ Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* **1972**, 37, 3570.

²⁵⁶ See Scherrer, R.A.; Beatty, H.R. *J. Org. Chem.* **1972**, 37, 1681.

It is possible to replace a halogen on an aromatic ring by another halogen²⁵⁷ if the ring is activated. In such cases, there is equilibrium, which is usually shifted in the desired direction by the use of an excess of added halide ion.²⁵⁸ A phenolic hydroxy group can be replaced by chloro with PCl_5 or POCl_3 , but only if the ring is activated. Unactivated phenols give phosphates when treated with POCl_3 : $3 \text{ ArOH} + \text{POCl}_3 \rightarrow (\text{ArO})_3\text{PO}$. Phenols, even unactivated ones, can be converted to aryl bromides by treatment with Ph_3PBr_2 ²⁵⁹ (see Reaction 10-47) and to aryl chlorides by treatment with PhPCl_4 .²⁶⁰

Halide exchange is particularly useful for putting fluorine into a ring, since there are fewer alternate ways of doing this than for the other halogens. Activated aryl chlorides give fluorides when treated with KF in DMF , DMSO , or dimethyl sulfone.²⁶¹ Reaction of aryl halides with $\text{Bu}_4\text{PF}/\text{HF}$ is also effective for exchanging a halogen with fluorine.²⁶²

Halide exchange can also be accomplished with copper halides. Since the leaving-group order in this case is $\text{I} > \text{Br} > \text{Cl} \gg \text{F}$, which means that iodides cannot normally be made by this method, the $\text{S}_{\text{N}}\text{Ar}$ mechanism is probably not operating.²⁶³ However, aryl iodides have been prepared from bromides, by the use of Cu supported on charcoal or Al_2O_3 ,²⁶⁴ with an excess of NaI and a Cu catalyst,²⁶⁵ and by treatment with excess KI and a Ni catalyst.²⁶⁶ Interestingly, aryl chlorides have been prepared from aryl iodides using 2 molar equivalents of NiCl_2 in DMF , with microwave irradiation.²⁶⁷ Aryl and vinyl triflates can be converted to the corresponding bromide or chloride using a Pd catalyst.²⁶⁸

Aryl iodides²⁶⁹ and fluorides can be prepared from arylthallium bis(trifluoroacetates) (see Reaction 12-23), indirectly achieving the $\text{ArH} \rightarrow \text{ArI}$ and $\text{ArH} \rightarrow \text{ArF}$ conversions. The bis(trifluoroacetates) react with KI to give ArI in high yields.²⁷⁰ Aryllead triacetates [$\text{ArPb}(\text{OAc})_3$] can be converted to aryl fluorides by treatment with BF_3 -etherate.²⁷¹ Treatment of $\text{PhB}(\text{OH})_2$ with NIS gives iodobenzene.²⁷² Arylboronic acids (Reaction 12-28) can be converted to the corresponding aryl bromides by reaction with

²⁵⁷ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 671–672.

²⁵⁸ Sauer, J.; Huisgen, R. *Angew. Chem.* **1960**, 72, 294, p. 297.

²⁵⁹ Schaefer, J.P.; Higgins, J. *J. Org. Chem.* **1967**, 32, 1607.

²⁶⁰ Bay, E.; Bak, D.A.; Timony, P.E.; Leone-Bay, A. *J. Org. Chem.* **1990**, 55, 3415.

²⁶¹ Kimura, Y.; Suzuki, H. *Tetrahedron Lett.* **1989**, 30, 1271. See Dolby-Glover, L. *Chem. Ind. (London)* **1986**, 518.

²⁶² Uchibori, Y.; Umeno, M.; Seto, H.; Qian, Z.; Yoshioka, H. *Synlett* **1992**, 345.

²⁶³ Bacon, R.G.R.; Hill, H.A.O. *J. Chem. Soc.* **1964**, 1097, 1108. See also, Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Res. (S)* **1989**, 238.

²⁶⁴ Clark, J.H.; Jones, C.W. *J. Chem. Soc. Chem. Commun.* **1987**, 1409.

²⁶⁵ Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, 124, 14844.

²⁶⁶ Yang, S.H.; Li, C.S.; Cheng, C.H. *J. Org. Chem.* **1987**, 52, 691.

²⁶⁷ Arvela, R.K.; Leadbeater, N.E. *Synlett* **2003**, 1145.

²⁶⁸ Shen, X.; Hyde, A.M.; Buchwald, S.L. *J. Am. Chem. Soc.* **2010**, 132, 14076.

²⁶⁹ See Merkushev, E.B. *Synthesis* **1988**, 923; *Russ. Chem. Rev.* **1984**, 53, 343.

²⁷⁰ Taylor, E.C.; Kienzie, F.; McKillop, A. *Org. Synth.* **VI**, 826; Taylor, E.C.; Katz, A.H.; Alvarado, S.I.; McKillop, A. *J. Organomet. Chem.* **1985**, 285, C9. See Ustyatinskii, A.Ya.; Bregadze, V.I. *Russ. Chem. Rev.* **1988**, 57, 1054; Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* **1975**, 40, 2351.

²⁷¹ De Meio, G.V.; Pinhey, J.T. *J. Chem. Soc. Chem. Commun.* **1990**, 1065.

²⁷² Thiebes, C.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *Synlett* **1998**, 141.

1,3-dibromo-5,5-dimethylhydantoin and 5 mol% NaOMe.²⁷³ Other aryl halides can be prepared using 1,3-dihalo-5,5-dimethylhydantoins.

OS **III**, 194, 272, 475; **V**, 142, 478; **VIII**, 57; **81**, 98.

The reduction of phenols and phenolic esters and ethers is discussed in Reactions **19-38** and **19-35**. The reaction $\text{ArX} \rightarrow \text{ArH}$ is treated in **11-39**, although, depending on reagent and conditions, it can be nucleophilic or free radical substitution, as well as electrophilic.

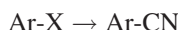
E. Carbon Nucleophiles²⁷⁴

Some formations of new aryl-carbon bonds formed from aryl substrates have been considered in Reactions **10-57**, **10-68**, **10-76**, and **10-77**.

13-8 Cyanation of Aromatic Rings

Cyano-de-halogenation

Cyano-de-metalation



The reaction between aryl halides and cuprous cyanide is called the *Rosenmund-von Braun reaction*.²⁷⁵ Reactivity of the aryl halide is in the order $\text{I} > \text{Br} > \text{Cl} > \text{F}$, indicating that the $\text{S}_{\text{N}}\text{Ar}$ mechanism does not apply.²⁷⁶ Cyanides (e.g., KCN and NaCN) do not react with aryl halides, even activated ones, but this reaction has been done in ionic liquids using CuCN.²⁷⁷ The reaction has also been done in water using CuCN, a phase-transfer catalyst, and microwave irradiation.²⁷⁸ L-Proline has been used to promote the reaction.²⁷⁹

Aryl halides react with metal cyanides, often with another transition metal catalyst, to give aryl nitriles (aryl cyanides). Alkali cyanides convert aryl halides to nitriles²⁸⁰ in dipolar aprotic solvents in the presence of Pd(II) salts²⁸¹ or Cu²⁸² or Ni²⁸³ complexes. In the presence of a Pd- catalyst,²⁸⁴ several cyanide-containing compounds react with aryl halides. Several different sources of cyanide may be used with the Pd catalyzed reaction, including: $\text{Zn}(\text{CN})_2$,²⁸⁵ CuCN,²⁸⁶ sodium cyanoborohydride/catechol,²⁸⁷

²⁷³ Szumigala, Jr., R.H.; Devine, P.N.; Gauthier, Jr., D.R.; Volante, R.P. *J. Org. Chem.* **2004**, 69, 566.

²⁷⁴ See Artamkina, G.A.; Kovalenko, S.V.; Beletskaya, I.P.; Reutov, O.A. *Russ. Chem. Rev.* **1990**, 59, 750.

²⁷⁵ See Ellis, G.P.; Romney-Alexander, T.M. *Chem. Rev.* **1987**, 87, 779.

²⁷⁶ See Connor, J.A.; Leeming, S.W.; Price, R. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1127.

²⁷⁷ Wu, J.X.; Beck, B.; Ren, R.X. *Tetrahedron Lett.* **2002**, 43, 387.

²⁷⁸ Arvela, R.K.; Leadbeater, N.W.; Torenus, H.M.; Tye, H. *Org. Biomol. Chem.* **2003**, 1, 1119.

²⁷⁹ Wang, D.; Kuang, L.; Li, Z.; Ding, K. *Synlett* **2008**, 69.

²⁸⁰ For a list of reagents that convert aryl halides to cyanides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1705–1709.

²⁸¹ Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* **1991**, 64, 1118.

²⁸² Connor, J.A.; Gibson, D.; Price, R. *J. Chem. Soc. Perkin Trans. 1* **1987**, 619.

²⁸³ Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1988**, 61, 1985.

²⁸⁴ See Stazi, F.; Palmisano, G.; Turconi, M.; Santagostino, M. *Tetrahedron Lett.* **2005**, 46, 1815; Zhu, Y.-Z.; Cai, C. *Eur. J. Org. Chem.* **2007**, 2401.

²⁸⁵ Marcantonio, K.M.; Frey, L.F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D.J.; Chen, C.-y. *Org. Lett.* **2004**, 6, 3723. See Erker, T.; Nemec, S. *Synthesis* **2004**, 23.

²⁸⁶ Sakamoto, T.; Ohsawa, K. *J. Chem. Soc. Perkin Trans. 1* **1999**, 2323.

²⁸⁷ Jiang, B.; Kan, Y.; Zhang, A. *Tetrahedron* **2001**, 57, 1581.

potassium ferricyanide,²⁸⁸ and KCN.²⁸⁹ Microwave irradiation has been used to facilitate Pd catalyzed cyanation.²⁹⁰ Aryl triflates may be used in aryl cyanation reactions, as well as aryl halides.²⁹¹ Benzylthiocyanate reacts with boronic acids to give aryl cyanides in a “cyanide-free” reaction, catalyzed by a Pd complex and mediated by Cu(I).²⁹² Cyanation reactions catalyzed by copper salts are common.²⁹³ Aryl bromides react with Ni(CN)₂ with microwave irradiation to give ArCN.²⁹⁴ A nickel complex also catalyzes the reaction between aryl triflates and KCN to give aryl nitriles.²⁹⁵ Iridium-catalyzed borylation of arenes also leads to aryl nitriles.²⁹⁶

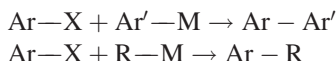
Alternative procedures are available. One uses excess aq KCN followed by photolysis of the resulting complex ion [ArTi(CN)₃][−] in the presence of excess KCN.²⁹⁷ Alternatively, arylthallium acetates react with Cu(CN)₂ or CuCN to give aryl nitriles.²⁹⁸ Yields from this procedure are variable, ranging from almost nothing to 90 or 100%.

Metal-free methods have been reported. For example, conversion of an aromatic compound to the corresponding iminium salt used POCl₃ and DMF, and subsequent reaction with molecular iodine in aq ammonia gave the nitrile.²⁹⁹ An indirect method involves the reaction of an aromatic ring with *tert*-butyllithium, particularly when there is a directing group (see Reaction 13-17), followed by reaction with PhOCN (phenyl cyanate) to give the aryl nitrile.³⁰⁰ Aromatic ethers (ArOR)³⁰¹ have been photochemically converted to ArCN.

OS III, 212, 631.

13-9 Coupling of Aryl and Alkyl Organometallic Compounds with Functionalized Aryl Compounds

Aryl-de-halogenation, and so on



A number of methods involving transition metals have been used to prepare unsymmetrical biaryls³⁰² (see also, Reaction 13-11). The uncatalyzed coupling of aryl halides and metalated aryls (particularly aryllithium reagents) is also known, including

²⁸⁸ Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372; Weissman, S.A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508; Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087; Velmathi, S.; Leadbeater, N.E. *Tetrahedron Lett.* **2008**, *49*, 4693.

²⁸⁹ Yang, C.; Williams, J.M. *Org. Lett.* **2004**, *6*, 2837.

²⁹⁰ Chobanian, H.R.; Fors, B.P.; Lin, L.S. *Tetrahedron Lett.* **2006**, *47*, 3303.

²⁹¹ Zhu, Y.-Z.; Cai, C. *Synth. Commun.* **2008**, *38*, 2753; Yeung, P.Y.; So, C.M.; Lau, C.-P.; Kwong, F.Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 8918.

²⁹² Zhang, Z.; Liebeskind, L.S. *Org. Lett.* **2006**, *8*, 4331.

²⁹³ Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chemistry: European J.* **2005**, *11*, 2483.

²⁹⁴ Arvela, R.K.; Leadbeater, N.E. *J. Org. Chem.* **2003**, *68*, 9122.

²⁹⁵ Chambers, M.R.I.; Widdowson, D.A. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1365; Takagi, K.; Sakakibara, Y. *Chem. Lett.* **1989**, 1957.

²⁹⁶ Liskey, C.W.; Liao, X.; Hartwig, J.F. *J. Am. Chem. Soc.* **2010**, *132*, 11389.

²⁹⁷ Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* **1975**, *40*, 2351.

²⁹⁸ Uemura, S.; Ikeda, Y.; Ichikawa, K. *Tetrahedron* **1972**, *28*, 3025.

²⁹⁹ Ushijima, S.; Togo, H. *Synlett* **2010**, 1067; Ushijima, S.; Togo, H. *Synlett* **2010**, 1562.

³⁰⁰ Sato, N. *Tetrahedron Lett.* **2002**, *43*, 6403.

³⁰¹ Letsinger, R.L.; Colb, A.L. *J. Am. Chem. Soc.* **1972**, *94*, 3665.

³⁰² Alberico, D.; Scott, M.E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

cyclization of organolithium reagents to aromatic rings.³⁰³ Noncatalyzed coupling reactions of aryllithium reagents and haloarenes can proceed via the well-known aryne route, but a novel addition–elimination pathway is possible when substituents facilitate a chelation-driven nucleophilic substitution pathway.³⁰⁴ Such noncatalyzed coupling reactions often proceed with high regioselectivity and high yield.³⁰⁴ 2-Bromopyridine reacts with pyrrolidine, at 130 °C with microwave irradiation, to give 2-(2-pyrrolidino)pyridine.³⁰⁵ Aryl iodides undergo homocoupling to give the biaryl by heating with triethylamine in an ionic liquid.³⁰⁶ Note that alkyl bromides are coupled to pyrrolidine by heating in an ionic liquid.³⁰⁷

Palladium-catalyzed coupling reactions that generate biaryls are increasingly important in synthesis. Aryl halides undergo homocoupling to give the biaryl with a Pd³⁰⁸ or a Ni catalyst.³⁰⁹ Aryl iodides have been coupled to form symmetric biphenyls with a Pd catalyst,³¹⁰ and homocoupling occurs with aryl triflates under electrolysis conditions with a Pd catalyst.³¹¹ A recyclable Pd catalyst for use in ionic liquids has been developed.³¹² Other alternative solvents include PEG.³¹³

Thiophene derivatives,³¹⁴ pyrrole,³¹⁵ azoles,³¹⁶ quinoline,³¹⁷ and indolizine³¹⁸ have been coupled to aryl halides using a Pd catalyst. Fused polycyclic aromatic compounds can also be prepared from halobiaryls.³¹⁹ Trimethylsilylpyridine derivatives are coupled to aryl halides in the presence of a Pd catalyst.³²⁰ A related reaction is the Pd catalyzed decarboxylative coupling of arylcarboxylic acids with aryl iodides.³²¹

Palladium catalysts are often used in conjunction with another metal compound or complex. Arylgermanium compounds are coupled with aryl iodides using tetrabutylammonium fluoride and a Pd catalyst.³²² Homocoupling of triphenylbismuth is known,³²³ as well as the coupling of arylbismuth reagents to arylodonium salts³²⁴ and to aryltin compounds³²⁵ with Pd compounds or complexes. Aryl triflates were coupled to triphenylbismuth using a Pd catalyst.³²⁶ Specialized arylbismuth compounds

³⁰³ See Clayden, J.; Kenworthy, M.N. *Synthesis* **2004**, 1721.

³⁰⁴ See Becht, J.-M.; Gissot, A.; Wagner, A.; Mioskowski, C. *Chem. Eur. J.* **2003**, *9*, 3209.

³⁰⁵ Narayan, S.; Seelhammer, T.; Gawley, R.E. *Tetrahedron Lett.* **2004**, *45*, 757.

³⁰⁶ Park, S.B.; Alper, H. *Tetrahedron Lett.* **2004**, *45*, 5515.

³⁰⁷ Jorapur, Y.R.; Lee, C.-H.; Chi, D.Y. *Org. Lett.* **2005**, *7*, 1231.

³⁰⁸ Silveira, P.B.; Lando, V.R.; Dupont, J.; Monteiro, A.L. *Tetrahedron Lett.* **2002**, *43*, 2327; Kuroboshi, M.; Waki, Y.; Tanaka, H. *Synlett* **2002**, 637. See also, Venkatraman, S.; Li, C.-J. *Org. Lett.* **1999**, *1*, 1133.

³⁰⁹ Leadbeater, N.E.; Resouly, S.M. *Tetrahedron Lett.* **1999**, *40*, 4243.

³¹⁰ Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, *39*, 2559.

³¹¹ de Franca, K.W.R.; Navarro, M.; Léonel, É.; Durandetti, M.; Nédélec, J.-Y. *J. Org. Chem.* **2002**, *67*, 1838.

³¹² Wang, R.; Twamley, B.; Shreeve, J.M. *J. Org. Chem.* **2006**, *71*, 426.

³¹³ Wang, L.; Zhang, Y.; Liu, L.; Wang, Y. *J. Org. Chem.* **2006**, *71*, 1284.

³¹⁴ Glover, B.; Harvey, K.A.; Liu, B.; Sharp, M.J.; Tymoschenko, M.F. *Org. Lett.* **2003**, *5*, 301.

³¹⁵ See Rieth, R.D.; Mankand, N.P.; Calimano, E.; Sadighi, J.P. *Org. Lett.* **2004**, *6*, 3981.

³¹⁶ Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607.

³¹⁷ Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 3547.

³¹⁸ Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159.

³¹⁹ Liu, Z.; Zhang, X.; Larock, R.C. *J. Am. Chem. Soc.* **2005**, *127*, 15716.

³²⁰ Napier, S.; Marcuccio, S.M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2008**, *49*, 6314. See also, Denmark, S.E.; Smith, R.C.; Chang, W.-T.T.; Muhuhi, J.M. *J. Am. Chem. Soc.* **2009**, *131*, 3104.

³²¹ Wang, Z.; Ding, Q.; He, X.; Wu, J. *Tetrahedron* **2009**, *65*, 4635.

³²² Nakamura, T.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3165.

³²³ Ohe, T.; Tanaka, T.; Kuroda, M.; Cho, C.S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1851.

³²⁴ Kang, S.-K.; Ryu, H.-C.; Kim, J.-W. *Synth. Commun.* **2001**, *31*, 1021.

³²⁵ Wang, J.; Scott, A.I. *Tetrahedron Lett.* **1996**, *37*, 3247; Kim, Y.M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696.

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have been used with a Pd catalyst to convert aryl chlorides to biaryls.³²⁷ An aryltin–aryl halide coupling has been done in ionic liquids.³²⁸ Aryl halides react with cyclopentadiene and Cp_2ZrCl_2 and a Pd catalyst to give pentaphenylcyclopentadiene.³²⁹ The homocoupling of arylzinc iodides with a Pd catalyst has been reported.³³⁰ In a related reaction, arylsulfonyl chlorides also react with ArSnBu_3 with Pd and Cu catalysts to give the biaryl.³³¹

Aryl triflates (halides) couple with $\text{ArZn}(\text{halide})$ reagents in the presence of a Ni catalyst.³³² A homocoupling-type reaction was reported in which PhSnBu_3 was treated with 10% CuCl_2 , 0.5 equiv of iodine, and heated in DMF to give biphenyl.³³³ Similar coupling was accomplished with aryltellurium compounds.³³⁴ A Co(II) catalyzed cross-coupling of arylcopper compounds with aryl halides gives the corresponding biaryl.³³⁵ Another homocoupling reaction of pyridyl bromides was reported using NiBr_2 under electrolytic conditions. Both alkylmanganese compounds (RMnCl)³³⁶ and Ph_3In ³³⁷ react with aryl halides or aryl triflates to give the arene. Aryl halides also react with phenols to form biaryls using a Rh catalyst.³³⁸ Diaryliodonium salts react with $\text{PhPb}(\text{OAc})_3$ and a Pd catalyst to give the biaryl.³³⁹ Coupling of trialkylbismuth compounds with aryl halides leads to the arene in the presence of a Pd catalyst.³⁴⁰ A cross-coupling reaction of benzylium compounds and aryl halides in the presence of a Pd catalyst has been reported.³⁴¹

Grignard reagents couple with aryl halides without a Pd catalyst, by the benzyne mechanism,³⁴² but metal-catalyzed reactions are known. Typical catalysts include Fe,³⁴³ Ni,³⁴⁴ Co,³⁴⁵ or Ti,³⁴⁶ and Pd-catalyzed reactions are important.³⁴⁷ Aryl *Grignard reagents* react with aryltrimethylammonium triflates in the presence of a Pd catalyst to give the corresponding biaryl.³⁴⁸ Arylmagnesium halides couple with aryl tosylates in the presence

³²⁷ Yamazaki, O.; Tanaka, T.; Shimada, S.; Suzuki, Y.; Tanaka, M. *Synlett* **2004**, 1921.

³²⁸ Grasa, G.A.; Nolan, S.P. *Org. Lett.* **2001**, 3, 119.

³²⁹ Dyker, G.; Heiermann, J.; Miura, M.; Inoh, J.-I.; Pivsa-Ast, S.; Satoh, T.; Nomura, M. *Chem. Eur. J.* **2000**, 6, 3426.

³³⁰ With NCS, Hossain, K.M.; Kameyama, T.; Shibata, T.; Takagi, K. *Bull. Chem. Soc. Jpn.* **2001**, 74, 2415. See also, Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* **2000**, 41, 4831.

³³¹ Dubbaka, S.R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, 125, 15292.

³³² Chen, C. *Synlett* **2000**, 1491. See Walla, P.; Kappe, C.O. *Chem. Commun.* **2004**, 564.

³³³ Kang, S.-K.; Baik, T.-G.; Jiao, X.H.; Lee, Y.-T. *Tetrahedron Lett.* **1999**, 40, 2383.

³³⁴ Kang, S.-K.; Lee, S.-W.; Kim, M.-S.; Kwon, H.S. *Synth. Commun.* **2001**, 31, 1721.

³³⁵ Korn, T.J.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, 44, 2947.

³³⁶ Cahiez, G.; Luart, D.; Lecomte, F. *Org. Lett.* **2004**, 6, 4395.

³³⁷ Pérez, I.; Sestelo, J.P.; Sarandeses, L.A. *J. Am. Chem. Soc.* **2001**, 123, 4155.

³³⁸ Bedford, R.B.; Limmert, M.E. *J. Org. Chem.* **2003**, 68, 8669.

³³⁹ Kang, S.-K.; Choi, S.-C.; Baik, T.-G. *Synth. Commun.* **1999**, 29, 2493.

³⁴⁰ Gagnon, A.; Duplessis, M.; Alsabeh, P.; Barabé, F. *J. Org. Chem.* **2008**, 73, 3604.

³⁴¹ Chupak, L.S.; Wolkowski, J.P.; Chantigny, Y.A. *J. Org. Chem.* **2009**, 74, 1388.

³⁴² Du, C.F.; Hart, H.; Ng, K.D. *J. Org. Chem.* **1986**, 51, 3162.

³⁴³ Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, 7, 1943.

³⁴⁴ Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, 127, 17978.

³⁴⁵ Korn, T.J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, 1892.

³⁴⁶ Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2000**, 56, 9601.

³⁴⁷ Manabe, K.; Ishikawa, S. *Synthesis* **2008**, 2645.

³⁴⁸ Reeves, J.T.; Fandrick, D.R.; Tan, Z.; Song, J.J.; Lee, H.; Yee, N.K.; Senanayake, C.H. *Org. Lett.* **2010**, 12, 4388.

of a Pd catalyst to give unsymmetrical biaryls,³⁴⁹ and to halopyridines to give the arylated pyridine.³⁵⁰ Aryl *Grignard reagents* are coupled to arylodonium salts, with ZnCl₂ and a Pd catalyst, to give the biaryl.³⁵¹

The coupling reaction of an excess of a *Grignard reagent* (RMgX) with methoxy aromatic compounds, when the aromatic ring contains multiple alkoxy groups, proceeds with replacement of the OMe group by R.³⁵² Aryl sulfones were coupled with aryl *Grignard reagents* in the presence of a Ni catalyst.³⁵³

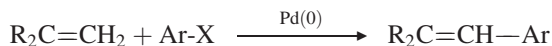
Unsymmetrical binaphthyls were synthesized by photochemically stimulated reaction of naphthyl iodides with naphthoxide ions in an S_{RN}1 reaction.³⁵⁴ Methyl chloroacetate coupled with aryl iodides under electrolysis conditions, using a Ni catalyst.³⁵⁵ Unsymmetrical biaryls were prepared from two aryl iodides using a CuI catalyst and microwave irradiation.³⁵⁶

It is possible to couple metalated alkyl compounds to aryl compounds. Alkyl halides³⁵⁷ are coupled to aryl halide using a Ni catalyzed reductive cross coupling.³⁵⁸ Organozinc compounds, available by reaction of an alkyl halide and zinc metal, are coupled to aryl halides using a Pd- catalyst.³⁵⁹ Specialized alkyl indium complexes have been used with a Pd catalyst to give arenes.³⁶⁰ Iron complexes have been used for coupling reactions.³⁶¹ Triarylbiomuth compounds are coupled with aryl bromides in the presence of a Pd catalyst.³⁶² Organolithium reagents are coupled to aryl bromides in the presence of a Ni catalyst,³⁶³ as are arylzinc compounds.³⁶⁴ The lithium enolate anion of an ester was coupled to an aryl halide using a Pd catalyst.³⁶⁵ Other ketones can be coupled to aryl triflates, in the presence of a Pd catalyst, and with good enantioselectivity.³⁶⁶

OS VI, 916; VIII, 430, 586; X, 9, 448.

13-10 Arylation and Alkylation of Alkenes

Alkylation or Alkyl-de-hydrogenation, and so on



³⁴⁹ Roy, A.H.; Hartwig, J.F. *J. Am. Chem. Soc.* **2003**, 125, 8704.

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³⁵² Kojima, T.; Ohishi, T.; Yamamoto, I.; Matsuoka, T.; Kotsuki, H. *Tetrahedron Lett.* **2001**, 42, 1709.

³⁵³ Clayden, J.; Cooney, J.J.A.; Julia, M. *J. Chem. Soc. Perkin Trans. 1* **1995**, 7.

³⁵⁴ Beugelmans, R.; Bois-Choussy, M.; Tang, Q. *Tetrahedron Lett.* **1988**, 29, 1705. See Pierini, A.B.; Baumgartner, M.T.; Rossi, R.A. *Tetrahedron Lett.* **1988**, 29, 3429.

³⁵⁵ Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *J. Org. Chem.* **1996**, 61, 1748.

³⁵⁶ He, H.; Wu, Y.-J. *Tetrahedron Lett.* **2003**, 44, 3445.

³⁵⁷ For a review of coupling reactions using various metals, see Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, 41, 1545.

³⁵⁸ Everson, D.A.; Shrestha, R.; Weix, D.J. *J. Am. Chem. Soc.* **2010**, 132, 920.

³⁵⁹ Hama, T.; Culkin, D.A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2006**, 128, 4976.

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³⁶¹ Sherry, B.D.; Fürstner, A. *Acc. Chem. Res.* **2008**, 41, 1500.

³⁶² Rao, M.L.N.; Banerjee, D.; Jadhav, D.N. *Tetrahedron Lett.* **2007**, 48, 2707.

³⁶³ Jhaveri, S.B.; Carter, K.R. *Chemistry: European J.* **2008**, 14, 685.

³⁶⁴ Wang, L.; Wang, Z.-X. *Org. Lett.* **2007**, 9, 4335.

³⁶⁵ Moradi, W.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2001**, 123, 7996.

³⁶⁶ Liao, X.; Weng, Z.; Hartwig, J.F. *J. Am. Chem. Soc.* **2008**, 130, 195.

Arylation of alkenes³⁶⁷ is an important reaction using an “arylpalladium” reagent, typically generated *in situ* from an aryl halide or other suitably functionalized aromatic compound and a Pd catalyst.³⁶⁸ The Pd catalyzed aryl–alkene coupling reaction is known as *the Heck reaction*.³⁶⁹ Mizoroki³⁷⁰ had earlier described the coupling between iodobenzene and styrene to form stilbene in methanol at 120 °C in the presence of potassium acetate and a palladium chloride catalyst leading some to call this the *Mizoroki–Heck reaction*. The reaction works best with aryl iodides, but conditions are available for aryl bromides and aryl chlorides.³⁷¹ Aryldiazonium salts (see Reactions **13-25** and **13-26**) have also been used.³⁷² Activated aromatic compounds couple readily,³⁷³ but unactivated aromatic compounds often require special reaction conditions. The *Heck reaction* can be done with heterocyclic compounds,³⁷⁴ and heteroaryl halides can be used in the coupling reaction.³⁷⁵ Intramolecular *Heck reactions* are increasingly important.³⁷⁶ A silane-tethered, intramolecular *Heck reaction* is known.³⁷⁷ Other nucleophiles can be coupled to aryl halides.³⁷⁸

Phosphine-free catalysts,³⁷⁹ halogen-free reactions,³⁸⁰ and base-free reactions³⁸¹ have been developed for the *Heck reaction*. Improvements to the Pd catalyst system are constantly being reported,³⁸² including polymer-supported³⁸³ silica-supported,³⁸⁴ and

³⁶⁷ See Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, **1985**, pp. 179–321; Ryabov, A.D. *Synthesis* **1985**, 233; Heck, R.F. *Org. React.* **1982**, 27, 345; Moritani, I.; Fujiwara, Y. *Synthesis* **1973**, 524. See Cabri, W.; Candiani, I. *Accts. Chem. Res.* **1995**, 28, 2.

³⁶⁸ See Heck, R.F. *Acc. Chem. Res.* **1979**, 12, 146; Kozhevnikov, I.V. *Russ. Chem. Rev.* **1983**, 52, 138. See also, Spencer, A. *J. Organomet. Chem.* **1983**, 258, 101; Andersson, C.; Karabelas, K.; Hallberg, A.; Andersson, C. *J. Org. Chem.* **1985**, 50, 3891; Larock, R.C.; Johnson, P.L. *J. Chem. Soc. Chem. Commun.* **1989**, 1368.

³⁶⁹ See Alonso, F.; Beletskaya, I.P.; Yus, M. *Tetrahedron* **2005**, 61, 11771.

³⁷⁰ Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn* **1971**, 4, 581.

³⁷¹ See Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* **2002**, 41, 4176.

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³⁷⁴ Pyridines: Draper, T.L.; Bailey, T.R. *Synlett* **1995**, 157.

³⁷⁵ See Park, S.B.; Alper, H. *Org. Lett.* **2003**, 5, 3209. See also, Zeni, G.; Larock, R.C. *Chem. Rev.* **2004**, 104, 2285.

³⁷⁶ See Firmansjah, L.; Fu, G.C. *J. Am. Chem. Soc.* **2007**, 129, 11340. Also see, Echavarren, A.M.; Gómez-Lor, B.; González, J.J.; de Frutos, Ó. *Synlett* **2003**, 585.

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³⁷⁸ For a review, see Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, 58, 2041.

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³⁸² Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, 4, 3031; Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2002**, 43, 2191. For the use of palladium nanoparticles, see Calò, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. *J. Org. Chem.* **2003**, 68, 2929. See Lindh, J.; Enquist, P.-A.; Pilotti, Å.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, 72, 7957. See also Seki, M. *Synthesis* **2006**, 2975.

³⁸³ Kim, J.-H.; Kim, J.W.; Shokouhimehr, M.; Lee, Y.-S. *J. Org. Chem.* **2005**, 70, 6714.

³⁸⁴ Polshettiwar, V.; Molnár, Á. *Tetrahedron* **2007**, 63, 6949.

recoverable catalysts.³⁸⁵ Considerable work has been done to study and improve the ligand.³⁸⁶ Efforts have been made to produce a homogeneous catalyst for the Heck reaction.³⁸⁷ The *Heck reaction* can be done in aq media,³⁸⁸ in perfluorinated solvents,³⁸⁹ in polyethylene glycol,³⁹⁰ in neat tricaprylmethylammonium chloride,³⁹¹ and in supercritical CO₂ (See Sec. 9.D.ii).³⁹² The reaction has been done on solid support,³⁹³ including Montmorillonite clay,³⁹⁴ glass beads,³⁹⁵ on a reverse-phase silica support,³⁹⁶ and using microwave irradiation.³⁹⁷ A microwave irradiated *Heck coupling* was done in water using a Pd catalyst.³⁹⁸ A noncatalytic reaction was reported using supercritical water.³⁹⁹ The effects of high pressure have been studied.⁴⁰⁰ The *Heck reaction* has also been done in ionic liquids,⁴⁰¹ and it is known that the nature of the halide is important in such reactions.⁴⁰² Ionic liquids have been shown to actually promote the *Heck reaction*.⁴⁰³

Ethylene is the most reactive alkene, and increasing substitution lowers the reactivity. Coupling generally takes place at the less highly substituted side of the double bond.⁴⁰⁴ Unlike the diazonium coupling reaction in Reaction 13-26, the *Heck reaction* is not limited

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³⁸⁸ See Botella, L.; Nájera, C. *J. Org. Chem.* **2005**, 70, 4360; Zhang, Z.; Zha, Z.; Gan, C.; Pan, C.; Zhou, Y.; Wang, Z.; Zhou, M.-M. *J. Org. Chem.* **2006**, 71, 4339; Bhattacharya, S.; Srivastava, A.; Sengupta, S. *Tetrahedron Lett.* **2005**, 46, 3557.

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³⁹⁶ Anson, M.S.; Mirza, A.R.; Tonks, L.; Williams, J.M.J. *Tetrahedron Lett.* **1999**, 40, 7147.

³⁹⁷ Arvela, R.K.; Leadbeater, N.E. *J. Org. Chem.* **2005**, 70, 1786; Leadbeater, N.E.; Williams, V.A.; Barnard, T. M.; Collins, Jr., M.J. *Synlett* **2006**, 2953; Declerck, V.; Martinez, J.; Lamaty, F. *Synlett* **2006**, 3029; Zhu, M.; Song, Y.; Cao, Y. *Synthesis* **2007**, 853; Du, L.-H.; Wang, Y.-G. *Synth. Commun.* **2007**, 37, 217. See Nilsson, P.; Gold, H.; Larhed, M.; Hallberg, A. *Synthesis* **2002**, 1611.

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³⁹⁹ Zhang, R.; Sato, O.; Zhao, F.; Sato, M.; Ikushima, Y. *Chem. Eur. J.* **2004**, 10, 1501.

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⁴⁰² Handy, S.T.; Okello, M. *Tetrahedron Lett.* **2003**, 44, 8395.

⁴⁰³ Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, 127, 751.

⁴⁰⁴ Heck, R.F. *J. Am. Chem. Soc.* **1969**, 91, 6707; **1971**, 93, 6896.

to activated substrates. Both electron-deficient alkenes (e.g., acrylates),⁴⁰⁵ and electron-rich alkenes⁴⁰⁶ undergo the *Heck reaction*. The substrate can be an unactivated alkene,⁴⁰⁷ and the alkene can contain a variety of functional groups (e.g., esters, ether,⁴⁰⁸ enol ethers,⁴⁰⁹ enamides,⁴¹⁰ carboxyl, phenolic, or cyano groups).⁴¹¹ The aryl halide or aryl triflate can be coupled to dienes,⁴¹² allenes,⁴¹³ allylic acetates,⁴¹⁴ allylic silanes,⁴¹⁵ allylic amines,⁴¹⁶ vinyl phosphonate esters,⁴¹⁷ and with terminal alkynes.⁴¹⁸ Aryliodonium salts can be coupled to conjugated alkenes in a *Heck-like* manner using a Pd catalyst.⁴¹⁹ Double-coupling reactions have been reported, generating diaryl aromatic compounds.⁴²⁰ *Heck-type reactions* have been reported with imines.⁴²¹

Control of regiochemistry is a serious problem in the coupling to unsymmetrical alkenes. Some regioselectivity can be obtained by the use of alkenes attached to an auxiliary coordinating group,⁴²² or by using special ligands and acrylate or styrene as substrates.⁴²³ Neighboring-group effects play a role in the *Heck reaction*.⁴²⁴ Steric effects are thought to control regioselectivity,⁴²⁵ but electronic influences have also been proposed.⁴²⁶ It has been shown that the presence of steric effects generally improves 1,2-selectivity, and that electronic effects can be used to favor 1,2- or 2,1-selectivity.⁴²⁷ A 1,4-Pd migration between the *o*- and *o'*-positions of biaryls has been observed in organopalladium intermediates derived from *o*-halobiaryls.⁴²⁸ Migration of the double bond is a problem in some cases, and reaction conditions play a significant role in such migrations.⁴²⁹ It has been

⁴⁰⁵ Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372.

⁴⁰⁶ Mo, J.; Xiao, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 4152.

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⁴²¹ Li, Z.; Fu, Y.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. *Chemistry: Asian J.* **2010**, *5*, 1475.

⁴²² Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217 and earlier references therein.

⁴²³ Ludwig, M.; Strömberg, S.; Svensson, M.; Åkermark, B. *Organometallics* **1999**, *18*, 970.

⁴²⁴ Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783.

⁴²⁵ Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, **1987**; Cornils, B.; Herrmann, A.W., Eds., *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley, NY, **1996**; Vol. 2; Heck, R.F. *Acc. Chem. Res.* **1979**, *12*, 146.

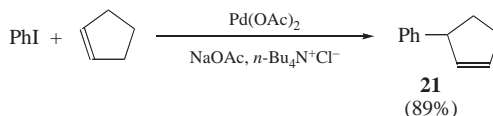
⁴²⁶ Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

⁴²⁷ von Schenck, H.; Åkermark, B.; Svensson, M. *J. Am. Chem. Soc.* **2003**, *125*, 3503.

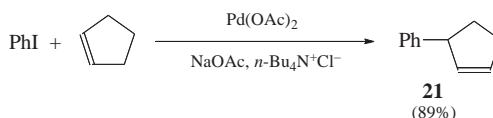
⁴²⁸ Campo, M.A.; Zhang, H.; Yao, T.; Ibdah, A.; McCulla, R.D.; Huang, Q.; Zhao, J.; Jenks, W.S.; Larock, R.C. *J. Am. Chem. Soc.* **2007**, *129*, 6298.

⁴²⁹ Fall, Y.; Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* **2007**, 1683.

reported that double-bond isomerization can be suppressed in intramolecular *Heck reactions* done in supercritical CO₂ (see Sec. 9.D.ii).⁴³⁰



The Pd catalyzed reactions are usually stereospecific,⁴³¹ yielding products expected from syn addition followed by syn elimination.⁴³² Because the product is formed by an elimination step, with suitable substrates, double-bond migration can occur, resulting in allylic rearrangement (as in the reaction of cyclopentene and iodobenzene to give **21**).⁴³³ Asymmetric *Heck reactions* are known,⁴³⁴ including asymmetric intramolecular *Heck reactions*.⁴³⁵ Dihydrofurans react with aryl triflates and a Pd catalyst that includes a chiral ligand, to give the 5-phenyl-3,4-dihydrofuran with good enantioselectivity.⁴³⁶ A similar reaction was reported for an *N*-carbamoyl dihydropyrrole.⁴³⁷



An addition–elimination mechanism (addition of ArPdX followed by elimination of HPdX) operates in most cases.⁴³⁸ In the conventionally accepted reaction mechanism,⁴³⁹ which is shown,⁴⁴⁰ a four-coordinate arylPd(II) intermediate (a palladacycle)⁴⁴¹ is formed by oxidative addition of the aryl halide to a Pd(0) complex prior to olefin addition.⁴⁴² This description suggests that cleavage of the dimeric precursor complex, reduction

⁴³⁰ Shezad, N.; Clifford, A.A.; Rayner, C.M. *Tetrahedron Lett.* **2001**, 42, 323.

⁴³¹ Su, Y.; Jiao, N. *Org. Lett.* **2009**, 11, 2980.

⁴³² Heck, R.F. *J. Am. Chem. Soc.* **1969**, 91, 6707; See Masllorens, J.; Moreno-Mañas, M.; Pla-Quintana, A.; Plexats, R.; Roglans, A. *Synthesis* **2002**, 1903. See Tan, Z.; Negishi, E. *Angew. Chem. Int. Ed.* **2006**, 45, 762.

⁴³³ Larock, R.C.; Baker, B.E. *Tetrahedron Lett.* **1988**, 29, 905. Also see, Larock, R.C.; Gong, W.H.; Baker, B.E. *Tetrahedron Lett.* **1989**, 30, 2603.

⁴³⁴ Wu, W.-Q.; Peng, Q.; Dong, D.-X.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2008**, 130, 9717.

⁴³⁵ Lapierre, A.J.B.; Geib, S.J.; Curran, D.P. *J. Am. Chem. Soc.* **2007**, 129, 494. See Dounay, A.B.; Overman, L.E. *Chem. Rev.* **2002**, 102, 2945.

⁴³⁶ Gilbertson, S.R.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, 66, 7240; Gilbertson, S.R.; Fu, Z. *Org. Lett.* **2001**, 3, 161; Hennessy, A.J.; Connolly, D.J.; Malone, Y.M.; Buiry, P.J. *Tetrahedron Lett.* **2000**, 41, 7757.

⁴³⁷ Servino, E.A.; Correia, C.R.D. *Org. Lett.* **2000**, 2, 3039.

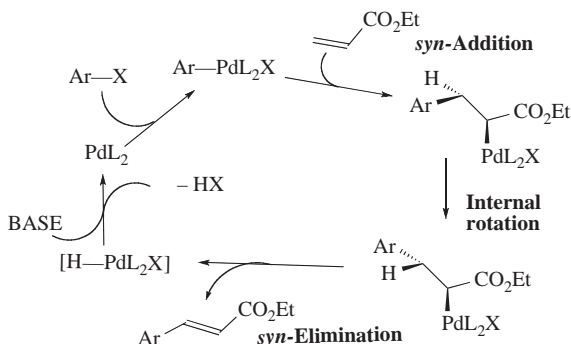
⁴³⁸ Heck, R.F.; Nolley, Jr., J.P. *J. Org. Chem.* **1972**, 3720; Henriksen, S.T.; Norrby, P.-O.; Kaukoranta, P.; Andersson, P.G. *J. Am. Chem. Soc.* **2008**, 130, 10414.

⁴³⁹ Heck, R.F. *Comprehensive Organic Synthesis* Vol. 4, Trost, B.M.; Fleming, I., Eds., Pergamon, Oxford, NY, **1991**, p. 833; de Meijere, A.; Meyer, F.E. *Angew. Chem. Int. Ed.* **1994**, 33, 2379; Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, 28, 2; Crisp, G.T. *Chem. Soc. Rev.* **1998**, 27, 427.

⁴⁴⁰ See Diederich, F.; Stang, P.J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **1998**; Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, **1985**.

⁴⁴¹ Masselot, D.; Charmant, J.P.H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, 128, 694.

⁴⁴² See Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Chemistry: European J.* **2007**, 13, 2002.



of Pd²⁺, and ligand dissociation combine to give a viable catalytic species.⁴⁴³ σ -Alkyl Pd(II) intermediates are thought to be involved.⁴⁴⁴ An analysis of reaction kinetics under dry conditions was reported.⁴³⁵ In this study, the mechanism requires a first-order dependence on olefin concentration, and anomalous kinetics may be observed when the rate-limiting step is not directly on the catalytic cycle.⁴³⁵ The mechanism requires a proton abstraction step, and there are substituent effects for this step.⁴⁴⁵ A mechanistic study has been reported for the Pd catalyzed decarboxylative reaction of alkenes and arylcarboxylic acids.⁴⁴⁶ The kinetics and mechanism of the *Heck reaction* promoted by a C—N palladacycle has been studied.⁴⁴⁷ The mechanistic implications of asymmetric Heck reactions have been examined.⁴⁴⁸

There are a number of variations of this reaction, including the use of transition metal catalysts other than Pd. Rhodium-catalyzed *Heck reactions* are known,⁴⁴⁹ and there are Co-,⁴⁵⁰ Ru-,⁴⁵¹ and Ni catalyzed variations.⁴⁵² Iron-mediated arylation of alkenes has been reported,⁴⁵³ and vinylgermanes are coupled to aryl halides with a Pd catalyst.⁴⁵⁴ Aryl chlorides were coupled to conjugated esters using a RuCl₃·3 H₂O, in an atmosphere of O₂ and CO.⁴⁵⁵ Aryl halides have been coupled to allenyltin compounds (C=C=C-SnR₃).⁴⁵⁶ Divinylindium chloride [(CH₂=CH)₂InCl] reacted with an aryl iodide in aq THF with a Pd catalyst to give the styrene derivative.⁴⁵⁷ Trialkenylindium reagents reacted similarly with

⁴⁴³ Rosner, T.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, 123, 4621.

⁴⁴⁴ For related work, see Kalyani, D.; Sanford, M.S. *J. Am. Chem. Soc.* **2008**, 130, 2150.

⁴⁴⁵ García-Cuadrado, D.; de Mendoza, P.; Braga, A.C.; Maseras, F.; Echavarren, A.M. *J. Am. Chem. Soc.* **2007**, 129, 6880.

⁴⁴⁶ Tanaka, D.; Romeril, S.P.; Myers, A.G. *J. Am. Chem. Soc.* **2005**, 127, 10323.

⁴⁴⁷ Consorti, C.S.; Flores, F.R.; Dupont, J. *J. Am. Chem. Soc.* **2005**, 127, 12054.

⁴⁴⁸ Hii, K.K.; Claridge, T.D.W.; Brown, J.M.; Smith, A.; Deeth, R.J. *Helv. Chim. Acta* **2001**, 84, 3043.

⁴⁴⁹ Kurahashi, T.; Shinokubo, H.; Osuka, A. *Angew. Chem. Int. Ed.* **2006**, 45, 6336.

⁴⁵⁰ Zhou, P.; Li, Y.; Sun, P.; Zhou, J.; Bao, J. *Chem. Commun.* **2007**, 1418; Amatore, M.; Gosmini, C.; Périchon, J. *Eur. J. Org. Chem.* **2005**, 989.

⁴⁵¹ Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, 129, 9858.

⁴⁵² Inamoto, K.; Kuroda, J.; Danjo, T.; Sakamoto, T. *Synlett* **2005**, 1624; Denmark, S.E.; Butler, C.R. *Chem. Commun.* **2009**, 20.

⁴⁵³ Wen, J.; Zhang, J.; Chen, S.-Y.; Li, J.; Yu, X.-Q. *Angew. Chem. Int. Ed.* **2008**, 47, 8897; Liu, W.; Cao, H.; Lei, A. *Angew. Chem. Int. Ed.* **2010**, 49, 2004.

⁴⁵⁴ Torres, N.M.; Lavis, J.M.; Maleczka, Jr., R.E. *Tetrahedron Lett.* **2009**, 50, 4407.

⁴⁵⁵ Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, 123, 337.

⁴⁵⁶ Huang, C.-W.; Shanmugasundaram, M.; Chang, H.-M.; Cheng, C.-H. *Tetrahedron* **2003**, 59, 3635.

⁴⁵⁷ Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, 3, 1997.

aryl halides in the presence of a Pd catalyst.⁴⁵⁸ Arylzinc chlorides (ArZnCl) were coupled to vinyl chlorides using a Pd catalyst,⁴⁵⁹ and vinyl zinc compounds were coupled to aryl iodides.⁴⁶⁰ In the presence of trimethylsilylmagnesium chloride, primary alkyl halides coupled to aryl alkenes to give the substituted alkene (R'—CH=CHAr), using a Co catalyst.⁴⁶¹

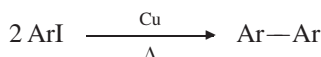
Potassium vinyltrifluoroborates can be coupled to aryl halides in *Heck-like* coupling reactions.⁴⁶² Likewise, the reaction of aryltrifluoroborates with vinyl halides, in the presence of a Pd catalyst, leads to the aryl alkene.⁴⁶³ In a related reaction, alkyltrifluoroborates react with aryl halides in the presence of a Pd and a Rh catalyst.⁴⁶⁴

Although related to chemistry found in Reaction 10-57, metal-catalyzed alkylation reactions are easily viewed as *Heck-like* reactions. For that reason, they are discussed here. Alkyl halides are coupled to alkenes to form substituted alkenes using a Co catalyst, promoted by Me₃SiCH₂MgCl.⁴⁶⁵ Alkylation requires that the alkyl group lacks a β-hydrogen, and the reaction is successful for the introduction of methyl, benzyl, and neopentyl groups.⁴⁶⁶ However, vinylic groups, even those possessing β-hydrogen atoms, have been successfully introduced (to give 1,3-dienes) by the reaction of the alkene with a vinylic halide in the presence of a trialkylamine and a Pd(0) catalyst.⁴⁶⁷

OS VI, 815; VII, 361; 81, 42, 54, 63, 263

13-11 Homo-Coupling of Aryl Halides: The Ullmann Reaction

de-halogen-coupling



The coupling of aryl halides with copper is called the *Ullmann reaction*.⁴⁶⁸ The reaction is clearly related to Reaction 13-9, but involves aryl copper intermediates. The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls.⁴⁶⁹ When a mixture of two different aryl halides is used, there are three possible products, but often only one is obtained. The best leaving group is iodo, and the reaction is most often done on aryl iodides, but bromides, chlorides, and even thiocyanates have been used. New ligands have been developed to promote the reaction, including an air-stable

⁴⁵⁸ Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* **2003**, 5, 2405.

⁴⁵⁹ Dai, C.; Fu, G.C. *J. Am. Chem. Soc.* **2001**, 123, 2719.

⁴⁶⁰ Jalil, A.A.; Kurono, N.; Tokuda, M. *Synlett* **2001**, 1944.

⁴⁶¹ Ikeda, Y.; Makamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, 124, 6514.

⁴⁶² Molander, G.A.; Brown, A.R. *J. Org. Chem.* **2006**, 71, 9681. Also see Alacid, E.; Njara, C. *J. Org. Chem.* **2009**, 74, 2321.

⁴⁶³ Molander, G.A.; Fumagalli, T. *J. Org. Chem.* **2006**, 71, 5743.

⁴⁶⁴ Molander, G.A.; Jean-Gérard, L. *J. Org. Chem.* **2007**, 72, 8422.

⁴⁶⁵ Affo, W.; Ohmiya, H.; Fujioka T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, 128, 8068.

⁴⁶⁶ Heck, R.F. *J. Organomet. Chem.* **1972**, 37, 389; Heck, R.F.; Nolley, Jr., J.P. *J. Org. Chem.* **1972**, 3720.

⁴⁶⁷ Kim, J.I.; Patel, B.A.; Heck, R.F. *J. Org. Chem.* **1981**, 46, 1067; Heck, R.F. *Pure Appl. Chem.* **1981**, 53, 2323. See also, Jeffery, T. *J. Chem. Soc. Chem. Commun.* **1991**, 324; Larock, R.C.; Gong, W.H. *J. Org. Chem.* **1989**, 54, 2047. Also see Varma, R.S.; Naicker, K.P.; Liesen, P.J. *Tetrahedron Lett.* **1999**, 40, 2075.

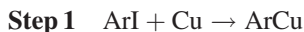
⁴⁶⁸ See Fanta, P.E. *Synthesis* **1974**, 9; Goshav, M.; Otroshchenko, O.S.; Sadykov, A.S. *Russ. Chem. Rev.* **1972**, 41, 1046.

⁴⁶⁹ See Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem, Int. Ed.* **1990**, 29, 977. Also see, Meyers, A.I.; Price, A. *J. Org. Chem.* **1998**, 63, 412.

diazaphospholane ligand.⁴⁷⁰ The Cu catalyst has been immobilized.⁴⁷¹ Intramolecular reactions are known.⁴⁷² The coupling reaction can be applied to heterocyclic compounds.⁴⁷³

The effects of other groups on the ring are not easily predicted. The nitro group is strongly activating, but only in the ortho (not meta or para) position.⁴⁷⁴ Both R and OR groups activate in all positions. Not only do OH, NH₂, NHR, and NHCOR inhibit the reaction, as would be expected for aromatic nucleophilic substitution, but so do CO₂H (but not CO₂R), SO₂NH₂, and similar groups for which the reaction fails completely. These groups inhibit the coupling reaction by causing side reactions.

The mechanism is not known with certainty. It seems likely that it is basically a two-step process, similar to that of the *Wurtz reaction* (**10-56**), which can be represented schematically by



Organocopper compounds have been trapped by coordination with organic bases.⁴⁷⁵ In addition, aryl copper compounds (ArCu) have been independently prepared and shown to give biaryls (Ar—Ar') when treated with aryl iodides (Ar'I).⁴⁷⁶ A similar reaction has been used for ring closure⁴⁷⁷: Copper-catalyzed coupling of aryl halides and heterocycles has been reported.⁴⁷⁸

An important alternative to the *Ullmann method* is the use of certain Ni complexes.⁴⁷⁹ Aryl halides (ArX) can also be converted to Ar—Ar⁴⁸⁰ by treatment with activated Ni metal,⁴⁸¹ with Zn and Ni complexes,⁴⁸² with aq alkaline sodium formate, Pd—C and a phase-transfer catalyst,⁴⁸³ and in an electrochemical process catalyzed by a Ni complex.⁴⁸⁴

An asymmetric *Ullmann reaction* has been reported.⁴⁸⁵

OS III, 339; V, 1120.

⁴⁷⁰ Yang, M.; Liu, F. *J. Org. Chem.* **2007**, 72, 8969.

⁴⁷¹ Wu, Q.; Wang, L. *Synthesis* **2008**, 2007.

⁴⁷² See for example, Karimipour, M.; Semones, A.M.; Asleson, G.L.; Heldrich, F.J. *Synlett*, **1990**, 525.

⁴⁷³ D'Angelo, N.D.; Peterson, J.J.; Booker, S.K.; Fellows, I.; Dominguez, C.; Hungate, R.; Reider, P.J.; Kim, T.-S. *Tetrahedron Lett.* **2006**, 47, 5045.

⁴⁷⁴ Forrest, J. *J. Chem. Soc.* **1960**, 592.

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⁴⁷⁶ See Mack, A.G.; Suschitzky, H.; Wakefield, B.J. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1682.

⁴⁷⁷ Salfeld, J.C.; Baume, E. *Tetrahedron Lett.* **1966**, 3365; Lothrop, W.C. *J. Am. Chem. Soc.* **1941**, 63, 1187.

⁴⁷⁸ Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, 129, 12404.

⁴⁷⁹ See Lourak, M.; Vanderesse, R.; Fort, Y.; Caubere, P. *J. Org. Chem.* **1989**, 54, 4840, 4844; Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, 63, 80. For a review of the mechanism, see Amatore, C.; Jutand, A. *Acta Chem. Scand.* **1990**, 44, 755.

⁴⁸⁰ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 82–84.

⁴⁸¹ Matsumoto, H.; Inaba, S.; Rieke, R.D. *J. Org. Chem.* **1983**, 48, 840; Chao, C.S.; Cheng, C.H.; Chang, C.T. *J. Org. Chem.* **1983**, 48, 4904.

⁴⁸² Takagi, K.; Hayama, N.; Sasaki, K. *Bull. Chem. Soc. Jpn.* **1984**, 57, 1887.

⁴⁸³ Bamfield, P.; Quan, P.M. *Synthesis* **1978**, 537.

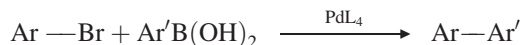
⁴⁸⁴ Meyer, G.; Rollin, Y.; Perichon, J. *J. Organomet. Chem.* **1987**, 333, 263.

⁴⁸⁵ Nelson, T.D.; Meyers, A.I. *J. Org. Chem.* **1994**, 59, 2655; Nelson, T.D.; Meyers, A.I. *Tetrahedron Lett.* **1994**, 35, 3259.

13-12 Coupling of Aryl Compounds with Arylboronic Acid Derivatives

Aryl-de-halogenation, and so on

Aryl-de-boronylation, and so on



Arylboronic acids are coupled to aryl halides using a Pd catalyst to give the arene in what is called *Suzuki coupling* (or *Suzuki–Miyaura coupling*).⁴⁸⁶ Aryl triflates react with arylboronic acids [ArB(OH)₂, Reaction 12-28],⁴⁸⁷ or with organoboranes,⁴⁸⁸ in the presence of a Pd catalyst.⁴⁸⁹ Even hindered boronic acids give good yields of the coupled product.⁴⁹⁰ Homocoupling of arylboronic acids has been reported.⁴⁹¹ Some aromatic compounds are so reactive that a catalyst may not be required. Using tetrabutylammonium bromide, phenylboronic acid was coupled to 2-bromofuran without a catalyst.⁴⁹²

Different conditions (including additives and solvent) for the reaction have been reported,⁴⁹³ often focusing on the Pd catalyst⁴⁹⁴ or the ligand.⁴⁹⁵ Phosphine-⁴⁹⁶ and

⁴⁸⁶ Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457; Alonso, F.; Beletskaya, I.P.; Yus, M. *Tetrahedron* **2008**, 64, 3047; Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013; Molander, G.A.; Yun, C.-S. *Tetrahedron* **2002**, 58, 1465. See Kotha, S.; Lahiri, K.; Kashshinath, D. *Tetrahedron* **2002**, 58, 9633.

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⁴⁸⁸ Fürstner, A.; Seidel, G. *Synlett*, **1998**, 161.

⁴⁸⁹ For a review, see Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.

⁴⁹⁰ Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

⁴⁹¹ Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, 43, 2525; Parrish, J.P.; Jung, Y.C.; Floyd, R.J.; Jung, K.W. *Tetrahedron Lett.* **2002**, 43, 7899.

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⁴⁹³ Fairlamb, I.J.S.; Kapdi, A.R.; Lee, A.F. *Org. Lett.* **2004**, 6, 4435; Arentsen, K.; Caddick, S.; Cloke, G.N.; Herring, A.P.; Hitchcock, P.B. *Tetrahedron Lett.* **2004**, 45, 3511; Artok, L.; Bulat, H. *Tetrahedron Lett.* **2004**, 45, 3881; Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* **2003**, 4080.

⁴⁹⁴ See Schweizer, S.; Becht, J.-M.; Le Drian, C. *Org. Lett.* **2007**, 9, 3777; Burns, M.J.; Fairlamb, I.J.S.; Kapdi, A. R.; Sehna, P.; Taylor, R.J.K. *Org. Lett.* **2007**, 9, 5397; Guo, M.; Jian, F.; He, R. *Tetrahedron Lett.* **2006**, 47, 2033; Li, J.-H.; Zhu, Q.-M.; Xie, Y.-X. *Tetrahedron* **2006**, 62, 10888; Kantam, M.L.; Subhas, M.S.; Roy, S.; Roy, M. *Synlett* **2006**, 633; Alonso, D.A.; Cívicos, J.F.; Nájera, C. *Synlett* **2009**, 3011; You, E.; Li, P.; Wang, L. *Synthesis* **2006**, 1465; Felpin, F.-X.; Ayad, T.; Mitra, S. *Eur. J. Org. Chem.* **2006**, 2679; Lee, D.-H.; Jung, J.-Y.; Lee, I.-M.; Jin, M.-J. *Eur. J. Org. Chem.* **2008**, 356; Subhas, M.S.; Racharlawar, S.S.; Sridhar, B.; Kennady, P.K.; Likhar, P.R.; Kantam, M.L.; Bhargava, S.K. *Org. Biomol. Chem.* **2010**, 8, 3001; Bhayana, B.; Fors, B.P.; Buchwald, S.L. *Org. Lett.* **2009**, 11, 3954; Nishikata, T.; Abela, A.R.; Huang, S.; Lipshutz, B.H. *J. Am. Chem. Soc.* **2010**, 132, 4978; Guo, M.; Zhang, Q. *Tetrahedron Lett.* **2009**, 50, 1965. For a discussion of catalysts in this reaction, see Barder, T.E.; Walker, S.D.; Martinelli, J.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, 127, 4685. For a precatalyst that is useful with unstable 2-heteroaryl boronic acids, see Kinzel, T.; Zhang, Y.; Buchwald, S.L. *J. Am. Chem. Soc.* **2010**, 132, 14073.

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ligand-free conditions⁴⁹⁷ have been developed. Recyclable catalysts have been developed.⁴⁹⁸ Catalysts have been developed for deactivated aryl chlorides.⁴⁹⁹ *Suzuki coupling* has also been done in ionic liquids,⁵⁰⁰ in supercritical CO₂⁵⁰¹ (see Sec. 9.D.ii), and there are solvent-free procedures.⁵⁰² Several procedures for coupling in aqueous media have been reported.⁵⁰³ The reaction has been done neat on alumina,⁵⁰⁴ and on alumina with microwave irradiation.⁵⁰⁵ Several procedures have been reported using microwave irradiation.⁵⁰⁶ Modifications to the basic procedure include tethering the aryl triflate⁵⁰⁷ or the boronic acid⁵⁰⁸ to a polymer, allowing a polymer-supported *Suzuki reaction*. Polymer-bound Pd complexes have been used.⁵⁰⁹ There is even a Pd free cross-coupling.⁵¹⁰

Arylboronic acids have been coupled to vinyl halides⁵¹¹ or vinyl tosylates⁵¹² using a Pd catalyst. Halogenated heteroaromatic compounds react, as do aryl carbamates, carbonates and sulfamates,⁵¹³ and aryl phosphoramides.⁵¹⁴ Aryl sulfonates have been used.⁵¹⁵

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Arylboronic acids couple with aryl sulfonate esters.⁵¹⁶ Many different heterocycles have been arylated.⁵¹⁷ 4-Pyridylboronic acids have been used.⁵¹⁸ 3-Iodopyridine reacted with NaBPh and palladium acetate, with microwave irradiation, to give 3-phenylpyridine.⁵¹⁹

A variety of functional groups are compatible with Suzuki coupling, including $\text{Ar}_2\text{P}=\text{O}$,⁵²⁰ CHO ,⁵²¹ $\text{C}=\text{O}$ of a ketone,⁵²² CO_2R ,⁵²³ cyclopropyl,⁵²⁴ NO_2 ,⁵²⁵ CN , and halogen substituents.⁵²⁶ Vinyl halides react with arylboronic acids to give alkenyl derivatives (vinyl arenes, $\text{C}=\text{C}-\text{Ar}$),⁵²⁷ in what is clearly a *Heck-like* reaction. In a variation, vinylboronic acids coupled to aryl halides to give the vinyl-coupling product.⁵²⁸ Vinylboronic acids have been coupled to aryldiazonium salts (see Reaction 13-25) without added base, using a Pd catalyst with an imidazolium ligand.⁵²⁹

Alkylation can accompany arylation if alkyl halides are added, as in the conversion of iodobenzene to 2,6-dibutylbiphenyl.⁵³⁰ Alkyl groups may be coupled to aryls, as in the Pd catalyzed reaction of arylboronic acids with benzylic carbonates.⁵³¹ Arylboronic acids also couple with alkyl halides using either a palladium(II) acetate⁵³² or a Ni catalyst.⁵³³ Conversely, arylboronic acids can be coupled to aliphatic halides.⁵³⁴ Arylboronic acids can be coupled to allylic alcohols as well.⁵³⁵ Benzylic phosphonates have also been used.⁵³⁶ Double *Suzuki coupling* reactions are known.⁵³⁷ An alkyl-alkyl coupling reaction has been classified as a *Suzuki cross-coupling* reaction.⁵³⁸ The reaction of an arylboronic acid and 1,2-dibromoethane, with KOH and a Pd catalyst, leads to the styrene derivative.⁵³⁹

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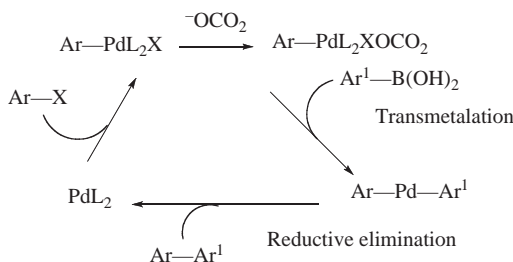
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Since many biaryls are chiral due to atropisomerism (see Sec. 4.C, category 5), the use of a chiral catalyst, and/or a chiral ligand can lead to enantioselectivity in the *Suzuki coupling*.⁵⁴⁰



For a mechanistic viewpoint,⁵⁴¹ the *Suzuki coupling* proceeds via oxidative addition of areneboronic acids to give a Pd species, followed by 1,2-arene migration to an electron-deficient Pd atom, eventually leading to very fast reductive elimination to afford biaryls.⁵⁴² This mechanism is illustrated.⁵⁴³ Several intermediates of the oxidative coupling process have been identified by electrospray ionization mass spectrometry.⁵⁴⁴ Palladium peroxo complexes have been shown to be key intermediates.⁵⁴⁵

Other transition metals have been employed in these coupling reactions, sometimes as cocatalysts. Arylboronic acids have been coupled to conjugated alkenes to give the aryl-alkene coupling product using a Pd catalyst,⁵⁴⁶ a Ru catalyst with copper(II) acetate,⁵⁴⁷ a Ni catalyst,⁵⁴⁸ or a Rh catalyst.⁵⁴⁹ Aryl boronic acids are coupled with aryl ammonium salts to give the biaryl, with a Ni catalyst.⁵⁵⁰ Allylic acetates have been coupled to arylboronic acids using nickel bis(acetylacetonate) and diisobutylaluminum hydride.⁵⁵¹ Arylboronic acids (Reaction 12-28) were shown to react directly with benzene in the presence of Mn(OAc)_3 .⁵⁵² Aryl halides couple with ArB(OR')_2 species with a Pd catalyst.⁵⁵³ Iron catalysts have been developed for coupling with alkyl halides.⁵⁵⁴ Arylboronic

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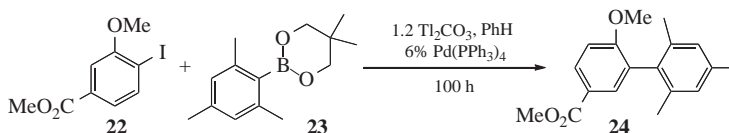
⁵⁵² Demir, A.S.; Reis, Ö.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 578.

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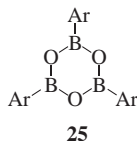
⁵⁵⁴ Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674. However, see Bedford, R.B.; Nakamura, M.; Gower, N.J.; Haddow, M.F.; Hall, M.A.; Huwe, M.; Hashimoto, T.; Okopie, R.A. *Tetrahedron Lett.* **2009**, *50*, 6110.

acids couple with the phenyl group of Ph_2TeCl_2 with a Pd catalyst.⁵⁵⁵ Tributyltin aryl compounds were coupled to the aryl group of $\text{Ar}_2\text{I}^+\text{BF}_4^-$ with a Ni catalyst.⁵⁵⁶

Suzuki-type coupling reactions have been reported involving acyl halides. When arylboronic acids were reacted with benzoyl chloride and PdCl_2 , the product was the diaryl ketone.⁵⁵⁷ This coupling reaction was also accomplished using a $\text{Pd}(0)$ catalyst.⁵⁵⁸ Cyclopropylboronic acids couple with benzoyl chloride, in the presence of Ag_2O and a Pd catalyst, to give the cyclopropyl ketone.⁵⁵⁹ A Ni catalyst has been used,⁵⁶⁰ and $\text{Ph}_3\text{P}/\text{Ni}/\text{C}-\text{BuLi}$ has also been used.⁵⁶¹ Arylboronic acids have also been coupled to anhydrides,⁵⁶² and the methoxy group of anisole derivatives has been replaced with phenyl using phenylboronic acid and a Ru catalyst.⁵⁶³



Arylborates (see Reaction **12-28**), $\text{ArB}(\text{OR})_2$, can be used in place of the boronic acid.⁵⁶⁴ The coupling reaction of aryl iodide (**22**) with boronate (**23**), for example, gave biaryl **24**.⁵⁶⁵ Base-free conditions, using nitrogen ligands, have been reported.⁵⁶⁶ Aryl and heteroarylboroxines (**25**) can be coupled to aryl halides using a Pd catalyst.⁵⁶⁷ Vinylboranes have been coupled to aryl iodides to give the aryl alkene, in the presence of a Pd catalyst.⁵⁶⁸ Organoboranes are coupled to aryl halides with a Pd catalyst.⁵⁶⁹



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In a useful variation, aryltrifluoroborates ($\text{ArBF}_3^+ \text{X}^-$) (Reaction **12-28**), are coupled to aryl halides with a Pd catalyst to give the biaryl.⁵⁷⁰ Alkyltrifluoroborates⁵⁷¹ (RBF_3K , see Reaction **12-28**) react with aryl triflates⁵⁷² aryl halides,⁵⁷³ or arylodonium salts⁵⁷⁴ with a Pd catalyst, to give the arene. In a related reaction, vinyltrifluoroborates ($\text{C}=\text{C}-\text{BF}_3^+ \text{X}^-$ see Reaction **12-28**), are coupled to aryl halides with a Pd catalyst to give the styrene derivative.⁵⁷⁵ *Suzuki coupling* with trifluoroborates has also been done using microwave irradiation.⁵⁷⁶ Aryltellurides have been used in this reaction.⁵⁷⁷ A Pd catalyzed reaction with enamino ketones, mediated by Cu(II) salts, led to coupling to give the aryl derivative.⁵⁷⁸ Ruthenium catalysts have also been used.⁵⁷⁹

OS 75, 53, 61

The coupling reactions of alkylboronic acids are covered in Reaction **13-17**.

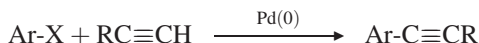
OS CV, 102, 467; OS 81, 89.

13-13 Aryl-Alkyne Coupling Reactions

Alkynyl-de-halogenation, and so on



When aryl halides react with copper acetylides to give 1-aryl alkynes, the reaction is known as *Stephens–Castro coupling*.⁵⁸⁰ Both aliphatic and aromatic substituents can be attached to the alkyne unit, and a variety of aryl iodides have been used. Benzonitrile was shown to react with alkynyl zinc bromides, with a Ni catalyst and after electrolysis to give the diarylalkyne, where the cyano unit was replaced with an alkyne unit.⁵⁸¹



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⁵⁸¹ Penney, J.M.; Miller, J.A. *Tetrahedron Lett.* **2004**, 45, 4989.

A Pd catalyzed variation is known in which an aryl halide reacts with a terminal alkyne to give 1-aryl alkynes is called *Sonogashira coupling*.⁵⁸² Terminal aryl alkynes react with aryl iodides and Pd(0)⁵⁸³ to give the corresponding diaryl alkyne,⁵⁸⁴ but monoalkynes are easily prepared.⁵⁸⁵ Aryl iodides are more reactive than aryl fluorides.⁵⁸⁶ Alkynes can be coupled to heteroaromatic compounds.⁵⁸⁷ As with all of the metal-catalyzed reactions in this chapter, work has been done to vary reaction conditions, including the catalyst,⁵⁸⁸ the ligand,⁵⁸⁹ the solvent, and additives.⁵⁹⁰ There are copper-⁵⁹¹ and ligand-free variations.⁵⁹² Transition metal free coupling has been reported using a 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical as an oxidant.⁵⁹³ Variations include *Sonogashira coupling* in water, without Cu,⁵⁹⁴ and other reactions are done in aqueous media.⁵⁹⁵ The coupling has been done in aq polyethylene glycol,⁵⁹⁶ and in ionic liquids.⁵⁹⁷ Microwave irradiation is an important tool in this reaction.⁵⁹⁸ *Sonogashira coupling* was reported on microbeads,⁵⁹⁹ with

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⁵⁸⁹ Mori, S.; Yanase, T.; Aoyagi, S.; Monguchi, Y.; Maegawa, T.; Sajiki, H. *Chemistry: European J.* **2008**, *14*, 6994.

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⁵⁹¹ Yi, C.; Hua, R. *J. Org. Chem.* **2006**, *71*, 2535; Cwik, A.; Hell, Z.; Figueras, F. *Tetrahedron Lett.* **2006**, *47*, 3023; Komáromi, A.; Tolnai, G.L.; Novák, Z. *Tetrahedron Lett.* **2008**, *49*, 7294; Teratani, T.; Ohtaka, A.; Kawashima, T.; Shimomura, O.; Nomura, R. *Synlett* **2010**, 2271; Li, J.-H.; Zhang, X.-D.; Xie, Y.-X. *Synthesis* **2005**, 804; Li, J.-H.; Zhang, X.-D.; Xie, Y.-X. *Eur. J. Org. Chem.* **2005**, 4256; Ren, T.; Zhang, Y.; Zhu, W.; Zhou, J. *Synth. Commun.* **2007**, *37*, 3279; Bakherad, M.; Keivanloo, A.; Bahramian, B.; Hashemi, M. *Tetrahedron Lett.* **2009**, *50*, 1557. For a variation using Au-nanoparticles, see de Souza, R.O.M.A.; Bittar, M.S.; Mendes, L.V.P.; da Silva, C.M.F.; da Silva, V.T.; Antunes, O.A.C. *Synlett* **2008**, 1777.

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⁵⁹⁴ Lipshutz, B.L.; Chung, D.W.; Rich, B. *Org. Lett.* **2008**, *10*, 3793; Guan, J.T.; Weng, T.Q.; Yu, G.-A.; Liu, S.H. *Tetrahedron Lett.* **2007**, *48*, 7129.

⁵⁹⁵ Özdemir, I.; Gürbüz, N.; Gök, Y.; Çetinkaya, E.; Çetinkaya, B. *Synlett* **2005**, 2394; Chen, G.; Zhu, X.; Cai, J.; Wan, Y. *Synth. Commun.* **2007**, *37*, 1355.

⁵⁹⁶ Leadbeater, N.E.; Marco, M.; Tominack, B.J. *Org. Lett.* **2003**, *5*, 3919.

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⁵⁹⁸ Appukkuttan, P.; Dehaen, W.; van der Eyken, E. *Eur. J. Org. Chem.* **2003**, 4713. See also, Kabalka, G.W.; Wang, L.; Namboodiri, V.; Pagni, R.M. *Tetrahedron Lett.* **2000**, *41*, 515.

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nanoparticulate nickel powder,⁶⁰⁰ and the aryl iodide was tethered to a polymer for a solid-state reaction.⁶⁰¹ Polymer-supported catalysts are known.⁶⁰² A variation scavenged the triphenylphosphine byproduct by addition of *Merrifield* resin.⁶⁰³

Coupling of the alkynes to form a diyne (see Reaction **14-16**) can be a problem in some cases, although the aryl–alkyne coupling usually predominates.⁶⁰⁴ There are many variations. Alkyl groups are coupled to alkynes under *Sonogashira conditions*, including unactivated secondary alkyl halides.⁶⁰⁵ Coupling propargyl bromide and an aryl iodide, in the presence of an amine, gives the aryl aminomethylalkyne.⁶⁰⁶ 4-Chloroacetophenone reacts with 1-phenylethyne, showing that the carbonyl group is compatible with this reaction.⁶⁰⁷ Arenediazonium salts can be used for the coupling reaction.⁶⁰⁸ Similar Pd catalyzed coupling of bromoalkynes with heterocycles also leads to the alkynyl derivative.⁶⁰⁹ Ynamides are coupled using copper-free conditions.⁶¹⁰

There are variations of the *Sonogashira reaction* that use other metals as catalysts or cocatalysts. A Pd free reaction is known, using Cu complexes as the catalyst.⁶¹¹ An In catalyzed reaction is known that does not use Cu, Pd, or phosphine ligands.⁶¹² Gold(I) has been used to catalyze *Sonogashira reactions*,⁶¹³ and there are Ni⁶¹⁴ and Fe catalyzed⁶¹⁵ reactions. Silver iodide has been used to catalyze the reaction.⁶¹⁶ Conversion of 1-lithioalkynes to the corresponding alkynyl zinc reagent allows coupling with aryl iodides when a Pd catalyst is used.⁶¹⁷ A 1-lithioalkyne was directly coupled to aryl bromides in the presence of B(OiPr)₃ and a Pd catalyst,⁶¹⁸ where an alkynylboronic acid was generated *in situ*. Lithium alkynyltrimethylborates are coupled to aryl chlorides as well.⁶¹⁹ Terminal alkynes are coupled to acylpyridinium salts in the presence of a Cu catalyst, giving a product with high enantioselectivity when a chiral ligand is used.⁶²⁰ Coupling with alkynyl tin compounds is known.⁶²¹ A triphenylstibine [Ph₃Sb(OAc)₂] was used to transfer a phenyl group to the alkyne carbon of PhC≡CSiMe₃, using Pd and CuI catalysts.⁶²²

⁶⁰⁰ Wang, M.; Li, P.; Wang, L. *Synth. Commun.* **2004**, *34*, 2803.

⁶⁰¹ Erdélyi, M.; Gogoll, A. *J. Org. Chem.* **2003**, *68*, 6431.

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⁶⁰³ Lipshutz, B.H.; Blomgren, P.A. *Org. Lett.* **2001**, *3*, 1869.

⁶⁰⁴ See Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910.

⁶⁰⁵ Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925.

⁶⁰⁶ Olivi, N.; Spruyt, P.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2004**, *45*, 2607.

⁶⁰⁷ Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2004**, *45*, 8443.

⁶⁰⁸ Fabrizi, G.; Goggiamani, A.A.; Sferrazza, A.; Cacchi, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 4067.

⁶⁰⁹ Seregin, I.V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742.

⁶¹⁰ Wakamatsu, H.; Takeshita, M. *Synlett* **2010**, 2322.

⁶¹¹ Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* **2008**, *10*, 3203. For a microwave induced variation of this reaction, see Colacino, E.; Daïch, L.; Martinez, J.; Lamaty, F. *Synlett* **2007**, 1279.

⁶¹² Borah, H.N.; Prajapati, D.; Boruah, R.C. *Synlett* **2005**, 2823.

⁶¹³ Li, P.; Wang, L.; Wang, M.; You, F. *Eur. J. Org. Chem.* **2008**, 5946. However, see Lauterbach, T.; Livendahl, M.; Roselln, A.; Espinet, P.; Echavarren, A.M. *Org. Lett.* **2010**, *12*, 3006, and Panda, B.; Sarkar, T.K. *Tetrahedron Lett.* **2010**, *51*, 301. See also, Beaumont, S.K.; Kyriakou, G.; Lambert, R.M. *J. Am. Chem. Soc.* **2010**, *132*, 12246.

⁶¹⁴ Bakherad, M.; Keivanloo, A.; Mihanparast, S. *Synth. Commun.* **2010**, *40*, 179.

⁶¹⁵ Sawant, D.N.; Tambade, P.J.; Wagh, Y.S.; Bhanage, B.M. *Tetrahedron Lett.* **2010**, *51*, 2758.

⁶¹⁶ Li, P.; Wang, L. *Synlett* **2006**, 2261.

⁶¹⁷ Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111.

⁶¹⁸ Castanet, A.-S.; Colobert, F.; Schlama, T. *Org. Lett.* **2000**, *2*, 3559.

⁶¹⁹ Torres, G.H.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* **2006**, 1450.

⁶²⁰ Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300.

⁶²¹ See Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2004**, *6*, 2821.

⁶²² Kang, S.-K.; Ryu, H.-C.; Hong, Y.-T. *J. Chem. Soc. Perkin Trans. 1* **2001**, 736.

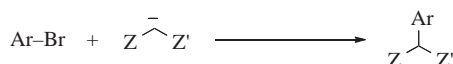
A variation of this aryl–alkyne coupling reaction reacted methylthioalkynes ($R-C\equiv C-SMe$) with arylboronic acids and a Pd catalyst to give the aryl alkyne ($R-C\equiv C-Ar$).⁶²³ The boron trifluoride induced Pd catalyzed cross-coupling reaction of 1-aryltriazenes with areneboronic acids has been reported.⁶²⁴ Aryl halides are coupled to alkynyltrifluoroboronates ($R-C\equiv C-BF_3K$, Reaction **12-28**) using a Pd catalyst.⁶²⁵ Aryl iodides were also coupled to lithium alkynyl borate complexes, $Li[R-C\equiv C-B(OR')_3]$, to give the aryl alkyne.⁶²⁶

Diaryliodonium salts react with terminal alkynes to give the phenyl alkyne.⁶²⁷ A variation couples the phenyl group of $Ph_2I^+OTf^-$ with an en-yne using a Pd catalyst.⁶²⁸ Aryl sulfonate esters can be coupled to terminal alkynes using a Pd catalyst in polymethylhydrosiloxane.⁶²⁹

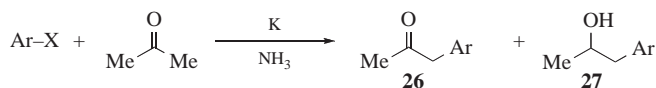
OS 11, 2009, 234.

13-14 Arylation at a Carbon Containing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on



The arylation of compounds of the form ZCH_2Z' is analogous to Reaction **10-67**, where Z is defined as an electron-withdrawing group (ester, cyano, sulfonyl, etc.). Activated aryl halides generally give good results.⁶³⁰ Treatment with an aryl halide in liquid ammonia containing Na or K, for example, leads in the formation of **26** and **27**.⁶³¹ When the solution is irradiated with near-UV light, but Na or K is omitted, the same products are



obtained (though in different proportions).⁶³² In either case, other leaving groups can be used instead of halogens (e.g., NR_3^+ , SAr) and the mechanism is the $S_{RN}1$ mechanism. *N*-Heterocyclic carbene ligands in the presence of alkoxide bases lead to coupling of ketones and aryl halides, at the α -position of the ketone.⁶³³ The reaction can also take place without an added initiator. The reaction of 2-fluoroanisole and KHMDS, and 4 equiv

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⁶²⁸ Radhakrishnan, U.; Stang, P.J. *Org. Lett.* **2001**, 3, 859.

⁶²⁹ Gallagher, W.P.; Maleczka, Jr., R.E. *J. Org. Chem.* **2003**, 68, 6775.

⁶³⁰ There is evidence for both the S_NAr mechanism (see Leffek, K.T.; Matinopoulos-Scordou, A.E. *Can. J. Chem.* **1977**, 55, 2656, 2664) and the $S_{RN}1$ mechanism (see Zhang, X.; Yang, D.; Liu, Y.; Chen, W.; Cheng, J. *Res. Chem. Intermed.* **1989**, 11, 281).

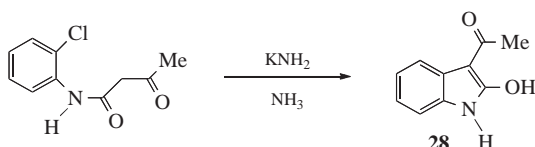
⁶³¹ Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* **1973**, 38, 3020; Bunnett, J.F.; Gloor, B.F. *J. Org. Chem.* **1973**, 38, 4156; **1974**, 39, 382.

⁶³² Rajan, S.; Muralimohan, K. *Tetrahedron Lett.* **1978**, 483; Rossi, R.A.; Alonso, R.A. *J. Org. Chem.* **1980**, 45, 1239; Beugelmans, R. *Bull. Soc. Chim. Belg.* **1984**, 93, 547.

⁶³³ Matsubara, K.; Ueno, K.; Koga, Y.; Hara, K. *J. Org. Chem.* **2007**, 72, 5069.

of 2-cyanopropane, leads to substitution of the fluorine atom by CMe_2CN .⁶³⁴ β -Keto esters were coupled to aryl fluorides using CsOH and a chiral quaternary ammonium salt, leading to the aryl substitution product with good enantioselectivity.⁶³⁵

Even unactivated aryl halides can be employed if the reaction is carried out in the presence of a strong base (e.g., NaNH_2 ⁶³⁶ or LDA). Compounds of the form $\text{ZCH}_2\text{Z}'$, and even simple ketones⁶³⁷ or carboxylic esters have been arylated in this manner. The reaction with unactivated halides proceeds by the benzyne mechanism and represents a method for extending the malonic ester (and similar) syntheses to aromatic compounds. The base performs two functions: It removes a proton from $\text{ZCH}_2\text{Z}'$ and catalyzes the benzyne mechanism. The reaction has been used for ring closure, as in the formation of indole **28**.⁶³⁸



A similar reaction was reported using a Pd catalyst.⁶³⁹ Nitroethane was converted to 2-phenylnitroethane using bromobenzene and a Pd catalyst.⁶⁴⁰ Palladium catalysts have been developed for the α -arylation of ketones.⁶⁴¹ α -Arylation of esters has been accomplished using Pd catalysts.⁶⁴² Malonate esters are coupled unactivated aryl halides using a Pd catalyst.⁶⁴³ Bis-(sulfones) $[\text{CH}_2(\text{SO}_2\text{Ar})_2]$, react with aryl halides in the presence of a Pd catalyst.⁶⁴⁴ Iron(II) salts have also been used to initiate this reaction.⁶⁴⁵ The coupling of active methylene compounds and unactivated aryl halides can also be done with copper halide catalysts¹⁰³ (the *Hurtley reaction*).⁶⁴⁶ Similar coupling was accomplished with $\text{CH}_2(\text{CN})_2$ and a Ni catalyst.⁶⁴⁷ A variation of α -arylation reacts α -halocarbonyl compounds with arylboronic acids, in the presence of a Ni catalyst.⁶⁴⁸ Malonic and β -keto esters can be arylated at the α -carbon in high yields by treatment

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⁶³⁷ See Caubere, P.; Guillaumet, G. *Bull. Soc. Chim. Fr.* **1972**, 4643, 4649.

⁶³⁸ Bunnett, J.F.; Kato, T.; Flynn, R.; Skorcz, J.A. *J. Org. Chem.* **1963**, 28, 1. See Biehl, E.R.; Khanapure, S.P. *Acc. Chem. Res.* **1989**, 22, 275; Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, **1967**, pp. 150–164. See also, Kessar, S.V. *Acc. Chem. Res.* **1978**, 11, 283.

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⁶⁴⁰ Vogl, E.M.; Buchwald, S.L. *J. Org. Chem.* **2002**, 67, 106.

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⁶⁴⁶ See Osuka, A.; Kobayashi, T.; Suzuki, H. *Synthesis* **1983**, 67; Hennessy, E.J.; Buchwald, S.L. *Org. Lett.* **2002**, 4, 269.

⁶⁴⁷ Cristau, H.J.; Vogel, R.; Taillefer, M.; Gadras, A. *Tetrahedron Lett.* **2000**, 41, 8457.

⁶⁴⁸ Liu, C.; He, C.; Shi, W.; Chen, M.; Lei, A. *Org. Lett.* **2007**, 9, 5601.

with aryllead tricarboxylates $[\text{ArPb}(\text{OAc})_3]$,⁶⁴⁹ with triphenylbismuth carbonate $(\text{Ph}_2\text{BiCO}_3)$,⁶⁵⁰ and other Bi reagents.⁶⁵¹ In a related process, manganese(III) acetate was used to convert a mixture of ArH and $\text{ZCH}_2\text{Z}'$ to ArCHZZ' .⁶⁵² Arylzinc reagents have also been used.⁶⁵³

Enolate ions of ketones react with PhI in the dark.⁶⁵⁴ In this case, it has been suggested⁶⁵⁵ that initiation takes place by formation of a radical (e.g., **29**).



This is a SET mechanism (see Sec. 10.B). The photostimulated reaction has also been used for ring closure.⁶⁵⁶ In certain instances of the intermolecular reaction, there is evidence that the leaving group exerts an influence on the product ratios, even when it has already departed at the time that product selection takes place.⁶⁵⁷

The reaction of the enolate anions of ketones and aldehydes, generated *in situ* by addition of a suitable base, with aryl halides can be accomplished by treatment with a Pd catalyst.⁶⁵⁸ Formation of an enolate anion of a conjugated ketone (cyclohexenone) via reaction with LDA (see Sec. 8.F, category 7), in the presence of Ph_3BiCl_2 , leads to the α -phenyl conjugated ketone (6-phenylcyclohex-2-enone).⁶⁵⁹ An ester reacted with TiCl_4 and *N,N*-dimethylaniline to give the para-substitution product ($\text{Me}_2\text{N}-\text{Ar}-2\text{Et}$).⁶⁶⁰ Nickel-catalyzed α -arylation of ketone enolate anions is also known.⁶⁶¹ The enolate anion of lactams will react with aryl halides in the presence of a Pd catalyst via the 3-aryl lactam.⁶⁶² When the enolate anion of a ketone is generated in the presence of a Pd catalyst and a chiral phosphine ligand, the α -aryl ketone is formed with good enantioselectivity.⁶⁶³

OS V, 12, 263; VI, 36, 873, 928; VII, 229.

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⁶⁵⁸ See Culkin, D.A.; Hartwig, J.F. *Acc. Chem. Res.* **2003**, *36*, 234.

⁶⁵⁹ Arnould, T.; Barton, D.H.R.; Normant, J.-F.; Doris, E. *J. Org. Chem.* **1999**, *64*, 6915.

⁶⁶⁰ Periasamy, M.; KishoreBabu N.; Jayakumar, K.N. *Tetrahedron Lett.* **2003**, *44*, 8939.

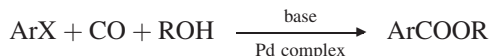
⁶⁶¹ Chen, G.; Kwong, F.Y.; Chan, H.O.; Yu, W.-Y.; Chan, A.S.C. *Chem. Commun.* **2006**, 1413.

⁶⁶² Cossy, J.; de Filippis, A.; Pardo, D.G. *Org. Lett.* **2003**, *5*, 3037.

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13-15 Conversion of Aryl Substrates to Carboxylic Acids, Their Derivatives, Aldehydes, and Ketones⁶⁶⁴

Alkoxycarbonyl-de-halogenation, and so on



Carbonylation of aryl halides⁶⁶⁵ and aryl triflates⁶⁶⁶ with CO, an alcohol and a base (which gives an alkoxide), and a Pd catalyst, gives carboxylic esters. Similar carbonylation reactions are possible with alkyl halides. Aryl carboxylic acids were also prepared from aryl iodides by heating in DMF with lithium formate, LiCl, acetic anhydride, and a Pd catalyst.⁶⁶⁷ Even very sterically hindered alkoxides can be used to produce the corresponding ester.⁶⁶⁸ The use of H₂O, RNH₂, or an alkali metal or calcium carboxylate⁶⁶⁹ instead of ROH, gives the carboxylic acid,⁶⁷⁰ amide,⁶⁷¹ or mixed anhydride, respectively.⁶⁷² Ester formation via carbonylation was done in supercritical CO₂ (see Sec. 9.D.ii).⁶⁷³ Microwave promoted carbonylation reactions have been reported.⁶⁷⁴

Variations including a silica-supported Pd reagent have been used to convert iodobenzene to butyl benzoate, in the presence of CO and butanol.⁶⁷⁵ 2-Chloropyridine was converted to the butyl pyridine 2-carboxylate with this procedure.⁶⁷⁶ Dicobalt octacarbonyl [Co₂(CO)₈] may be used as a surrogate reagent for CO.⁶⁷⁷ Heating an aryl iodide, CO in ethanol and DBU, with a Pd catalyst, gave the ethyl ester of the aryl carboxylic acid.⁶⁷⁸ A similar result was obtained when an aryl iodide was heated in ethanol with triethylamine, CO, and Pd/C.⁶⁷⁹ Phenols and aryl halides react with a Pd catalyst, and carbonylation leads to the phenyl ester.⁶⁸⁰ Arylthallium bis(trifluoroacetates) [ArTl(O₂CCF₃)₂], (see Reaction 12-23), can be carbonylated with CO, an alcohol, and a PdCl₂ catalyst to give esters.⁶⁸¹ Note that seleno esters (ArCOSeAr) were prepared

⁶⁶⁴ See Weil, T.A.; Cassar, L.; Foà, M. in Wender, I.; Pino, P. *Organic Synthesis Via Metal Carbonyls*, Vol. 2, Wiley, NY, **1977**, pp. 517–543.

⁶⁶⁵ Liu, J.; Liang, B.; Shu, D.; Hu, Y.; Yang, Z.; Lei, A. *Tetrahedron* **2008**, *64*, 9581; Berger, P.; Bessmerlykh, A.; Caille, J.-C.; Mignonac, S. *Synthesis* **2006**, 3106.

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⁶⁷⁹ Ramesh, C.; Nakamura, R.; Kubota, Y.; Miwa, M.; Sugi, Y. *Synthesis* **2003**, 501.

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⁶⁸¹ Larock, R.C.; Fellows, C.A. *J. Am. Chem. Soc.* **1982**, *104*, 1900.

from aryl iodides, CO, PhSeSnBu₃, and a Pd catalyst.⁶⁸² Aminocarbonylation reactions are known.⁶⁸³

Modification of this approach allows the synthesis of ketones, and aryl iodides can be converted to aldehydes.⁶⁸⁴ Aryl ketones can be prepared from aryltrimethylsilanes (ArSiMe₃) and acyl chlorides in the presence of AlCl₃.⁶⁸⁵ Aryllithium and *Grignard reagents* react with iron pentacarbonyl to give aldehydes ArCHO.⁶⁸⁶ The reaction of CO with aryllithium may occur by electron transfer.⁶⁸⁷ Aryl iodides are converted to unsymmetrical diaryl ketones on treatment with arylmercury halides and nickel carbonyl: ArI + Ar'HgX + Ni(CO)₄ → ArCOAr'.⁶⁸⁸ Aryl iodides are carbonylated to give the aryl alkyl ketone with CO and R₃In.⁶⁸⁹ Aryl iodides are coupled with aryl acid chlorides in the presence of an In complex to form a diaryl ketone.⁶⁹⁰ Organomercury compounds undergo a similar reaction.⁶⁹¹ The aryllead reagent [PhPb(OAc)₂] was converted to benzophenone using NaOMe, CO, and a Pd catalyst.⁶⁹² Aryl iodides containing an ortho substituent with a β-cyano group that served as the source of a carbonyl group, was converted to a bicyclic ketone with a Pd catalyst at 130 °C in aq DMF.⁶⁹³

Diaryl ketones can also be prepared by coupling aryl iodides with phenylboronic acid (Reaction 12-28), in the presence of CO and a Pd catalyst.⁶⁹⁴ This reaction has been extended to heteroaromatic systems, with the preparation of phenyl 4-pyridyl ketone from phenylboronic acid and 4-iodopyridine.⁶⁹⁵ 2-Bromopyridine as coupled with phenylboronic acid, CO, and a Pd catalyst to give phenyl 2-pyridyl ketone.⁶⁹⁶ Carbonylation of an alkyne and an aryl halide, with CO and Pd and Cu catalysts, gave the alkynyl ketone RC≡C(C=O)Ar.⁶⁹⁷

13-16 Arylation of Silanes

Silyl and Silyloxy-de-halogenation, Aryl-de-silylation, and so on



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⁶⁹⁰ Papoian, V.; Minehan, T. J. *Org. Chem.* **2008**, 73, 7376.

⁶⁹¹ Baird, Jr., W.C.; Hartgerink, R.L.; Surridge, J.H. *J. Org. Chem.* **1985**, 50, 4601.

⁶⁹² Kang, S.-K.; Ryu, H.-C.; Choi, S.-C. *Synth. Commun.* **2001**, 31, 1035.

⁶⁹³ Pletnev, A.A.; Larock, R.C. *J. Org. Chem.* **2002**, 67, 9428.

⁶⁹⁴ Ishiyama, T.; Kizaki, H.; Miyauro, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, 34, 7595.

⁶⁹⁵ Couve-Bonnaire, S.; Caprentier, J.-F.; Mortreux, A.; Castanet, Y. *Tetrahedron Lett.* **2001**, 42, 3689.

⁶⁹⁶ Maerten, E.; Hassouna, F.; Couve-Bonnaire, S.; Mortreux, A.; Carpentiere, J.-F.; Castanet, Y. *Synlett* **2003**, 1874.

⁶⁹⁷ Ahmed, M.S.M.; Mori, A. *Org. Lett.* **2003**, 5, 3057. For a Pd-catalyzed reaction, see Liang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, 70, 6097.

In the presence of transition metal catalysts (e.g., Pd), trialkoxysilanes [$\text{HSi}(\text{OR})_3$] react with aryl halides to give the corresponding arylsilane.⁶⁹⁸ This transformation is an alternative to the *Suzuki coupling* (Reaction 13-12).⁶⁹⁹ The influence of silicon substituents on the cross-coupling reaction has been studied.⁷⁰⁰ A similar reaction was reported using a Rh catalyst.⁷⁰¹ Similar coupling of aryl halides with trialkylsilanes (HSiR_3) in the presence of a Pd,⁷⁰² or Rh catalyst,⁷⁰³ or PtO_2 ⁷⁰⁴ gives the arylsilane. Cyclic alkoxy silanes are prepared using Pd catalyzed cross-coupling reactions.⁷⁰⁵ Vinylsilanes are coupled to aryl halides to give the aryl alkene.⁷⁰⁶ Disilanes have also been employed, using a Pd catalyst.⁷⁰⁷ Arylsilanes can be coupled to aryl iodides using a Pd catalyst⁷⁰⁸ and in aqueous media.⁷⁰⁹ Arylsilanes react with alkyl halides to give the corresponding arene, in the presence of a Pd catalyst.⁷¹⁰

Other variations include the conversion of vinyl silanes to styrene derivatives upon treatment with Bu_4NF (TBAF), an aryl iodide and a Pd catalyst.⁷¹¹ Arylsilanes were coupled to alkenes to give the styrene derivative using palladium acetate in an oxygen atmosphere,⁷¹² or TBAF and an Ir catalyst.⁷¹³ Aryl iodides can be coupled to 1-methyl-1-vinyl- and 1-methyl-1-(prop-2-enyl)silacyclobutane with desilylation, using a Pd catalyst and TBAF, to give the corresponding styrene derivative.⁷¹⁴ Aryl silanes can be coupled to aryl iodides using Ag_2O and a Pd catalyst,⁷¹⁵ and arylsiloxanes [$\text{ArSi}(\text{OR})_3$] are coupled to aryl halides with TBAF and a Pd catalyst.⁷¹⁶ 1-Trialkylsilylalkynes ($\text{R}_3\text{Si}-\text{C}\equiv\text{C}-\text{R}'$) were coupled to aryl iodides using a Pd catalyst.⁷¹⁷

An alternative approach reacts aryllithium reagents with siloxanes [$\text{Si}(\text{OR})_4$], to give the aryl derivative $\text{ArSi}(\text{OR})_3$.⁷¹⁸ Biaryl derivatives are similarly prepared from

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⁷⁰² Yamanoi, Y. *J. Org. Chem.* **2005**, *70*, 9607.

⁷⁰³ Omachi, H.; Itami, K. *Chem. Lett.* **2009**, 38, 186.

⁷⁰⁴ Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* **2006**, *8*, 931.

⁷⁰⁵ Nakao, Y.; Imanaka, H.; Sahoo, A.K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952.

⁷⁰⁶ Denmark, S.E.; Tymonko, S.A. *J. Am. Chem. Soc.* **2005**, *127*, 8004; Denmark, S.E.; Butler, C.R. *J. Am. Chem. Soc.* **2008**, *130*, 3690.

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⁷⁰⁸ Denmark, S.E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495; Lee, H.M.; Nolan, S.P. *Org. Lett.* **2000**, *2*, 2053.

⁷⁰⁹ Denmark, S.E.; Ober, M.H. *Org. Lett.* **2003**, *5*, 1357.

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⁷¹² Parrish, J.P.; Jung, Y.C.; Shin, S.I.; Jung, K.W. *J. Org. Chem.* **2002**, *67*, 7127.

⁷¹³ Koike, T.; Du, X.; Sanada, T.; Danda, Y.; Mori, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 89.

⁷¹⁴ Denmark, S.E.; Wang, Z. *Synthesis* **2000**, 999.

⁷¹⁵ Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299.

⁷¹⁶ Mowery, M.E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137.

⁷¹⁷ Kabalka, G.W.; Wang, L.; Pagni, R.M. *Tetrahedron* **2001**, *57*, 8017; Denmark, S.E.; Tymonko, S.A. *J. Org. Chem.* **2003**, *68*, 9151.

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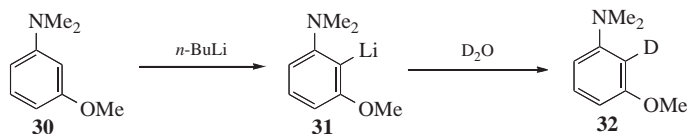
aryl halides.⁷¹⁹ Arylsiloxanes are similarly coupled at the ortho position of anilide derivatives.⁷²⁰

The reaction of NaBPh₄ (sodium tetraphenylborate) and a silyl dichloride (Ph₂SiCl₂) gives biphenyl.⁷²¹

13.C.ii. Hydrogen as Leaving Group⁷²²

13-17 Alkylation and Arylation

Alkylation or Alkyl-de-hydrogenation, and so on



The alkylation of aromatic rings was introduced, in part, in Reaction **10-57**. The reaction of an aromatic ring with an organolithium reagent can give H–Li exchange to form an aryllithium. This reaction tends to be slow if there are activating substituents on the aryl halide, or in the absence of diamine additives.⁷²³ When heteroatom substituents are present as in **30**, however, the reaction is facile and the Li goes into the 2 position (as in **31**).⁷²⁴ This regioselectivity can be quite valuable synthetically, and is now known as *directed ortho metalation*⁷²⁵ (see Reaction **10-57**). Subsequent reaction with a suitable electrophilic agent (e.g., D₂O) leads to **32** in this case. Aryllithium reagents give arylation. The reaction occurs by an addition–elimination mechanism and the adduct can be isolated.⁷²⁶ Upon heating of the adduct, elimination of LiH occurs and an alkylated product is obtained. With respect to C-2, the first step is the same as that of the S_NAr mechanism. The difference is that the unshared pair of electrons on the nitrogen combines with the lithium, so the extra pair of ring electrons has a place to go: It becomes the new unshared pair on the nitrogen.

With TMEDA/*n*-butyllithium mediated arene lithiation reactions, the viability of directive effects (complex-induced proximate effects) has been questioned,⁷²⁷ although it is not clear if this extends to other systems (particularly when there is a strong coordinating group (e.g., carbamate)).⁷²⁸ The 2 position is much more acidic than the 3 position (see Table 8.1), but a negative charge at C-3 is in a more favorable position to be

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⁷²² See Chupakhin, O.N.; Postovskii, I.Ya. *Russ. Chem. Rev.* **1976**, 45, 454. See Chupakhin, O.N.; Charushin, V.N.; van der Plas, H.C. *Tetrahedron* **1988**, 44, 1.

⁷²³ See Becht, J.-M.; Gissot, A.; Wagner, A.; Misokowski, C. *Tetrahedron Lett.* **2004**, 45, 9331.

⁷²⁴ Slocum, D.W.; Jennings, C.A. *J. Org. Chem.* **1976**, 41, 3653. However, the regioselectivity can depend on reaction conditions: See Meyers, A.I.; Avila, W.B. *Tetrahedron Lett.* **1980**, 3335.

⁷²⁵ See Snieckus, V. *Chem. Rev.* **1990**, 90, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* **1979**, 26, 1; Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* **1999**, 36, 1453. Also see, Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* **1999**, 36, 1453; Slocum, D.W.; Dietzel, P. *Tetrahedron Lett.* **1999**, 40, 1823.

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⁷²⁸ Hay, D. R.; Song, Z.; Smith, S.G.; Beak, P. *J. Am. Chem. Soc.* **1988**, 110, 8145.

stabilized by the Li^+ . Lithiation reactions do not necessarily rely on a complex-induced proximity effect.⁷²⁹ *N,N*-Dialkyl aryl-*O*-sulfamates are substrates for ortho metalation.⁷³⁰ Phenylaziridines also undergo this reaction.⁷³¹ Formation of the ortho arylmagnesium compound has been accomplished with bases of the form $(\text{R}_2\text{N})_2\text{Mg}$.⁷³² A directed meta metalation has been reported, using alkali metal mediated zincation.⁷³³ Note that the substrate-dependent mechanism of the ortho lithiation of aryloxazolines using butyllithium has been studied.⁷³⁴

Benzene, naphthalene, and phenanthrene have been alkylated with alkyllithium reagents, although the usual reaction with these reagents is Reaction **12-22**,⁷³⁵ and *Grignard reagents* have been used to alkylate naphthalene.⁷³⁶ The addition–elimination mechanism apparently applies in these cases too. A protected form of benzaldehyde (protected as the benzyl imine) has been similarly alkylated at the ortho- position with butyllithium.⁷³⁷ The alkylation of heterocyclic nitrogen compounds⁷³⁸ with alkyllithium reagents is called *Ziegler alkylation*. The reaction of 2-chloropyridine with 3 equiv of butyllithium– $\text{Me}_2\text{NCH}_2\text{CH}_2\text{OLi}$ and then iodomethane gave 2-chloro-6-methylpyridine.⁷³⁹ Note that H–Li exchange can be faster than Cl–Li exchange. Treatment of 2-chloro-5-phenylpyridine with *tert*-butyllithium leads to lithiation on the phenyl ring rather than Li–Cl exchange, and subsequent treatment with dimethyl sulfate gave 2-chloro-5-(2-methylphenyl)pyridine.⁷⁴⁰ The reaction of *N*-triisopropylsilyl indole with *tert*-butyllithium and then iodomethane gave the 3-methyl derivative.⁷⁴¹ Heteroaromatic compounds can be alkylated. Pyrrole, for example, reacts with an allylic halide and zinc to give primarily the 3-substituted pyrrole.⁷⁴²

Mercuration of aromatic compounds⁷⁴³ can be accomplished with mercuric salts, most often $\text{Hg}(\text{OAc})_2$,⁷⁴⁴ to give ArHgOAc . This is ordinary electrophilic aromatic substitution and takes place by the arenium ion mechanism (Sec. 11.A.i).⁷⁴⁵ Aromatic compounds can also be converted to arylthallium bis(trifluoroacetates) $[\text{ArTl}(\text{OOCF}_3)_2]$ by treatment

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⁷³¹ Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005**, *7*, 3749.

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⁷³⁴ Chadwick, S.T.; Ramirez, A.; Gupta, L.; Collum, D.B. *J. Am. Chem. Soc.* **2007**, *129*, 2259.

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⁷³⁸ See Vorbrüggen, H.; Maas, M. *Heterocycles*, **1988**, *27*, 2659. Also see Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199.

⁷³⁹ Choppin, S.; Gros, P.; Fort, Y. *Org. Lett.* **2000**, *2*, 803.

⁷⁴⁰ Fort, Y.; Rodriguez, A.L. *J. Org. Chem.* **2003**, *68*, 4918.

⁷⁴¹ Matsuzono, M.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **2001**, *42*, 7621.

⁷⁴² Yadav, J.S.; Reddy, B.V.S.; Reddy, P.M.; Srinivas, Ch. *Tetrahedron Lett.* **2002**, *43*, 5185.

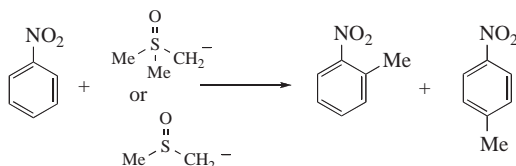
⁷⁴³ See Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, **1985**, pp. 60–97; Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, **1988**, pp. 308–318.

⁷⁴⁴ See Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, **1981**, pp. 1–145.

⁷⁴⁵ See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, **1972**, pp. 186–194. An alternative mechanism, involving radical cations, has been reported: Courtneidge, J.L.; Davies, A.G.; McGuchan, D.C.; Yazdi, S.N. *J. Organomet. Chem.* **1988**, *341*, 63.

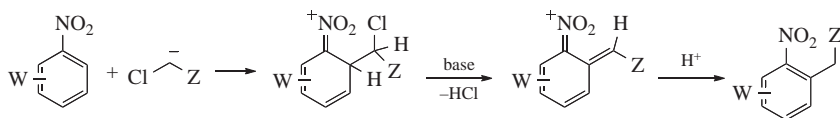
with thallium(III) trifluoroacetate⁷⁴⁶ in trifluoroacetic acid.⁷⁴⁷ These arylthallium compounds can be converted to phenols, aryl iodides or fluorides (Reaction 12-31), aryl cyanides (Reaction 12-34), aryl nitro compounds,⁷⁴⁸ or aryl esters (Reaction 12-33). The mechanism of thallation appears to be complex, with electrophilic and electron-transfer mechanisms both taking place.⁷⁴⁹ Transient metalated aryl complexes can be formed that react with another aromatic compound. Aryl iodides reacted with benzene to form a biaryl in the presence of an Ir catalyst.⁷⁵⁰ Aniline derivatives reacted with TiCl_4 to give the para-homo coupling product ($\text{R}_2\text{N}-\text{Ar}-\text{Ar}-\text{NR}_2$).⁷⁵¹

Aromatic nitro compounds can be methylated with dimethyloxosulfonium methylid⁷⁵² or the methylsulfinyl carbanion (obtained by treatment of DMSO with a strong base)⁷⁵³:



The reactions with the sulfur carbanions are especially useful, since none of these substrates can be methylated by the *Friedel-Crafts* procedure (Reaction 11-10).

A different kind of alkylation of nitro compounds uses carbanion nucleophiles that have a chlorine at the carbanionic carbon. The following process takes place:⁷⁵⁴



This type of process is called *vicarious nucleophilic substitution of hydrogen*.⁷⁵⁵ The Z group is electron withdrawing (e.g., SO_2R , SO_2OR , SO_2NR_2 , COOR , or CN); it stabilizes the negative charge. The carbanion attacks the activated ring ortho or para to the nitro group.⁷⁵⁶ Hydride ion (H^-) is not normally a leaving group, but in this case the presence of the adjacent Cl allows the hydrogen to be replaced. Hence, Cl is a “vicarious” leaving group. Other leaving groups have been used (e.g., OMe and SPh), but Cl is generally the best. Many W groups in the ortho, meta, or para positions do not interfere. The reaction is

⁷⁴⁶ See Uemura, S. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, **1983**, pp. 165–241.

⁷⁴⁷ Taylor, E.C.; Kienzle, F.; McKillop, A. *Org. Synth.* **VI**, 826; Taylor, E.C.; Katz, A.H.; Alvarado, S.I.; McKillop, A. *J. Organomet. Chem.* **1985**, 285, C9. See Usyatinskii, A.Ya.; Bregadze, V.I. *Russ. Chem. Rev.* **1988**, 57, 1054.

⁷⁴⁸ Uemura, S.; Toshimitsu, A.; Okano, M. *Bull. Chem. Soc. Jpn.* **1976**, 49, 2582.

⁷⁴⁹ Lau, W.; Kochi, J.K. *J. Am. Chem. Soc.* **1984**, 106, 7100; **1986**, 108, 6720.

⁷⁵⁰ Fujita, K.-i.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004**, 1926.

⁷⁵¹ Periasamy, M.; Jayakumar, K.N.; Bharathi, P. *J. Org. Chem.* **2000**, 65, 3548.

⁷⁵² Traynelis, V.J.; McSweeney, J.V. *J. Org. Chem.* **1966**, 31, 243.

⁷⁵³ Russell, G.A.; Weiner, S.A. *J. Org. Chem.* **1966**, 31, 248.

⁷⁵⁴ See Stahly, G.P.; Stahly, B.C.; Maloney, J.R. *J. Org. Chem.* **1988**, 53, 690.

⁷⁵⁵ See Makosza, M. *Synthesis* **1991**, 103; *Russ. Chem. Rev.* **1989**, 58, 747; Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, 20, 282.

⁷⁵⁶ For a discussion of the mechanism of vicarious nucleophilic aromatic substitution, see Makosza, M.; Lemek, T.; Kwast, A.; Terrier, F. *J. Org. Chem.* **2002**, 67, 394.

also successful for di- and trinitro compounds, for nitronaphthalenes,⁷⁵⁷ and for many nitro heterocycles, $^-Z-CR-Cl$ may also be used.⁷⁵⁸ When the nucleophile is Br_3C^- or Cl_3C^- , the product is $ArCHX_2$, which can easily be hydrolyzed to $ArCHO$.⁷⁵⁹ This is therefore an indirect way of formylating an aromatic ring containing one or more NO_2 groups, which cannot be done by any of the formylations mentioned in Reaction 11-1-11-18.

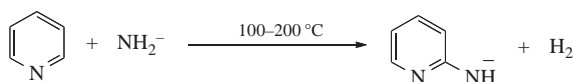
Replacement of an amino group is possible. When aniline derivatives were treated with allyl bromide and *tert*-butyl nitrite (*t*-BuONO), the aryl-allyl coupling product was formed ($Ar-NH_2 \rightarrow Ar-CH_2CH=CH_2$).⁷⁶⁰

For the introduction of CH_2SR groups into phenols, see Reaction 11-23. See also, Reaction 14-19.

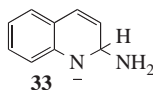
OS II, 517.

13-18 Amination of Nitrogen Heterocycles

Amination or Amino-de-hydrogenation



Pyridine and other heterocyclic nitrogen compounds can be aminated with alkali metal amides in a process called the *Chichibabin reaction*.⁷⁶¹ The attack is always in the 2 position unless both such positions are filled, in which case the 4 position is attacked. Substituted alkali metal amides (e.g., RNH^- and R_2N^-), have also been used. The mechanism is probably similar to that of Reaction 13-17. The existence of intermediate ions (e.g., 33)



(from quinoline) has been demonstrated by NMR spectra.⁷⁶² A pyridyne type of intermediate was ruled out by several observations including the facts that 3-ethylpyridine gave 2-amino-3-ethylpyridine⁷⁶³ and that certain heterocycles that cannot form an aryne could nevertheless be successfully aminated. Nitro compounds do not give this reaction,⁷⁶⁴ but they have been aminated ($ArH \rightarrow ArNH_2$ or $ArNHR$) via the vicarious substitution principle (see Reaction 13-17), using 4-amino- or 4-alkylamino-1,2,4-triazoles as nucleophiles.⁷⁶⁵ The vicarious leaving group in this case is the triazole ring. Note, however, that 3-nitropyridine was converted to 6-amino-3-nitropyridine by reaction with KOH, hydroxylamine, and $ZnCl_2$.⁷⁶⁶

⁷⁵⁷ Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1987**, 711.

⁷⁵⁸ See Mudryk, B.; Makosza, M. *Tetrahedron* **1988**, 44, 209.

⁷⁵⁹ Makosza, M.; Owczarczyk, Z. *J. Org. Chem.* **1989**, 54, 5094.

⁷⁶⁰ Ek, F.; Axelsson, O.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* **2002**, 67, 6376.

⁷⁶¹ See Vorbrüggen, H. *Adv. Heterocycl. Chem.* **1990**, 49, 117; McGill, C.K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988**, 44, 1; Pozharskii, A.F.; Simonov, A.M.; Doron'kin, V.N. *Russ. Chem. Rev.* **1978**, 47, 1042.

⁷⁶² Wozniak, M.; Baránski, A.; Nowak, K.; van der Plas, H.C. *J. Org. Chem.* **1987**, 52, 5643.

⁷⁶³ Ban, Y.; Wakamatsu, T. *Chem. Ind. (London)* **1964**, 710.

⁷⁶⁴ See Levitt, L.S.; Levitt, B.W. *Chem. Ind. (London)* **1975**, 520.

⁷⁶⁵ Katritzky, A.R.; Laurenzo, K.S. *J. Org. Chem.* **1986**, 51, 5039; **1988**, 53, 3978.

⁷⁶⁶ Bakke, J.M.; Svensen, H.; Trevisan, R. *J. Chem. Soc. Perkin Trans. 1* **2001**, 376.

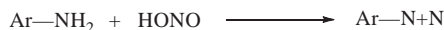
Analogous reactions have been carried out with hydrazide ions (R_2NNH^-).⁷⁶⁷ A mixture of NO_2 and O_3 , with excess $NaHSO_3$, converted pyridine to 3-aminopyridine.⁷⁶⁸ For other methods of aminating aromatic rings, see Reaction 11-6.

There are no *Organic Syntheses* references, but see OS V, 977, for a related reaction.

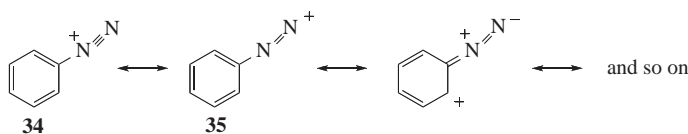
13.C.iii. Nitrogen as Leaving Group

The diazonium group can be replaced by a number of groups.⁷⁶⁹ Some of these are nucleophilic substitutions, with S_N1 mechanisms (Sec. 10.A.ii), but others are free radical reactions and are treated in Chapter 14. The solvent in diazonium group reactions is usually water. With other solvents it has been shown that the S_N1 mechanism is favored by solvents of low nucleophilicity, while those of high nucleophilicity favor free radical mechanisms.⁷⁷⁰ The N_2^+ group⁷⁷¹ can be replaced by Cl^- , Br^- , and CN^- , by a nucleophilic mechanism (see OS IV, 182), but the *Sandmeyer reaction* is much more useful (Reaction 14-20). Transition metal catalyzed reactions are known involving aryldiazonium salts, and diazonium variants of the *Heck reaction* (13-10) and *Suzuki coupling* (13-12) were mentioned previously. As mentioned in Section 13.B.i, it must be kept in mind that the N_2^+ group can activate the removal of another group on the ring. In a few cases, nitrogen groups (e.g., nitro or ammonium) can be replaced.

13-19 Diazotization



When primary aromatic amines are treated with nitrous acid, diazonium salts are formed.⁷⁷² The reaction also occurs with aliphatic primary amines, but aliphatic diazonium ions are extremely unstable, even in solution (see Sec. 10.G.iii). Aromatic diazonium ions are more stable, because of the resonance interaction between the nitrogen atoms and the ring:



⁷⁶⁷ Kauffmann, T.; Hansen, J.; Kosel, C.; Schoeneck, W. *Liebigs Ann. Chem.* **1962**, 656, 103.

⁷⁶⁸ Suzuki, H.; Iwaya, M.; Mori, T. *Tetrahedron Lett.* **1997**, 38, 5647.

⁷⁶⁹ See Wulfman, D.S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1; Wiley, NY, **1978**, pp. 286–297.

⁷⁷⁰ Szele, I.; Zollinger, H. *Helv. Chim. Acta* **1978**, 61, 1721.

⁷⁷¹ See Pérez, P. *J. Org. Chem.* **2003**, 68, 5886.

⁷⁷² See in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, Wiley, NY, **1978**, the articles by Hegarty, A.F. pt. 2, pp. 511–591, and Schank, K. pt. 2, pp. 645–657; Godovikova, T.I.; Rakitin, O.A.; Khmel'nitskii, L.I. *Russ. Chem. Rev.* **1983**, 52, 440; Challis, B.C.; Butler, A.R. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, **1968**, pp. 305–320. See Butler, A.R. *Chem. Rev.* **1975**, 75, 241.

Incidentally, **34** contributes more than **35**, as shown by bond-distance measurements.⁷⁷³ In benzenediazonium chloride, the C—N distance is $\sim 1.42 \text{ \AA}$, and the N—N distance $\sim 1.08 \text{ \AA}$,⁷⁷⁴ and these values fit more closely to a single and a triple bond than to two double bonds (see Table 1.5). Even aromatic diazonium salts are unstable at temperatures other than about $<5^\circ\text{C}$. A few are more stable (e.g., the diazonium salt obtained from sulfanilic acid), which is stable up to 10 or 15°C . Diazonium salts are usually prepared in aqueous solution and *used without isolation*.⁷⁷⁵ While it is possible to prepare solid diazonium salts (see Reaction **13-23**), many dry diazonium salts are explosive if not handled with great care and extreme caution should be exercised. The stability of aryl diazonium salts can be increased by crown ether complexion.⁷⁷⁶

For aromatic amines, the reaction is very general. Halogen, nitro, alkyl, aldehyde, sulfonic acid, and so on, groups do not interfere. Since aliphatic amines do not react with nitrous acid below a pH of ~ 3 , it is even possible, by working at a pH ~ 1 , to diazotize an aromatic amine without disturbing an aliphatic amino group in the same molecule.⁷⁷⁷



If an aliphatic amino group is α to a COOR, CN, CHO, COR, and so on, and has a hydrogen, treatment with nitrous acid gives not a diazonium salt, but a *diazo compound*.⁷⁷⁸ Such diazo compounds can also be prepared, often more conveniently, by treatment of the substrate with isoamyl nitrite ($\text{Me}_2\text{CHCH}_2\text{CH}_2\text{ONO}$) and a small amount of acid.⁷⁷⁹ Certain heterocyclic amines also give diazo compounds rather than diazonium salts.⁷⁸⁰

Despite the fact that diazotization takes place in acid solution, the actual reactive species is not the salt of the amine, but is the small amount of free amine present.⁷⁸¹ Because aliphatic amines are stronger bases than aromatic ones that at pH values <3 there is not enough free amine present for the former to be diazotized, while the latter still undergo the reaction. In dilute acid, the actual attacking species is N_2O_3 , which acts as a carrier of NO^+ . Evidence is that the reaction is second order in nitrous acid and, at sufficiently low acidities, the amine does not appear in the rate expression.⁷⁸² Under these conditions the mechanism is

⁷⁷³ See Sorriso, S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, **1978**, pp. 95–105.

⁷⁷⁴ Rømming, C. *Acta Chem. Scand.* **1963**, 17, 1444; Sorriso, S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, **1978**, p. 98; Ball, R.G.; Eloffson, R.M. *Can. J. Chem.* **1985**, 63, 332.

⁷⁷⁵ See Wulfman, D.S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, **1978**, pp. 247–339.

⁷⁷⁶ Korzeniowski, S.H.; Leopold, A.; Beadle, J.R.; Ahern, M.F.; Sheppard, W.A.; Khanna, R.K.; Gokel, G.W. *J. Org. Chem.* **1981**, 46, 2153, and references cited therein; Bartsch, R.A. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt.1, Wiley, NY, **1983**, pp. 889–915.

⁷⁷⁷ Kornblum, N.; Iffland, D.C. *J. Am. Chem. Soc.* **1949**, 71, 2137.

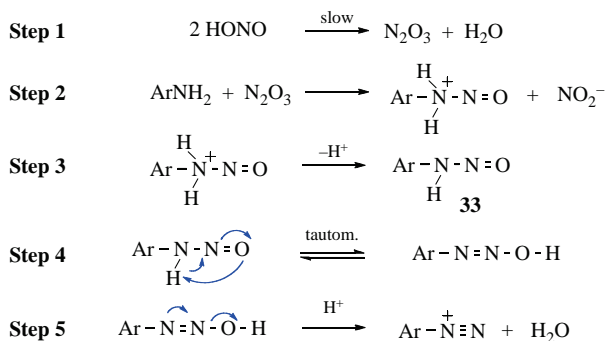
⁷⁷⁸ See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, **1986**. For reviews, see, in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, **1978**, the articles by Regitz, M. pt. 2, pp. 659–708, 751–820, and Wulfman, D.S.; Linstumelle, G.; Cooper, C.F. pt. 2, pp. 821–976.

⁷⁷⁹ Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* **1975**, 31, 227.

⁷⁸⁰ Butler, R.N. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, **1968**, p. 305.

⁷⁸¹ Challis, B.C.; Larkworthy, L.F.; Ridd, J.H. *J. Chem. Soc.* **1962**, 5203.

⁷⁸² Hughes, E.D.; Ingold, C.K.; Ridd, J.H. *J. Chem. Soc.* **1958**, 58, 65, 77, 88; Hughes, E.D.; Ridd, J.H. *J. Chem. Soc.* **1958**, 70, 82.



Other evidence exists for this mechanism.⁷⁸³ Other attacking species can be NOCl, H_2NO_2^+ , and at high acidities even NO^+ . Nucleophiles (e.g., Cl^- , SCN^- , and thiourea) catalyze the reaction by converting the HONO to a better electrophile (e.g., $\text{HNO}_2 + \text{Cl}^- + \text{H}^+ \rightarrow \text{NOCl} + \text{H}_2\text{O}$).⁷⁸⁴

N-Aryl ureas are converted to the aryldiazonium nitrate upon treatment with NaNO_2 and H_2SO_4 in dioxane⁷⁸⁵ or with $\text{DMF}-\text{NO}_2$ in DMF.⁷⁸⁶

There are many preparations of diazonium salts listed in *Organic Syntheses*, but they are always prepared for use in other reactions. They are listed under reactions in which they are used. The preparation of aliphatic diazo compounds can be found in OS **III**, 392; **IV**, 424. See also, OS **VI**, 840.

13-20 Hydroxylation of Aryldiazonium Salts

Hydroxy-de-diazoniatio



This reaction is formally analogous to **13-1**, but with a N_2^+ leaving group rather than a halide. Water is usually present whenever diazonium salts are made, but at these temperatures (0–5 °C) the reaction proceeds very slowly. When it is *desired* to have OH replace the diazonium group, the excess nitrous acid is destroyed and the solution is usually boiled. Some diazonium salts require even more vigorous treatment, for example, boiling with aq H_2SO_4 or with trifluoroacetic acid containing potassium trifluoroacetate.⁷⁸⁷ The reaction can be performed on solutions of any diazonium salts, but hydrogen sulfates are preferred to chlorides or nitrates, since in these cases there is competition from the nucleophiles Cl^- or NO_3^- .

A better method, which is faster, avoids side reactions, takes place at room temperature, and gives higher yields consists of adding Cu_2O to a dilute solution of the diazonium salt dissolved in a solution containing a large excess of $\text{Cu}(\text{NO}_3)_2$.⁷⁸⁸ Aryl radicals are intermediates when this method is used. It has been shown that aryl radicals are at least

⁷⁸³ See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, **1988**, pp. 95–109; Ridd, J.H. *Q. Rev. Chem. Soc.* **1961**, *15*, 418, p. 422.

⁷⁸⁴ Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, **1988**, pp. 84–93.

⁷⁸⁵ Zhang, Z.; Zhang, Q.; Zhang, S.; Liu, X.; Zhao, G. *Synth. Commun.* **2001**, *31*, 329.

⁷⁸⁶ Zhang, O.Z.; Zhang, S.; Zhang, J. *Synth. Commun.* **2001**, *31*, 1243.

⁷⁸⁷ Horning, D.E.; Ross, D.A.; Muchowski, J.M. *Can. J. Chem.* **1973**, *51*, 2347.

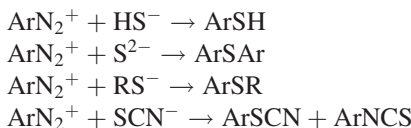
⁷⁸⁸ Cohen, T.; Dietz, Jr., A.G.; Miser, J.R. *J. Org. Chem.* **1977**, *42*, 2053.

partly involved when ordinary hydroxy-de-diazonation is carried out in weakly alkaline aqueous solution.⁷⁸⁹ Decomposition of arenediazonium tetrafluoroborates in F_3CSO_2OH gives aryl triflates directly, in high yields.⁷⁹⁰

OS I, 404; **III**, 130, 453, 564; **V**, 1130.

13-21 Replacement by Sulfur-Containing Groups

Mercapto-de-diazonation, and so on



These reactions are convenient methods for incorporating a sulfur-containing group onto an aromatic ring. With Ar'S^- , diazosulfides (Ar-N=N-S-Ar') are intermediates,⁷⁹¹ which can in some cases be isolated.⁷⁹² Thiophenols can be made as shown above, but more often the diazonium ion is treated with EtO-CSS^- or S_2^{2-} , which give the expected products, and these are easily convertible to thiophenols. Aryldiazonium salts are prepared by the reaction of an aniline derivative with an alkyl nitrite (RONO), and when formed in the presence of dimethyl disulfide (MeS-SMe), the product is the thioether (Ar-S-Me).⁷⁹³ Aryl triflates have been converted to the aryl thiol using NaST(P5) and a Pd catalyst, followed by treatment with tetrabutylammonium fluoride⁷⁹⁴ (see also, Reaction **14-22**).

OS **II**, 580; **III**, 809 (but see OS **V**, 1050). Also see, OS **II**, 238.

13-22 Replacement by Iodine

Iodo-de-diazonation



One of the best methods for the introduction of iodine into aromatic rings (see Reaction **13-7**) is the reaction of diazonium salts with iodide ions.⁷⁹⁵ Analogous reactions with chloride, bromide, and fluoride ions give poorer results, and Reactions **14-20** and **13-23** are preferred for the preparation of aryl chlorides, bromides, and fluorides. However, when other diazonium reactions are carried out in the presence of these ions, halides are usually side products. Aniline has also been converted to fluorobenzene by treatment with *t*-BuONO and SiF_4 followed by heating.⁷⁹⁶ A related reaction between PhN=N-NR_2 and iodine gave iodobenzene.⁷⁹⁷

⁷⁸⁹ Dreher, E.; Niederer, P.; Rieker, A.; Schwarz, W.; Zollinger, H. *Helv. Chim. Acta* **1981**, 64, 488.

⁷⁹⁰ Yoneda, N.; Fukuhara, T.; Mizokami, T.; Suzuki, A. *Chem. Lett.* **1991**, 459.

⁷⁹¹ Abeywickrema, A.N.; Beckwith, A.L.J. *J. Am. Chem. Soc.* **1986**, 108, 8227, and references cited therein.

⁷⁹² See Price, C.C.; Tsunawaki, S. *J. Org. Chem.* **1963**, 28, 1867.

⁷⁹³ Allaire, F.S.; Lyga, J.W. *Synth. Commun.* **2001**, 31, 1857.

⁷⁹⁴ Arnould, J.C.; Didelot, M.; Cadilhac, C.; Pasquet, M.J. *Tetrahedron Lett.* **1996**, 37, 4523.

⁷⁹⁵ See Krasnokutskaya, E.A.; Semenischeva, N.I.; Filimonov, V.D.; Knochel, P. *Synthesis* **2007**, 81; Filimonov, V.D.; Semenischeva, N.I.; Krasnokutskaya, E.A.; Tretyakov, A.N.; Hwang, H.Y.; Chi, K.W. *Synthesis* **2008**, 185.

⁷⁹⁶ Tamura, M.; Shibakami, M.; Sekiya, A. *Eur. J. Org. Chem.* **1998**, 725.

⁷⁹⁷ Wu, Z.; Moore, J.S. *Tetrahedron Lett.* **1994**, 35, 5539.

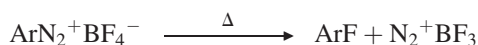
The actual attacking species is probably not only I^- if it is I^- at all. The iodide ion is oxidized (by the diazonium ion, nitrous acid, or some other oxidizing agent) to iodine, which in a solution containing iodide ions is converted to I_3^- ; this is the actual attacking species, at least partly. This was shown by isolation of $\text{ArN}_2^+ \text{I}_3^-$ salts, which, on standing, gave ArI .⁷⁹⁸ From this, it can be inferred that the reason the other halide ions give poor results is *not* that they are poor nucleophiles but *rather* they are poor reducing agents (compared with iodide). There is also evidence for a free radical mechanism.⁷⁹⁹

The hydroxyl group of a phenol can be replaced with iodine. The reaction of phenol with a boronic ester and a Pd catalyst, followed by reaction with NaI and chloramine-T (see Reaction 15-52) converts phenol to iodobenzene.⁸⁰⁰ Arylboronic acids are converted to the aryl fluoride with Selectfluor, in the presence of a Pd catalyst.⁸⁰¹

OS II, 351, 355, 604; V, 1120.

13-23 The Schiemann Reaction

Fluoro-de-diazonation (overall transformation)



Heating diazonium fluoroborates (the *Schiemann* or *Balz–Schiemann reaction*) is by far the best way to introduce fluorine into an aromatic ring.⁸⁰² In the most common procedure, the tetrafluoroborate salts are prepared by diazotizing as usual with nitrous acid and HCl and then adding a cold aqueous solution of NaBF_4 , HBF_4 , or NH_4BF_4 . A precipitate forms, which is dried, and the salt is heated in the dry state. These salts are unusually stable for diazonium salts, and the reaction is usually successful (since diazonium salts are generally unstable, care should be exercised any time a diazonium salt is dried). In general, any aromatic amine that can be diazotized will form a BF_4^- salt, usually with high yields. The diazonium fluoroborates can be formed directly from primary aromatic amines with *tert*-butyl nitrite and BF_3 -etherate.⁸⁰³ The reaction has also been carried out on $\text{ArN}_2^+ \text{PF}_6^-$, $\text{ArN}_2^+ \text{SbF}_6^-$, and $\text{ArN}_2^+ \text{AsF}_6^-$ salts, in many cases with better yields.⁸⁰⁴ Aryl chlorides and bromides are commonly prepared by the *Sandmeyer reaction* (14-20). In an alternative procedure, aryl fluorides are prepared by treatment of aryltriazenes $\text{Ar}-\text{N}=\text{N}-\text{NR}_2$ with 70% HF in pyridine.⁸⁰⁵

The mechanism is of the $\text{S}_{\text{N}}1$ type. That aryl cations are intermediates was shown by the following experiments⁸⁰⁶: Aryl diazonium chlorides are known to arylate other aromatic rings by a free radical mechanism (see Reaction 13-27). In radical arylation it does not matter whether the other ring contains electron-withdrawing or electron-donating groups; in either case a mixture of isomers is obtained, since the attack is not by a charged species.

⁷⁹⁸ Carey, J.G.; Millar, I.T. *Chem. Ind. (London)* **1960**, 97.

⁷⁹⁹ Packer, J.E.; Taylor, R.E.R. *Aust. J. Chem.* **1985**, 38, 991; Abeywickrema, A.N.; Beckwith, A.L.J. *J. Org. Chem.* **1987**, 52, 2568.

⁸⁰⁰ Thompson, A.L.S.; Kabalka, G.W.; Akula, M.R.; Huffman, J.W. *Synthesis* **2005**, 547.

⁸⁰¹ Furuya, T.; Kaiser, H.M.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, 47, 5993.

⁸⁰² See Suschitzky, H. *Adv. Fluorine Chem.* **1965**, 4, 1.

⁸⁰³ Doyle, M.P.; Bryker, W.J. *J. Org. Chem.* **1979**, 44, 1572.

⁸⁰⁴ Sellers, C.; Suschitzky, H. *J. Chem. Soc. C* **1968**, 2317.

⁸⁰⁵ Rosenfeld, M.N.; Widdowson, D.A. *J. Chem. Soc. Chem. Commun.* **1979**, 914. For another alternative procedure, see Yoneda, N.; Fukuhara, T.; Kikuchi, T.; Suzuki, A. *Synth. Commun.* **1989**, 19, 865.

⁸⁰⁶ See also, Swain, C.G.; Sheats, J.E.; Harbison, K.G. *J. Am. Chem. Soc.* **1975**, 97, 783, 796; Becker, H.G.O.; Israel, G. *J. Prakt. Chem.* **1979**, 321, 579.

If an aryl radical were an intermediate in the *Schiemann reaction* and the reaction were run in the presence of other rings, it should not matter what kinds of groups were on these other rings: Mixtures of biaryls should be obtained in all cases. But if an aryl cation is an intermediate in the *Schiemann reaction*, compounds containing meta-directing groups (i.e., meta-directing for *electrophilic* substitutions), should be meta arylated and those containing ortho–para directing groups should be ortho and para arylated, since an aryl cation should behave in this respect like any electrophile (see Chapter 11). Experiments have shown⁸⁰⁷ that such orientation is observed, demonstrating that the *Schiemann reaction* has a positively charged intermediate. The attacking species, in at least some instances, is not F^- but BF_4^- .⁸⁰⁸

OS II, 188, 295, 299; V, 133.

13-24 Conversion of Amines to Azo Compounds

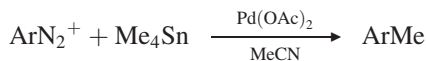
N-Arylimino-de-dihydro-bisubstitution



Aromatic nitroso compounds combine with primary arylamines in glacial acetic acid to give symmetrical or unsymmetrical azo compounds (the *Mills reaction*).⁸⁰⁹ A wide variety of substituents may be present in both aryl groups. Unsymmetrical azo compounds have also been prepared by the reaction between aromatic nitro compounds ($ArNO_2$) and *N*-acyl aromatic amines ($Ar'NHAc$).⁸¹⁰ The use of phase-transfer catalysis increased the yields.

13-25 Methylation, Vinylation, and Arylation of Diazonium Salts

Methyl-de-diazonation, and so on



A methyl group can be introduced into an aromatic ring by treatment of diazonium salts with tetramethyltin and a Pd catalyst.⁸¹¹ The reaction has been performed with Me, Cl, Br, and NO_2 groups on the ring. A vinylic group can be introduced with $CH_2=CHSnBu_3$. When an aryl amine is treated with *tert*-butyl hyponitrite (*t*-BuONO) and allyl bromide, the nitrogen is displaced to give the allyl–aryl compound.⁸¹²

Aryl diazonium salts can be used coupled with alkenes in a *Heck-like reaction* (Reaction 13-10).⁸¹³ Other reactive aryl species also couple with aryldiazonium salts in the presence of a Pd catalyst.⁸¹⁴ A *Suzuki-type* coupling (Reaction 13-12) has also been reported using arylboronic acids, aryldiazonium salts, and a Pd catalyst.⁸¹⁵

⁸⁰⁷ Makarova, L.G.; Matveeva, M.K. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1958**, 548; Makarova, L.G.; Matveeva, M.K.; Gribchenko, E.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1958**, 1399.

⁸⁰⁸ Swain, C.G.; Rogers, R.J. *J. Am. Chem. Soc.* **1975**, 97, 799.

⁸⁰⁹ See Boyer, J.H. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, **1969**, pp. 278–283.

⁸¹⁰ Ayyangar, N.R.; Naik, S.N.; Srinivasan, K.V. *Tetrahedron Lett.* **1989**, 30, 7253.

⁸¹¹ Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1983**, 48, 1333.

⁸¹² Ek, F.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* **2003**, 68, 1911.

⁸¹³ Sengupta, S.; Bhattacharya, S. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1943.

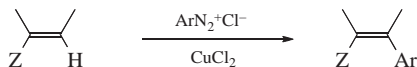
⁸¹⁴ Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1997**, 38, 4393.

⁸¹⁵ Darses, S.; Jeffery, T.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1996**, 37, 3857.

Aryltrifluoroborates (Reaction **12-28**) react with aryldiazonium salts in the presence of a Pd catalyst to give the corresponding biaryl.⁸¹⁶ See Reaction **13-12**. Arylborate esters also react using a Pd catalyst, and the aryl diazonium unit reacts faster than an aryl halide.⁸¹⁷

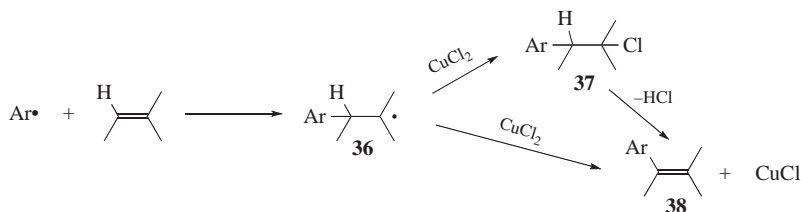
13-26 Arylation of Activated Alkenes by Diazonium Salts: Meerwein Arylation

Arylation or Aryl-de-hydrogenation



Alkenes activated by an electron-withdrawing group (Z may be C=C, halogen, C=O, Ar, CN, etc.) can be arylated by treatment with a diazonium salt and a cupric chloride⁸¹⁸ catalyst. This is called the *Meerwein arylation reaction*.⁸¹⁹ Addition of ArCl to the double bond (to give Z(Cl)C—CHAr) is a side reaction (**15-46**). In an improved procedure, an arylamine is treated with an alkyl nitrite (generating ArN₂⁺ *in situ*) and a copper(II) halide in the presence of the alkene.⁸²⁰

The mechanism is probably of the free radical type, with Ar• (**36**) forming as in Reaction **14-20**, and then halogen transfer to give **37** or elimination to give **38**.⁸²¹

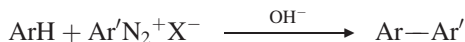


The radical **36** can react with cupric chloride by two pathways, one of which leads to addition and the other to substitution. Even when the addition pathway is taken, however, the substitution product may still be formed by subsequent elimination of HCl. Note that radical reactions are presented in Chapter 14, but the coupling of an alkene with an aromatic compound containing a leaving group prompted its placement here. Note the similarity to the *Heck reaction* in Reaction **13-10**.

OS IV, 15.

13-27 Arylation of Aromatic Compounds by Diazonium Salts

Arylation or Aryl-de-hydrogenation



⁸¹⁶ Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875.

⁸¹⁷ Willis, D.M.; Strongin, R.M. *Tetrahedron Lett.* **2000**, 41, 6271.

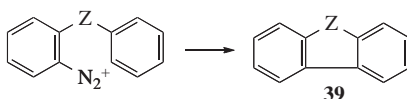
⁸¹⁸ See Ganushchak, N.I.; Obushak, N.D.; Luka, G.Ya. *J. Org. Chem. USSR* **1981**, 17, 765.

⁸¹⁹ Dombrovskii, A.V. *Russ. Chem. Rev.*, **1984**, 53, 943; Rondestvedt, Jr., C.S. *Org. React.*, **1976**, 24, 225.

⁸²⁰ Doyle, M.P.; Siegfried, B.; Elliott, R.C.; Dellaria, Jr., J.F. *J. Org. Chem.* **1977**, 42, 2431.

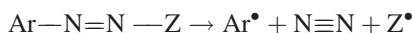
⁸²¹ Dickerman, S.C.; Vermont, G.B. *J. Am. Chem. Soc.* **1962**, 84, 4150; Morrison, R.T.; Cazes, J.; Samkoff, N.; Howe, C.A. *J. Am. Chem. Soc.* **1962**, 84, 4152.

When the normally acidic solution of a diazonium salt is made alkaline, the aryl portion of the diazonium salt can couple with another aromatic ring. Known as the *Gomberg* or *Gomberg–Bachmann reaction*,⁸²² it has been performed on several types of aromatic rings and on quinones. Yields are not high (usually <40%) because of the many side reactions undergone by diazonium salts, although higher yields have been obtained under phase-transfer conditions.⁸²³ The conditions of the *Meerwein reaction* (**13-26**), treatment of the solution with a copper-ion catalyst, have also been used, as has the addition of sodium nitrite in DMSO (to benzenediazonium tetrafluoroborate).⁸²⁴ When the *Gomberg–Bachmann reaction* is performed intramolecularly as in the formation of **39**, either by the alkaline solution or by the copper-ion procedure, it is called the *Pschorr reaction*⁸²⁵ and yields are usually somewhat higher. Still higher yields have been obtained by carrying out the *Pschorr reaction* electrochemically.⁸²⁶ The *Pschorr reaction* has been carried out for $Z = \text{CH}=\text{CH}$, CH_2CH_2 , NH , $\text{C}=\text{O}$, CH_2 , and quite a few others. A rapid and convenient way to diazotize the amine substrate uses isopropyl nitrite in the presence of sodium iodide, in which case the ring-closed product is formed in one step.⁸²⁷ Palladium-catalyzed arylation of arenediazonium salts are known.⁸²⁸



Other compounds with nitrogen–nitrogen bonds have been used instead of diazonium salts. Among these are *N*-nitroso amides [$\text{ArN}(\text{NO})\text{COR}$], triazenes,⁸²⁹ and azo compounds. Still another method involves treatment of an aromatic primary amine directly with an alkyl nitrite in an aromatic substrate as solvent.⁸³⁰

In each case, the mechanism involves generation of an aryl radical from a covalent azo compound. In acid solution, diazonium salts are ionic and their reactions are polar. When they cleave, the product is an aryl cation (see Sec. 13.A.i). However, in neutral or basic solution, diazonium ions are converted to covalent compounds, and these cleave to give free radicals (Ar^\bullet and Z^\bullet). Note that radical reactions are presented in Chapter 14, but the coupling of an aromatic ring with an aromatic compound containing a leaving group prompted its placement here. Note the similarity to the *Suzuki Reaction* in **13-12**.



⁸²² See Bolton, R.; Williams, G.H. *Chem. Soc. Rev.*, **1986**, 15, 261; Hey, D.H. *Adv. Free-Radical Chem.* **1966**, 2, 47. Also see Verrin, G.; Dou, H.J.; Metzger, J. *Bull. Soc. Chim. Fr.* **1972**, 1173.

⁸²³ Beadle, J.R.; Korzeniowski, S.H.; Rosenberg, D.E.; Garcia-Slanga, B.J.; Gokel, G.W. *J. Org. Chem.* **1984**, 49, 1594.

⁸²⁴ Kamigata, N.; Kurihara, T.; Minato, H.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* **1971**, 44, 3152.

⁸²⁵ For a review, see Abramovitch, R.A. *Adv. Free-Radical Chem.* **1966**, 2, 87.

⁸²⁶ Eloffson, R.M.; Gadallah, F.F. *J. Org. Chem.* **1971**, 36, 1769.

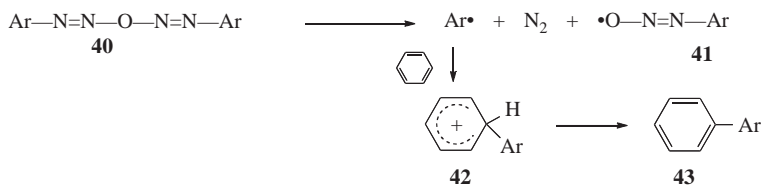
⁸²⁷ Chauncy, B.; Gellert, E. *Aust. J. Chem.* **1969**, 22, 993. See also, Duclos, Jr., R.I.; Tung, J.S.; Rappoport, H. *J. Org. Chem.* **1984**, 49, 5243.

⁸²⁸ Robinson, M.K.; Kochurina, V.S.; Hanna, Jr., J.M. *Tetrahedron Lett.* **2007**, 48, 7687.

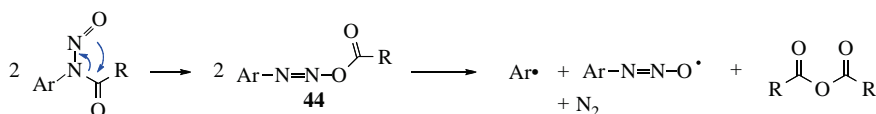
⁸²⁹ See Butler, R.N.; O'Shea, P.D.; Shelly, D.P. *J. Chem. Soc. Perkin Trans. 1*, **1987**, 1039.

⁸³⁰ Fillipi, G.; Verrin, G.; Dou, H.J.; Metzger, J.; Perkins, M.J. *Bull. Soc. Chim. Fr.* **1974**, 1075.

Under *Gomberg–Bachmann* conditions, the species that cleaves is the anhydride (**40**).⁸³¹



The aryl radical thus formed attacks the substrate to give the aryl cation⁸³² intermediate **42** (see Sec. 14.A.iii), from which the radical **41** abstracts hydrogen to give the product (**43**). *N*-Nitroso amides probably rearrange to *N*-acyloxy compounds (**44**), which cleave to give aryl radicals.⁸³³ There is evidence that the reaction with alkyl nitrites also involves attack by aryl radicals.⁸³⁴

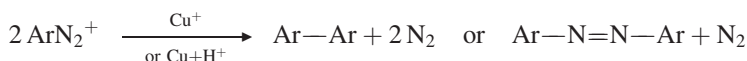


The *Pschorr reaction* can take place by two different mechanisms, depending on conditions: (1) attack by an aryl radical (as in the *Gomberg–Bachmann reaction*) or (2) attack by an aryl cation (similar to the $\text{S}_{\text{N}}1$ mechanism discussed in Sec. 13.A.ii).⁸³⁵ Under certain conditions the ordinary *Gomberg–Bachmann reaction* can also involve attack by aryl cations.⁸³⁶

OS **I**, 113; **IV**, 718.

13-28 Aryl Dimerization with Diazonium Salts

De-diazonio-coupling; Arylazo-de-diazonio-substitution



When diazonium salts are treated with cuprous ion (or with Cu and acid, in which case it is called the *Gatterman method*), two products are possible. If the ring contains electron-withdrawing groups, the main product is the biaryl, but the presence of electron-donating groups leads mainly to the azo compound. This reaction is different from Reaction **13-27** (and from **19-14**) in that *both* aryl groups in the product originate from ArN_2^+ , that is, hydrogen is not a leaving group in this reaction. The mechanism probably involves free radicals.⁸³⁷

OS **I**, 222; **IV**, 872. Also see, OS **IV**, 273.

⁸³¹ Eliel, E.L.; Saha, J.G.; Meyerson, S. *J. Org. Chem.* **1965**, 30, 2451.

⁸³² For an alternative method to generate aryl cations, see Milanesi, S.; Fagnoni, M.; Albin, A. *J. Org. Chem.* **2005**, 70, 603.

⁸³³ Cadogan, J.I.G.; Murray, C.D.; Sharp, J.T. *J. Chem. Soc. Perkin Trans. 2*, **1976**, 583, and references cited therein.

⁸³⁴ Gragerov, I.P.; Levit, A.F. *J. Org. Chem. USSR* **1968**, 4, 7.

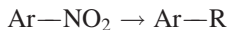
⁸³⁵ See Gadallah, F.F.; Cantu, A.A.; Eloffson, R.M. *J. Org. Chem.* **1973**, 38, 2386.

⁸³⁶ See Burri, P.; Zollinger, H. *Helv. Chim. Acta* **1973**, 56, 2204; Eustathopoulos, H.; Rinaudo, J.; Bonnier, J.M. *Bull. Soc. Chim. Fr.* **1974**, 2911; Zollinger, H. *Acc. Chem. Res.* **1973**, 6, 335, p. 338.

⁸³⁷ See Cohen, T.; Lewarchik, R.J.; Tarino, J.Z. *J. Am. Chem. Soc.* **1974**, 96, 7753.

13-29 Replacement of Nitro

Alkyl-de-nitration, Hydroxy and alkoxy-de-nitration, Halo-de-nitration



In some cases, the nitrogen group of an aromatic nitro compound can be replaced with an alkyl group. The reaction of 1,4-dinitrobenzene with potassium *tert*-butoxide in the presence of BEt_3 , for example, gave 4-ethylnitrobenzene.⁸³⁸

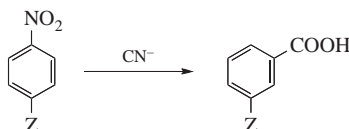
Other nucleophiles can replace a nitrogen-containing group. The reaction of hydroxide with $\text{Ar}-\text{Y}$, where $\text{Y} = \text{nitro},^{839} \text{ azide}, \text{NR}_3^+$, and so on gives the corresponding phenol. This latter reaction works with alkoxide nucleophiles to give the corresponding aryl ether. The nitro can be replaced with chloro by use of NH_4Cl , PCl_5 , SOCl_2 , HCl , Cl_2 , or CCl_4 . Some of these reagents operate only at high temperatures and the mechanism is not always nucleophilic substitution. Activated aromatic nitro compounds can be converted to fluorides with fluoride ion.⁸⁴⁰

The reaction of vinyl nitro compounds ($\text{C}=\text{C}-\text{NO}_2$) and aryl iodide to give the styrene compound ($\text{C}=\text{C}-\text{Ar}$) was reported using BEt_3 and exposure to air.⁸⁴¹

13.C.iv. REARRANGEMENTS

13-30 The von Richter Rearrangement

Hydro-de-nitro-cine-substitution



When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters with cine substitution (Sec. 13.A.iii), always ortho to the displaced group, never meta or para. The scope of this reaction, called the *von Richter rearrangement*, is variable.⁸⁴² As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in ortho and para positions, but yields are low, usually <20% and never >50%.

At one time, it was believed that a nitrile (ArCN) was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions (16-4). However, a remarkable series of results proved this belief to be in error. Bunnett and Rauhut⁸⁴³ demonstrated that α -naphthyl cyanide is *not* hydrolyzable to α -naphthoic acid under conditions at which β -nitronaphthalene undergoes the *von Richter rearrangement* to give α -naphthoic acid. This proved that the nitrile could not be an intermediate. It was subsequently demonstrated that N_2 is a major product of the reaction.⁸⁴⁴ It had

⁸³⁸ Palani, N.; Jayaprakash, K.; Hoz, S. *J. Org. Chem.* **2003**, 68, 4388.

⁸³⁹ See Knudsen, R.D.; Snyder, H.R. *J. Org. Chem.* **1974**, 39, 3343.

⁸⁴⁰ Suzuki, H.; Yazawa, N.; Yoshida, Y.; Furusawa, O.; Kimura, O. *Bull. Chem. Soc. Jpn.* **1990**, 63, 2010; Effenberger, F.; Streicher, W. *Chem. Ber.* **1991**, 124, 157.

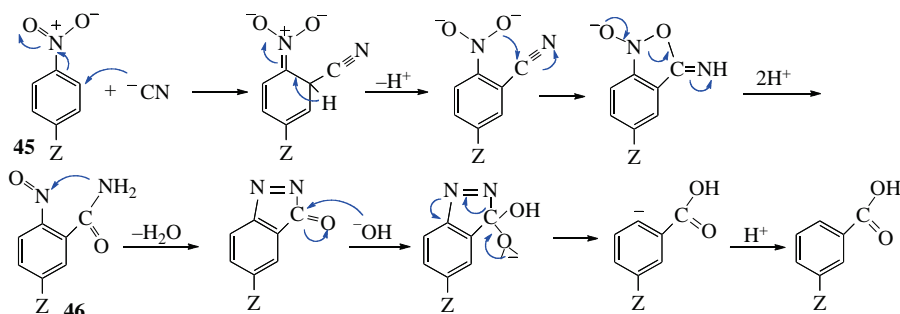
⁸⁴¹ Liu, J.-T.; Jang, Y.-J.; Shih, Y.-K.; Hu, S.-R.; Chu, C.-M.; Yao, C.-F. *J. Org. Chem.* **2001**, 66, 6021.

⁸⁴² For a review, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 326–335.

⁸⁴³ Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* **1956**, 21, 934, 944.

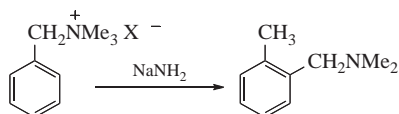
⁸⁴⁴ Rosenblum, M. *J. Am. Chem. Soc.* **1960**, 82, 3796.

previously been assumed that all the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles. At the same time it was shown that NO_2^+ is not a major product. The discovery of nitrogen indicated that a nitrogen–nitrogen bond must be formed during the course of the reaction. Rosenblum proposed a mechanism in accord with all the facts⁸⁴³:



Note that **46** is a stable compound: Hence, it should be possible to prepare it independently and to subject it to the conditions of the *von Richter rearrangement*. This was done and the correct products are obtained.⁸⁴⁵ Further evidence is that when **45** ($Z = \text{Cl}$ or Br) was treated with cyanide in H_2^{18}O , half the oxygen in the product was labeled, showing that one of the oxygen atoms of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.⁸⁴⁶

13-31 The Sommelet–Hauser Rearrangement



Benzylic quaternary ammonium salts, when treated with alkali metal amides, undergo a rearrangement called the *Sommelet–Hauser rearrangement*.⁸⁴⁷ Since the product is a benzylic tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an ortho position is blocked.⁸⁴⁸

The rearrangement occurs with high yields and can be performed with various groups present in the ring.⁸⁴⁹ The reaction is most often carried out with three methyl groups on the

⁸⁴⁵ Ibne-Rasa, K.M.; Koubek, E. *J. Org. Chem.* **1963**, 28, 3240.

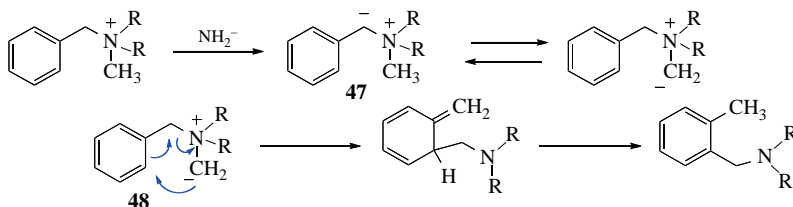
⁸⁴⁶ Samuel, D. *J. Chem. Soc.* **1960**, 1318. For other evidence, see Cullen, E.; L'Ecuyer, P. *Can. J. Chem.* **1961**, 39, 144, 155, 382; Ullman, E.F.; Bartkus, E.A. *Chem. Ind. (London)* **1962**, 93.

⁸⁴⁷ See Pine, S.H. *Org. React.*, **1970**, 18, 403; Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* **1971**, 3, 297; Wittig, G. *Bull. Soc. Chim. Fr.* **1971**, 1921; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand–Reinhold, Princeton, **1973**, pp. 81–88; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 316–326. Also see, Klunder, J.M. *J. Heterocyclic Chem.* **1995**, 32, 1687.

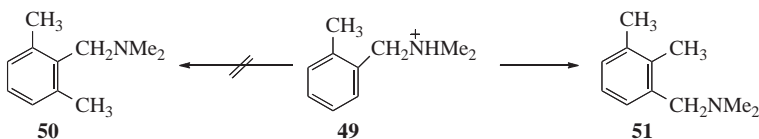
⁸⁴⁸ Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* **1960**, 25, 334.

⁸⁴⁹ Jones, G.C.; Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* **1963**, 28, 199.

nitrogen, but other groups can also be used, though if a β -hydrogen is present, *Hofmann elimination* (Reaction 17-7) often competes. The *Stevens rearrangement* (Reaction 18-21) is also a competing process.⁸⁵⁰ When both rearrangements are possible, the *Stevens rearrangement* is favored at high temperatures and the *Sommelet–Hauser* at low temperatures.⁸⁵¹ The mechanism is:



The benzylic hydrogen is most acidic and is the one that first loses a proton to give the ylide (47). However, 48, which is present in a smaller amount, is the species that undergoes the rearrangement, shifting the equilibrium in its favor. This mechanism is an example of a [2,3]-sigmatropic rearrangement (see Reaction 18-35). Another mechanism that might be proposed is one in which a methyl group actually breaks away (in some form) from the nitrogen and then attaches itself to the ring. That this is not so was shown by a product study.⁸⁵² If the second mechanism were true, 49 should give 50, but the first mechanism predicts the formation of 51, which is what was actually obtained.⁸⁵³



The mechanism as shown can lead only to an ortho product. However, a small amount of para product has been obtained in some cases.⁸⁵⁴ A mechanism⁸⁵⁵ in which there is a dissociation of the $\text{ArC}-\text{N}$ bond (similar to the ion-pair mechanism of the *Stevens rearrangement*, Reaction 18-21) has been invoked to explain the para products that are observed.

Sulfur ylids containing a benzylic group (analogous to 48) undergo an analogous rearrangement.⁸⁵⁶

OS IV, 585.

⁸⁵⁰ See, however, Nakano, M.; Sato, Y. *J. Org. Chem.* **1987**, 52, 1844; Shirai, N.; Sato, Y. *J. Org. Chem.* **1988**, 53, 194.

⁸⁵¹ Wittig, G.; Streib, H. *Liebigs Ann. Chem.* **1953**, 584, 1.

⁸⁵² See Puterbaugh, W.H.; Hauser, C.R. *J. Am. Chem. Soc.* **1964**, 86, 1105; Pine, S.H.; Sanchez, B.L. *Tetrahedron Lett.* **1969**, 1319; Shirai, N.; Watanabe, Y.; Sato, Y. *J. Org. Chem.* **1990**, 55, 2767.

⁸⁵³ Kantor, S.W.; Hauser, C.R. *J. Am. Chem. Soc.* **1951**, 73, 4122.

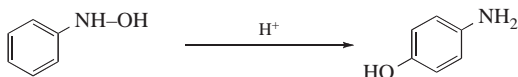
⁸⁵⁴ Pine, S.H. *Tetrahedron Lett.* **1967**, 3393; Pine, S.H. *Org. React.* **1970**, 18, 403, p. 418.

⁸⁵⁵ Bumgardner, C.L. *J. Am. Chem. Soc.* **1963**, 85, 73.

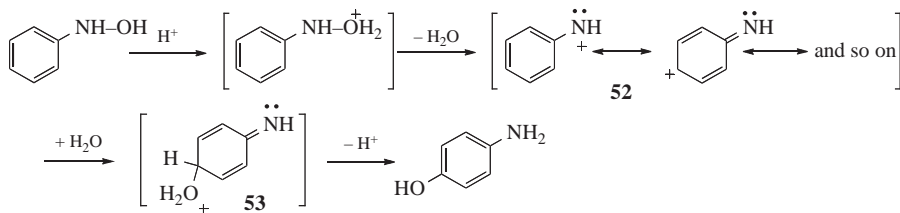
⁸⁵⁶ See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**, pp. 118–124.

13-32 Rearrangement of Aryl Hydroxylamines

1/C-Hydro-5/N-hydroxy-interchange



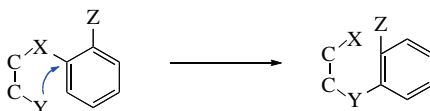
Aryl hydroxylamines treated with acids rearrange to aminophenols.⁸⁵⁷ Although this reaction (known as the *Bamberger rearrangement*) is similar in appearance to Reactions **11-28–11-32**, the attack on the ring is not electrophilic but nucleophilic. The rearrangement is intermolecular, with the following mechanism:



Among the evidence⁸⁵⁸ for this mechanism are the facts that other products are obtained when the reaction is run in the presence of competing nucleophiles (e.g., *p*-ethoxyaniline) when ethanol is present, and that when the para position is blocked, compounds similar to **53** are isolated. In the case of 2,6-dimethylphenylhydroxylamine, the intermediate nitrenium ion (**52**) was trapped, and its lifetime in solution was measured.⁸⁵⁹ The reaction of **52** with water was found to be diffusion controlled.⁸⁶⁰

There is a base-mediated rearrangement of aromatic hydroxamic acids to anilines.⁸⁶¹ OS IV, 148.

13-33 The Smiles Rearrangement



The *Smiles rearrangement* actually comprises a group of rearrangements that follow the pattern given above.⁸⁶² A specific example is the reaction of **54** with hydroxide to give **55**.

⁸⁵⁷ See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 182–190.

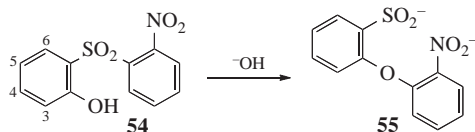
⁸⁵⁸ Also see Kohnstam, G.; Petch, W.A.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* **1984**, 423; Sternson, L.A.; Chandrasakar, R. *J. Org. Chem.* **1984**, *49*, 4295, and references cited therein.

⁸⁵⁹ Fishbein, J.C.; McClelland, R.A. *J. Am. Chem. Soc.* **1987**, *109*, 2824.

⁸⁶⁰ Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 1661.

⁸⁶¹ Hoshino, Y.; Okuno, M.; Kawamura, E.; Honda, K.; Inoue, S. *Chem. Commun* **2009**, 2281.

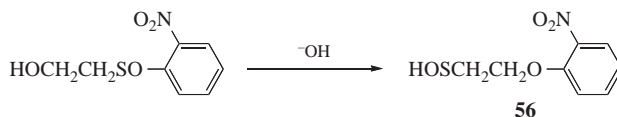
⁸⁶² See Truce, W.E.; Kreider, E.M.; Brand, W.W. *Org. React.*, **1971**, *18*, 99; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1967**, pp. 307–316; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, **1973**, pp. 120–126.



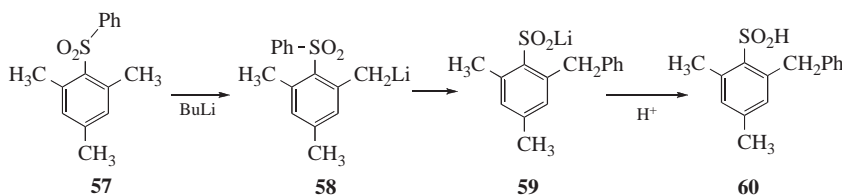
Smiles rearrangements are simply intramolecular nucleophilic substitutions. In the example given, SO_2Ar is the leaving group and ArO^- is the nucleophile. The nitro group serves to activate its ortho position. Halogens also serve as activating groups.⁸⁶³ The ring at which the substitution takes place is nearly always activated, usually by ortho or para nitro groups. Here X is usually S, SO, SO_2 ,⁸⁶⁴ O, or CO_2 , and Y is usually the conjugate base of OH, NH_2 , NHR , or SH. The reaction has even been carried out with $\text{Y} = \text{CH}_2^-$ (phenyllithium was the base here).⁸⁶⁵

The reaction rate is greatly enhanced by substitution in the 6 position of the attacking ring, for steric reasons. For example, a methyl, chloro, or bromo group in the 6 position of **54** caused the rate to be $\sim 10^5$ times faster than when the same groups were in the 4 position,⁸⁶⁶ although electrical effects should be similar at these positions. The enhanced rate comes about because the most favorable conformation of the molecule can adapt to suit the bulk of the 6-substituent is also the conformation required for the rearrangement. Thus, less entropy of activation is required.

Although the *Smiles rearrangement* is usually carried out on compounds containing two rings, this need not be the case, as in the formation of **56**.⁸⁶⁷



In this case the, sulfenic acid (**56**) is unstable⁸⁶⁸ and the actual products isolated were the corresponding sulfinic acid (RSO_2H) and disulfide (R_2S_2).



In the *Smiles rearrangement*, the nucleophile Y is most often the conjugate base of SH, SO_2NHR , SO_2NH_2 , NH_2 , NHR , OH, and OR. There are few examples where Y is a

⁸⁶³ Grundon, M.F.; Matier, W.L. *J. Chem. Soc., B* **1966**, 266; Schmidt, D.M.; Bonvicino, G.E. *J. Org. Chem.* **1984**, *49*, 1664.

⁸⁶⁴ See Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, **1968**, pp. 262–274.

⁸⁶⁵ Truce, W.E.; Robbins, C.R.; Kreider, E.M. *J. Am. Chem. Soc.* **1966**, *88*, 4027; Drozd, V.N.; Nikonova, L.A. *J. Org. Chem., USSR* **1969**, *5*, 313.

⁸⁶⁶ Bunnett, J.F.; Okamoto, T. *J. Am. Chem. Soc.* **1956**, *78*, 5363.

⁸⁶⁷ Kent, B.A.; Smiles, S. *J. Chem. Soc.* **1934**, 422.

⁸⁶⁸ For a stable sulfenic acid, see Nakamura, N. *J. Am. Chem. Soc.* **1983**, *105*, 7172.

carbanion, and the most common example is probably the *Truce–Smiles rearrangement*, where L—YH is an *o*-tolyl group.⁸⁶⁹ The prototypical *Truce–Smiles rearrangement* requires use of a strong base to form the benzylic carbanion that undergoes the rearrangement. When sulfone (**57**) was treated with butyllithium, for example, deprotonation led to the benzylic lithium compound (**58**). *Truce–Smiles rearrangement* led to **59**, and hydrolysis gave the sulfinic acid (**60**).⁸⁷⁰ *Truce–Smiles rearrangements* with stabilized benzylic carbanions are known,⁸⁷⁰ and rearrangements of carbanions in general fall under this category.⁸⁷¹ Relatively few examples have been reported, however.⁸⁷² *Truce–Smiles rearrangements* of sulfones that proceed through a six-membered transition state have been reported.⁸⁷³ In another example, displacement of an activated aryl fluoride with *o*-hydroxyacetophenone gave a product that was C-arylated adjacent to the ketone.⁸⁷⁴

⁸⁶⁹ Truce, W.E.; Ray, Jr., W.J.; Norman, O.L.; Eickemeyer, D.B. *J. Am. Chem. Soc.* **1958**, *80*, 3625.

⁸⁷⁰ Erickson, W.R.; McKennon, M.J. *Tetrahedron Lett.* **2000**, *41*, 4541.

⁸⁷¹ Fukazawa, Y.; Kato, N.; Ito, S. *Tetrahedron Lett.* **1982**, *23*, 437.

⁸⁷² Hirota, T.; Tomita, K.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. *Heterocycles* **2001**, *55*, 741.

⁸⁷³ Truce, W.E.; Hampton, D.C. *J. Org. Chem.* **1963**, *28*, 2276.

⁸⁷⁴ Mitchell, L.H.; Barvian, N.C. *Tetrahedron Lett.* **2004**, *45*, 5669.

Substitution Reactions: Radical

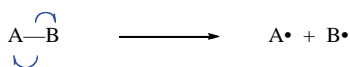
This chapter discusses many types of radical reactions, including reactions in which radicals may be intermediates. Radicals are increasingly important in organic synthesis.¹ The formation, fate, and properties of radicals were introduced in Section 5.C. Additional information concerning radicals may be found in Section 7.A, in the discussion of photochemical processes.

For the most part, this chapter discusses radical substitution reactions. Free radical additions to unsaturated compounds and rearrangements are discussed in Chapters 15 and 18, respectively. Fragmentation reactions are covered, in part, in Chapter 17. In addition, many of the oxidation–reduction reactions considered in Chapter 19 involve free radical mechanisms. Several important types of free radical reactions do not usually lead to reasonable yields of pure products and are not generally treated in this book.

14.A. MECHANISMS

14.A.i. Radical Mechanisms in General²

A free radical process (or just a radical process) consists of at least two steps. Any radical reaction first step involve the *formation* of free radicals, usually by homolytic cleavage of a bond; that is, a cleavage in which each fragment retains one electron:



This is called an *initiation* step. It may happen spontaneously or may be induced by heat³ or light (see the discussion in Sec. 5.C.ii), depending on the type of bond.⁴ Peroxides,

¹ Rowlands, G.J. *Tetrahedron* **2009**, 65, 8603; **2010**, 66, 1593.

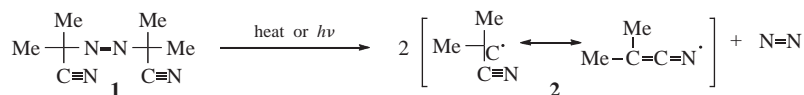
² Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radical*, Cambridge University Press, Cambridge, **1979**; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, **1974**; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, **1970**; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, **1966**. See Huyser, E.S. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, **1973**, pp. 1–59; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, **1986**; Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis*, Springer, NY, **1978**; Curran, D.P. *Synthesis* **1988**, 417, 489; Ramaiah, M. *Tetrahedron* **1987**, 43, 3541.

³ See Engel, P.S.; Pan, L.; Ying, Y.; Alemany, L.B. *J. Am. Chem. Soc.* **2001**, 123, 3706.

⁴ See Fokin, A.A.; Schreiner, P.R. *Chem. Rev.* **2002**, 102, 1551.

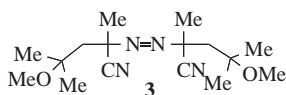
including hydrogen peroxide, dialkyl, diacyl, alkyl acyl peroxides, and peroxyacids are the most common source of free radicals. However, other organic compounds with low-energy bonds (e.g., azo compounds) are also used. Chlorine, bromine, and various ketones (see Chapter 7) are most commonly cleaved by light. Radicals can also be formed by a one-electron transfer (loss or gain) (e.g., $A^+ + e^- \rightarrow A^\bullet$). One-electron transfers usually involve inorganic ions or electrochemical processes.⁵

Dialkyl peroxides (ROOR) or alkyl hydroperoxides (ROOH) decompose to hydroxy radicals (HO^\bullet) or alkoxy radicals (RO^\bullet) when heated.⁶ Cumene hydroperoxide ($PhCMe_2OOH$), bi-*tert*-butylperoxide ($Me_3COOCMe_3$),⁷ and benzoyl peroxide [$(PhCO)O_2$] undergo homolytic cleavage at temperatures compatible with many organic reactions. They are also reasonably soluble in organic solvents.⁸ In general, when a peroxide decomposes, the oxygen radical remains in a “cage” for $\sim 10^{-11}$ s before diffusing away. The radical can



recombine (dimerize), or react with other molecules. Azo compounds, characterized by a $-\text{N}=\text{N}-$ bond, are free radical precursors that liberate nitrogen gas (N_2) upon decomposition. Azo bisisobutyronitrile (AIBN, **1**) is a well-known example, which decomposes to give nitrogen gas and the cyano stabilized radical (**2**).⁹ Homolytic dissociation of symmetrical diazo compounds may be stepwise.¹⁰ A derivative has been developed that decomposes at room temperature: 2,2'-azobis(2,4-dimethyl-4-methoxyvaleronitrile), **3**.¹¹ Water soluble azo compounds are known, and can be used as radical initiators.¹²

Alkyl hypochlorites ($\text{R}-\text{O}-\text{Cl}$) generate chlorine radicals (Cl^\bullet) and alkoxy radicals (RO^\bullet) when heated.¹³ Heating *N*-alkoxydithiocarbamates is another useful source of alkoxy radicals (RO^\bullet).¹⁴ Alkoxy radicals, particularly those derived from cyclic compounds, may undergo β -scission reactions to give carbonyl derivatives.¹⁵



⁵ For a review of bond formation and bond dissociation, see Houmam, A. *Chem. Rev.* **2008**, *108*, 2180.

⁶ For a table of approximate decomposition temperatures, see Lazár, M.; Rychly, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology* CRC Press, Washington, DC, **1989**, p 12.

⁷ Lazár, M.; Rychly, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology*, CRC Press, Washington, DC, **1989**, p 13.

⁸ Hydrogen bonding affects the persistency of alkyl peroxy radicals. See Mugnaini, V.; Lucarini, M. *Org. Lett.* **2007**, *9*, 2725.

⁹ Yoshino, K.; Ohkatsu, J.; Tsuruta, T. *Polym. J.* **1977**, *9*, 275; von J. Hinz, A.; Oberlinner, A.; Rüchardt, C. *Tetrahedron Lett.* **1973**, 1975.

¹⁰ Dannenberg, J.J.; Rocklin, D. *J. Org. Chem.* **1982**, *47*, 4529. See also, Newman, Jr, R.C.; Lockyer, Jr, G.D. *J. Am. Chem. Soc.* **1983**, *105*, 3982.

¹¹ Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *Tetrahedron Lett.* **1997**, *38*, 3549.

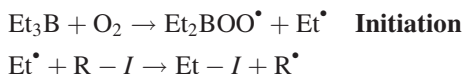
¹² Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 519.

¹³ Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis* Springer-Verlag, Berlin, **1978**, p. 9; Chattaway, F.D.; Baekberg, O.G. *J. Chem. Soc.* **1923**, 123, 2999.

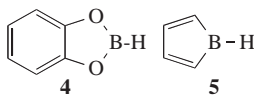
¹⁴ Kim, S.; Lim, C.J.; Song, S.-E.; Kang, H.-Y. *Synlett* **2001**, 688.

¹⁵ See Bietti, M.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 417.

It has been known for many years that boron compounds participate in radical reactions.¹⁶ Trialkylboranes (R_3B ; see Reactions **15-27** and **12-27**), such as triethylborane (Et_3B), can be used to initiate radical reactions. Indeed, Et_3B is widely used.¹⁷ In radical reactions, Et_3B functions as both a radical initiator and also as a chain-propagation agent.¹⁸ Reactions are usually run in open vessels exposed to oxygen or under an oxygen atmosphere. It is known that O_2 is involved in the initiation step, as shown, in this case using an atom-transfer reaction with an alkyl iodide to give the alkyl radical, (R^\bullet). Trialkylborane/water-mediated radical reactions are also known.¹⁹



In general, the order of reactivity is $R_3B > R_2BOR > RB(OR)_2$ where $R = \text{alkyl}$.²⁰ Boronic acids are less reactive, presumably due to π -bonding between B and O.¹⁷ However, B-alkylcatecholboranes are very reactive, and highly useful for initiating radical reactions.²¹ Reaction conditions usually involve addition of catecholborane (**4**, abbreviated CatBH), and the B-alkyl derivative is presumably generated *in situ* by reaction with an alkene.²² Note that borole derivatives (the B analogue of pyrrole, **5**) have been used to initiate radical reactions.²³



Aldehydes can be a source of acyl radicals ($^\bullet C=O$) via reaction with transition metal salts (e.g., Mn(III) acetate or Fe(II) compounds).²⁴ α,β -Unsaturated acyl radicals are subject to an isomerization that generates α -ketenyl radicals.²⁵ Another useful variation employs imidoyl radicals as synthons for unstable aryl radicals.²⁶

¹⁶ See Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed.* **1972**, *11*, 692; Ghosez, A.; Giese, B.; Zipse, H. *Houben-Weyl*, Vol. E19a, **1989**, p. 753; Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415.

¹⁷ Renaud, P.; Beauseigneur, A.; Brecht-Forster, A.; Becattini, B.; Darmency, V.; Kandhasamy, S.; Montermini, F.; Ollivier, C.; Panchaud, P.; Pozzi, D.; Scanlan, E.M.; Schaffner, A.-P.; Weber, V. *Pure Appl. Chem.* **2007**, *79*, 223; Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547; Yorimitsu, H.; Oshima, K. in *Radicals in Organic Synthesis*, Vol. 1, Renaud, P.; Sibi, M.P. (Eds.) p. 11, Wiley-VCH, Weinheim, **2001**.

¹⁸ See Darmency, V.; Renaud, P. in *Topics in Current Chemistry*, Vol. 263 Gansaeuer, A. (Ed.), Springer, Berlin, **2006**, p. 71.

¹⁹ Medeiros, M.R.; Schacherer, L.N.; Spiegel, D.A.; Wood, J.L. *Org. Lett.* **2007**, *9*, 4427.

²⁰ Davies, A.G.; Roberts, B.P. *Free Radicals*, Vol. 1 Kochi, J.K. (Ed.), p. 457, J Wiley, NY, **1973**, p. 457; Baban, J.A.; Goodchild, N.J.; Roberts, B.P. *J. Chem. Soc., Perkin Trans. 2* **1986**, 157.

²¹ Ollivier, C.; Renaud, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 925; Ollivier, C.; Renaud, P. *Chem. Eur. J.* **1999**, *5*, 1468; Schaffner, A.-P.; Renaud, P. *Eur. J. Org. Chem.* **2004**, 2291; Darmency, V.; Renaud, P. *Top. Curr. Chem.* **2006**, *263*, 71.

²² See Garrett, C.E.; Fu, G.C. *J. Org. Chem.* **1996**, *61*, 3224.

²³ Montgomery, I.; Parsons, A.F.; Ghelfi, F.; Roncaglia, F. *Tetrahedron Lett.* **2008**, *49*, 628.

²⁴ Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis* Springer-Verlag, Berlin, **1978**, p 69; Nikishin, G.I.; Vinogradov, M.G.; Il'ina, G.P. *Synthesis* **1972**, 376; Nikishin, G.I.; Vinogradov, M.G.; Verenchikov, S.P.; Kostyukov, I.N.; Kereselidze, R.V. *J. Org. Chem., USSR* **1972**, *8*, 539 (Engl. p. 544).

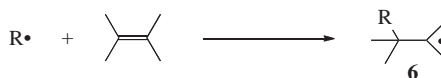
²⁵ Matsubara, H.; Ryu, I.; Schiesser, C.H. *J. Org. Chem.* **2005**, *70*, 3610.

²⁶ Fujiwara, S.-i.; Matsuya, T.; Maeda, H.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **2001**, *66*, 2183.

An important step in radical reactions involves the *destruction* of free radicals. This usually happens by a process opposite to the first, namely, a combination of two like or unlike radicals to form a new bond:²⁷



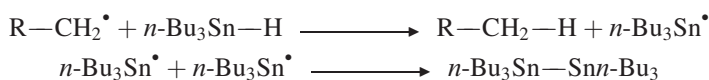
This type of step is called *termination* because the product of the reaction is a neutral compound and not a radical.²⁸ Note that this reaction constitutes a radical coupling process. The termination step rarely follows initiation because most radicals are very reactive, and there are several radical processes that occur faster than the termination step. In the usual situation, in which the concentration of radicals is low, a radical is more likely to react with a molecule rather than another radical (i.e., the radical coupling reaction is usually slower). When a radical, which has an odd number of electrons, reacts with a molecule, which has an even number, the total number of electrons in the products must be odd. In other words, the product is another radical. When a radical



reacts with a π bond, for example, the product is free radical (**6**). This reaction is called a *radical addition*. Another reaction constitutes an *atom-transfer reaction*. The abstraction of an atom (e.g., hydrogen atom) from an alkyl fragment gives two particles: $R-H$ and the new radical (R'^{\bullet}), as shown. This type of atom-transfer reaction is called a *hydrogen-transfer reaction*.



Once again, the product is a free radical. This type of step is called *propagation*, since the newly formed radical can now react with another molecule and produce another radical, and so on, until two radicals undergo coupling and terminate the sequence. The process of initiation, propagation, and then termination constitutes what is called a *chain reaction*,²⁹ and there may be hundreds or thousands of propagation steps between an initiation and a termination. Two other types of propagation reactions do not involve a molecule at all. These are (1) cleavage of a radical into, necessarily, a radical and a molecule and (2) rearrangement of one radical to another (see Chapter 18). When radicals are highly reactive (e.g., alkyl radicals), chains are long, since reactions occur with many molecules; but with radicals of low reactivity (e.g., aryl radicals), the radical may be unable to react with anything until it meets another radical, so that chains are short. Alternatively, the reaction may be a nonchain process. In any particular chain process, there is usually a wide variety of propagation and termination steps so there may be many products. Such reaction are often difficult to treat kinetically.³⁰



²⁷ For a review of stereochemistry, see Porter, N.A.; Krebs, P.J. *Top. Stereochem.* **1988**, 18, 97.

²⁸ Another type of termination step is *disproportionation* (see Sec. 5.C.ii).

²⁹ See Walling, C. *Tetrahedron* **1985**, 41, 3887.

³⁰ See Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, **1970**, pp. 39–65.

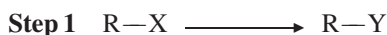
Is it possible to terminate a radical reaction under controlled conditions? The answer is yes, using an atom-transfer reaction. When a carbon radical (R^\bullet) is generated in the presence of tributyltin hydride ($n\text{-Bu}_3\text{SnH}$), a hydrogen atom is transferred to the radical to give $R\text{—H}$ and a new radical ($n\text{-Bu}_3\text{Sn}^\bullet$). The tin radical usually undergoes rapid coupling to another tin radical to give $n\text{-Bu}_3\text{Sn—Sn—}n\text{-Bu}_3$, which effectively terminates the chain-radical process. The carbon radical is *reduced* ($R^\bullet \rightarrow R\text{—H}$) as a result of the hydrogen-atom transfer, and the tin dimer can be removed from the reaction. Again, hydrogen-atom transfer³¹ is simply a variation of the radical reaction known as atom transfer. Silanes (e.g., triethylsilane, Et_3SiH), have also been used as an effective radical reducing agent.³² The rate constants for the reaction of both tributyltin hydride and $(\text{Me}_3\text{Si})_3\text{Si—H}$ with acyl radical have been measured and the silane quenches the radical faster than the tin hydride.³³ Thermolysis of bis(tri-*n*-butylstannyl)benzopinacolate has also been used as a source of $n\text{-Bu}_3\text{Sn}^\bullet$, used to mediate radical reactions.³⁴

The following are some general characteristics of free radical reactions³⁵:

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase, but solvation of free radicals in solution does cause some differences.³⁶
2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents, except that nonpolar solvents may suppress competing ionic reactions.
3. They are initiated or accelerated by typical free radical sources (e.g., the peroxides or diazo compounds) noted above, or by light. In the latter case, the concept of quantum yield applies (Sec. 7.A.viii). Quantum yields can be quite high (e.g., 1000), if each quantum generates a long chain, or low, in the case of nonchain processes.
4. Their rates are decreased or the reactions are suppressed entirely by substances that scavenge free radicals (e.g., nitric oxide, molecular oxygen, or benzoquinone). These substances are called *inhibitors*.³⁷ Note that there are C-centered radicals in thermal equilibrium with their dimers that show poor reactivity with molecular oxygen, but good reactivity with peroxy radicals.³⁸

14.A.ii. Free Radical Substitution Mechanisms³⁹

In a free radical substitution reaction



there must first be a cleavage of the substrate RX so that R^\bullet radicals are produced. This can happen by a spontaneous cleavage,

³¹ For a discussion of barriers to degenerate hydrogen transfer, see Isborn, C.; Hrovat, D.A.; Borden, W.T.; Mayer, J.M.; Carpenter, B.K. *J. Am. Chem. Soc.* **2005**, *127*, 5794. For a discussion of hydrogen atom transfer from phenols, see Nielsen, M.F.; Ingold, K.U. *J. Am. Chem. Soc.* **2006**, *128*, 1172.

³² Chatgililoglu, C.; Ferreri, C.; Lucarini, M. *J. Org. Chem.* **1993**, *58*, 249.

³³ Chatgililoglu, C.; Lucarini, M. *Tetrahedron Lett.* **1995**, *36*, 1299.

³⁴ Hart, D.J.; Krishnamurthy, R.; Pook, L.M.; Seely, F.L. *Tetrahedron Lett.* **1993**, *34*, 7819.

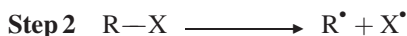
³⁵ See Beckwith, A.L.J. *Chem. Soc. Rev.* **1993**, *22*, 143 for a discussion of selectivity in radical reactions.

³⁶ See Mayo, F.R. *J. Am. Chem. Soc.* **1967**, *89*, 2654.

³⁷ See Denisov, E.T.; Khudyakov, I.V. *Chem. Rev.* **1987**, *87*, 1313.

³⁸ Korth, H.-G. *Angew. Chem. Int. Ed.* **2008**, *47*, 5274.

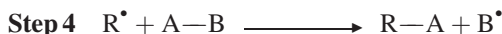
³⁹ See Poutsma, M.L. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, pp. 113–158.



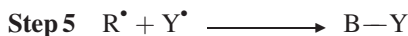
or it can be caused by light or heat, or, more often, there is no actual cleavage, but R^\bullet is produced by an *abstraction* of another atom, X by the radical W^\bullet .



The radical W^\bullet is produced by adding a compound (e.g., peroxide) that spontaneously forms free radicals. Such a compound is called an *initiator* (see above). Once R^\bullet is formed, it can go to product in this system, by another atom abstraction, such as the reaction with $\text{A}-\text{B}$ to form $\text{R}-\text{A}$ and a new radical B^\bullet (atom transfer).



Another reaction is coupling with another radical to form the neutral product $\text{R}-\text{Y}$.



In a reaction with a moderately long chain, much more of the product will be produced by abstraction (4) than by coupling (5). Cleavage steps like (2) have been called $\text{S}_{\text{H}}1$ (H for homolytic), and abstraction steps like (3) and (4) have been called $\text{S}_{\text{H}}2$; reactions can be classified as $\text{S}_{\text{H}}1$ or $\text{S}_{\text{H}}2$ on the basis of whether RX is converted to R by (2) or (3).⁴⁰ Most chain substitution mechanisms follow the pattern (3), (4), (3), (4) ... Chains are long and reactions go well where both (3) and (4) are energetically favored (no worse than slightly endothermic, see Sec. 14.B.i and 14.C.i). The IUPAC designation of a chain reaction that follows the pattern (3),(4) ... is $\text{A}_\text{r}\text{D}_\text{R} + \text{A}_\text{r}\text{D}_\text{r}$ (R stands for radical).

With certain radicals the transition state in an abstraction reaction has some polar character. Consider the abstraction of hydrogen from the methyl group of toluene by a bromine atom. Since bromine is more electronegative than carbon, it is reasonable to assume that there is a separation of charge in the transition state, with a partial negative charge on the halogen and a partial positive charge on the carbon:



Evidence for the polar character of the transition state is that electron-withdrawing groups in the para position of toluene, which would destabilize a positive charge, decrease the rate of hydrogen abstraction by bromine while electron-donating groups increase it.⁴¹ However, substituents have a smaller effect here ($\rho \approx -1.4$) than they do in reactions where a completely ionic intermediate is involved (e.g., the $\text{S}_{\text{N}}1$ mechanism, Sec. 10.A.ii). Other evidence for polar transition states in radical abstraction reactions is mentioned in Section 14.B.i, category 4. For abstraction by radicals such as methyl or phenyl, polar effects are very small or completely absent. For example, rates of hydrogen-atom abstraction from ring-substituted toluenes by methyl radical were relatively unaffected by the presence of electron-donating or electron-withdrawing substituents.⁴² Those radicals (e.g., Br^\bullet) that have a tendency to abstract electron-rich hydrogen atoms are called *electrophilic radicals*.

When the reaction step $\text{R}-\text{X} \rightarrow \text{R}^\bullet$ takes place at a stereogenic carbon, *racemization is almost always observed because free radicals do not retain configuration*. Exceptions

⁴⁰ Eliel, E.L. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, **1956**, pp. 142–143.

⁴¹ See Kim, S.S.; Choi, S.Y.; Kang, C.H. *J. Am. Chem. Soc.* **1985**, *107*, 4234.

⁴² See Pryor, W.A.; Tonellato, U.; Fuller, D.L.; Jumonville, S. *J. Org. Chem.* **1969**, *34*, 2018.

to this rule are found with cyclopropyl substrates, where both inversion⁴³ and retention⁴⁴ of configuration have been reported, and in the reactions mentioned in Section 14.A.iv. Enantioselective radical processes have been reviewed.⁴⁵

14.A.iii. Mechanisms at an Aromatic Substrate⁴⁶

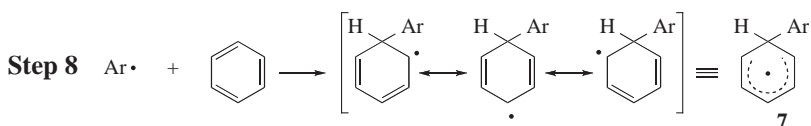
When R in reaction (1) is aromatic, the simple abstraction mechanism just discussed may be operating, especially in gas-phase reactions. However, mechanisms of this type cannot account for all reactions of aromatic substrates. In processes such as Reactions 13-27, 14-17, and 14-18:



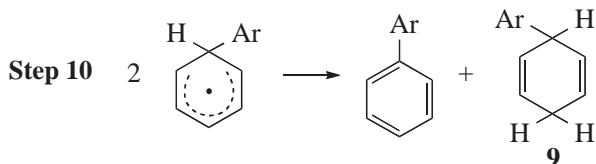
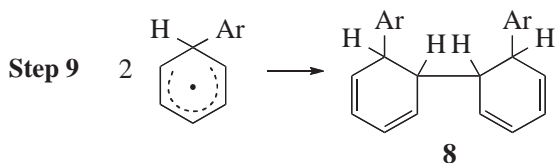
which occur in solution, the simple coupling of two rings by abstraction of an entire group (e.g., phenyl) to generate H^\bullet by the free radical mechanism shown here is very unlikely (see Sec. 14.B.i).



The products can be explained by a mechanism similar to that of electrophilic and nucleophilic aromatic substitution. In the first step, the radical attacks the ring in much the same way as would an electrophile or a



nucleophile to generate 7. The intermediate radical (7) is relatively stable because of the resonance. The reaction can terminate in three ways: by simple coupling to give 8, by disproportionation to give 9,



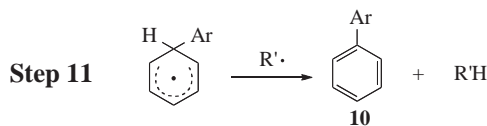
⁴³ Altman, L.J.; Nelson, B.W. *J. Am. Chem. Soc.* **1969**, 91, 5163.

⁴⁴ Jacobus, J.; Pensak, D. *Chem. Commun.* **1969**, 400.

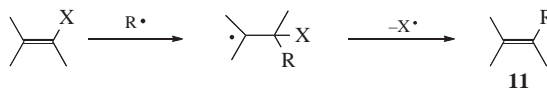
⁴⁵ Sibi, M.P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, 103, 3263.

⁴⁶ See Kobrina, L.S. *Russ. Chem. Rev.* **1977**, 46, 348; Perkins, M.J. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, 231–271; Bolton, R.; Williams, G.H. *Adv. Free-Radical Chem.* **1975**, 5, 1; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, **1974**, pp. 417–469.

or, if a species (R'^{\bullet}) is present that abstracts hydrogen, by abstraction to give **10**.⁴⁷



Coupling product **8** is a partially hydrogenated *o*-quaterphenyl (an *o,o'*-diphenylbiphenyl). Of course, the coupling need not be ortho–ortho, and other isomers can also be formed. Among the evidence (9) and (10) was isolation of compounds of types **8** and **9**.⁴⁸ However, under the reaction conditions dihydrobiphenyls like **9** are normally oxidized to the corresponding biphenyls. Other evidence for this mechanism is the detection of the intermediate **7** by CIDNP⁴⁹ and the absence of isotope effects, expected if the rate-determining step were (7), which involves cleavage of the Ar—H bond. In the mechanism just given, the rate-determining step (8) does not involve loss of hydrogen. The reaction between aromatic rings and the HO^{\bullet} radical takes place by the same mechanism. Intramolecular hydrogen-transfer reactions of aryl radicals are known.⁵⁰ A similar mechanism has been shown for substitution at some vinylic⁵¹ and acetylenic substrates, giving the substituted alkene (**11**).⁵² The kinetics of radical heterolysis reactions that form alkene radical cations has been studied.⁵³



This is reminiscent of the nucleophilic tetrahedral mechanism at a vinylic carbon (Sec. 10.F).

There are many transition metal mediated coupling reactions of aromatic substrates that probably proceed by radical coupling. It is likely that many of these reactions do *not* proceed by free radicals, but rather by metal-mediated radicals or by ligand transfer at the metal. Reactions in these categories were presented in Chapter 13 for convenient correlation with other displacement reactions of aryl halides, aryl diazonium salts, and so on.

14.A.iv. Neighboring-Group Assistance in Free Radical Reactions

In a few cases, it has been shown that cleavage steps (2) and abstraction steps (3) were accelerated by the presence of neighboring groups. Photolytic halogenation (Reaction **14-1**) is a process that normally leads to mixtures of many products. However, bromination of carbon chains containing a bromine atom occurs with high regioselectivity. Bromination of

⁴⁷ See Narita, N.; Tezuka, T. *J. Am. Chem. Soc.* **1982**, *104*, 7316.

⁴⁸ DeTar, D.F.; Long, R.A.J.; Rendleman, J.; Bradley, J.; Duncan, P. *J. Am. Chem. Soc.* **1967**, *89*, 4051; DeTar, D. F. *J. Am. Chem. Soc.* **1967**, *89*, 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* **1985**, 88.

⁴⁹ Fahrenholtz, S.R.; Trozzolo, A.M. *J. Am. Chem. Soc.* **1972**, *94*, 282.

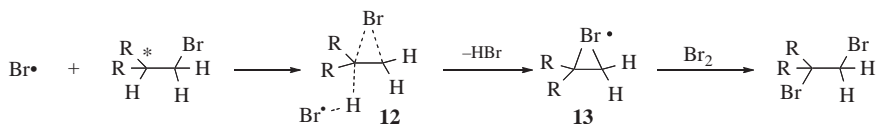
⁵⁰ Curran, D.P.; Fairweather, N. *J. Org. Chem.* **2003**, *68*, 2972.

⁵¹ See Bach, R.D.; Baboul, A.G.; Schlegel, H.B. *J. Am. Chem. Soc.* **2001**, *123*, 5787.

⁵² Russell, G.A.; Ngoviwatchai, P. *Tetrahedron Lett.* **1986**, *27*, 3479, and references cited therein.

⁵³ Horner, J.H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* **2004**, *126*, 14979. See also, Maruyama, T.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 7324.

alkyl bromides gave 84–94% substitution at the carbon adjacent to the bromine already in the molecule.⁵⁴ This result may seem surprising because, as will be seen (Sec. 14.B.i, category 3), positions close to a polar group (e.g., bromine) should actually be *deactivated* by the electron-withdrawing field effect of the bromine. However, the unusual regioselectivity is explained by a mechanism in which abstraction (3) is assisted by a neighboring bromine atom, as in **12**.⁵⁵ In the normal mechanism, Br^\bullet abstracts a hydrogen atom from RH , leaving R^\bullet . When a bromine is present in the proper position, it assists this process, giving a cyclic intermediate (a *bridged free radical*, **13**).⁵⁶ In the final step (very similar to $\text{R}^\bullet + \text{Br}_2 \rightarrow \text{RBr} + \text{Br}^\bullet$) the ring is broken. If this mechanism is correct, the configuration at the substituted carbon (marked *) should be retained. This has been shown to be the case: Optically active 1-bromo-2-methylbutane gave 1,2-dibromo-2-methylbutane with retention of configuration.⁵⁵ Furthermore, when this reaction was carried out in



the presence of DBr , the “recovered” 1-bromo-2-methylbutane was found to be deuterated in the 2 position, and its configuration was retained.⁵⁷ This is just what would be predicted if some of the **11** present abstracted D from DBr . There is evidence that Cl can form bridged radicals,⁵⁸ though ESR spectra show that the bridging is not necessarily symmetrical.⁵⁹ Still more evidence for bridging by Br has been found in isotope effects and other studies.⁶⁰ However, evidence from CIDNP shows that the methylene protons of the β -bromoethyl radical are not equivalent, at least while the radical is present in the radical pair $[\text{PhCOO}^\bullet \cdot \text{CH}_2\text{CH}_2\text{Br}]$ within a solvent cage.⁶¹ This evidence indicates that under these conditions $\text{BrCH}_2\text{CH}_2^\bullet$ is not a symmetrically bridged radical, but it could be unsymmetrically bridged. A bridged intermediate has also been invoked, when a bromo group is in the proper position, in the *Hunsdiecker reaction*⁶² (**14-30**), and in abstraction of iodine atoms by the phenyl radical.⁶³ Participation by other neighboring groups (e.g. SR, SiR_3 , SnR_3) has also been reported.⁶⁴

⁵⁴ Thaler, W.A. *J. Am. Chem. Soc.* **1963**, 85, 2607. See also, Hargis, J.H. *J. Org. Chem.* **1973**, 38, 346.

⁵⁵ Skell, P.S.; Tuleen, D.L.; Read, P.D. *J. Am. Chem. Soc.* **1963**, 85, 2849; Huyser, E.S.; Feng, R.H.C. *J. Org. Chem.* **1971**, 36, 731. For another explanation, see Lloyd, R.V.; Wood, D.E. *J. Am. Chem. Soc.* **1975**, 97, 5986. Also see, Cope, A.C.; Fenton, S.W. *J. Am. Chem. Soc.* **1951**, 73, 1668.

⁵⁶ See Kaplan, L. *Bridged Free Radicals*; Marcel Dekker, NY, **1972**; Skell, P.S.; Traynham, J.G. *Acc. Chem. Res.* **1984**, 17, 160; Skell, P.S.; Shea, K.J. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, pp. 809–852.

⁵⁷ Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* **1973**, 95, 283.

⁵⁸ Everly, C.R.; Schweinsberg, F.; Traynham, J.G. *J. Am. Chem. Soc.* **1978**, 100, 1200; Wells, P.R.; Franke, F.P. *Tetrahedron Lett.* **1979**, 4681.

⁵⁹ Cooper, J.; Hudson, A.; Jackson, R.A. *Tetrahedron Lett.* **1973**, 831; Chen, K.S.; Elson, I.H.; Kochi, J.K. *J. Am. Chem. Soc.* **1973**, 95, 5341.

⁶⁰ Cain, E.N.; Solly, R.K. *J. Chem. Soc., Chem. Commun.* **1974**, 148; Howard, J.A.; Chenier, J.H.B.; Holden, D.A. *Can. J. Chem.* **1977**, 55, 1463. See, however, Tanner, D.D.; Blackburn, E.V.; Kosugi, Y.; Ruo, T.C.S. *J. Am. Chem. Soc.* **1977**, 99, 2714.

⁶¹ Hargis, J.H.; Shevlin, P.B. *J. Chem. Soc., Chem. Commun.* **1973**, 179.

⁶² Applequist, D.E.; Werner, N.D. *J. Org. Chem.* **1963**, 28, 48.

⁶³ Danen, W.C.; Winter, R.L. *J. Am. Chem. Soc.* **1971**, 93, 716.

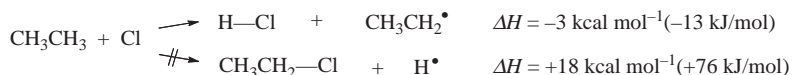
⁶⁴ Ingold, K.U.; Griller, D.; Nazran, A.S. *J. Am. Chem. Soc.* **1985**, 107, 208. See Reetz, M.T. *Angew. Chem. Int. Ed.* **1979**, 18, 173.

Note that a traditional explanation for the selectivity of bromine relative to chlorine is that abstraction of hydrogen by a bromine radical has a later transition state relative to abstraction of hydrogen by a chlorine radical. In a later transition state, the relative stability of the radical plays a greater role than the strength of the C—H bond. Since a tertiary radical is more stable than a secondary, which is more stable than a primary radical, bromination favors formation of the secondary radical over the primary, and a tertiary over secondary. This analysis is supported by the relative rates of hydrogen-atom abstraction by Br^\bullet when compared to Cl^\bullet , where there is a large difference between 1° , 2° , and 3° for Br^\bullet and a small difference for Cl^\bullet . This effect is discussed in more detail in Section 14.B.i, categories 1–5.

14.B. REACTIVITY

14.B.i. Reactivity for Aliphatic Substrates⁶⁵

In a chain reaction, the step that determines what the product will be is most often an abstraction (atom-transfer) step. The atom abstracted by a free radical is almost never a tetra-⁶⁶ or trivalent atom⁶⁷ (except in strained systems, see Sec. 15.B.iv)⁶⁸ and seldom a divalent one.⁶⁹ Nearly always it is univalent, and for organic compounds, it is commonly hydrogen or halogen. Further, in a reaction between a chlorine radical and ethane, formation of an ethyl radical is preferred (H atom transfer) to formation of a hydrogen-atom radical (Cl atom transfer):



The principal reason for this preference is steric. A univalent atom is much more exposed to attack by the incoming radical than an atom with a higher valence. Also, in many cases abstraction of a univalent atom is energetically more favored. For example, in the reaction given above, a $\text{C}_2\text{H}_5\text{—H}$ bond is broken ($D = 100 \text{ kcal mol}^{-1}$, 419 kJ mol^{-1} , from Table 5.3) whichever pathway is taken, but in the former case an H—Cl bond is formed ($D = 103 \text{ kcal mol}^{-1}$, 432 kJ mol^{-1}) while in the latter case it is a $\text{C}_2\text{H}_5\text{—Cl}$ bond ($D = 82 \text{ kcal mol}^{-1}$, 343 kJ mol^{-1}). Thus the first reaction is favored because it is exothermic by 3 kcal mol^{-1} ($100-103$) [13 kJ mol^{-1} ($419-432$)], while the latter is endothermic by 18 kcal mol^{-1} ($100-82$) [76 kJ mol^{-1} ($419-343$)].⁷⁰ However, the steric reason is more important, because even in cases where ΔH is not very different for the two possibilities, the univalent atom is chosen.⁷¹ *Ab initio* studies have probed the transition structures for radical hydrogen abstractions.⁷²

⁶⁵ See Tedder, J.M. *Angew. Chem. Int. Ed.* **1982**, 21, 401.

⁶⁶ See Firouzbakht, M.L.; Ferrieri, R.A.; Wolf, A.P.; Rack, E.P. *J. Am. Chem. Soc.* **1987**, 109, 2213.

⁶⁷ See Back, R.A. *Can. J. Chem.* **1983**, 61, 916.

⁶⁸ See Jackson, R.A.; Townson, M. *J. Chem. Soc. Perkin Trans. 2* **1980**, 1452. See also, Johnson, M.D. *Acc. Chem. Res.* **1983**, 16, 343.

⁶⁹ See Ingold, K.U.; Roberts, B.P. *Free-Radical Substitution Reactions*, Wiley, NY, **1971**.

⁷⁰ The parameter ΔH for a free radical abstraction reaction can be regarded simply as the difference in D values for the bond being broken and the one formed.

⁷¹ Giese, B.; Hartung, J. *Chem. Ber.* **1992**, 125, 1777.

⁷² Eksterowicz, J.E.; Houk, K.N. *Tetrahedron Lett.* **1993**, 34, 427; Damm, W.; Dickhaut, J.; Wetterich, F.; Giese, B. *Tetrahedron Lett.* **1993**, 34, 431.

TABLE 14.1 Relative Susceptibility to Attack by Cl[•] of Primary, Secondary, and Tertiary Positions at 100 and 600 °C in the Gas Phase^a

Temp (°C)	Primary	Secondary	Tertiary
100	1	4.3	7.0
600	1	2.1	2.6

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^aSee Ref. 78.

Most studies of aliphatic reactivity have been made with hydrogen as the leaving atom and chlorine atoms as the abstracting species.⁷³ In these reactions, every hydrogen atom in the substrate is potentially replaceable and mixtures of several products may be obtained. However, the abstracting radical is not totally unselective, and some positions on a molecule lose hydrogen more easily than others. *Ab initio* studies have studied the factors controlling hydrogen abstraction by radicals.⁷⁴ For hydrogen abstraction by the *tert*-butoxy radical (*t*-Bu—O[•]) the factors that influence rate in their order of importance are structure of the radical > substituent effects⁷⁵ > solvent effects.⁷⁶ The position of attack will be discussed under several headings⁷⁷:

1. *Alkanes*. If a tertiary hydrogen atoms is present in an alkane, it is preferentially abstracted by almost any radical, with secondary hydrogen atoms being next preferred. This is in the same order as *D* values for these types of C—H bonds (Table 5.3). The extent of the preference depends on the selectivity of the abstracting radical and on the temperature. Table 14.1 shows⁷⁸ that at high temperatures selectivity decreases, as might be expected.⁷⁹ An example of the effect of radical selectivity is the comparison of fluorine atoms with bromine atoms. For the former, the ratio of primary to tertiary abstraction (of hydrogen) is 1:1.4, while for the less reactive bromine atom this ratio is 1:1600. With certain large radicals there is a steric factor that may change the selectivity pattern. For example, in the photochemical chlorination of isopentane in H₂SO₄ with *N*-chloro-di-*tert*-butylamine and *N*-chloro-*tert*-butyl-*tert*-pentylamine, the primary hydrogen atoms are abstracted 1.7 times *faster* than the tertiary hydrogen.⁸⁰ In this case, the attacking

⁷³ See Hendry, D.G.; Mill, T.; Piszkievicz, L.; Howard, J.A.; Eigenmann, H.K. *J. Phys. Chem. Ref. Data* **1974**, 3, 937; Roberts, B.P.; Steel, A.J. *Tetrahedron Lett.* **1993**, 34, 5167. See Tanko, J.M.; Blackert, J.F. *J. Chem. Soc. Perkin Trans. 2* **1996**, 1775.

⁷⁴ Zavitsas, A.A. *J. Chem. Soc. Perkin Trans. 2* **1998**, 499.

⁷⁵ See Wen, Z.; Li, Z.; Shang, Z.; Cheng, J.-P. *J. Org. Chem.* **2001**, 66, 1466.

⁷⁶ Kim, S.S.; Kim, S.Y.; Ryou, S.S.; Lee, C.S.; Yoo, K.H. *J. Org. Chem.* **1993**, 58, 192.

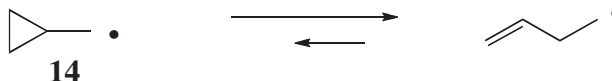
⁷⁷ See Tedder, J.M. *Tetrahedron* **1982**, 38, 313; Kerr, J.A. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 18, Elsevier, NY, **1976**, pp. 39–109; Russell, G.A. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, pp. 275–331; Rüchardt, C. *Angew. Chem. Int. Ed.* **1970**, 9, 830; Poutsma, M.L. *Methods Free-Radical Chem.* **1969**, 1, 79; Davidson, R.S. *Q. Rev. Chem. Soc.* **1967**, 21, 249; Pryor, W.A.; Fuller, D.L.; Stanley, J. *P. J. Am. Chem. Soc.* **1972**, 94, 1632.

⁷⁸ Hass, H.B.; McBee, E.T.; Weber, P. *Ind. Eng. Chem.* **1936**, 28, 333.

⁷⁹ With phenyl radicals: Kopinke, F.; Zimmermann, G.; Anders, K. *J. Org. Chem.* **1989**, 54, 3571.

⁸⁰ Deno, N.C.; Fishbein, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* **1971**, 93, 2065. See Dneprovskii, A.N.; Mil'tsov, S. *A. J. Org. Chem. USSR* **1988**, 24, 1836.

radicals (the radical ions $R_2NH^{\bullet+}$, see Reaction 14-1) are bulky enough for steric hindrance to become a major factor.



Cyclopropylcarbinyl radicals (**14**) are alkyl radicals, but because of the cyclopropane ring with its relatively weak bonds, they undergo rapid ring opening to give butenyl radicals.⁸¹ The rate constant for this process has been measured by picosecond radical kinetic techniques to be in the range of $10^7 \text{ M}^{-1} \text{ s}^{-1}$ for the parent⁸² to $10^{10} \text{ M}^{-1} \text{ s}^{-1}$ for substituted derivatives.⁸³ Cyclobutylcarbinyl radicals undergo the cyclobutylcarbinyl to 4-pentenyl radical process,⁸⁴ but examples are generally limited to the parent system and phenyl-substituted derivatives.⁸⁵ Cyclization of the 4-pentenyl radical is usually limited to systems where a stabilized radical can be formed.⁸⁶ The effect of substituents has been studied.⁸⁷ Note that 2-aziridinylmethyl radicals also undergo ring opening via C—N or C—C cleavage to give a nitrogen or carbon radical, respectively, and the ring opening is strongly influenced by substituents at C-1 rather than those on nitrogen.⁸⁸ An alkyl substituent at the C-1 substituent generally leads to C—N cleavage, whereas a carbonyl substituent at C-1 usually favors C—C cleavage.⁸⁸

The rate of the ring-opening reaction of **5**,⁸⁹ and other substrates have been determined using an indirect method for the calibration⁹⁰ of fast radical reactions, applicable for radicals with lifetimes as short as 1 ps.⁹¹ This 'radical clock'⁹² method is based on the use of pyridine-2-thione-*N*-oxycarbonyl esters as radical precursors and radical trapping by the highly reactive thiophenol and benzeneselenenol.⁹³ A number of radical clock substrates are known.⁹⁴ Other radical clock processes include: racemization of radicals with chiral conformations,⁹⁵ one-carbon

⁸¹ Nonhebel, D.C. *Chem. Soc. Rev.* **1993**, 22, 347. For a discussion of solvent/counterion reorganization, see Tanko, J.M.; Gillmore, J.G.; Friedline, R.; Chahma, M. *J. Org. Chem.* **2005**, 70, 4170.

⁸² Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Luszytk, J. *J. Org. Chem.* **1997**, 62, 1210.

⁸³ Toy, P.H.; Newcomb, M. *J. Org. Chem.* **1998**, 63, 8609. See Martinez, F.N.; Schlegel, H.B.; Newcomb, M. *J. Org. Chem.* **1996**, 61, 8547; **1998**, 63, 3618 for *ab initio* studies to determine rate constants.

⁸⁴ See Jin, J.; Newcomb, M. *J. Org. Chem.* **2007**, 72, 5098. For a discussion of ring opening versus ring expansion in bicyclic cyclopropyl radicals, see Shi, J.; Chong, S.-S.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Org. Chem.* **2008**, 73, 974.

⁸⁵ Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* **2000**, 65, 4447.

⁸⁶ Cerreti, A.; D'Annibale, A.; Trogolo, C.; Umani, F. *Tetrahedron Lett.* **2000**, 41, 3261.

⁸⁷ Baker, J.M.; Dolbier, Jr., W.R. *J. Org. Chem.* **2001**, 66, 2662. See Kirschberg, T.; Mattay, J. *Tetrahedron Lett.* **1994**, 35, 7217.

⁸⁸ Wang, Y.-M.; Fu, Y.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* **2005**, 70, 3633.

⁸⁹ Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, 108, 7981; Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Luszytk, J. *J. Org. Chem.* **1997**, 62, 1210, 5656.

⁹⁰ See Hollis, R.; Hughes, L.; Bowry, V.W.; Ingold, K.U. *J. Org. Chem.* **1992**, 57, 4284.

⁹¹ Newcomb, M.; Toy, P.H. *Acc. Chem. Res.* **2000**, 33, 449. See Horn, A.H.C.; Clark, T. *J. Am. Chem. Soc.* **2003**, 125, 2809.

⁹² See Griller, D.; Ingold, K.U. *Acc. Chem. Res.* **1980**, 13, 317.

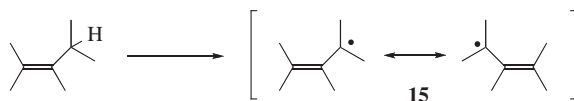
⁹³ Newcomb, M.; Johnson, C.C.; Manek, M.B.; Varick, T.R. *J. Am. Chem. Soc.* **1992**, 114, 10915; Newcomb, M.; Varick, T.R.; Ha, C.; Manek, M.B.; Yue, X. *J. Am. Chem. Soc.* **1992**, 114, 8158.

⁹⁴ See Kumar, D.; de Visser, S.P.; Sharma, P.K.; Cohen, S.; Shaik, S. *J. Am. Chem. Soc.* **2004**, 126, 1907.

⁹⁵ Rychnovsky, S.D.; Hata, T.; Kim, A.I.; Buckmelter, A.J. *Lett. Org. Chem.* **2001**, 3, 807.

ring expansion in cyclopentanones,⁹⁶ norcarane and spiro[2,5]octane,⁹⁷ α - and β -thujone radical rearrangements,⁹⁸ and cyclopropylcarbinyl radicals or alkoxy-carbonyl radicals containing stabilizing substituents,⁹⁹ and cyclobutylcarbinyl radicals.¹⁰⁰ *Ab initio* and density functional theory have been used to study radical clock reactions.¹⁰¹

2. *Alkenes*. When the substrate molecule contains a double bond, treatment with chlorine or bromine usually leads to addition rather than substitution, as described in Reaction 15-39. However, for other radicals (and even for chlorine or bromine atoms when they react by hydrogen transfer) the position of attack is at the allylic carbon. Vinylic hydrogen atoms are practically never abstracted, and allylic hydrogen atoms are greatly preferred to other positions of the molecule. Allylic hydrogen abstraction from a cyclic alkene is usually faster than abstraction from an acyclic alkene.¹⁰² This is generally attributed¹⁰³ to resonance stabilization of the allylic radical (15). As might be expected, allylic rearrangements (see Reaction 14-7) are common in these cases.¹⁰⁴



3. *Alkyl Side Chains of Aromatic Rings*. The preferential position of attack on a side chain is usually the one directly attached to the ring (the benzylic position). Both for active radicals (e.g., chlorine and phenyl) and for more selective ones (e.g., bromine), hydrogen exchange is faster than that at a primary carbon. For active radicals, hydrogen exchange at the benzylic position is slower than for tertiary positions, while for the selective ones it is faster. Two or three aryl groups on a carbon activate its hydrogen atoms even more, as would be expected from the resonance involved. These statements can be illustrated by the following abstraction ratios:¹⁰⁵

	Me—H	MeCH ₂ —H	Me ₂ CH—H	Me ₃ C—H	PhCH ₂ —H	Ph ₂ CH—H	Ph ₃ C—H
Br	0.0007	1	220	19,400	64,000	1.1×10^6	6.4×10^6
Cl	0.004	1	4.3	6.0	1.3	2.6	9.5

However, many anomalous results have been reported for these substrates. The benzylic position is not always the most favored. One thing certain is that *aromatic* hydrogen atoms are seldom abstracted if there are aliphatic ones to compete (note from Table 5.3, that *D* for Ph—H is higher than that for any alkyl H bond). Several

⁹⁶ Chatgililoglu, C.; Timokhin, V. I.; Ballestri, M. *J. Org. Chem.* **1998**, 63, 1327.

⁹⁷ See Auclair, K.; Hu, Z.; Little, D. M.; Ortiz de Montellano, P. R.; Groves, J. T. *J. Am. Chem. Soc.* **2002**, 124, 6020.

⁹⁸ He, X.; Ortiz de Montellano, P. R. *J. Org. Chem.* **2004**, 69, 5684.

⁹⁹ Beckwith, A.L.J.; Bowry, V.W. *J. Am. Chem. Soc.* **1994**, 116, 2710. See Cooksy, A.L.; King, H.F.; Richardson, W.H. *J. Org. Chem.* **2003**, 68, 9441.

¹⁰⁰ Jin, J.; Newcomb, M. *J. Org. Chem.* **2008**, 73, 4740.

¹⁰¹ Jäger, C.M.; Hennemann, M.; Mieszala, A.; Clark, T. *J. Org. Chem.* **2008**, 73, 1536.

¹⁰² Rothenberg, G.; Sasson, Y. *Tetrahedron* **1998**, 54, 5417.

¹⁰³ See, however, Kwart, H.; Brechbiel, M.; Miles, W.; Kwart, L.D. *J. Org. Chem.* **1982**, 47, 4524.

¹⁰⁴ See Wilt, J.W. in Kochi, J.K. *Free Radicals*, Vol. 1 Wiley, NY, **1973**, pp. 458–466.

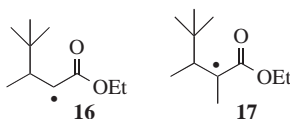
¹⁰⁵ Russell, G.A. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, p. 289.

σ^\bullet scales (similar to the σ , σ^+ , and σ^- scales discussed in Chapter 9) have been developed for benzylic radicals.¹⁰⁶

4. *Compounds Containing Electron-Withdrawing Substituents.* In halogenations, electron-withdrawing groups greatly deactivate adjacent positions. Compounds of the type $Z-CH_2-CH_3$ are attacked predominantly or exclusively at the β position when Z is CO_2H , $COCl$, $COOR$, SO_2Cl , or CX_3 . Compounds, such as acetic acid and acetyl chloride, are not attacked at all, in sharp contrast to electrophilic halogenations (Reactions 12-4–12-6), where *only* the α position is substituted. This deactivation of α positions is also at variance with the expected stability of the resulting radicals, since they would be expected to be stabilized by resonance similar to that for allylic and benzylic radicals. This behavior is a result of the polar transition states discussed in Section 14.A.ii. Halogen atoms are electrophilic radicals and look for positions of high electron density. Hydrogen atoms on carbon atoms next to electron-withdrawing groups have low-electron densities (because of the field effect of Z) and are therefore shunned. Radicals that are not electrophilic do not display this behavior. For example, the methyl radical is essentially nonpolar and does not avoid positions next to electron-withdrawing groups; relative rates of abstraction at the α and β carbons of propionic acid are¹⁰⁷

CH ₃ —CH ₂ —COOH		
Me [•]	1	7.8
Cl [•]	1	0.02

It is possible to generate radicals adjacent to electron-withdrawing groups. Radical **16** can be generated and undergoes coupling reactions with little selectivity. When **17** is generated, it rapidly disproportionates rather than couples, giving the corresponding alkene and alkane.¹⁰⁸ Such radicals have also been shown to have a conformational preference for orientation of the orbital containing the single electron. In such cases, hydrogen abstraction proceeds with good stereoselectivity.¹⁰⁹



Some radicals (e.g., *tert*-butyl,¹¹⁰ benzyl,¹¹¹ and cyclopropyl)¹¹² are *nucleophilic* (they tend to abstract electron-poor hydrogen atoms).¹¹³ The phenyl radical appears to have a very small degree of nucleophilic character.¹¹⁴ For longer chains, the field effect

¹⁰⁶ See Fisher, T.H.; Dershem, S.M.; Prewitt, M.L. *J. Org. Chem.* **1990**, 55, 1040.

¹⁰⁷ Russell, G.A. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, p. 311.

¹⁰⁸ Porter, N.A.; Rosenstein, I.J. *Tetrahedron Lett.* **1993**, 34, 7865.

¹⁰⁹ Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G. *Tetrahedron Lett.* **1992**, 33, 1863.

¹¹⁰ Pryor, W.A.; Tang, F.Y.; Tang, R.H.; Church, D.F. *J. Am. Chem. Soc.* **1982**, 104, 2885; Dütsch, H.R.; Fischer, H. *Int. J. Chem. Kinet.* **1982**, 14, 195.

¹¹¹ Clerici, A.; Minisci, F.; Porta, O. *Tetrahedron* **1973**, 29, 2775.

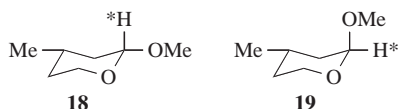
¹¹² Stefani, A.; Chuang, L.; Todd, H.E. *J. Am. Chem. Soc.* **1970**, 92, 4168.

¹¹³ Nucleophilicity and electrophilicity indices have been developed for radicals. See De Vleeschouwer, F.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. *Org. Lett.* **2007**, 9, 2721.

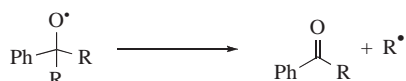
¹¹⁴ Suehiro, T.; Suzuki, A.; Tsuchida, Y.; Yamazaki, J. *Bull. Chem. Soc. Jpn.* **1977**, 50, 3324.

continues, and the β position is also deactivated to attack by halogen, though much less so than the α position. Note that in Section 14.A.ii the abstraction of an α hydrogen atom from ring-substituted toluenes can be correlated by the *Hammett equation*.

5. *Stereoelectronic Effects*. In Section 16.A.i, category 4, there is an example of a stereoelectronic effect. It has been shown that such effects are important where a hydrogen is abstracted from a carbon adjacent to a C—O or C—N bond. In such cases, hydrogen is abstracted from C—H bonds that have a relatively small dihedral angle ($\approx 30^\circ$) with the unshared orbitals of the O or N much more easily than from those with a large angle ($\sim 90^\circ$). For example, the starred hydrogen of **18** was abstracted about eight times faster than the starred hydrogen of **19**.¹¹⁵



The presence of an OR or SiR₃ substituent β - to the carbon bearing the radical accelerates the rate of halogen abstraction.¹¹⁶ Tertiary arylcarbinyloxy radicals undergo β -scission to give a ketone:¹¹⁷

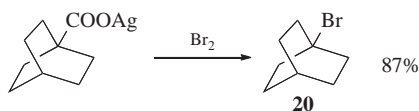


Abstraction of a halogen has been studied much less,¹¹⁸ but the order of reactivity is RI > RBr > RCl \gg RF.

There are now many cases where free radical reactions are promoted by transition metals.¹¹⁹

14.B.ii. Reactivity at a Bridgehead¹²⁰

Many free radical reactions have been observed at bridgehead carbons, as in formation of bromide **20** (see Reaction 14-30),¹²¹ demonstrating that the free radical need not be planar. However, treatment of norbornane with sulfuryl chloride and benzoyl peroxide gave mostly 2-chloronorbornane, although the bridgehead position is tertiary.¹²² So, while bridgehead free radical substitution is possible, it is not preferred, presumably because of the strain involved.¹²³



¹¹⁵ Hayday, K.; McKelvey, R.D. *J. Org. Chem.* **1976**, *41*, 2222. Also see Beckwith, A.L.J.; Westwood, S.W. *Aust. J. Chem.* **1983**, *36*, 2123; Griller, D.; Bunce, N.J.; Cheung, H.K.Y.; Langshaw, J. *J. Org. Chem.* **1986**, *51*, 5421.

¹¹⁶ Roberts, B.P.; Steel, A.J. *J. Chem. Soc. Perkin Trans. 2* **1994**, 2411.

¹¹⁷ Bietti, M.; Gente, G.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 6820.

¹¹⁸ See Danen, W.C. *Methods Free-Radical Chem.* **1974**, *5*, 1.

¹¹⁹ Iqbal, J.; Bhatia, B.; Nayyar, N.K. *Chem. Rev.* **1994**, *94*, 519.

¹²⁰ See Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* **1971**, *18*, 1, see pp. 79–81.

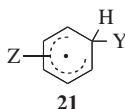
¹²¹ Grob, C.A.; Ohta, M.; Renk, E.; Weiss, A. *Helv. Chim. Acta* **1958**, *41*, 1191.

¹²² Roberts, J.D.; Urbanek, L.; Armstrong, R. *J. Am. Chem. Soc.* **1949**, *71*, 3049. See also, Kooyman, E.C.; Vegter, G.C. *Tetrahedron* **1958**, *4*, 382; Walling, C.; Mayahi, M.F. *J. Am. Chem. Soc.* **1959**, *81*, 1485.

¹²³ See Koch, V.R.; Gleicher, G.J. *J. Am. Chem. Soc.* **1971**, *93*, 1657.

14.B.iii. Reactivity in Aromatic Substrates

Free radical substitution at an aromatic carbon seldom takes place by a mechanism in which a hydrogen atom is abstracted to give an aryl radical. Reactivity considerations here are similar to those in Chapters 11 and 13; that is, which position on the ring will be attacked to give the intermediate **21**.



The obvious way to obtain this information is to carry out reactions with various Z groups and to analyze the products for percent ortho, meta, and para isomers, as has so often been done for electrophilic substitution. However, this procedure is much less accurate in the case of free radical substitutions because of the many side reactions. It may be, for example, that in a given case the ortho position is more reactive than the para, but the intermediate from the para attack may go on to product while that from the ortho attack gives a side reaction. In such a case, analysis of the three products does not give a true picture of which position is most susceptible to attack. The following generalizations can nevertheless be drawn, though there has been much controversy over just how meaningful such conclusions are¹²⁴

1. All substituents increase reactivity at ortho and para positions over that of benzene. There is no great difference between electron-donating and electron-withdrawing groups.
2. Reactivity at meta positions is usually similar to that of benzene, perhaps slightly higher or lower. This fact, coupled with the preceding one, means that all substituents are activating and ortho–para directing; none are deactivating or (chiefly) meta directing.
3. Reactivity at ortho positions is usually somewhat greater than at para positions, except where a large group decreases ortho reactivity for steric reasons.
4. In direct competition, electron-withdrawing groups exert a somewhat greater influence than electron-donating groups. Arylation of para-disubstituted compounds ($\text{XC}_6\text{H}_4\text{Y}$) showed that substitution ortho to the group X became increasingly preferred as the electron-withdrawing character of X increases (with Y held constant).¹²⁵ The increase could be correlated with the Hammett σ_p values for X.
5. Substituents have a much smaller effect than in electrophilic or nucleophilic substitution; hence the partial rate factors (see Sec. 11.C) are not great.¹²⁶ Partial rate factors for a few groups are given in Table 14.2.¹²⁷
6. Although hydrogen is the leaving group in most free radical aromatic substitutions, ipso attack (Sec. 11.B.iii) and ipso substitution (e.g., with Br, NO_2 , or CH_3CO as the leaving group) have been found in certain cases.¹²⁸

¹²⁴ Vidal, S.; Court, J.; Bonnier, J. *J. Chem. Soc. Perkin Trans. 2* **1973**, 2071; Tezuka, T.; Ichikawa, K.; Marusawa, H.; Narita, N. *Chem. Lett.* **1983**, 1013.

¹²⁵ Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* **1970**, 2653.

¹²⁶ For a quantitative treatment, see Charton, M.; Charton, B. *Bull. Soc. Chim. Fr.* **1988**, 199.

¹²⁷ Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* **1971**, 2681.

¹²⁸ See Traynham, J.G. *J. Chem. Educ.* **1983**, 60, 937; *Chem. Rev.* **1979**, 79, 323; Tiecco, M. *Acc. Chem. Res.* **1980**, 13, 51; *Pure Appl. Chem.* **1981**, 53, 239.

TABLE 14.2 Partial Rate Factors for Attack of Substituted Benzenes by Phenyl Radicals Generated from Bz₂O₂ (Reaction 14–21)^a

Z	Partial Rate Factor		
	<i>o</i>	<i>m</i>	<i>p</i>
H	1	1	1
NO ₂	5.50	0.86	4.90
CH ₃	4.70	1.24	3.55
CMe ₃	0.70	1.64	1.81
Cl	3.90	1.65	2.12
Br	3.05	1.70	1.92
MeO	5.6	1.23	2.31

Reproduced from Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* **1971**, 2681 with permission from the Royal Society of Chemistry

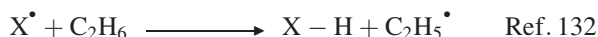
^aSee Ref. 127.

Note that interconvertible 1,4-hydrogen atom shifts are possible in radicals derived from biaryls.¹²⁹

14.B.iv. Reactivity in the Attacking Radical¹³⁰

As seen above, some radicals are much more selective than others (Sec. 14.B.i). The bromine atom is so selective that when only primary hydrogen atoms are available, as in neopentane or *tert*-butylbenzene, the reaction is slow; and isobutane can be selectively brominated to give *tert*-butyl bromide in high yields. However, toluene reacts with bromine atoms instantly. Bromination of other alkylbenzenes (e.g., ethylbenzene and cumene) takes place exclusively at the α position,¹³¹ emphasizing the selectivity of Br \cdot . The dissociation energy (*D*) of the C—H bond is more important for radicals of low reactivity than for highly reactive radicals, since bond breaking in the transition state is greater. Thus, bromine shows a greater tendency than chlorine to attack α to an electron-withdrawing group because the energy of the C—H bond there is lower than in other places in the molecule.

Some radicals (e.g., triphenylmethyl) are so unreactive that they abstract hydrogen atoms very poorly if at all. Table 14.3 lists some common free radicals in approximate order of reactivity.¹³²



iPr \cdot is < Me \cdot and *t-Bu* \cdot is still less¹³³

As mentioned earlier, some free radicals (e.g., chloro) are electrophilic and some (e.g., *tert*-butyl) are nucleophilic. Bear in mind that these tendencies are relatively slight compared with the electrophilicity of a positive ion or the nucleophilicity of a negative ion. The predominant character of a free radical is neutral, whether it has slight electrophilic or nucleophilic tendencies.

¹²⁹ Peng, L.; Scott, L.T. *J. Am. Chem. Soc.* **2005**, 127, 16518.

¹³⁰ See Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* **1965**, 1, 1; Gray, P.; Herod, A.A.; Jones, A. *Chem. Rev.* **1971**, 71, 247.

¹³¹ Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, **1970**, p. 97.

¹³² Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* **1965**, 1, 1.

¹³³ Kharasch, M.S.; Hambling, J.K.; Rudy, T.P. *J. Org. Chem.* **1959**, 24, 303.

TABLE 14.3 Some Common Free Radicals in Decreasing Order of Activity⁵

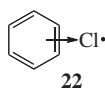
Radical	E		Radical	E	
	(kcal mol ⁻¹)	(kJ mol ⁻¹)		(kcal mol ⁻¹)	(kJ mol ⁻¹)
F [•]	0.3	1.3	H [•]	9.0	38
Cl [•]	1.0	4.2	Me [•]	11.8	49.4
MeO [•]	7.1	30	Br [•]	13.2	55.2
CF ₃ [•]	7.5	31			

^aThe *E* values represent activation energies for the reaction

[Reprinted with permission from Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* **1965**, 1, 1, Copyright © 1965, with permission from Elsevier Science.]

14.B.v. The Effect of Solvent on Reactivity¹³⁴

As noted earlier, the solvent usually has little effect on free radical substitutions in contrast to ionic substitution reactions: Indeed, reactions in solution are often quite similar in character to those in the gas phase, where there is no solvent at all. However, in certain cases the solvent *can* make an appreciable difference. Chlorination of 2,3-dimethylbutane in aliphatic solvents gave ~60% (CH₃)₂CHCH(CH₃)CH₂Cl and 40% (CH₃)₂CHCCl(CH₃)₂, while in aromatic solvents the ratio became 10:90.¹³⁵ This result is attributed to



complex formation between the aromatic solvent and the chlorine atom that makes the chlorine more selective.¹³⁶ This type of effect is not found in cases where the differences in ability to abstract the atom are caused by field effects of electron-withdrawing groups (Sec 14.B.i). In such cases, aromatic solvents make little difference.¹³⁷ Complex **22** has been detected¹³⁸ as a very short-lived species by observation of its visible spectrum in the pulse radiolysis of a solution of benzene in CCl₄.¹³⁹ Differences caused by solvents have also been reported in reactions of other radicals.¹⁴⁰ Some of the anomalous results obtained in the chlorination of aromatic side chains (Sec 14.B.i) can also be explained by this type of complexing, in this case not with the solvent but with the reacting species.¹⁴¹ Much smaller, though real, differences in selectivity have been found when the solvent in the chlorination of 2,3-dimethylbutane is changed from an alkane to CCl₄.¹⁴² However,

¹³⁴ See Reichardt, C. *Solvent Effects in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, **1979**, pp. 110–123; Martin, J.C. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, pp. 493–524; Huyser, E.S. *Adv. Free-Radical Chem.* **1965**, 1, 77.

¹³⁵ Russell, G.A. *J. Am. Chem. Soc.* **1958**, 80, 4987, 4997, 5002; *J. Org. Chem.* **1959**, 24, 300.

¹³⁶ See also, Ingold, K.U.; Luszyk, J.; Raner, K.D. *Acc. Chem. Res.* **1990**, 23, 219.

¹³⁷ Nagai, T.; Horikawa, Y.; Ryang, H.S.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1971**, 44, 2771.

¹³⁸ See, however, Skell, P.S.; Baxter III, H.N.; Tanko, J.M.; Chebolu, V. *J. Am. Chem. Soc.* **1986**, 108, 6300. For arguments against this proposal, see Walling, C. *J. Org. Chem.* **1988**, 53, 305; Aver'yanov, V.A.; Shvets, V.F.; Semenov, A.O. *J. Org. Chem. USSR* **1990**, 26, 1261.

¹³⁹ Bühler, R.E. *Helv. Chim. Acta* **1968**, 51, 1558; Raner, K.D.; Luszyk, J.; Ingold, K.U. *J. Phys. Chem.* **1989**, 93, 564.

¹⁴⁰ Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* **1987**, 52, 730.

¹⁴¹ See Newkirk, D.D.; Gleicher, G.J. *J. Am. Chem. Soc.* **1974**, 96, 3543 and reference cited therein.

¹⁴² See Raner, K.D.; Luszyk, J.; Ingold, K.U. *J. Org. Chem.* **1988**, 53, 5220.

these differences are not caused by formation of a complex between Cl^\bullet and the solvent. There are cases, however, where the rate of reaction for trapping a radical depends on the polarity of the solvent, particularly in water.¹⁴³

14.C. REACTIONS

The reactions in this chapter are classified according to leaving group. The most common leaving groups are hydrogen and nitrogen (generally the diazonium ion); these are considered first.

14.C.i. Hydrogen as a Leaving Group

A. Substitution by Halogen

14-1 Halogenation at an Alkyl Carbon¹⁴⁴

Halogenation or Halo-de-hydrogenation



Alkanes can be chlorinated or brominated by treatment with chlorine or bromine in the presence of visible or UV light, or with heat.¹⁴⁵ These reactions require an added chemical reagent as the radical chain initiator, or exposure to light, or higher temperatures.¹⁴⁶ The reaction can also be applied to alkyl chains containing many functional groups. The chlorination reaction is usually not useful for preparative purposes precisely because it is so general: Not only does substitution take place at virtually every alkyl carbon in the molecule, but di- and polychloro substitution almost invariably occur even if there is a large molar ratio of substrate to halogen. Note that benzylic halogenation (e.g., the *Wohl-Ziegler bromination*) is discussed in Reaction 14-3.

When functional groups are present, the principles are those outlined in Section 14.B.i. Tertiary carbons are most likely to be functionalized and primary are least likely. Favored positions are those α to aromatic rings, while positions α to electron-withdrawing groups are least likely to be substituted. Hydrogen atoms α to an OR group are very readily replaced. Nevertheless, mixtures are nearly always obtained. This can be contrasted to the regioselectivity of electrophilic halogenation (Reactions 12-4–12-6), which always takes place α to a carbonyl group (except when the reaction is catalyzed by AgSbF_6). Of course, if a *mixture* of chlorides is wanted, the reaction is usually quite satisfactory. For obtaining pure compounds, the chlorination reaction is essentially limited to substrates with only one type of replaceable hydrogen (e.g., ethane, cyclohexane, and neopentane). The most common are methylbenzenes and other substrates with methyl groups on aromatic rings,

¹⁴³ Tronche, C.; Martinez, F.N.; Horner, J.H.; Newcomb, M.; Senn, M.; Giese, B. *Tetrahedron Lett.* **1996**, 37, 5845.

¹⁴⁴ For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, **1999**, pp. 611–617.

¹⁴⁵ See Poutsma, M.L. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, pp. 159–229; Huyser, E.S. in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 1, Wiley, NY, **1973**, pp. 549–607; Poutsma, M.L. *Methods Free-Radical Chem.* **1969**, 1, 79 (chlorination); Thaler, W.A. *Methods Free-Radical Chem.* **1969**, 2, 121 (bromination).

¹⁴⁶ Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, **1989**.

since few cases are known where halogen atoms substitute at an aromatic position.¹⁴⁷ Of course, ring substitution *does* take place in the presence of a positive-ion-forming catalyst (Reaction 11-10). In addition to mixtures of various alkyl halides, traces of other products are obtained. These include H₂, alkenes, higher alkanes, lower alkanes, and halogen derivatives of these compounds. Solvent plays an important role in this process.¹⁴⁸

The bromine atom is much more selective than the chlorine atom. As indicated in Section 14.B.iv, it is often possible to brominate tertiary and benzylic positions selectively. High regioselectivity can also be obtained where the neighboring-group mechanism (Sec 14.A.iv) can operate.

As already mentioned, halogenation can be performed with chlorine or bromine. Fluorine has also been used,¹⁴⁹ but seldom, because it is too reactive and hard to control.¹⁵⁰ It often breaks carbon chains down into smaller units, a side reaction that sometimes becomes troublesome in chlorinations as well. Fluorination¹⁵¹ has been achieved by the use of chlorine trifluoride (ClF₃) at -75°C.¹⁵² For example, cyclohexane gave 41% fluorocyclohexane and methylcyclohexane gave 47% 1-fluoro-1-methylcyclohexane. Fluorox-ytrifluoromethane (CF₃OF) fluorinates tertiary positions of certain molecules in good yields with high regioselectivity.¹⁵³ For example, adamantane gave 75% 1-fluoroadamantane. Fluorine at -70 °C, diluted with N₂,¹⁵⁴ and bromine trifluoride at 25–35 °C¹⁵⁵ are also highly regioselective for tertiary positions. These reactions probably have electrophilic,¹⁵⁶ not free radical mechanisms. In fact, the success of the F₂ reactions depends on the suppression of free radical pathways, by dilution with an inert gas, by working at low temperatures, and/or by the use of radical scavengers. Fluorination of 1,3-dicarbonyl compounds and activated aromatic compounds was achieved under solvent-free conditions using SelectfluorTM F–TEDA–BF₄.¹⁵⁷

Iodine can be used if the activating light has a wavelength of 184.9 nm,¹⁵⁸ but iodinations using I₂ alone are seldom attempted, largely because the HI formed reduces the alkyl iodide. The direct free radical halogenation of aliphatic hydrocarbons with iodine is significantly endothermic relative to the other halogens, and the requisite chain reaction does not occur.¹⁵⁹ On the other hand, when iodine (CCl₄ • 2 AlI₃) reacts with an alkane in

¹⁴⁷ Dermer, O.C.; Edmison, M.T. *Chem. Rev.* **1957**, 57, 77, pp. 110–112. See Kooyman, E.C. *Adv. Free-Radical Chem.* **1965**, 1, 137.

¹⁴⁸ Dneprovskii, A.S.; Kuznetsov, D.V.; Eliseenkov, E.V.; Fletcher, B.; Tanko, J.M. *J. Org. Chem.* **1998**, 63, 8860.

¹⁴⁹ Rozen, S. *Acc. Chem. Res.* **1988**, 21, 307; Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* **1986**, 86, 997, pp. 1003–1005; Gerstenberger, M.R.C.; Haas, A. *Angew. Chem. Int. Ed.* **1981**, 20, 647; Hudlicky, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, **1976**; pp. 67–91. For descriptions of the apparatus necessary for handling F₂, see Vypel, H. *Chimia* **1985**, 39, 305.

¹⁵⁰ See Rozhkov, I.N. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, **1983**, pp. 805–825; Lagow, R.J.; Margrave, J.L. *Prog. Inorg. Chem.* **1979**, 26, 161. See also, Adcock, J.L.; Evans, W.D. *J. Org. Chem.* **1984**, 49, 2719; Huang, H.; Lagow, R.J. *Bull. Soc. Chim. Fr.* **1986**, 993.

¹⁵¹ See German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, **1989**.

¹⁵² Brower, K.R. *J. Org. Chem.* **1987**, 52, 798.

¹⁵³ Alker, D.; Barton, D.H.R.; Hesse, R.H.; Lister-James, J.; Markwell, R.E.; Pechet, M.M.; Rozen, S.; Takeshita, T.; Toh, H.T. *Nouv. J. Chem.* **1980**, 4, 239.

¹⁵⁴ Rozen, S.; Gal, C. *J. Org. Chem.* **1988**, 53, 2803. (See Ref. 153.)

¹⁵⁵ Boguslavskaya, L.S.; Kartashov, A.V.; Chuvatkin, N.N. *J. Org. Chem. USSR* **1989**, 25, 1835.

¹⁵⁶ See, for example, Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, 52, 2769.

¹⁵⁷ Stavber, G.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2007**, 48, 2671.

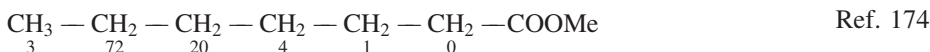
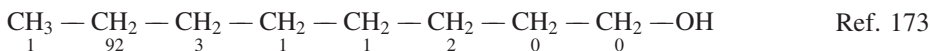
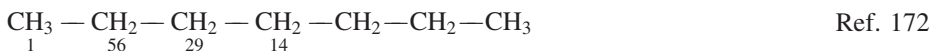
¹⁵⁸ Gover, T.A.; Willard, J.E. *J. Am. Chem. Soc.* **1960**, 82, 3816.

¹⁵⁹ Liguori, L.; Bjørsvik, H.-R.; Bravo, A.; Fontana, R.; Minisci, F. *Chem. Commun.* **1997**, 1501.

dibromomethane at -20°C , good yields of the iodoalkane are obtained.¹⁶⁰ The reaction of an alkane with *tert*-butylhypoiodite (*t*-BuOI) at 40°C gave the iodoalkane in good yield.¹⁶¹ The reaction of alkanes with iodine and $\text{PhI}(\text{OAc})_2$ generates the iodoalkane.¹⁶² A radical protocol was developed using Cl_4 with base. Cyclohexane could be iodinated, for example, with Cl_4 in the presence of powdered NaOH .¹⁶³ The reaction led to the use of iodoform on solid NaOH as the iodination reagent of choice. A base-induced bromination has been reported. 2-Methyl butane reacts with 50% aq NaOH and CBr_4 , in a phase-transfer catalyst, to give a modest yields of 2-bromo-2-methylbutane. α -Iodo ethers and α -iodolactones have been prepared from the parent ether or lactone via treatment with $\text{Et}_4\text{N}^+\text{HF}$ under electrolytic conditions.¹⁶⁴

Many other halogenation agents have been employed, and a common reagent is sulfuryl chloride (SO_2Cl_2).¹⁶⁵ Among other agents used have been NBS (see Reaction 14-3), CCl_4 ,¹⁶⁶ PCl_5 ,¹⁶⁷ *N*-haloamines, and sulfuric acid.¹⁶⁸ In all these cases, an initiator is required, usually peroxides or UV light.¹⁶⁹

When chlorination is carried out with *N*-haloamines and sulfuric acid (catalyzed by either UV light or metal ions), selectivity is much greater than with other reagents.¹⁶⁸ In particular, alkyl chains are chlorinated with high regioselectivity at the position next to the end of the chain (the $\omega - 1$ position).¹⁷⁰ Some typical selectivity values are¹⁷¹



Furthermore, di- and polychlorination are much less prevalent. Dicarboxylic acids are predominantly chlorinated in the middle of the chain,¹⁷⁵ and adamantane and bicyclo [2.2.2]octane at the bridgeheads¹⁷⁶ by this procedure. The reasons for the high $\omega - 1$

¹⁶⁰ Akhrem, I.; Orlinkov, A.; Vitt, S.; Chistyakov, A. *Tetrahedron Lett.* **2002**, 43, 1333.

¹⁶¹ Montoro, R.; Wirth, T. *Org. Lett.* **2003**, 5, 4729.

¹⁶² Barluenga, J.; González-Bobes, F.; González, J.M. *Angew. Chem. Int. Ed.* **2002**, 41, 2556.

¹⁶³ Schreiner, P.R.; Lauenstein, O.; Butova, E.D.; Fokin, A.A. *Angew. Chem. Int. Ed.* **1999**, 38, 2786.

¹⁶⁴ Hasegawa, M.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* **2002**, 43, 1503.

¹⁶⁵ See Tabushi, I.; Kitaguchi, H. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, **1981**, pp. 336–396.

¹⁶⁶ See Hawari, J.A.; Davis, S.; Engel, P.S.; Gilbert, B.C.; Griller, D. *J. Am. Chem. Soc.* **1985**, 107, 4721.

¹⁶⁷ Wyman, D.P.; Wang, J.Y.C.; Freeman, W.R. *J. Org. Chem.* **1963**, 28, 3173.

¹⁶⁸ See Minisci, F. *Synthesis* **1973**, 1; Deno, N.C. *Methods Free-Radical Chem.* **1972**, 3, 135; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* **1972**, 4, 203.

¹⁶⁹ Schreiner, P.R.; Lauenstein, O.; Kolomitsyn, I.V.; Nadi, S.; Kokin, A.A. *Angew. Chem. Int. Ed.* **1998**, 37, 1895.

¹⁷⁰ The ($\omega - 1$) regioselectivity diminishes when the chains are >10 carbon atoms; see Deno, N.C.; Jedziniak, E.J. *Tetrahedron Lett.* **1976**, 1259; Konen, D.A.; Maxwell, R.J.; Silbert, L.S. *J. Org. Chem.* **1979**, 44, 3594.

¹⁷¹ See, however, Deno, N.C.; Pohl, D.G. *J. Org. Chem.* **1975**, 40, 380.

¹⁷² Bernardi, R.; Galli, R.; Minisci, F. *J. Chem. Soc. B* **1968**, 324. See also, Fuller, S.E.; Lindsay Smith, J.R.; Norman, R.O.C.; Higgins, R. *J. Chem. Soc. Perkin Trans. 2* **1981**, 545.

¹⁷³ Deno, N.C.; Billups, W.E.; Fishbein, R.; Pierson, C.; Whalen, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* **1971**, 93, 438.

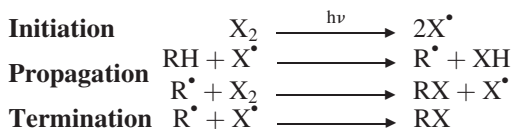
¹⁷⁴ Minisci, F.; Gardini, G.P.; Bertini, F. *Can. J. Chem.* **1970**, 48, 544.

¹⁷⁵ Kämper, F.; Schäfer, H.J.; Luftmann, H. *Angew. Chem. Int. Ed.* **1976**, 15, 306.

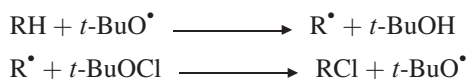
¹⁷⁶ Smith, C.V.; Billups, W.E. *J. Am. Chem. Soc.* **1974**, 96, 4307.

specificity are not clearly understood.¹⁷⁷ Alkyl chlorides can be converted to *vic*-dichlorides by treatment with MoCl_5 .¹⁷⁸ Enhanced selectivity at a terminal position of *n*-alkanes has been achieved by absorbing the substrate onto a pentasil zeolite.¹⁷⁹ For regioselective chlorination at certain positions of the steroid nucleus, see Reaction 19-2.

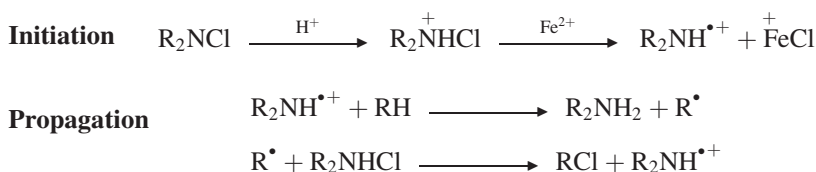
In almost all cases, the mechanism involves a free radical chain:



When the reagent is halogen, initiation occurs as shown above.¹⁸⁰ When it is another reagent, a similar cleavage occurs (catalyzed by light or, more commonly, peroxides), followed by propagation steps that do not necessarily involve abstraction by halogen. For example, the propagation steps for chlorination by *tert*-butyl hypochlorite (*t*-BuOCl) have been formulated as:¹⁸¹

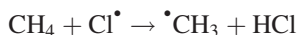


and the abstracting radicals in the case of *N*-haloamines are the aminium radical cations ($\text{R}_2\text{NH}^{\bullet+}$, Reaction 11-5), with the following mechanism (in the case of initiation by Fe^{2+}):¹⁶⁸



This mechanism is similar to that of the *Hofmann–Löffler Reaction* (18-40).

The two propagation steps shown above for X_2 are those that lead directly to the principal products (RX and HX), but many other propagation steps are possible and many occur. Similarly, the only termination step shown is the one that leads to RX, but any two radicals may combine (H^\bullet , CH_3^\bullet , Cl^\bullet , $\text{CH}_2\text{CH}_3^\bullet$ in all combinations). Thus, products like H_2 , higher alkanes, and higher alkyl halides can be accounted for. When methane is the substrate, the rate-determining step is



since an isotope effect of 12.1 was observed at 0 °C.¹⁸² For chlorinations, chains are very long, typically 10^4 – 10^6 propagations before a termination step takes place.

¹⁷⁷ See, however, Dneprovskii, A.S.; Mil'tsov, S.A.; Arbuzov, P.V. *J. Org. Chem. USSR* **1988**, 24, 1826. See also, Tanner, D.D.; Arhart, R.; Meintzer, C.P. *Tetrahedron* **1985**, 41, 4261.

¹⁷⁸ San Filippo, Jr., J.; Sowinski, A.F.; Romano, L.J. *J. Org. Chem.* **1975**, 40, 3463.

¹⁷⁹ Turro, N.J.; Fehlner, J.R.; Hessler, D.P.; Welsh, K.M.; Ruderman, W.; Firnberg, D.; Braun, A.M. *J. Org. Chem.* **1988**, 53, 3731.

¹⁸⁰ There is evidence radicals within a solvent cage, see Raner, K.D.; Luszyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* **1988**, 110, 3519; Tanko, J.M.; Anderson III, F.E. *J. Am. Chem. Soc.* **1988**, 110, 3525.

¹⁸¹ See Walling, C.; McGuiness, J.A. *J. Am. Chem. Soc.* **1969**, 91, 2053. See also, Zhulin, V.M.; Rubinshtein, B.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1977**, 26, 2082.

¹⁸² Wiberg, K.B.; Motell, E.L. *Tetrahedron* **1963**, 19, 2009.

TABLE 14.4 Some D Values^a

Bond	D	
	(kcal mol ⁻¹)	(kJ mol ⁻¹)
H—F	136	570
H—Cl	103	432
H—Br	88	366
H—I	71	298
F—F	38	159
Cl—Cl	59	243
Br—Br	46	193
I—I	36	151
CH ₃ —F	108	452
CH ₃ —Cl	85	356
CH ₃ —Br	70	293
CH ₃ —I	57	238

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^aSee Ref. 183.

The order of reactivity of the halogens can be explained by energy considerations. For the substrate methane, ΔH values for the two principal propagation steps follow:

	F ₂	Cl ₂	Br ₂	I ₂	F ₂	Cl ₂	Br ₂	I ₂
	(kcal mol ⁻¹)				(kJ mol ⁻¹)			
CH ₄ + X [•] → CH ₃ [•] + HX	-31	+2	+17	+34	-132	+6	+72	+140
CH ₄ + X ₂ → CH ₃ X + X [•]	-70	-26	-24	-21	-293	-113	-100	-87

In each case, D for CH₃—H is 105 kcal mol⁻¹ (438 kJ mol⁻¹), while D values for the other bonds involved are given in Table 14.4.¹⁸³ Fluorine (F₂) is so reactive¹⁸⁴ that neither UV light nor any other initiation is needed (total $\Delta H = -101$ kcal mol⁻¹, -425 kJ mol⁻¹)¹⁸⁵; while Br₂ and I₂ essentially do not react with methane. The second step is exothermic in all four cases, but it cannot take place before the first, and it is this step that is very unfavorable for Br₂ and I₂. It is apparent that the most important single factor causing the order of halogen reactivity to be F₂ > Cl₂ > Br₂ > I₂ is the decreasing strength of the HX bond in the order HF > HCl > HBr > HI. The increased reactivity of secondary and tertiary positions is in accord with the decrease in D values for R—H in the order primary > secondary > tertiary (Table 5.3). (Note that for chlorination, step 1 is exothermic for practically all substrates other than CH₄, since most other aliphatic C—H bonds are weaker than those in CH₄.)

¹⁸³ Lide, D.R. (Ed.), *Handbook of Chemistry and Physics*, 87th ed., CRC Press, Boca Raton, FL, **2007**, pp. 5-4-5-42.

¹⁸⁴ See Johnson, G.L.; Andrews, L. *J. Am. Chem. Soc.* **1980**, 102, 5736.

¹⁸⁵ For F₂ the following initiation step is possible: F₂ + RH → R[•] + F[•] + HF (first demonstrated by Miller, Jr., W.T.; Koch, Jr., S.D.; McLafferty, F.W. *J. Am. Chem. Soc.* **1956**, 78, 4992).

Metal mediated halogenation reactions are known. Heating alkenes with bromine in the presence of MnO_2 leads to monobromination.¹⁸⁶ Hydrogen peroxide–HBr in water has been used for radical bromination.¹⁸⁷ Bromination and chlorination of alkanes and cycloalkanes can also take place by an electrophilic mechanism if the reaction is catalyzed by AgSbF_6 .¹⁸⁸ Direct chlorination at a vinylic position by an electrophilic mechanism has been achieved with benzeneselenenyl chloride [PhSe(O)Cl] and AlCl_3 or AlBr_3 .¹⁸⁹ However, while some substituted alkenes give high yields of chloro-substitution products, others (e.g., styrene) undergo addition of Cl_2 to the double bond (Reaction 15-39).¹⁵¹ Electrophilic fluorination has already been mentioned (Sec. 14.C.i).

OS II, 89, 133, 443, 549; III, 737, 788; IV, 807, 921, 984; V, 145, 221, 328, 504, 635, 825; VI, 271, 404, 715; VII, 491; VIII, 161.

14-2 Halogenation at Silicon

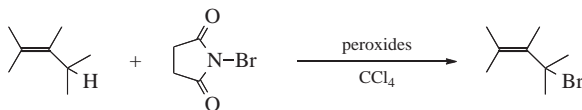
Halogenation or Halo-de-hydrogenation



Just as free radical halogenation occurs at the carbon of an alkane, via hydrogen abstraction to form the radical, a similar reaction occurs at silicon. When triisopropylsilane ($i\text{Pr}_3\text{Si}-\text{H}$) reacts with *tert*-butyl hypochlorite at -10°C , the product is triisopropylchlorosilane ($i\text{Pr}_3\text{Si}-\text{Cl}$).¹⁹⁰

14-3 Allylic and Benzylic Halogenation

Halogenation or Halo-de-hydrogenation



This reaction is a special case of Reaction 14-1, but is important enough to be treated separately.¹⁹¹ Alkenes can be brominated in the allylic position and also a benzylic position by a number of reagents, of which NBS¹⁹² is by far the most common. When this reagent is used, the reaction is known as *Wohl–Ziegler bromination*. A nonpolar solvent is used, most often CCl_4 , but the reaction has been done in an ionic liquid.¹⁹³ A variation in the reaction used NBS with 5% Yb(OTf)_3 and 5% ClSiMe_3 .¹⁹⁴ Other *N*-bromo amides have also been used. With any reagent an initiator is needed; this is usually AIBN (**1**), a peroxide (e.g., di-*tert*-butyl peroxide) or benzoyl peroxide or, less often, UV light. Boron trifluoride has been used for benzylic bromination.¹⁹⁵

¹⁸⁶ Jiang, X.; Shen, M.; Tang, Y.; Li, C. *Tetrahedron Lett.* **2005**, 46, 487.

¹⁸⁷ Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Tetrahedron Lett.* **2006**, 47, 7245.

¹⁸⁸ Olah, G.A.; Renner, R.; Schilling, P.; Mo, Y.K. *J. Am. Chem. Soc.* **1973**, 95, 7686. See also, Olah, G.A.; Wu, A.; Farooq, O. *J. Org. Chem.* **1989**, 54, 1463.

¹⁸⁹ Kamigata, N.; Satoh, T.; Yoshida, M. *Bull. Chem. Soc. Jpn.* **1988**, 44, 449.

¹⁹⁰ Chawla, R.; Larson, G.L. *Synth. Commun.* **1999**, 29, 3499.

¹⁹¹ See Nechvatal, A. *Adv. Free-Radical Chem.* **1972**, 4, 175.

¹⁹² See Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, **1974**, pp. 1–63.

¹⁹³ Togo, H.; Hirai, T. *Synlett* **2003**, 702.

¹⁹⁴ Yamanaka, M.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2002**, 43, 2403.

¹⁹⁵ Chen, H.; Shen, L.; Lin, Y. *Synth. Commun.* **2010**, 40, 998.

1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) has been used for benzylic bromination in the presence of a Lewis acid (e.g., ZrCl_4).¹⁹⁶ Similarly, *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, in the presence of a Pd catalyst and microwave irradiation, led to benzylic fluorides.¹⁹⁷

Allylic chlorination has also been carried out¹⁹⁸ with NCS and either arylselenenyl chlorides (ArSeCl), aryl diselenides (ArSeSeAr), or TsNSO as catalysts. Allylic chlorination has been carried out with *tert*-butyl hypochlorite¹⁹⁹ or $\text{NaClO/CeCl}_3 \cdot 7\text{H}_2\text{O}$.²⁰⁰

The reaction is usually quite specific at an allylic or benzylic position and good yields are obtained. However, when the allylic radical intermediate is unsymmetrical, allylic rearrangements can take place, so that mixtures of both possible products are obtained (**23** and **24**). Use of the selenium catalysts produces almost entirely the allylically rearranged chlorides in high yields. With TsNSO the products are the unrearranged chlorides in lower yields. Dichlorine monoxide (Cl_2O), with no catalyst, also leads to allylically rearranged chlorides in high yields.²⁰¹ A free radical mechanism is unlikely in these latter reactions.



When a double bond has two different allylic positions (e.g., $\text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_3$), a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.²⁰² It is possible to brominate both sides of the double bond.²⁰³ Because of the electron-withdrawing nature of bromine, the second bromine substitutes on the other side of the double bond rather than α to the first bromine. Molecules with a benzylic hydrogen (e.g., toluene) react rapidly to give α -bromomethyl benzene (e.g., $\text{PhCH}_3 \rightarrow \text{PhCH}_2\text{Br}$).

N-Bromosuccinimide is a highly regioselective brominating agent at other positions, including positions α to a carbonyl group, to a $\text{C}\equiv\text{C}$ triple bond, and to an aromatic ring (benzylic position). When both a double and a triple bond are in the same molecule, the preferred position is α to the triple bond.²⁰⁴

Dauben and McCoy²⁰⁵ demonstrated that the mechanism of allylic bromination is of the free radical type, showing that the reaction is very sensitive to free radical initiators and inhibitors and indeed does not proceed at all unless at least a trace of initiator is present. Subsequent work indicated that the species that actually abstracts hydrogen from the

¹⁹⁶ Shibatomi, K.; Zhang, Y.; Yamamoto, H. *Chemistry: Asian J.* **2008**, *3*, 1581.

¹⁹⁷ Hull, K.I.; Anani, W.Q.; Sanford, M.S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.

¹⁹⁸ Hori, T.; Sharpless, K.B. *J. Org. Chem.* **1979**, *44*, 4204.

¹⁹⁹ Walling, C.; Thaler, W.A. *J. Am. Chem. Soc.* **1961**, *83*, 3877.

²⁰⁰ Moreno-Dorado, F.J.; Guerra, F.M.; Manzano, F.L.; Aladro, F.J.; Jorge, Z.S.; Massanet, G.M. *Tetrahedron Lett.* **2003**, *44*, 6691.

²⁰¹ Torii, S.; Tanaka, H.; Tada, N.; Nagao, S.; Sasaoka, M. *Chem. Lett.* **1984**, 877.

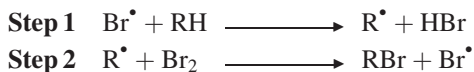
²⁰² Dauben, Jr, H.J.; McCoy, L.L. *J. Org. Chem.* **1959**, *24*, 1577.

²⁰³ Ucciani, E.; Naudet, M. *Bull. Soc. Chim. Fr.* **1962**, 871.

²⁰⁴ Peiffer, G. *Bull. Soc. Chim. Fr.* **1963**, 537.

²⁰⁵ Dauben, Jr, H.J.; McCoy, L.L. *J. Am. Chem. Soc.* **1959**, *81*, 4863.

substrate is the bromine atom. The reaction is initiated by small amounts of Br^\bullet . Once it is formed, the main propagation steps are

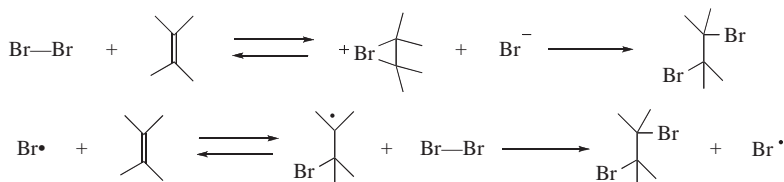


The source of the Br_2 is a fast ionic reaction between NBS and the HBr liberated in step 1:



The function of the NBS is therefore to provide a source of Br_2 , as shown in the reaction, in a low, steady-state concentration, which effectively uses up the HBr liberated in step 1.²⁰⁶ The main evidence for this mechanism is that NBS and Br_2 show similar selectivity²⁰⁷ and that the various *N*-bromo amides also show similar selectivity,²⁰⁸ which is consistent with the hypothesis that the same species is abstracting in each case.²⁰⁹

It may be asked why, if Br_2 is the reacting species, it does not add to the double bond, either by an ionic or by a free radical mechanism (see Reaction 15-39). Apparently, the concentration is too low. In bromination of a double bond, only one atom of an attacking bromine molecule becomes attached to the substrate, whether the addition is electrophilic or free radical:



The other bromine atom comes from another bromine-containing molecule or ion. This result is clearly not a problem in reactions with benzylic species since the benzene ring is not prone to such addition reactions. If the concentration is sufficiently low, there is a low probability that the proper species will be in the vicinity once the intermediate forms. The intermediate in either case reverts to the initial species and the allylic substitution competes successfully. If this is true, it should be possible to brominate an alkene in the allylic position without competition from addition, even in the absence of NBS or a similar compound, if a very low concentration of bromine is used and if the HBr is

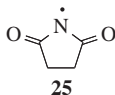
²⁰⁶ See Adam, J.; Gosselain, P.A.; Goldfinger, P. *Nature (London)* **1953**, 171, 704; *Bull. Soc. Chim. Belg.* **1956**, 65, 533.

²⁰⁷ Walling, C.; Rieger, A.L.; Tanner, D.D. *J. Am. Chem. Soc.* **1963**, 85, 3129; Russell, G.A.; Desmond, K.M. *J. Am. Chem. Soc.* **1963**, 85, 3139; Pearson, R.; Martin, J.C. *J. Am. Chem. Soc.* **1963**, 85, 3142; Skell, P.S.; Tuleen, D.L.; Readio, P.D. *J. Am. Chem. Soc.* **1963**, 85, 2850.

²⁰⁸ Incremona, J.H.; Martin, J.C. *J. Am. Chem. Soc.* **1970**, 92, 627.

²⁰⁹ For other evidence, see Day, J.C.; Lindstrom, M.J.; Skell, P.S. *J. Am. Chem. Soc.* **1974**, 96, 5616.

removed as it is formed so that it is not available to complete the addition step. This has indeed been demonstrated.²¹⁰



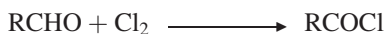
When NBS is used to brominate non-alkenyl substrates (e.g., alkanes) another mechanism, involving abstraction of the hydrogen of the substrate by the succinimidyl radical²¹¹ **25** can operate.²¹² This mechanism is facilitated by certain solvents (e.g., CH_2Cl_2 , CHCl_3 , or MeCN) in which NBS is more soluble, and by the presence of small amounts of an alkene that lacks an allylic hydrogen (e.g., ethene). The alkene serves to scavenge any Br^\bullet that forms from the reagent. Among the evidence for the mechanism involving **25** are abstraction selectivities similar to those of Cl^\bullet atoms and the isolation of β -bromopropionyl isocyanate ($\text{BrCH}_2\text{CH}_2\text{CONCO}$), which is formed by ring opening of **25**.

Allyl silanes react with transition metals bearing chlorine ligands to give allyl chlorides, where a chlorine replaces a Me_3Si unit.²¹³

OS IV, 108; V, 825; VI, 462; IX, 191.

14-4 Halogenation of Aldehydes

Halogenation or Halo-de-hydrogenation



The α -halogenation reaction of carbonyl compounds was mentioned in Reaction **14-2**. A different halogenation reaction is possible in which aldehydes can be directly converted to acyl chlorides by treatment with chlorine, but the reaction operates only when the aldehyde does not contain an α hydrogen and even then it is not very useful. When there is an α hydrogen, α halogenation (Reactions **14-2** and **12-4**) occurs instead. Other sources of chlorine have also been used, among them SO_2Cl_2 ²¹⁴ and t -BuOCl.²¹⁵ The mechanisms are probably of the free radical type. *N*-Bromosuccinimide, with AIBN (Sec. 14.A.i) as a catalyst, has been used to convert aldehydes to acyl bromides.²¹⁶ In the presence of benzoyl peroxide as an initiator, $\text{Br}_3\text{CCO}_2\text{Et}$ converts aldehydes to acyl bromides under radical conditions.²¹⁷

OS I, 155.

²¹⁰ McGrath, B.P.; Tedder, J.M. *Proc. Chem. Soc.* **1961**, 80.

²¹¹ See Chow, Y.L.; Naguib, Y.M.A. *Rev. Chem. Intermed.* **1984**, 5, 325.

²¹² Luning, U.; Seshadri, S.; Skell, P.S. *J. Org. Chem.* **1986**, 51, 2071; Zhang, Y.; Dong, M.; Jiang, X.; Chow, Y.L. *Can. J. Chem.* **1990**, 68, 1668.

²¹³ Fujii, T.; Hirao, Y.; Ohshiro, Y. *Tetrahedron Lett.* **1993**, 34, 5601.

²¹⁴ Arai, M. *Bull. Chem. Soc. Jpn.* **1964**, 37, 1280; **1965**, 38, 252.

²¹⁵ Walling, C.; Mintz, M.J. *J. Am. Chem. Soc.* **1967**, 89, 1515.

²¹⁶ Markó, I.E.; Mekhafia, A. *Tetrahedron Lett.* **1990**, 31, 7237. For a related procedure, see Cheung, Y. *Tetrahedron Lett.* **1979**, 3809.

²¹⁷ Kang, D.H.; Joo, T.Y.; Chavasiri, W.; Jang, D.O. *Tetrahedron Lett.* **2007**, 48, 285.

B. Substitution by Oxygen

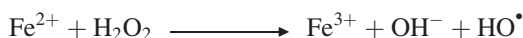
14-5 Hydroxylation at an Aromatic Carbon²¹⁸

Hydroxylation or Hydroxy-de-hydrogenation



A mixture of hydrogen peroxide and ferrous sulfate,²¹⁹ called *Fenton's reagent*,²²⁰ can be used to hydroxylate aromatic rings, although yields are usually not high.²²¹ Biaryls are typical side products.²²² Among other reagents used H_2O_2 and titanous ion; O_2 and Cu(I) ²²³ or Fe(III) ,²²⁴ a mixture of ferrous ion, oxygen, ascorbic acid, and ethylenetetraaminetetraacetic acid (*Udenfriend's reagent*)²²⁵; O_2 and KOH in liquid NH_3 ²²⁶; and peroxyacids (e.g., peroxyntrous and trifluoroperoxyacetic acids).

Much work has been done on the mechanism of the reaction with *Fenton's reagent*, and it is known that free aryl radicals (formed by a process, e.g., $\text{HO}^\bullet + \text{ArH} \rightarrow \text{AR}^\bullet + \text{H}_2\text{O}$) are *not* intermediates. The mechanism is essentially that outlined in Section 14.A.iii, with HO^\bullet as the attacking species,²²⁷ formed by



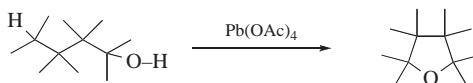
The rate-determining step is formation of HO^\bullet and not its reaction with the aromatic substrate.

An alternative oxidation of arene to phenol was reported using $\text{Cu(NO}_3)_3 \cdot 3 \text{H}_2\text{O}$, 30% hydrogen peroxide and a phosphate buffer.²²⁸

See also, Reaction 11-26

14-6 Formation of Cyclic Ethers

(5)OC-cyclo- Alkoxy-de-hydro-substitution



²¹⁸ See Vysotskaya, N.A. *Russ. Chem. Rev.* **1973**, 42, 851; Sangster, D.F. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, pp. 133–191; Metelitsa, D.I. *Russ. Chem. Rev.* **1971**, 40, 563; Loudon, J.D. *Prog. Org. Chem.* **1961**, 5, 47.

²¹⁹ See Sosnovsky, G.; Rawlinson, D.J. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, **1970**, pp. 269–336. See also, Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press, NY, **1981**.

²²⁰ See Walling, C. *Acc. Chem. Res.* **1975**, 8, 125.

²²¹ Yields can be improved with phase-transfer catalysis: Karakhanov, E.A.; Narin, S.Yu.; Filippova, T.Yu.; Dedov, A.G. *Doklad. Chem.* **1987**, 292, 81.

²²² See the discussion of the aromatic free-radical substitution mechanism in Sec. 14.A.ii.

²²³ See Cruse, R.W.; Kaderli, S.; Meyer, C.J.; Zuberbühler, A.D.; Karlin, K.D. *J. Am. Chem. Soc.* **1988**, 110, 5020; Ito, S.; Kunai, A.; Okada, H.; Sasaki, K. *J. Org. Chem.* **1988**, 53, 296.

²²⁴ Funabiki, T.; Tsujimoto, M.; Ozawa, S.; Yoshida, S. *Chem. Lett.* **1989**, 1267.

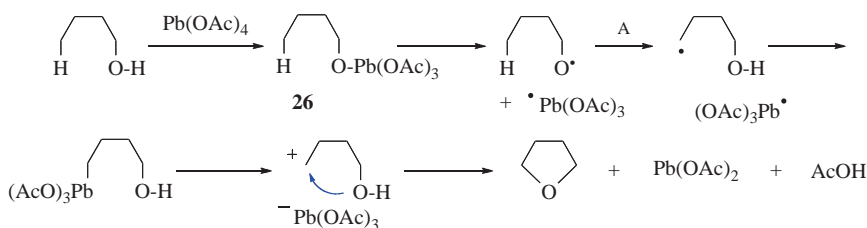
²²⁵ Udenfriend, S.; Clark, C.T.; Axelrod, J.; Brodie, B.B. *J. Biol. Chem.* **1954**, 208, 731; Brodie, B.B.; Shore, P.A.; Udenfriend, S. *J. Biol. Chem.* **1954**, 208, 741. See also, Tamagaki, S.; Suzuki, K.; Tagaki, W. *Bull. Chem. Soc. Jpn.* **1989**, 62, 148, 153, 159.

²²⁶ Malykhin, E.V.; Kolesnichenko, G.A.; Shteingarts, V.D. *J. Org. Chem. USSR* **1986**, 22, 720.

²²⁷ Brook, M.A.; Castle, L.; Lindsay Smith, J.R.; Higgins, R.; Morris, K.P. *J. Chem. Soc. Perkin Trans. 2* **1982**, 687; Kunai, A.; Hata, S.; Ito, S.; Sasaki, K. *J. Am. Chem. Soc.* **1986**, 108, 6012.

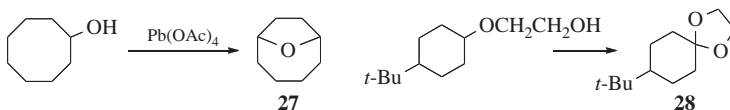
²²⁸ Nasreen, A.; Adapa, S.R. *Org. Prep. Proceed. Int.* **2000**, 32, 373.

Alcohols with hydrogen in the δ position can be cyclized with lead tetraacetate.²²⁹ The reaction is usually carried out at $\sim 80^\circ\text{C}$ (most often in refluxing benzene), but can also be done at room temperature if the reaction mixture is irradiated with UV light. Tetrahydrofurans are formed in high yields. Little or no four- and six-membered cyclic ethers (oxetanes and tetrahydropyrans, respectively) are obtained even when γ and ϵ hydrogen atoms are present. The reaction has also been carried out with a mixture of halogen (Br_2 or I_2) and a salt or oxide of silver or mercury (especially HgO or AgOAc),²³⁰ with iodosobenzene diacetate and I_2 ,²³¹ and with ceric ammonium nitrate (CAN).²³² The following mechanism is likely for the lead tetraacetate reaction²³³:



although **26** has never been isolated. The step marked **A** is a 1,5-internal hydrogen abstraction. Such abstractions are well known (see Reaction **18-40**) and are greatly favored over 1,4 or 1,6 abstractions (the small amounts of tetrahydropyran formed result from 1,6-abstractions).²³⁴

Oxidation to the aldehyde or acid (Reactions **19-3** and **19-22**) and fragmentation of the substrate sometimes compete. When the OH group is on a ring of at least seven members, a transannular product can be formed, as in the cyclization reaction of 1-octanol to **27**.²³⁵ β -Hydroxy ethers can give cyclic acetals (e.g., **28**).²³⁶



There are no references in *Organic Syntheses*, but see OS **V**, 692; **VI**, 958, for related reactions.

²²⁹ See Mihailovic, M.Lj.; Partch, R. *Sel. Org. Transform.* **1972**, 2, 97; Mihailovic, M.Lj.; Cekovic, Z. *Synthesis* **1970**, 209; Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, **1977**, pp. 277–419.

²³⁰ Roscher, N.M.; Shaffer, D.K. *Tetrahedron* **1984**, 40, 2643. See Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, **1999**, pp. 889–890.

²³¹ Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, 29, 2215.

²³² See Doyle, M.P.; Zuidema, L.J.; Bade, T.R. *J. Org. Chem.* **1975**, 40, 1454.

²³³ Mihailovic, M.Lj.; Cekovic, Z.; Maksimovic, Z.; Jeremic, D.; Lorenc, Lj.; Mamuzic, R.I. *Tetrahedron* **1965**, 21, 2799.

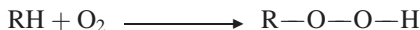
²³⁴ Mihailovic, M.Lj.; Cekovic, Z.; Jeremic, D. *Tetrahedron* **1965**, 21, 2813.

²³⁵ Mihailovic, M.Lj.; Cekovic, Z.; Andrejevic, V.; Matic, R.; Jeremic, D. *Tetrahedron* **1968**, 24, 4947.

²³⁶ Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, 29, 2215.

14-7 Formation of Hydroperoxides

Hydroperoxy-dehydrogenation



The slow atmospheric oxidation (*slow* meaning without combustion) of C—H to C—O—O—H is called *autoxidation*.²³⁷ The reaction occurs when compounds are allowed to stand in air and is catalyzed by light, so unwanted autoxidations can be greatly slowed by keeping the compounds in dark places. Most autoxidations proceed by free radical chain processes that involve peroxy radicals.²³⁸ To suppress autoxidation, an antioxidant can be added that will prevent or retard the reaction with atmospheric oxygen.²³⁹ Although some lactone compounds are sold as antioxidants, many radicals derived from lactones show poor or no reactivity toward oxygen.²³⁹ The hydroperoxides produced often react further to give alcohols, ketones, and more complicated products, so the reaction is not often used for preparative purposes, although in some cases hydroperoxides have been prepared in good yield.²⁴⁰ It is because of autoxidation that foods, rubber, paint, lubricating oils, and so on deteriorate on exposure to the atmosphere over periods of time. On the other hand, a useful application of autoxidation is the atmospheric drying of paints and varnishes. As with other free radical reactions of C—H bonds, some bonds are attacked more readily than others,²⁴¹ and these are the ones seen before (Sec. 14.B.i), although the selectivity is very low at high temperatures and in the gas phase. The reaction can be carried out successfully at tertiary (to a lesser extent, secondary), benzylic,²⁴² and allylic (though allylic rearrangements are common) R.²⁴³ 2-Phenylpropane reacted with oxygen to give PhMe₂C—OOH, for example. Another susceptible position is aldehydic C—H, but the peroxyacids so produced are not easily isolated²⁴⁴ since they are converted to the corresponding carboxylic acids (Reaction 19-23). The α positions of ethers are also easily attacked by oxygen [RO—C—H \rightarrow RO—C—OOH], but the resulting hydroperoxides are seldom isolated. However, this reaction constitutes a hazard in the storage of ethers since solutions of these hydroperoxides and their rearrangement products in ethers are potential spontaneous explosives.²⁴⁵

Oxygen itself (a diradical) is not reactive enough to be the species that actually abstracts the hydrogen. But if a trace of free radical (say R') is produced by some initiating process, it reacts with oxygen²⁴⁶ to give R'—O—O'; since this type of radical *does* abstract

²³⁷ The term autoxidation actually applies to any slow oxidation with atmospheric oxygen. See Goosen, A.; Morgan, D.H. *J. Chem. Soc. Perkin Trans. 2* **1994**, 557. For reviews, see Sheldon, R.A.; Kochi, J.K. *Adv. Catal.* **1976**, 25, 272; Howard, W.G. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, pp. 3–62; Lloyd, W.G. *Methods Free-Radical Chem.* **1973**, 4, 1; Betts, J. *Q. Rev. Chem. Soc.* **1971**, 25, 265; Ingold, K.U. *Acc. Chem. Res.* **1969**, 2, 1; Mayo, F.R. *Acc. Chem. Res.* **1968**, 1, 193.

²³⁸ Ingold, K.U. *Acc. Chem. Res.* **1969**, 2, 1.

²³⁹ Bejan, E.V.; Font-Sanchis, E.; Scaiano, J.C. *Org. Lett.* **2001**, 3, 4059.

²⁴⁰ See Sheldon, R.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, **1983**, pp. 161–200.

²⁴¹ See Korcek, S.; Chenier, J.H.B.; Howard, J.A.; Ingold, K.U. *Can. J. Chem.* **1972**, 50, 2285, and other papers in this series.

²⁴² See Santamaria, J.; Jroundi, R.; Rigaudy, J. *Tetrahedron Lett.* **1989**, 30, 4677.

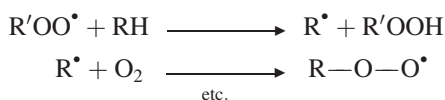
²⁴³ See Voronenkov, V.V.; Vinogradov, A.N.; Belyaev, V.A. *Russ. Chem. Rev.* **1970**, 39, 944.

²⁴⁴ Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, **1970**, p. 313.

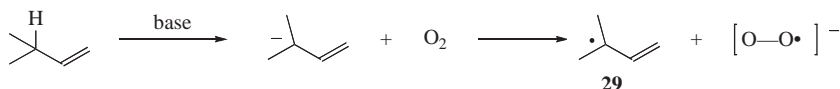
²⁴⁵ For methods of detection and removal of peroxides from ether solvents, see Gordon, A.J.; Ford, R.A. *The Chemist's Companion*, Wiley, NY, **1972**, p. 437; Burfield, D.R. *J. Org. Chem.* **1982**, 47, 3821.

²⁴⁶ See Schwetlick, K. *J. Chem. Soc. Perkin Trans. 2* **1988**, 2007.

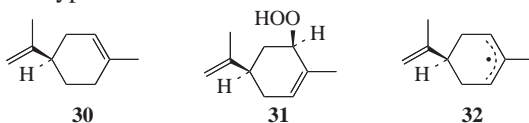
hydrogen, the chain is



In at least some cases (in alkaline media),²⁴⁷ the radical R^\bullet can be produced by formation of a carbanion and its oxidation (by O_2) to a radical, such as allylic radical **29**.²⁴⁸ Autoxidations in alkaline media can also proceed by a different mechanism: $\text{R}-\text{H} + \text{base} \rightarrow \text{R}^- + \text{O}_2 \rightarrow \text{ROO}^-$.²⁴⁹



When alkenes are treated with oxygen that has been photosensitized (Sec. 7.A.vi, category 6), they are substituted by OOH in the allylic position in a synthetically useful reaction.²⁵⁰ Although superficially similar to autoxidation, this reaction is clearly different because 100% allylic rearrangement always takes place. The reagent here is not the ground-state oxygen (a triplet), but an excited singlet state²⁵¹ (in which all electrons are paired), and the function of the photosensitization is to promote the oxygen to this singlet state. Singlet oxygen can also be produced by nonphotochemical means,²⁵² for example, by the reaction between H_2O_2 and NaOCl ²⁵³ or between ozone and triphenyl phosphite.²⁵⁴ Calcium peroxide diperoxohydrate ($\text{CaO}_2 \cdot 2\text{H}_2\text{O}_2$) has been reported as a storable compound used for the chemical generation of singlet oxygen.²⁵⁵ The oxygen generated by either photochemical or nonphotochemical methods reacts with alkenes in the same way;²⁵⁶ this is evidence that singlet oxygen is the reacting species in the photochemical reaction and not some hypothetical



²⁴⁷ Sosnovsky, G.; Zaret, E.H. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, **1970**, pp. 517–560.

²⁴⁸ Barton, D.H.R.; Jones, D.W. *J. Chem. Soc.* **1965**, 3563; Russell, G.A.; Bemis, A.G. *J. Am. Chem. Soc.* **1966**, 88, 5491.

²⁴⁹ Gersmann, H.R.; Bickel, A.F. *J. Chem. Soc. B* **1971**, 2230.

²⁵⁰ See Frimer, A.A.; Stephenson, L.M. in Frimer, A.A. *Singlet O₂*, Vol. 2, CRC Press, Boca Raton, FL, **1985**, pp. 67–91; Wasserman, H.H.; Ives, J.L. *Tetrahedron* **1981**, 37, 1825; Gollnick, K.; Kuhn, H.J. in Wasserman, H. H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, **1979**, pp. 287–427; Denny, R.W.; Nickon, A. *Org. React.* **1973**, 20, 133; Adams, W.R. in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, **1969**, pp. 65–112.

²⁵¹ See Frimer, A.A. *Singlet O₂*, 4 Vols., CRC Press, Boca Raton, FL, **1985**; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, **1979**; Frimer, A.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, **1983**, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* **1981**, 10, 205; Ohloff, G. *Pure Appl. Chem.* **1975**, 43, 481; Kearns, D.R. *Chem. Rev.* **1971**, 71, 395; Wayne, R.P. *Adv. Photochem.* **1969**, 7, 311.

²⁵² See Turro, N.J.; Ramamurthy, V. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, **1980**, pp. 1–23; Murray, R.W. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, **1979**, pp. 59–114; Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*, Academic Press, NY, **1982**.

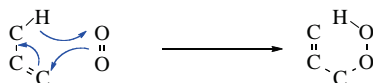
²⁵³ Foote, C.S.; Wexler, S. *J. Am. Chem. Soc.* **1964**, 86, 3879.

²⁵⁴ See Bartlett, P.D.; Mendenhall, G.D.; Durham, D.L. *J. Org. Chem.* **1980**, 45, 4269.

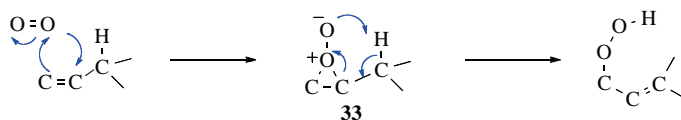
²⁵⁵ Pierlot, C.; Nardello, V.; Schrive, J.; Mabilie, C.; Barbillat, J.; Sombret, B.; Aubry, J.-M. *J. Org. Chem.* **2002**, 67, 2418.

²⁵⁶ Foote, C.S.; Wexler, S.; Ando, W.; Higgins, R. *J. Am. Chem. Soc.* **1968**, 90, 975. See also, McKeown, E.; Waters, W.A. *J. Chem. Soc. B* **1966**, 1040.

complex between triplet oxygen and the photosensitizer, as had previously been suggested. The fact that 100% allylic rearrangement always takes place is incompatible with a free radical mechanism. Further evidence that free radicals are not involved comes from the treatment of optically active limonene (**30**) with singlet oxygen. Among other products is the optically active hydroperoxide **31**, though if **32** were an intermediate, it could not give an optically active product since it possesses a plane of symmetry.²⁵⁷ In contrast, autoxidation of **30** gave optically inactive **31** (a mixture of four diastereomers in which the two pairs of enantiomers are present as racemic mixtures). As this example shows, singlet oxygen reacts faster with more highly substituted than with less highly substituted alkenes. The order of alkene reactivity is tetrasubstituted > trisubstituted > disubstituted. Electron-withdrawing substituents deactivate the alkene.²⁵⁸ In simple trisubstituted alkenes, there is a general preference for the hydrogen to be removed from the more highly congested side of the double bond.²⁵⁹ With *cis*-alkenes of the form RCH=CHR', the hydrogen is removed from the larger R group.²⁶⁰ Many functional groups in an allylic position cause the hydrogen to be removed from that side rather than the other (geminal selectivity).²⁶¹ Also, in alkyl-substituted alkenes, the hydrogen that is preferentially removed is the one geminal to the larger substituent on the double bond.²⁶²



Several mechanisms have been proposed for the reaction with singlet oxygen.²⁶³ One of these is a pericyclic mechanism, similar to that of the ene synthesis (Reaction **15-23**) and to the first step of the reaction between alkenes and SeO₂ (Reaction **19-14**). However, there is strong evidence against this mechanism,²⁶⁴ and a more likely mechanism involves addition of singlet oxygen to the double bond to give a perepoxide (**33**),²⁶⁵ followed by internal proton transfer.²⁶⁶



Still other proposed mechanisms involve diradicals or dipolar intermediates.²⁶⁷
OS IV, 895.

²⁵⁷ See Schenck, G.O.; Neumüller, O.; Ohloff, G.; Schroeter, S. *Liebigs Ann. Chem.* **1965**, 687, 26.

²⁵⁸ See Foote, C.S.; Denny, R.W. *J. Am. Chem. Soc.* **1971**, 93, 5162.

²⁵⁹ Rautenstrauch, V.; Thommen, W.; Schulte-Elte, K.H. *Helv. Chim. Acta* **1986**, 69, 1638 and references cited therein.

²⁶⁰ Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *Tetrahedron Lett.* **1989**, 30, 4875.

²⁶¹ Clennan, E.L.; Chen, X.; Koola, J.J. *J. Am. Chem. Soc.* **1990**, 112, 5193, and references cited therein.

²⁶² Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* **1990**, 112, 6417.

²⁶³ See Frimer, A.A.; Stephenson, L.M. in Frimer, A.A. *Singlet O₂*, Vol. 2, CRC Press, Boca Raton, FL, **1985**, pp. 80–87; Stephenson, L.M.; Grdina, M.J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, 13, 419; Gollnick, K.; Kuhn, H.J.; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, **1979**, pp. 288–341; Frimer, A.A. *Chem. Rev.* **1979**, 79, 359; Foote, C.S. *Pure Appl. Chem.* **1971**, 27, 635; Gollnick, K. *Adv. Photochem.* **1968**, 6, 1; Kearns, D.R. *Chem. Rev.* **1971**, 71, 395.

²⁶⁴ Asveld, E.W.H.; Kellogg, R.M. *J. Org. Chem.* **1982**, 47, 1250.

²⁶⁵ See Mitchell, J.C. *Chem. Soc. Rev.* **1985**, 14, 399, p. 401.

²⁶⁶ See Wilson, S.L.; Schuster, G.B. *J. Org. Chem.* **1986**, 51, 2056; Davies, A.G.; Schiesser, C.H. *Tetrahedron Lett.* **1989**, 30, 7099; Orfanopoulos, M.; Smonou, I.; Foote, C.S. *J. Am. Chem. Soc.* **1990**, 112, 3607.

²⁶⁷ See Jefford, C.W. *Helv. Chim. Acta* **1981**, 64, 2534.

14-8 Formation of Peroxides

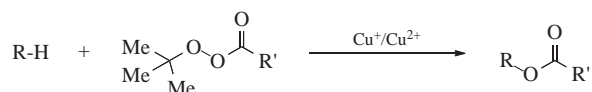
Alkyldioxy-de-hydrogenation



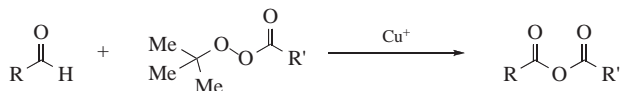
Peroxy groups (ROO) can be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of cuprous chloride or other catalysts (e.g., cobalt and manganese salts).²⁶⁸ Very high yields can be obtained. The type of hydrogen replaced is similar to that with NBS (Reaction 14-3); that is, mainly benzylic, allylic, and tertiary. The mechanism is therefore of the free radical type, involving ROO^\bullet formed from ROOH and the metal ion. The reaction can be used to demethylate tertiary amines of the form R_2NCH_3 , since the product $\text{R}_2\text{NHCH}_2\text{OOR}'$ can easily be hydrolyzed by acid (Reaction 10-6) to give R_2NH .²⁶⁹

14-9 Acyloxylation

Acyloxylation or Acyloxy-de-hydrogenation



Susceptible positions of organic compounds can be directly acyloxylated²⁷⁰ by *tert*-butyl peroxyesters, the most frequently used being acetic and benzoic ($\text{R}' = \text{Me}$ or Ph).²⁷¹ The reaction requires a catalyst (cuprous ion is the actual catalyst, but a trace is all that is necessary, and such traces are usually present in cupric compounds, so that these are often used) and without it is not selective. Susceptible positions are similar to those in Reaction 14-6: benzylic, allylic, and the α position of ethers and sulfides. Terminal alkenes are substituted almost entirely in the 3 position; that is, with only a small amount of allylic rearrangement, but internal alkenes generally give mixtures containing a large amount of allylic-shift product. If the reaction with alkenes is carried out in an excess of another acid ($\text{R}''\text{CO}_2\text{H}$), the ester produced is of *that* acid ROCOR'' . Aldehydes give anhydrides:



Acyloxylation has also been achieved with metallic acetates (e.g., lead tetraacetate,²⁷² mercuric acetate,²⁷³ and palladium(II) acetate).²⁷⁴ In the case of the lead and mercuric acetates, not only does the reaction take place at allylic and benzylic positions and at those α

²⁶⁸ See Sosnovsky, G.; Rawlinson, D.J. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, **1970**, pp. 153–268. See also, Murahashi, S.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820; Sheldon, R.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, **1983**, p. 161.

²⁶⁹ See Murahashi, S.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256.

²⁷⁰ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, **1999**, pp. 1625–1630 ff, 1661–1663.

²⁷¹ See Rawlinson, D.J.; Sosnovsky, G. *Synthesis* **1972**, 1; Sosnovsky, G.; Rawlinson, D.J. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, **1970**, pp. 585–608; Doumaux Jr, A.R. in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, **1971**, pp. 141–185.

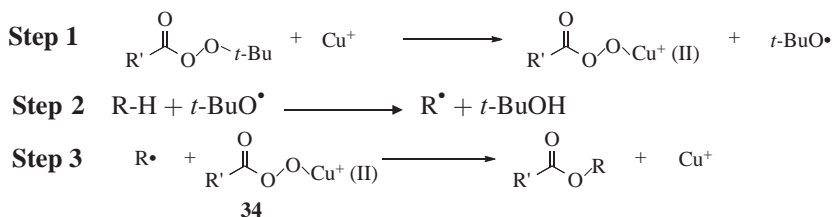
²⁷² See Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, p. 277.

²⁷³ Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, **1985**, pp. 190–208; Rawlinson, D.J.; Sosnovsky, G. *Synthesis* **1973**, 567.

²⁷⁴ Hansson, S.; Heumann, A.; Rein, T.; Åkermärk, B. *J. Org. Chem.* **1990**, *55*, 975; Byström, S.E.; Larsson, E.M.; Åkermärk, B. *J. Org. Chem.* **1990**, *55*, 5674.

to an OR or SR group, but also at positions α to the carbonyl groups of aldehydes, ketones, or esters and at those α to two carbonyl groups (ZCH_2Z'). It is likely that in the latter cases it is the enol forms that react. Ketones can be α -acyloxyated indirectly by treatment of various enol derivatives with metallic acetates (e.g., silyl enol ethers with silver carboxylates-iodine,²⁷⁵ enol thioethers with lead tetraacetate,²⁷⁶ and enamines²⁷⁷ with lead tetraacetate).²⁷⁸ Lead tetraacetate even acyloxyates alkanes, in a slow reaction (10 days–2 weeks), with tertiary and secondary positions greatly favored over primary ones.²⁷⁹ α,β -Unsaturated ketones can be acyloxyated in good yields in the α' position with manganese triacetate.²⁸⁰ Palladium acetate converts alkenes to vinylic and/or allylic acetates.²⁸¹ Acyloxylation of certain alkanes has also been reported with palladium(II) acetate.²⁸²

Studies of the mechanism of the cuprous-catalyzed reaction show that the most common mechanism is the following²⁸³:



This mechanism, involving a free radical R^\bullet , is compatible with the allylic rearrangements found.²⁸⁴ The fact that *tert*-butyl peroxyesters labeled with ^{18}O in the carbonyl oxygen gave an ester with 50% of the label in each oxygen²⁸⁵ is in accord with coupling of R^\bullet with intermediate **34**, in which the Cu is ionically bound, so that the oxygen atoms are essentially equivalent. Other evidence is that *tert*-butoxy radicals have been trapped with dienes.²⁸⁶ Much less is known about the mechanisms of the reactions with other metal acetates.²⁸⁷

Free radical acyloxylation of aromatic substrates²⁸⁸ has been accomplished with a number of reagents, including copper(II) acetate,²⁸⁹ silver(II) complexes,²⁹⁰ and cobalt(III) trifluoroacetate.²⁹¹

²⁷⁵ Rubottom, G.M.; Mott, R.C.; Juve Jr., H.D. *J. Org. Chem.* **1981**, *46*, 2717.

²⁷⁶ Trost, B.M.; Tanigawa, Y. *J. Am. Chem. Soc.* **1979**, *101*, 4413.

²⁷⁷ See Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, **1988**, pp. 251–258.

²⁷⁸ See Butler, R.N. *Chem. Ind. (London)* **1976**, 499.

²⁷⁹ See Mosher, M.W.; Cox, J.L. *Tetrahedron Lett.* **1985**, *26*, 3753.

²⁸⁰ Demir, A.S.; Sayrac, T.; Watt, D.S. *Synthesis* **1990**, 1119.

²⁸¹ See Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, **1973**, pp. 80–87; Jira, R.; Freiesleben, W. *Organomet. React.* **1972**, *3*, 1, pp. 44–84; Heck, R.F. *Fortschr. Chem. Forsch.* **1971**, *16*, 221, pp. 231–237; Tsuji, J. *Adv. Org. Chem.* **1969**, *6*, 109, pp. 132–143.

²⁸² See Sen, A.; Gretz, E.; Oliver, T.F.; Jiang, Z. *New J. Chem.* **1989**, *13*, 755.

²⁸³ Kochi, J.K.; Mains, H.E. *J. Org. Chem.* **1965**, *30*, 1862. See also, Beckwith, A.L.J.; Zavitsas, A.A. *J. Am. Chem. Soc.* **1986**, *108*, 8230.

²⁸⁴ Goering, H.L.; Mayer, U. *J. Am. Chem. Soc.* **1964**, *86*, 3753.

²⁸⁵ Denney, D.B.; Denney, D.Z.; Feig, G. *Tetrahedron Lett.* **1959**, no. 15, p. 19.

²⁸⁶ Kochi, J.K. *J. Am. Chem. Soc.* **1962**, *84*, 2785, 3271; Story, P.R. *Tetrahedron Lett.* **1962**, 401.

²⁸⁷ See, for example, Jones, S.R.; Mellor, J.H. *J. Chem. Soc. Perkin Trans. 2* **1977**, 511.

²⁸⁸ See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1985**, pp. 177–180, 351–355.

²⁸⁹ Takizawa, Y.; Tateishi, A.; Sugiyama, J.; Yoshida, H.; Yoshihara, N. *J. Chem. Soc., Chem. Commun.* **1991**,

104. See also, Kaeding, W.W.; Kerlinger, H.O.; Collins, G.R. *J. Org. Chem.* **1965**, *30*, 3754.

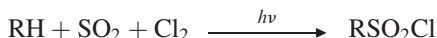
²⁹⁰ Nyberg, K.; Wistrand, L.G. *J. Org. Chem.* **1978**, *43*, 2613.

²⁹¹ See DiCosimo, R.; Szabo, H. *J. Org. Chem.* **1986**, *51*, 1365.

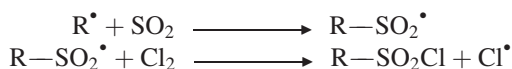
OS III, 3; V, 70, 151; VIII, 137.

C. Substitution by Sulfur

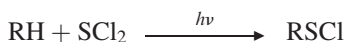
14-10 Chlorosulfonation or Chlorosulfo-de-hydrogenation



The chlorosulfonation of organic molecules with chlorine and sulfur dioxide is called the *Reed reaction*.²⁹² In scope and range of products obtained, the reaction is similar to 14-1. The mechanism is also similar, except that there are two additional main propagation steps:



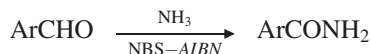
*Chlorosulfenation*²⁹³ can be accomplished by treatment with SCl_2 and UV light:



D. Substitution by Nitrogen

14-11 The Direct Conversion of Aldehydes to Amides

Amination or Amino-de-hydrogenation



Aliphatic and aromatic aldehydes have been converted to the corresponding amides with ammonia or a primary or secondary amine, NBS, and a catalytic amount of AIBN (Sec. 14.A.i).²⁹⁴ In a reaction of more limited scope, amides are obtained from aromatic and α,β -unsaturated aldehydes by treatment with dry ammonia gas and nickel peroxide.²⁹⁵ Best yields (80–90%) are obtained at -25 to -20 °C. In the nickel peroxide reaction, the corresponding alcohols (ArCH_2OH) have also been used as substrates.

Oxidative amidation of aldehydes has been done using AgIO_3 in the presence of a CuI catalyst.²⁹⁶ Similar oxidative amidation was accomplished using H_2O_2 and a Pd-catalyst.²⁹⁷ Amides were prepared from aldehydes using NBS with a Cu catalyst.²⁹⁸ Hypervalent iodine with a Fe catalyst has also been used.²⁹⁹ Oxidative amidation of aromatic aldehydes using Oxone and ball milling without solvent gave the corresponding amide.³⁰⁰ Amidation using nucleophilic *N*-heterocyclic carbenes leads to amidation

²⁹² See Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, **1965**, pp. 126–131.

²⁹³ Müller, E.; Schmidt, E.W. *Chem. Ber.* **1964**, 97, 2614; Kühle, E. *Synthesis* **1970**, 561; **1971**, 563, 617.

²⁹⁴ Markó, I.E.; Mekhafia, A. *Tetrahedron Lett.* **1990**, 31, 7237. See Ekoue-Kovi, K.; Wolf, C. *Chemistry: European J.* **2008**, 14, 6302.

²⁹⁵ Nakagawa, K.; Onoue, H.; Minami, K. *Chem. Commun.* **1966**, 17.

²⁹⁶ Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, 128, 13064.

²⁹⁷ Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* **2008**, 49, 5732.

²⁹⁸ Wang, L.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.: Eur. J.* **2008**, 14, 10722.

²⁹⁹ Fang, C.; Qian, W.; Bao, W. *Synlett* **2008**, 2529.

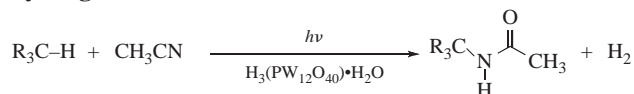
³⁰⁰ Gao, J.; Wang, G.-W. *J. Org. Chem.* **2008**, 73, 2955.

accompanied by ring opening of proximal epoxides³⁰¹ or cyclopropane moieties.³⁰² Aromatic aldehydes are converted to the corresponding amide by treatment with LiN(TMS)₂ in the presence of LnCl₃, and a stoichiometric reaction was reported using (Me₃Si)₂N]₃Ln(*i*-Cl)Li(THF)₃.³⁰³

The reaction has been performed with MnO₂ and NaCN along with ammonia or an amine at 0 °C in isopropyl alcohol.³⁰⁴ Treatment of an aldehyde with iodine in aq ammonia, followed by oxidation with aq H₂O₂ generates a primary amide.³⁰⁵ Secondary amines react with aldehydes to give an amide using a Pd³⁰⁶ or a Rh catalyst.³⁰⁷ For an indirect way of converting aldehydes to amides, see Reaction 12-32. Thioamides (RCSNR'₂) have been prepared in good yield from thioaldehydes (produced *in situ* from phosphoranes and sulfur) and secondary amines.³⁰⁸

14-12 Amidation and Amination at an Alkyl Carbon

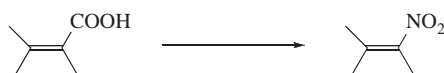
Acylamino-de-hydrogenation



When alkanes bearing a tertiary hydrogen are exposed to UV light in acetonitrile containing a heteropolytungstic acid, they are amidated.³⁰⁹ The oxygen in the product comes from the tungstic acid. When the substrate bears two adjacent tertiary hydrogen atoms, alkenes are formed (by loss of two hydrogen atoms), rather than amides (Reaction 19-2). Amidyl radicals can be generated by other means.³¹⁰

14-13 Substitution by Nitro

Nitro-de-carboxylation



In a reaction termed a “nitro-Hunsdiecker” (see Reaction 14-30), vinyl carboxylic acids (conjugated acids) are treated with nitric acid and a catalytic amount of AIBN (Sec. 14.A.i). The product is the vinyl nitro compound, generated via decarboxylation of a radical intermediate.³¹¹

Aryl halides are converted to aromatic nitro compounds via a Cu catalyzed reaction with nitrite salts (Ar—X → Ar—NO₂).³¹² Ceric ammonium nitrate in acetonitrile also facilitates this reaction.³¹³

³⁰¹ Vora, H.U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796.

³⁰² Bode, J.W.; Sohn, S.S. *J. Am. Chem. Soc.* **2007**, *129*, 13798.

³⁰³ Zhang, L.; Wang, S.; Zhou, S.; Yang, G.; Sheng, E. *J. Org. Chem.* **2006**, *71*, 3149.

³⁰⁴ Gilman, N.W. *Chem. Commun.* **1971**, 733.

³⁰⁵ Shie, J.-J.; Fang, J.-M. *J. Org. Chem.* **2003**, *68*, 1158.

³⁰⁶ Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* **1983**, 474.

³⁰⁷ Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523.

³⁰⁸ Okuma, K.; Komiya, Y.; Ohta, H. *Chem. Lett.* **1988**, 1145.

³⁰⁹ Renneke, R.F.; Hill, C.L. *J. Am. Chem. Soc.* **1986**, *108*, 3528.

³¹⁰ Moutrille, C.; Zard, S.Z. *Chem. Commun.* **2004**, 1848.

³¹¹ Das, J.P.; Sinha, P.; Roy, S. *Org. Lett.* **2002**, *4*, 3055.

³¹² Saito, S.; Koizumi, Y. *Tetrahedron Lett.* **2005**, *46*, 4715.

³¹³ Rao, A.S.; Srinivas, P.V.; Babu, K.S.; Rao, J.M. *Tetrahedron Lett.* **2005**, *46*, 8141.

Conjugated amides were coupled via the γ -carbon to give good yields of the dimeric diamide, with an excess of samarium(II) iodide, and with modest enantioselectivity using a chiral additive.³¹⁴

E. Substitution by Carbon

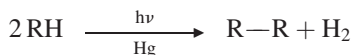
In these reactions, a new carbon–carbon bond is formed, and they may be given the collective title *coupling reactions*. In each case, an alkyl or aryl radical is generated and then combines with another radical (a termination process) or attacks an aromatic ring or alkene to give the coupling product.³¹⁵

14-14 Simple Coupling at a Susceptible Position

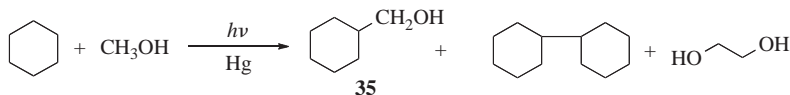
De-hydrogen-coupling



Alkane and alkyl substrates RH are treated with peroxides, which decompose to give a radical that abstracts a hydrogen from RH to give R^\cdot , which dimerizes. Dialkyl and diacyl peroxides have been used, as well as *Fenton's reagent* (Reaction 14-5). This reaction is far from general, although in certain cases respectable yields have been obtained. Among susceptible positions are those at a tertiary carbon,³¹⁶ as well as those α to a phenyl group (especially if there is also an α -alkyl or α -chloro group),³¹⁷ an ether group,³¹⁸ a carbonyl group,³¹⁹ a cyano group,³²⁰ a dialkylamino group,³²¹ or a carboxylic ester group (either the acid or alcohol side).³²² Cross-coupling is possible in some cases. When toluene was heated with allyl bromide, in the presence of di-*tert*-butyl peroxide, 4-phenyl-1-butene was formed quantitatively.³²³



Alkanes can be dimerized by vapor-phase mercury photosensitization³²⁴ in a synthetically useful process. Best results are obtained for coupling at tertiary positions, but compounds lacking tertiary hydrogen atoms (e.g., cyclohexane) also give good yields. Dimerization of *n*-alkanes gives secondary–secondary coupling in a nearly statistical distribution, with primary positions essentially unaffected. Alcohols and ethers dimerize at the position α to the oxygen [e.g., $2 \text{ EtOH} \rightarrow \text{MeCH(OH)CH(OH)Me}$].



³¹⁴ Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1999**, 40, 7497.

³¹⁵ See Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, **1986**.

³¹⁶ Meshcheryakov, A.P.; Érzyutova, E.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1966**, 94.

³¹⁷ Johnston, K.M.; Williams, G.H. *J. Chem. Soc.* **1960**, 1168.

³¹⁸ Pfordte, K.; Leuschner, G. *Liebigs Ann. Chem.* **1961**, 643, 1.

³¹⁹ Hawkins, E.G.E.; Large, R. *J. Chem. Soc. Perkin Trans. 1* **1974**, 280.

³²⁰ Kharasch, M.S.; Sosnovsky, G. *Tetrahedron* **1958**, 3, 97.

³²¹ Schwetlick, K.; Jentsch, J.; Karl, R.; Wolter, D. *J. Prakt. Chem.* **1964**, [4] 25, 95.

³²² Boguslavskaya, L.S.; Razuvaev, G.A. *J. Gen. Chem. USSR* **1963**, 33, 1967.

³²³ Tanko, J.M.; Sadeghipour, M. *Angew. Chem. Int. Ed.* **1999**, 38, 159.

³²⁴ Brown, S.H.; Crabtree, R.H. *J. Am. Chem. Soc.* **1989**, 111, 2935, 2946; *J. Chem. Educ.* **1988**, 65, 290.

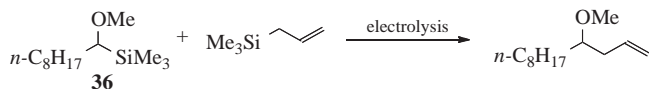
When a mixture of compounds is treated, cross-dimerization (to give **35**) and homo-dimerization take place statistically. Even with the limitation on yield implied by the statistical process, cross-dimerization is still useful when one of the reactants is an alkane, because the products are easy to separate, and because of the few other ways to functionalize an alkane. The cross-coupling of an alkane with trioxane is especially valuable, because hydrolysis of the product (Reaction **10-6**) gives an aldehyde, thus achieving the conversion $\text{RH} \rightarrow \text{RCHO}$. The mechanism probably involves abstraction of H by the excited Hg atom, and coupling of the resulting radicals.

The reaction has been extended to ketones, carboxylic acids and esters (all of which couple α to the C=O group), and amides (which couple α to the nitrogen) by running it in the presence of H_2 .³²⁵ Under these conditions it is likely that the excited Hg abstracts H^\bullet from H_2 , and that the remaining H^\bullet abstracts H from the substrate. Radicals have also been generated at benzylic positions and shown to couple with epoxides, forming an alcohol.³²⁶

OS IV, 367; V, 1026; VII, 482.

14-15 Coupling at a Susceptible Position via Silanes

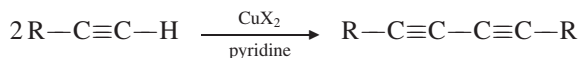
De-silyl-coupling



Under electrochemical conditions it is possible to couple two silanes. The reaction of **36** and allyltrimethylsilane, for example, gave the corresponding homoallylic ether.³²⁷

14-16 Coupling of Alkynes³²⁸

De-hydrogen-coupling



Terminal alkynes can be coupled by heating with stoichiometric amounts of cupric salts in pyridine or a similar base. This reaction, which produces symmetrical diynes in high yields, is called the *Eglinton reaction*.³²⁹ The large-ring annulenes (see Sec. 2.K) were prepared by rearrangement and hydrogenation of cyclic polyynes,³³⁰ prepared by the *Eglinton reaction* with terminal diynes to give **37**, a cyclic trimer of 1,5-hexadiyne.³³¹ The corresponding tetramers (C_{24}), pentamers (C_{30}), and hexamers

³²⁵ Boojamra, C.G.; Crabtree, R.H.; Ferguson, R.R.; Muedas, C.A. *Tetrahedron Lett.* **1989**, 30, 5583.

³²⁶ Rawal, V.H.; Krishnamurthy, V.; Fabre, A. *Tetrahedron Lett.* **1993**, 34, 2899.

³²⁷ Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2000**, 122, 10244.

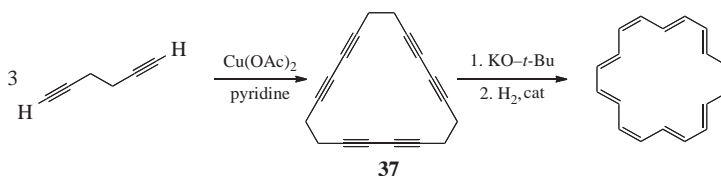
³²⁸ See Siemsen, P.; Livingston, R.C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, 39, 2632.

³²⁹ See Simándi, L.I. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, **1983**, pp. 529–534; Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, **1973**, pp. 11–31; Cadot, P.; Chodkiewicz, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 597–647.

³³⁰ See Nakagawa, M. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, **1978**, pp. 635–712. See Sondheimer et al. in Ref. 331 also.

³³¹ Sondheimer, F.; Wolovsky, R. *J. Am. Chem. Soc.* **1962**, 84, 260; Sondheimer, F.; Wolovsky, R.; Amiel, Y. *J. Am. Chem. Soc.* **1962**, 84, 274.

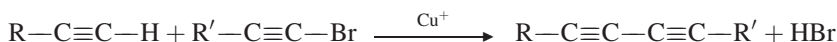
(C₃₆) were also formed. The *Eglinton reaction* is of wide scope and many functional groups can be present on the alkyne. The oxidation is usually quite specific for triple-bond hydrogen.



Another common procedure is the use of catalytic amounts of cuprous salts in the presence of ammonia or ammonium chloride (this method is called the *Glaser reaction*). Atmospheric oxygen or some other oxidizing agent (e.g., permanganate or hydrogen peroxide) is required in the latter procedure. This method is not satisfactory for cyclic coupling. Hydrogen peroxide, potassium permanganate, potassium ferricyanide, iodine, or Cu(II) can be used instead of oxygen as oxidants.³³² Isolation of copper acetylide during the reaction can be avoided by doing the reaction in pyridine or cyclohexylamine, in the presence of a catalytic amount of CuCl₂.³³³ If the *Glaser reaction* is done with a *N,N,N',N'*-tetramethylethylenediamine–CuCl complex, the reaction proceeds in good yield in virtually any organic solvent.³³⁴ When molecular oxygen is the oxidant, this modification of the *Glaser reaction* is known as the *Hay reaction*.

A variation couples terminal alkynes using CuCl₂ in supercritical CO₂ (see Sec. 9.D.ii),³³⁵ and in ionic liquids.³³⁶ Coupling was also achieved using CuCl₂ on KF–Al₂O₃ with microwave irradiation.³³⁷ A Co catalyzed *Glaser coupling* has been reported³³⁸ and also a transition metal free coupling.³³⁹ A modified *Glaser coupling* has been reported using KF/Alumina.³⁴⁰ Coupling has been achieved under ambient conditions using cupric acetate.³⁴¹ Copper(II) promoted homocoupling of terminal alkynes has been done in supercritical CO₂.³⁴² Another variation is a Ni catalyzed cross-coupling.³⁴³ Terminal alkynes give 1,3-diynes upon treatment with Cu–iodine.³⁴⁴

Unsymmetrical diynes can be prepared by *Cadiot–Chodkiewicz coupling*³⁴⁵:



This may be regarded as a variation of Reaction 10-74, but it must have a different mechanism since acetylenic halides give the reaction but ordinary alkyl halides do not,

³³² Gunter, H.V. *Chemistry of Acetylenes*, Marcel Dekker, NY, **1969**, pp. 597–647 and references cited therein.

³³³ Stansbury, H.A.; Proops, W.R. *J. Org. Chem.* **1962**, 27, 320.

³³⁴ Hay, A.S. *J. Org. Chem.* **1960**, 25, 1275; Hay, A. S. *J. Org. Chem.* **1962**, 27, 3320.

³³⁵ Li, J.; Jiang, H. *Chem. Commun.* **1999**, 2369.

³³⁶ Yadav, J.S.; Reddy, B.V.S.; Reddy, K.B.; Gayathri, K.U.; Prasad, A.R. *Tetrahedron Lett.* **2003**, 44, 6493.

³³⁷ Kabalka, G.W.; Wang, L.; Pagni, R.M. *Synlett* **2001**, 108.

³³⁸ Hilt, G.; Hengst, C.; Arndt, M. *Synthesis* **2009**, 395.

³³⁹ Yan, J.; Wang, L. *Synth. Commun.* **2005**, 35, 2333.

³⁴⁰ Sharifi, A.; Mirzaei, M.; Naimi-Jamal, M.R. *Monat. Chemie* **2006**, 137, 213.

³⁴¹ Balaraman, K.; Kesavan, V. *Synthesis* **2010**, 3461.

³⁴² Jiang, H.-F.; Tang, J.Y.; Wang, A.-Z.; Deng, G.-H.; Yang, S.-R. *Synthesis* **2006**, 1155.

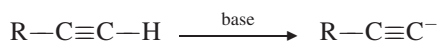
³⁴³ Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, 11, 709.

³⁴⁴ Li, D.; Yin, K.; Li, J.; Jia, X. *Tetrahedron Lett.* **2008**, 49, 5918.

³⁴⁵ Chodkiewicz, W. *Ann. Chim. (Paris)* **1957**, [13] 2, 819.

which is hardly compatible with a nucleophilic mechanism. However, the mechanism is not fully understood. One version of this reaction binds the alkynyl bromide unit to a polymer, and the di-yne is released from the polymer after the solid-state transformation.³⁴⁶ Alkynes have also been coupled using CuI and a Pd catalyst.³⁴⁷ A variation of the *Cadiot–Chodkiewicz method* consists of treating a haloalkyne ($R'C\equiv CX$) with a copper acetylide ($RC\equiv CCu$).³⁴⁸ The *Cadiot–Chodkiewicz procedure* can be adapted to the preparation of diynes in which $R'=H$ by the use of $BrC\equiv CSiEt_3$ and subsequent cleavage of the $SiEt_3$ group.³⁴⁹ This protecting group can also be used in the *Eglinton* or *Glaser* methods.³⁵⁰

The mechanism of the *Eglinton* and *Glaser reactions* probably begins with loss of a proton



since there is a base present and acetylenic protons are acidic. It is known, of course, that cuprous ion can form complexes with triple bonds. The last step is probably the coupling of two radicals:



but just how the carbanion becomes oxidized to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,³⁵¹ and depend on the oxidizing agent. One proposed mechanism postulated Cu(II) as the oxidant.³⁵² It has been shown that molecular oxygen forms adducts with Cu(I) supported by tertiary amines, which might be the intermediates in the *Glaser reaction* where molecular oxygen is the oxidant.³⁵³ For the *Hay reaction*, the mechanism involves a Cu(I)/Cu(III)/Cu(II)/Cu(I) catalytic cycle, and the key step for this reaction is the dioxygen activation during complexation of two molecules of acetylide with molecular oxygen, giving a Cu(III) complex.³⁵⁴ This mechanism is supported by isolation and characterization of Cu(III) complexes formed under the conditions of the *Glaser coupling*.

Sonogashira coupling, which involves aryl halides and terminal alkynes in the presence of a Pd catalyst, has been extended to the coupling of two alkynes.³⁵⁵ Indeed, the Pd catalyzed coupling of two alkynes to form a diyne³⁵⁶ is often referred to as *Sonogashira cross-coupling*, or *Sonogashira-like coupling*. An example is the

³⁴⁶ Montierth, J.M.; DeMario, D.R.; Kurth, M.J.; Schore, N.E. *Tetrahedron* **1998**, *54*, 11741.

³⁴⁷ Liu, Q.; Burton, D.J. *Tetrahedron Lett.* **1997**, *38*, 4371.

³⁴⁸ Curtis, R.F.; Taylor, J.A. *J. Chem. Soc. C* **1971**, 186.

³⁴⁹ Ghose, B.N.; Walton, D.R.M. *Synthesis* **1974**, 890.

³⁵⁰ Johnson, T.R.; Walton, D.R.M. *Tetrahedron* **1972**, *28*, 5221.

³⁵¹ See Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, **1973**, pp. 27–31; Fedenok, L.G.; Berdnikov, V.M.; Shvartsberg, M.S. *J. Org. Chem. USSR* **1973**, *9*, 1806; Clifford, A.A.; Waters, W.A. *J. Chem. Soc.* **1963**, 3056.

³⁵² Bohlmann, F.; Schönowsky, H.; Inhoffen, E.; Grau, G. *Chem. Ber.* **1964**, *97*, 794.

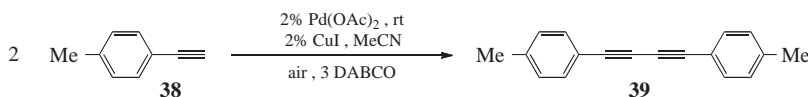
³⁵³ Wiegardt, K.; Chaudhuri, P. *Prog. Inorg. Chem.* **1987**, *37*, 329.

³⁵⁴ Fomina, L.; Vazquez, B.; Tkatchouk, E.; Fomine, S. *Tetrahedron* **2002**, *58*, 6741.

³⁵⁵ See Henriksen, S.T.; Tanner, D.; Skrydstrup, T.; Norrby, P.-O. *Chemistry: Eur. J.* **2010**, *16*, 9494.

³⁵⁶ See Kurita, T.; Abe, M.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Synlett* **2007**, 2521.

conversion of **38** to **39**.³⁵⁷ Here rt = room temperature and DABCO = 1,4-diazabicyclo [2.2.2]octane.



Terminal alkynes are not the only reaction partners. 1-Trimethylsilyl alkynes ($\text{R}-\text{C}\equiv\text{C}-\text{SiMe}_3$) give the diyne $\text{R}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{R}$ upon reaction with CuCl ³⁵⁸ or $\text{Cu(OAc)}_2/\text{Bu}_4\text{NF}$.³⁵⁹

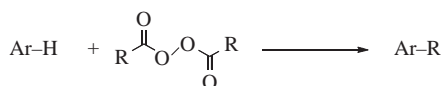
Alkynylboronates undergo homocoupling to give symmetrical 1,3-diynes in the presence of a Cu salt.³⁶⁰ The Cu-catalyzed homocoupling of alkynyltrifluoroborates leads to 1,3-diynes.³⁶¹

In related reactions, alkynyltrifluoroborates react with vinylic tellurides to give 1,3-enynes.³⁶² The Pd catalyzed reaction of vinyl bromides and terminal alkynes gives enynes.³⁶³ 1,3-Dienes are prepared by the Pd catalyzed homocoupling of alkenyltrifluoroborates.³⁶⁴

OS V, 517; VI, 68, 925; VIII, 63.

14-17 Alkylation and Arylation of Aromatic Compounds by Peroxides

Alkylation or Alkyl-de-hydrogenation



This reaction is most often carried out with $\text{R} = \text{aryl}$, so the net result is the same as in Reaction 13-27, though the reagent is different.³⁶⁵ It is used less often than Reaction 13-27, but the scope is similar. When $\text{R} = \text{alkyl}$, the scope is more limited.³⁶⁶ Only certain aromatic compounds, particularly benzene rings with two or more nitro groups, and fused ring systems, can be alkylated by this procedure. 1,4-Quinones can be alkylated with diacyl peroxides or with lead tetraacetate (methylation occurs with this reagent).

³⁵⁷ Li, J.-H.; Liang, Y.; Xie, Y.-X. *J. Org. Chem.* **2005**, 70, 4393.

³⁵⁸ Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, 65, 1780.

³⁵⁹ Heuft, M.A.; Collins, S.K.; Yap, G.P.A.; Fallis, A.E. *Org. Lett.* **2001**, 3, 2883.

³⁶⁰ Nishihara, Y.; Okamoto, M.; Inoue, Y.; Miyazaki, M.; Miyasaka, M.; Takagi, K. *Tetrahedron Lett.* **2005**, 46, 8661.

³⁶¹ Paixão, M.W.; Weber, M.; Braga, A.L.; de Azeredo, J.B.; Deobald, A.M.; Stefani, H.A. *Tetrahedron Lett.* **2008**, 49, 2366.

³⁶² Stefani, H.A.; Cella, R.; Dörr, F.A.; Pereira, C.M.P.; Zeni, G.; Gomes, Jr., M. *Tetrahedron Lett.* **2005**, 46, 563.

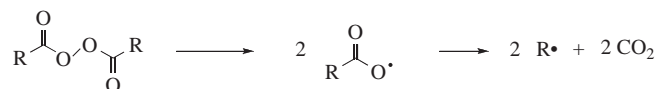
³⁶³ Feuerstein, M.; Chahen, L.; Doucet, H.; Santelli, M. *Tetrahedron* **2006**, 62, 112.

³⁶⁴ Weber, M.; Singh, F.V.; Vieira, A.S.; Stefani, H.A.; Paixão, M.W. *Tetrahedron Lett.* **2009**, 50, 4324.

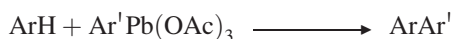
³⁶⁵ See Bolton, R.; Williams, G.H. *Chem. Soc. Rev.* **1986**, 15, 261; Hey, D.H. *Adv. Free-Radical Chem.* **1966**, 2, 47.

³⁶⁶ See Tiecco, M.; Testaferri, L. *React. Intermed. (Plenum)* **1983**, 3, 61.

The mechanism is as shown in Section 14.A.iii (CIDNP has been observed³⁶⁷); the radicals are produced by



Since no relatively stable free radical is present (e.g., $^\bullet\text{O}-\text{N}=\text{N}-\text{Ar}$ in Reaction **13-27**), most of the product arises from dimerization and disproportionation.³⁶⁸ The addition of a small amount of nitrobenzene increases the yield of arylation product because the nitrobenzene is converted to diphenyl nitroxide, which abstracts a hydrogen atom and diminishes the extent of side reactions.³⁶⁹ The Pd catalyzed methylation of aromatic rings in the presence of dicumyl peroxide is another variation.³⁷⁰

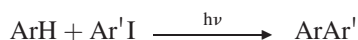


Aromatic compounds can also be arylated by aryllead tricarboxylates.³⁷¹ Best yields (~ 70 – 85%) are obtained when the substrate contains alkyl groups; an electrophilic mechanism is likely. Phenols are phenylated ortho to the OH group (and enols are a phenylated) by triphenylbismuth dichloride or by certain other Bi(V) reagents.³⁷² *O*-Phenylation is a possible side reaction. As with the aryllead tricarboxylate reactions, a free radical mechanism is unlikely.³⁷³

OS V, 51. See also, OS V, 952; VI, 890.

14-18 Photochemical Arylation of Aromatic Compounds

Arylation or Aryl-de-hydrogenation



Another free radical arylation method consists of the photolysis of aryl iodides in an aromatic solvent.³⁷⁴ Yields are generally higher than in Reactions **13-27** or **14-17**. The aryl iodide may contain OH or COOH groups. The coupling reaction of iodobenzene and azulene to give a phenylazulene was reported (41% conversion and 85% yield).³⁷⁵ The mechanism is similar to that of Reaction **13-27**. The aryl radicals are generated by the photolytic cleavage $\text{ArI} \rightarrow \text{AR}^\bullet + \text{I}^\bullet$. The reaction has been applied to intramolecular arylation (analogous to the *Pschorr reaction*).³⁷⁶ A similar reaction is photolysis of an

³⁶⁷ Kaptein, R.; Freeman, R.; Hill, H.D.W.; Bargon, J. *J. Chem. Soc., Chem. Commun.* **1973**, 953.

³⁶⁸ The mechanism is actually more complicated. See DeTar, D.F.; Long, R.A.J.; Rendleman, J.; Bradley, J.; Duncan, P. *J. Am. Chem. Soc.* **1967**, 89, 4051; DeTar, D.F. *J. Am. Chem. Soc.* **1967**, 89, 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* **1985**, 88.

³⁶⁹ Chalfont, G.R.; Hey, D.H.; Liang, K.S.Y.; Perkins, M.J. *J. Chem. Soc. B* **1971**, 233.

³⁷⁰ Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, 130, 2900.

³⁷¹ Bell, H.C.; Kalman, J.R.; May, G.L.; Pinhey, J.T.; Sternhell, S. *Aust. J. Chem.* **1979**, 32, 1531.

³⁷² See Abramovitch, R.A.; Barton, D.H.R.; Finet, J. *Tetrahedron* **1988**, 44, 3039, pp. 3040–3047.

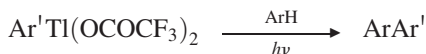
³⁷³ Barton, D.H.R.; Finet, J.; Giannotti, C.; Halley, F. *J. Chem. Soc. Perkin Trans. 1* **1987**, 241.

³⁷⁴ See Sharma, R.K.; Kharasch, N. *Angew. Chem. Int. Ed.* **1968**, 7, 36.

³⁷⁵ Ho, T.-I.; Ku, C.-K.; Liu, R.S.H. *Tetrahedron Lett.* **2001**, 42, 715.

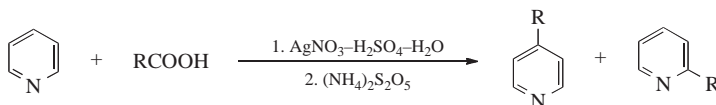
³⁷⁶ See Jeffs, P.W.; Hansen, J.F. *J. Am. Chem. Soc.* **1967**, 89, 2798; Thyagarajan, B.S.; Kharasch, N.; Lewis, H.B.; Wolf, W. *Chem. Commun.* **1967**, 614.

arylthallium bis(trifluoroacetate) (**12-23**) in an aromatic solvent. Here too, an unsymmetrical biaryl is produced in good yields.³⁷⁷ In this case, it is the C—Tl bond that is cleaved to give aryl radicals.



14-19 Alkylation, Acylation, and Carbalkoxylation of Nitrogen Heterocycles³⁷⁸

Alkylation or **Alkyl-de-hydrogenation**, and so on

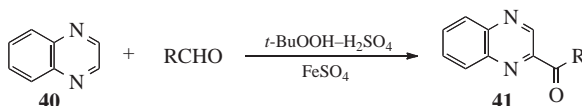


Alkylation of protonated nitrogen heterocycles (e.g., pyridines, quinolines) can be accomplished by treatment with a carboxylic acid, silver nitrate, sulfuric acid, and ammonium peroxydisulfate.³⁷⁹ The R group can be primary, secondary, or tertiary. The attacking species is R^\bullet , formed by³⁸⁰



A hydroxymethyl group can be introduced ($\text{ArH} \rightarrow \text{ArCH}_2\text{OH}$) by several variations of this method.³⁸¹ Alkylation of these substrates can also be accomplished by generating the alkyl radicals in other ways: from hydroperoxides and FeSO_4 ,³⁸² from alkyl iodides and H_2O_2 — Fe(II) ,³⁸³ from carboxylic acids and lead tetraacetate, or from the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate.³⁸⁴

Protonated nitrogen heterocycles (e.g., quinoxaline, **40**) can be acylated by treatment with an aldehyde, *tert*-butyl hydroperoxide, sulfuric acid, and ferrous sulfate, in this case giving **41**.³⁸⁵



Photochemical alkylation of protonated quinoline occurred with $\text{Ph}_2\text{Se}(\text{O}_2\text{Cc-C}_6\text{H}_{11})_2$.³⁸⁶

³⁷⁷ Taylor, E.C.; Kienzle, F.; McKillop, A. *J. Am. Chem. Soc.* **1970**, 92, 6088.

³⁷⁸ See Heinisch, G. *Heterocycles* **1987**, 26, 481; Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, 28, 489; Vorbrüggen, H.; Maas, M. *Heterocycles* **1988**, 27, 2659.

³⁷⁹ Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Tetrahedron* **1990**, 46, 2525.

³⁸⁰ Anderson, J.M.; Kochi, J.K. *J. Am. Chem. Soc.* **1970**, 92, 1651.

³⁸¹ See Katz, R.B.; Mistry, J.; Mitchell, M.B. *Synth. Commun.* **1989**, 19, 317.

³⁸² Minisci, F.; Selva, A.; Porta, O.; Barilli, P.; Gardini, G.P. *Tetrahedron* **1972**, 28, 2415.

³⁸³ Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Acta Chem. Scand.* **1989**, 43, 995.

³⁸⁴ Minisci, F.; Vismara, E.; Fontana, F.; Barbosa, M.C.N. *Tetrahedron Lett.* **1989**, 30, 4569.

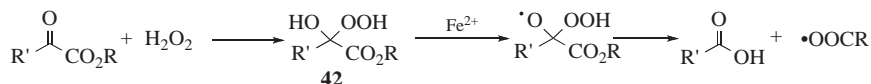
³⁸⁵ Arnoldi, A.; Bellatti, M.; Caronna, T.; Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *Gazz. Chim. Ital.* **1977**, 107, 491.

³⁸⁶ Togo, H.; Miyagawa, N.; Yokoyama, M. *Chem. Lett.* **1992**, 1677.

Other positively charged heterocycles react as well. When *N*-fluoropyridinium triflate was treated with the enolate anion of acetone, 2-(2-oxopropyl)pyridine was formed in modest yield.³⁸⁷

These alkylation and acylation reactions are important because *Friedel–Crafts* alkylation and acylation (Reactions **11-11** and **11-17**) cannot be applied to most nitrogen heterocycles (see also, Reaction **13-17**).

Protonated nitrogen heterocycles can be carbalkoxylated³⁸⁸ by treatment with esters of α -keto acids and *Fenton's reagent*. Pyridine is carbalkoxylated at C-2 and C-4, for example. The attack is by $\cdot\text{COOR}$ radicals generated from the esters via a hydroperoxide (**42**).



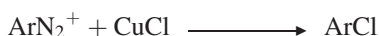
Similarly, a carbamoyl group can be introduced³⁸⁹ by the use of the radicals $\text{H}_2\text{N}-\dot{\text{C}}=\text{O}$ or $\text{Me}_2\text{N}-\dot{\text{C}}=\text{O}$ generated from formamide or DMF and H_2SO_4 , H_2O_2 , and FeSO_4 or other oxidants.

14.C.ii. N_2 as Leaving Group³⁹⁰

In these reactions, diazonium salts are cleaved to aryl radicals,³⁹¹ in most cases with the assistance of copper salts. Reactions **13-27** and **13-26** may also be regarded as belonging to this category with respect to the attacking compound. For nucleophilic substitutions of diazonium salts (see Reactions **13-20–13-23**). Removal of nitrogen and replacement with a hydrogen atom is a reduction, found in Chapter 19.

14-20 Replacement of the Diazonium Group by Chlorine or Bromine

Chloro-de-diazonation, and so on



Treatment of diazonium salts with cuprous chloride or bromide leads to aryl chlorides or bromides, respectively. In either case, the reaction is called the *Sandmeyer Reaction*.³⁹² The reaction can also be carried out with copper and HBr or HCl, in which case it is called the *Gatterman Reaction* (not to be confused with **11-18**). However, a Cu catalyzed *Sandmeyer bromination* reaction is known.³⁹³ The *Sandmeyer reaction* is not useful for the preparation of fluorides or iodides, but for bromides and chlorides it is

³⁸⁷ Kiselyov, A.S.; Strekowski, L. *J. Org. Chem.* **1993**, 58, 4476.

³⁸⁸ See Heinisch, G.; Lötsch, G. *Angew. Chem. Int. Ed.* **1985**, 24, 692.

³⁸⁹ Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* **1985**, 41, 4157.

³⁹⁰ See Wulfman, D.S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, **1978**, pp. 286–297.

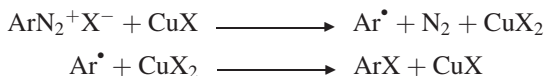
³⁹¹ See Galli, C. *Chem. Rev.* **1988**, 88, 765; Zollinger, H. *Acc. Chem. Res.* **1973**, 6, 355, pp. 339–341.

³⁹² Rate constants for this reaction have been determined. See Hanson, P.; Hammond, R.C.; Goodacre, P.R.; Purcell, J.; Timms, A.W. *J. Chem. Soc. Perkin Trans. 2* **1994**, 691.

³⁹³ Beletskaya, I.P.; Sigeev, A.S.; Peregudov, A.S.; Petrovskii, P.V. *Synthesis* **2007**, 2534.

of wide scope and is probably the best way of introducing bromine or chlorine into an aromatic ring. The yields are usually high.

The mechanism is not known with certainty, but is believed to take the following course³⁹⁴:



The first step involves a reduction of the diazonium ion by the cuprous ion, which results in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it. CuX is regenerated and is thus a true catalyst.

Aryl bromides and chlorides can be prepared from primary aromatic amines in one step by several procedures,³⁹⁵ including treatment of the amine (1) with *tert*-butyl nitrite and anhydrous CuCl₂ or CuBr₂ at 65 °C,³⁹⁶ and (2) with *tert*-butyl thionitrite or *tert*-butyl thionitrate and CuCl₂ or CuBr₂ at room temperature.³⁹⁷ These procedures are, in effect, a combination of Reaction **13-19** and the *Sandmeyer Reaction*. A further advantage is that cooling to 0 °C is not needed. A mixture of Me₃SiCl and NaNO₂ was used to convert aniline to chlorobenzene in a related reaction.³⁹⁸

For the preparation of fluorides and iodides from diazonium salts, see Reactions **13-32** and **13-31**.

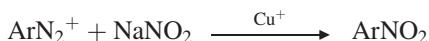


Note that the reaction of aryl diazonium salts with CuCN to give benzonitrile derivatives is also called the *Sandmeyer Reaction*. It is usually conducted in neutral solution to avoid liberation of HCN.

OS **I**, 135, 136, 162, 170; **II**, 130; **III**, 185; **IV**, 160. Also see, OS **III**, 136; **IV**, 182. For the reaction with CuCN see OS **I**, 514.

14-21 Replacement of the Diazonium Group by Nitro

Nitro-de-diazoniatio



Nitro compounds can be formed in good yields by treatment of diazonium salts with sodium nitrite in the presence of cuprous ion. The reaction occurs only in neutral or alkaline solution. This is not usually called the *Sandmeyer Reaction*, although, like Reaction **14-20**, it was discovered by Sandmeyer. Tetrafluoroborate (BF₄[−]) is often used as the negative ion, since the diminished nucleophilicity avoids competition from the chloride ion. The mechanism is probably like that of Reaction **14-20**.³⁹⁹ If electron-withdrawing groups

³⁹⁴ Galli, C. J. *Chem. Soc. Perkin Trans. 2* **1984**, 897. See also, Hanson, P.; Jones, J.R.; Gilbert, B.C.; Timms, A.W. *J. Chem. Soc. Perkin Trans. 2* **1991**, 1009.

³⁹⁵ Also see Brackman, W.; Smit, P.J. *Recl. Trav. Chim. Pays-Bas*, **1966**, 85, 857; Cadogan, J.I.G.; Roy, D.A.; Smith, D.M. *J. Chem. Soc. C* **1966**, 1249.

³⁹⁶ Doyle, M.P.; Siegfried, B.; Dellaria, Jr., J.F. *J. Org. Chem.* **1977**, 42, 2426.

³⁹⁷ Oae, S.; Shinhama, K.; Kim, Y.H. *Bull. Chem. Soc. Jpn.* **1980**, 53, 1065.

³⁹⁸ Lee, J.G.; Cha, H.T. *Tetrahedron Lett.* **1992**, 33, 3167.

³⁹⁹ See Singh, P.R.; Kumar, R.; Khanna, R.K. *Tetrahedron Lett.* **1982**, 23, 5191.

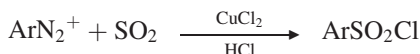
are present, the catalyst is not needed; NaNO_2 alone gives nitro compounds in high yields.⁴⁰⁰

An alternative procedure used electrolysis, in 60% HNO_3 to convert 1-aminonaphthalene to naphthalene.⁴⁰¹

OS II, 225; III, 341.

14-22 Replacement of the Diazonium Group by Sulfur-Containing Groups

Chlorosulfo-de-diazoniatio

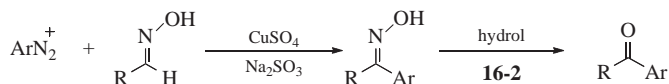


Diazonium salts can be converted to sulfonyl chlorides by treatment with sulfur dioxide in the presence of cupric chloride.⁴⁰² The use of FeSO_4 and copper metal instead of CuCl_2 gives sulfinic acids (ArSO_2H)⁴⁰³ (see also, Reaction 13-21).

OS V, 60; VII, 508.

14-23 Conversion of Diazonium Salts to Aldehydes, Ketones, or Carboxylic Acids

Acyl-de-diazoniatio



Diazonium salts react with oximes to give aryl oximes, which are easily hydrolyzed to aldehydes ($\text{R} = \text{H}$) or ketones.⁴⁰⁴ A copper sulfate–sodium sulfite catalyst is essential. In most cases, higher yields (40–60%) are obtained when the reaction is used for aldehydes rather than for ketones. In another method⁴⁰⁵ for achieving the conversion $\text{ArN}_2^+ \rightarrow \text{ArCOR}$, diazonium salts are treated with R_4Sn and CO with palladium acetate as catalyst.⁴⁰⁶ In a different kind of reaction, silyl enol ethers of aryl ketones ($\text{Ar}'\text{C}(\text{OSiMe}_3)=\text{CHR}$) react with solid diazonium fluoroborates ($\text{ArN}_2^+ \text{BF}_4^-$) to give ketones ($\text{ArCHRCOAr}'$).⁴⁰⁷ This is, in effect, an arylation of the aryl ketone.

Carboxylic acids can be prepared in moderate-to-high yields by treatment of diazonium fluoroborates with carbon monoxide and palladium acetate⁴⁰⁸ or copper(II) chloride.⁴⁰⁹ The mixed anhydride (ArCOOCOMe) is an intermediate that can be isolated. Other mixed anhydrides can be prepared by the use of other salts instead of sodium acetate.⁴¹⁰ An arylpalladium compound is probably an intermediate.³⁶⁸

OS V, 139.

⁴⁰⁰ Bagal, L.I.; Pevzner, M.S.; Frolov, A.N. *J. Org. Chem. USSR* **1969**, 5, 1767.

⁴⁰¹ Torii, S.; Okumoto, H.; Satoh, H.; Minoshima, T.; Kurozumi, S. *SynLett*, **1995**, 439.

⁴⁰² Gilbert, E.E. *Synthesis* **1969**, 1, p. 6.

⁴⁰³ Wittig, G.; Hoffmann, R.W. *Org. Synth.* **V**, 60.

⁴⁰⁴ Beech, W.F. *J. Chem. Soc.* **1954**, 1297.

⁴⁰⁵ See Citterio, A.; Serravalle, M.; Vimara, E. *Tetrahedron Lett.* **1982**, 23, 1831.

⁴⁰⁶ Kikukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1511.

⁴⁰⁷ Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1545.

⁴⁰⁸ Nagira, K.; Kikukawa, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1980**, 45, 2365.

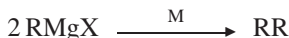
⁴⁰⁹ Olah, G.A.; Wu, A.; Bagno, A.; Prakash, G.K.S. *Synlett*, **1990**, 596.

⁴¹⁰ Kikukawa, K.; Kono, K.; Nagira, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1981**, 46, 4413.

14.C.iii. Metals as Leaving Groups

14-24 Coupling of Grignard Reagents

De-metallo-coupling



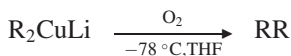
This organometallic coupling reaction is clearly related to the *Wurtz coupling*, discussed in Reaction **10-56**, and the coupling of other organometallic compounds is discussed in Reaction **14-25**. *Grignard reagents* can be coupled to give symmetrical dimers⁴¹¹ by treatment with either thallium(I) bromide⁴¹² or with a transition metal halide (e.g., Fe compounds,⁴¹³ CrCl₂, CrCl₃, CoCl₂, CoBr₂, or CuCl₂).⁴¹⁴ The metallic halide is an oxidizing agent and becomes reduced. Both aryl and alkyl *Grignard reagents* can be dimerized by either procedure, though the TlBr method cannot be applied to R = primary alkyl or to aryl groups with ortho substituents. Aryl *Grignard reagents* can also be dimerized by treatment with 1,4-dichloro-2-butene, 1,4-dichloro-2-butyne, or 2,3-dichloropropene.⁴¹⁵ Vinylic and alkynyl *Grignard reagents* can be coupled (to give 1,3-dienes and 1,3-diynes, respectively) by treatment with thionyl chloride.⁴¹⁶ Primary alkyl, vinylic, aryl, and benzylic *Grignard reagents* give symmetrical dimers in high yield (~90%) when treated with a silver(I) salt in the presence of a nitrogen-containing oxidizing agent (e.g., lithium nitrate, methyl nitrate, or NO₂).⁴¹⁷ This method has been used to close rings of four, five, and six members.⁴¹⁸

The mechanisms of the reactions with metal halides, at least in some cases, probably begin with conversion of RMgX to the corresponding RM (Reaction **12-36**), followed by its decomposition to free radicals.⁴¹⁹

OS VI, 488.

14-25 Coupling of Other Organometallic Reagents³³²

De-metallo-coupling



Lithium dialkylcopper reagents can be oxidized to symmetrical dimers by O₂ at -78 °C in THF.⁴²⁰ The reaction is successful for R = primary and secondary alkyl, vinylic, or aryl. Other oxidizing agents (e.g., nitrobenzene) can be used instead of O₂. Vinylic

⁴¹¹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, **1999**, pp. 85–88.

⁴¹² McKillop, A.; Elsom, L.F.; Taylor, E.C. *Tetrahedron* **1970**, 26, 4041.

⁴¹³ Liu, W.; Lei, A. *Tetrahedron Lett.* **2008**, 49, 610.

⁴¹⁴ See Kauffmann, T. *Angew. Chem. Int. Ed.* **1974**, 13, 291; Elsom, L.F.; Hunt, J.D.; McKillop, A. *Organomet. Chem. Rev. Sect. A* **1972**, 8, 135; Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B; Academic Press, NY, **1973**, pp. 85–91. See Terao, J.; Todo, H.; Begum, S.A.; Kuniyasu, H.; Kambe, N. *Angew. Chem. Int. Ed.* **2007**, 46, 2086.

⁴¹⁵ Cheng, J.; Luo, F. *Tetrahedron Lett.* **1988**, 29, 1293.

⁴¹⁶ Uchida, A.; Nakazawa, T.; Kondo, I.; Iwata, N.; Matsuda, S. *J. Org. Chem.* **1972**, 37, 3749.

⁴¹⁷ Tamura, M.; Kochi, J.K. *Bull. Chem. Soc. Jpn.* **1972**, 45, 1120.

⁴¹⁸ Whitesides, G.M.; Gutowski, F.D. *J. Org. Chem.* **1976**, 41, 2882.

⁴¹⁹ See Kashin, A.N.; Beletskaya, I.P. *Russ. Chem. Rev.* **1982**, 51, 503.

⁴²⁰ Whitesides, G.M.; San Filippo Jr., J.; Casey, C.P.; Panek, E.J. *J. Am. Chem. Soc.* **1967**, 89, 5302. See also Bertz, S.H.; Gibson, C.P. *J. Am. Chem. Soc.* **1986**, 108, 8286.

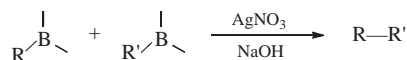
copper reagents dimerize on treatment with oxygen, or simply on standing at 0 °C for several days or at 25 °C for several hours, to yield 1,3-dienes.⁴²¹ The finding of retention of configuration for this reaction demonstrates that free radical intermediates are not involved.

The coupling reaction of *Grignard reagents* was discussed in Reaction **14-24**. There are iron-catalyzed cross-coupling reactions.⁴²² Lithium organoaluminates (LiAlR_4) are dimerized to $\text{R}-\text{R}$ by treatment with $\text{Cu}(\text{OAc})_2$.⁴²³ Terminal vinylic alanes (prepared by Reaction **15-17**) can be dimerized to 1,3-dienes with CuCl in THF.⁴²⁴ Symmetrical 1,3-dienes can also be prepared in high benzylic bromides to give the coupling product.⁴²⁵ Coupling products are obtained by treatment of vinylic mercury chlorides⁴²⁶ with LiCl and a Rh catalyst⁴²⁷ and by treatment of vinylic tin compounds with a Pd catalyst.⁴²⁸ Vinylic, alkynyl, and aryl tin compounds were dimerized with $\text{Cu}(\text{NO}_3)_2$.⁴²⁹ Allylindium reagents were coupled to alkyl- and aryllithium compounds can be dimerized by transition metal halides in a reaction similar to Reaction **14-24**.⁴³⁰

Unsymmetrical coupling of vinylic, alkynyl, and arylmercury compounds was achieved in moderate-to-good yields by treatment with alkyl and vinylic dialkylcopper reagents (e.g., $\text{PhCH}=\text{CHHgCl} + \text{Me}_2\text{CuLi} \rightarrow \text{PhCH}=\text{CHMe}$).⁴³¹ A radical coupling reaction has been reported, in which an aryl halide reacted with Bu_3SnH , AIBN, and benzene, followed by treatment with methyllithium to give the biaryl.⁴³²

14-26 Coupling of Boranes

Alkyl-de-dialkylboration



Alkylboranes can be coupled by treatment with silver nitrate and base.⁴³³ Since alkylboranes are easily prepared from alkenes (Reaction **15-16**), this is essentially a way of coupling and reducing alkenes; in fact, alkenes can be hydroborated and coupled in the same flask. For symmetrical coupling ($\text{R} = \text{R}'$) yields range from 60 to 80% for terminal alkenes and from 35 to 50% for internal ones. Unsymmetrical coupling has also been

⁴²¹ Rao, S.A.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1987**, 495. See also, Lambert, G.J.; Duffley, R.P.; Dalzell, H.C.; Razdan, R.K. *J. Org. Chem.* **1982**, 47, 3350.

⁴²² Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, 34, 624.

⁴²³ Sato, F.; Mori, Y.; Sato, M. *Chem. Lett.* **1978**, 1337.

⁴²⁴ Zweifel, G.; Miller, R.L. *J. Am. Chem. Soc.* **1970**, 92, 6678.

⁴²⁵ Ranu, B.C.; Banerjee, S.; Adak, L. *Tetrahedron Lett.* **2007**, 48, 7374.

⁴²⁶ See Russell, G.A. *Acc. Chem. Res.* **1989**, 22, 1; Larock, R.C. *Organomercury Compounds in Organic Synthesis* Springer, NY, **1985**, pp. 240–248.

⁴²⁷ Larock, R.C.; Bernhardt, J.C. *J. Org. Chem.* **1977**, 42, 1680; Larock, R.C.; Riefling, B. *J. Org. Chem.* **1978**, 43, 1468.

⁴²⁸ Tolstikov, G.A.; Miftakhov, M.S.; Danilova, N.A.; Vel'der, Ya.L.; Spirikhin, L.V. *Synthesis* **1989**, 633.

⁴²⁹ Ghosal, S.; Luke, G.P.; Kyler, K.S. *J. Org. Chem.* **1987**, 52, 4296.

⁴³⁰ Morizur, J. *Bull. Soc. Chim. Fr.* **1964**, 1331.

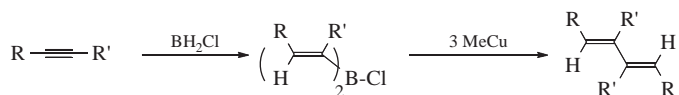
⁴³¹ Larock, R.C.; Leach, D.R. *Organometallics* **1982**, 1, 74. Also see Larock, R.C.; Hershberger, S.S. *Tetrahedron Lett.* **1981**, 22, 2443.

⁴³² Studer, A.; Bossart, M.; Vasella, T. *Org. Lett.* **2000**, 2, 985.

⁴³³ Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, pp. 306–308.

carried out,⁴³⁴ but with lower yields. Arylboranes react similarly, yielding biaryls.⁴³⁵ The mechanism is probably of the free radical type.

Dimerization of two vinylborane units to give a conjugated diene can be achieved by treatment of divinylchloroboranes (prepared by addition of BH_2Cl to alkynes; see Reaction 15-16) with methylcopper. (*E,E*)-1,3-Dienes are prepared in high yields.⁴³⁶



In a similar reaction, symmetrical conjugated diynes $\text{RC}\equiv\text{C}-\text{C}\equiv\text{CR}$ can be prepared by reaction of lithium dialkyldialkynylborates, $\text{Li}^+ [\text{R}'_2\text{B}(\text{C}\equiv\text{CR})_2]^-$, with iodine.⁴³⁷

14.C.iv. Halogen as Leaving Group

The conversion of RX to RH can occur by a free radical mechanism, but is treated at Reaction 19-53.

14.C.v. Sulfur as Leaving Group

14-27 Desulfurization

Hydro-de-thio-substitution, and so on



Thiols and thioethers,⁴³⁸ both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.⁴³⁹ The hydrogen is usually not applied externally, since Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, among them disulfides (RSSR), thiono esters (RCSOR'),⁴⁴⁰ thioamides (RCDNHR'), sulfoxides, and dithioacetals. The last reaction, which is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see

⁴³⁴ Brown, H.C.; Verbrugge, C.; Snyder, C.H. *J. Am. Chem. Soc.* **1961**, 83, 1001.

⁴³⁵ Breuer, S.W.; Broster, F.A. *Tetrahedron Lett.* **1972**, 2193.

⁴³⁶ Yamamoto, Y.; Yatagai, H.; Maruyama, K.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* **1977**, 99, 5652; *Bull. Chem. Soc. Jpn.* **1977**, 50, 3427. See Rao, V.V.R.; Kumar, C.V.; Devaprabhakara, D. *J. Organomet. Chem.* **1979**, 179, C7; Campbell, Jr., J.B.; Brown, H.C. *J. Org. Chem.* **1980**, 45, 549.

⁴³⁷ Pelter, A.; Smith, K.; Tabata, M. *J. Chem. Soc., Chem. Commun.* **1975**, 857; Pelter, A.; Hughes, R.; Smith, K.; Tabata, M. *Tetrahedron Lett.* **1976**, 4385; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* **1976**, 41, 1078.

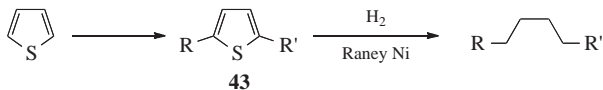
⁴³⁸ See Block, E. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, **1980**, pp. 585–600.

⁴³⁹ See Belen'kii, L.I. in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, **1990**, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* **1962**, 12, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* **1962**, 62, 347.

⁴⁴⁰ See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* **1981**, 46, 831.

Reaction **19-61**), can also give the alkene if a hydrogen atom is present.⁴⁴¹ In most of the examples given, R can also be aryl. Other reagents⁴⁴² have also been used,⁴⁴³ including Sm in acetic acid for desulfurization of vinyl sulfones.⁴⁴⁴

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene (see **39**), followed by reduction to the corresponding alkane.



Thiophenes can also be desulfurized to alkenes ($\text{RCH}_2\text{CH}=\text{CHCH}_2\text{R}'$ from **43**) with a nickel boride catalyst prepared from nickel(II) chloride and NaBH_4 in methanol.⁴⁴⁵ It is possible to reduce just one SR group of a dithioacetal by treatment with borane–pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of AlCl_3 .⁴⁴⁶ Phenyl selenides (RSePh) can be reduced to RH with Ph_3SnH ⁴⁴⁷ and with nickel boride.⁴⁴⁸

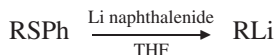
The exact mechanisms of the Raney nickel reactions are still in doubt, though they are probably of the free radical type.⁴⁴⁹ It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds; that is, the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the olefins and the failure to isolate any potential sulfur-containing intermediates.⁴⁵⁰

See Chapter 19 for other reduction reactions involving sulfur compounds.

OS IV, 638; V, 419; VI, 109, 581, 601. See also, OS VII, 124, 476.

14-28 Conversion of Sulfides to Organolithium Compounds

Lithio-de-phenylthio-substitution



Sulfides can be cleaved, with a phenylthio group replaced by a lithium,⁴⁵¹ by treatment with Li or lithium naphthalenide in THF.⁴⁵² Good yields have been obtained

⁴⁴¹ Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* **1963**, 28, 1443.

⁴⁴² For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, **1999**, pp. 53–60. See Luh, T.; Ni, Z. *Synthesis* **1990**, 89; Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* **1989**, 54, 4848.

⁴⁴³ See Shigemasa, Y.; Ogawa, M.; Sashiwa, H.; Saimoto, H. *Tetrahedron Lett.* **1989**, 30, 1277; Ho, K.M.; Lam, C.H.; Luh, T. *J. Org. Chem.* **1989**, 54, 4474.

⁴⁴⁴ Liu, Y.; Zhang, Y. *Org. Prep. Proceed. Int.* **2001**, 33, 376.

⁴⁴⁵ Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* **1972**, 2, 415.

⁴⁴⁶ Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* **1984**, 609.

⁴⁴⁷ Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc., Chem. Commun.* **1978**, 41.

⁴⁴⁸ Back, T.G. *J. Chem. Soc., Chem. Commun.* **1984**, 1417.

⁴⁴⁹ See Bonner, W.A.; Grimm, R.A. in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, NY, **1966**, pp. 35–71, 410–413. Also see Friend, C.M.; Roberts, J.T. *Acc. Chem. Res.* **1988**, 21, 394.

⁴⁵⁰ Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* **1962**, 40, 941.

⁴⁵¹ See Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, 22, 152.

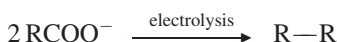
⁴⁵² Screttas, C.G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, 43, 1064; **1979**, 44, 713.

with R = primary, secondary, or tertiary alkyl, or allylic,⁴⁵³ and containing groups, such as double bonds or halogens. Dilithio compounds can be made from compounds containing two separated SPh groups, but it is also possible to replace just one SPh from a compound with two such groups on a single carbon, to give an α -lithio sulfide.⁴⁵⁴ The reaction has also been used to prepare α -lithio ethers and α -lithio organosilanes.⁴⁵¹ For some of these compounds, lithium 1-(dimethylamino)naphthalenide is a better reagent than either Li or lithium naphthalenide.⁴⁵⁵ The mechanism is presumably of the free radical type.

14.C.vi. Carbon as Leaving Group

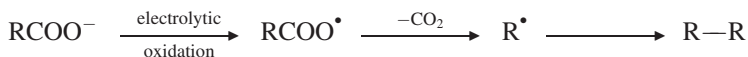
14-29 Decarboxylative Dimerization: The Kolbe Reaction

De-carboxylic-coupling



Electrolysis of carboxylate ions, results in decarboxylation and combination of the resulting radicals to give the coupling product R—R. This coupling reaction is called the *Kolbe Reaction* or the *Kolbe electrosynthesis*.⁴⁵⁶ It is used to prepare symmetrical R—R, where R is straight chained, since little or no yield is obtained when there is a branching. The reaction is not successful for R = aryl. Many functional groups may be present, though many others inhibit the reaction.⁴⁵⁶ Unsymmetrical R—R' have been made by coupling mixtures of acid salts. The *Kolbe reaction* has been done using solid-supported bases.⁴⁵⁷

A free radical mechanism is involved



There is much evidence⁴⁵⁸ for this mechanism, including side products (RH, alkenes) characteristic of free radical intermediates and the fact that electrolysis of acetate ion in the presence of styrene caused some of the styrene to polymerize to polystyrene (such polymerizations can be initiated by free radicals, see Sec. 15.B.i). Other side products (ROH, RCO₂R) are sometimes found, stemming from further oxidation of the radical R[•] to a carbocation R⁺.⁴⁵⁹

⁴⁵³ See Cohen, T.; Guo, B. *Tetrahedron* **1986**, 42, 2803.

⁴⁵⁴ See Cohen, T.; Sherbine, J.P.; Matz, J.R.; Hutchins, R.R.; McHenry, B.M.; Willey, P.R. *J. Am. Chem. Soc.* **1984**, 106, 3245; Ager, D.J. *J. Chem. Soc. Perkin Trans. 1* **1986**, 183.

⁴⁵⁵ See Cohen, T.; Matz, J.R. *Synth. Commun.* **1980**, 10, 311.

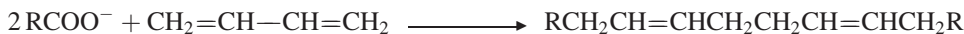
⁴⁵⁶ See Nuding, G.; Vögtle, F.; Danielmeier, K.; Steckhan, E. *Synthesis* **1996**, 71; Schäfer, H.J. *Top. Curr. Chem.* **1990**, 152, 91; *Angew. Chem. Int. Ed.* **1981**, 20, 911; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed, Wiley, NY, **1989**, pp. 238–253; Ebersson, L.; Utley, J.H.P. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, **1983**, pp. 435–462.

⁴⁵⁷ Kurihara, H.; Fuchigami, T.; Tajima, T. *J. Org. Chem.* **2008**, 73, 6888.

⁴⁵⁸ See Kraeutler, B.; Jaeger, C.D.; Bard, A.J. *J. Am. Chem. Soc.* **1978**, 100, 4903.

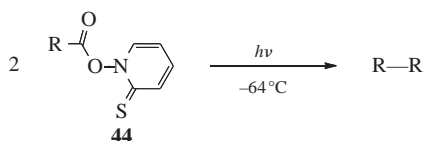
⁴⁵⁹ See Corey, E.J.; Bauld, N.L.; La Londe, R.T.; Casanova Jr, J.; Kaiser, E.T. *J. Am. Chem. Soc.* **1960**, 82, 2645.

When the reaction is conducted in the presence of 1,3-dienes, additive dimerization can occur.⁴⁶⁰



The radical R^\bullet adds to the conjugated system to give $\text{RCH}_2\text{CH}=\text{CHCH}_2^\bullet$, which dimerizes. Another possible product is $\text{RCH}_2\text{CH}=\text{CHCH}_2\text{R}$, from coupling of the two kinds of radicals.⁴⁶¹

In a nonelectrolytic reaction, which is limited to R = primary alkyl, the thiohydroxamic esters (**44**) give dimers when irradiated at -64°C in an Ar atmosphere.⁴⁶²

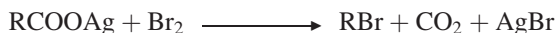


In another nonelectrolytic process, aryl acetic acids are converted to *vic*-diaryl compounds ($2\text{ArCR}_2\text{COOH} \rightarrow \text{ArCR}_2\text{CR}_2\text{Ar}$) by treatment with sodium persulfate ($\text{Na}_2\text{S}_2\text{O}_8$) and a catalytic amount of AgNO_3 .⁴⁶³ Photolysis of carboxylic acids in the presence of Hg_2F_2 leads to the dimeric alkane via decarboxylation.⁴⁶⁴ Both of these reactions involve dimerization of free radicals. In still another process, electron-deficient aromatic acyl chlorides are dimerized to biaryls ($\text{Ar}-\text{Ar}$) by treatment with a disilane R_3SiSiR_3 and a Pd catalyst.⁴⁶⁵

OS III, 401; V, 445, 463; VII, 181.

14-30 The Hunsdiecker Reaction

Bromo-de-carboxylation



Reaction of a silver salt of a carboxylic acid with bromine is called the *Hunsdiecker reaction*⁴⁶⁶ and is a method of decreasing the length of a carbon chain by one unit.⁴⁶⁷ The reaction is of wide scope, giving good results for *n*-alkyl R from 2 to 18 carbons and for many branched R too, producing primary, secondary, and tertiary bromides. Many functional groups may be present as long as they are not a substituted. The R group may also be aryl. However, if R contains unsaturation, the reaction seldom gives good results. Although bromine is the most often used halogen, chlorine, and iodine have also

⁴⁶⁰ Khrizolitova, M.A.; Mirkind, L.A.; Fioshin, M.Ya. *J. Org. Chem. USSR* **1968**, 4, 1640; Bruno, F.; Dubois, J.E. *Bull. Soc. Chim. Fr.* **1973**, 2270.

⁴⁶¹ See Schäfer, H.; Pistorius, R. *Angew. Chem. Int. Ed.* **1972**, 11, 841.

⁴⁶² Barton, D.H.R.; Bridon, D.; Fernandez-Picot, I.; Zard, S.Z. *Tetrahedron* **1987**, 43, 2733.

⁴⁶³ Fristad, W.E.; Klang, J.A. *Tetrahedron Lett.* **1983**, 24, 2219.

⁴⁶⁴ Habibi, M.H.; Farhadi, S. *Tetrahedron Lett.* **1999**, 40, 2821.

⁴⁶⁵ Krafft, T.E.; Rich, J.D.; McDermott, P.J. *J. Org. Chem.* **1990**, 55, 5430.

⁴⁶⁶ This reaction was first reported by the Russian composer-chemist Alexander Borodin: *Liebigs Ann. Chem.* **1861**, 119, 121.

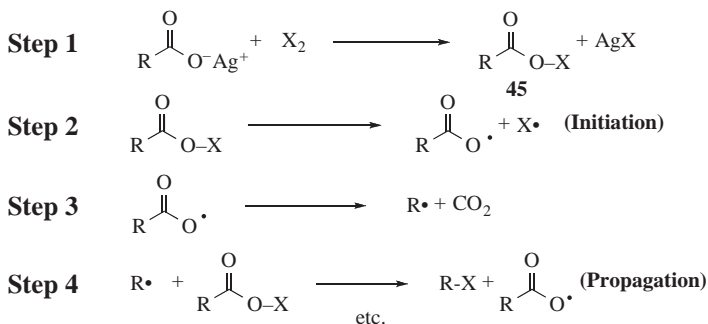
⁴⁶⁷ See Wilson, C.V. *Org. React.* **1957**, 9, 332; Johnson, R.G.; Ingham, R.K. *Chem. Rev.* **1956**, 56, 219. Also see, Naskar, D.; Chowdhury, S.; Roy, S. *Tetrahedron Lett.* **1998**, 39, 699.

been used. Catalytic Hunsdiecker reactions are known,⁴⁶⁸ and microwave enhancement has been employed.⁴⁶⁹

When iodine is the reagent, the ratio between the reactants is very important and determines the products. A 1:1 ratio of salt/iodine gives the alkyl halide, as above. A 2:1 ratio, however, gives the ester RCOOR. This is called the *Simonini Reaction* and is sometimes used to prepare carboxylic esters. The *Simonini reaction* can also be carried out with lead salts of acids.⁴⁷⁰ A more convenient way to perform the *Hunsdiecker Reaction* is by use of a mixture of the acid and mercuric oxide instead of the salt, since the silver salt must be very pure and dry and such pure silver salts are often not easy to prepare.⁴⁷¹

Other methods for accomplishing the conversion $\text{RCOOH} \rightarrow \text{RX}$ are⁴⁷² (1) treatment of thallium(I) carboxylates with bromine;⁴⁷³ (2) treatment of carboxylic acids with lead tetraacetate and halide ions (Cl^- , Br^- , or I^-);⁴⁷⁴ (3) reaction of the acids with lead tetraacetate and NCS, which gives tertiary and secondary chlorides in good yields, but is not good for R = primary alkyl or phenyl;⁴⁷⁵ (4) treatment of thiohydroxamic esters with CCl_4 , BrCCl_3 (which gives bromination), CHI_3 , or CH_2I_2 in the presence of a radical initiator;⁴⁷⁶ (5) photolysis of benzophenone oxime esters of carboxylic acids in CCl_4 ($\text{RCON}=\text{CPh}_2 \rightarrow \text{RCl}$).⁴⁷⁷ Alkyl fluorides can be prepared in moderate-to-good yields by treating carboxylic acids (RCOOH) with XeF_2 .⁴⁷⁸ This method works best for R = primary and tertiary alkyl, and benzylic. Aromatic and vinylic acids do not react.

The mechanism of the *Hunsdiecker reaction* is believed to be as follows:



⁴⁶⁸ Das, J.P.; Roy, S. *J. Org. Chem.* **2002**, *67*, 7861.

⁴⁶⁹ Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Synthesis* **2005**, 1319.

⁴⁷⁰ Bachman, G.B.; Kite, G.F.; Tuccarbasu, S.; Tullman, G.M. *J. Org. Chem.* **1970**, *35*, 3167.

⁴⁷¹ Cristol, S.J.; Firth, W.C. *J. Org. Chem.* **1961**, *26*, 280. See also, Meyers, A.I.; Fleming, M.P. *J. Org. Chem.* **1979**, *44*, 3405, and references cited therein.

⁴⁷² For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, **1999**, pp. 741–744.

⁴⁷³ Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* **1981**, 2608.

⁴⁷⁴ Kochi, J.K. *J. Am. Chem. Soc.* **1965**, *87*, 2500; *J. Org. Chem.* **1965**, *30*, 3265; Sheldon, R.A.; Kochi, J.K. *Org. React.* **1972**, *19*, 279, pp. 326–334, 390–399.

⁴⁷⁵ Becker, K.B.; Geisel, M.; Grob, C.A.; Kuhn, F. *Synthesis* **1973**, 493.

⁴⁷⁶ Barton, D.H.R.; Lacher, B.; Zard, S.Z. *Tetrahedron* **1987**, *43*, 4321; Stofer, E.; Lion, C. *Bull. Soc. Chim. Belg.* **1987**, *96*, 623; Della, E.W.; Tsanaktsidis, J. *Aust. J. Chem.* **1989**, *42*, 61.

⁴⁷⁷ Hasebe, M.; Tsuchiya, T. *Tetrahedron Lett.* **1988**, *29*, 6287.

⁴⁷⁸ Patrick, T.B.; Johri, K.K.; White, D.H.; Bertrand, W.S.; Mokhtar, R.; Kilbourn, M.R.; Welch, M.J. *Can. J. Chem.* **1986**, *64*, 138. For another method, see Grakauskas, V. *J. Org. Chem.* **1969**, *34*, 2446.

The first step is not a free radical process, and its actual mechanism is not known.⁴⁷⁹ Compound **45** is an acyl hypohalite and is presumed to be an intermediate, though it has never been isolated from the reaction mixture. Among the evidence for the mechanism is that optical activity at R is lost (except when a neighboring bromine atom is present, see Sec. 14.A.iv); if R is neopentyl, there is no rearrangement, which would certainly happen with a carbocation; and the side products, notably R-R, are consistent with a free radical mechanism. There is evidence that the *Simonini reaction* involves the same mechanism as the *Hunsdiecker reaction*, but that the alkyl halide formed then reacts with excess RCOOAg (Reaction **10-17**) to give the ester⁴⁸⁰ (see also, Reaction **19-12**).

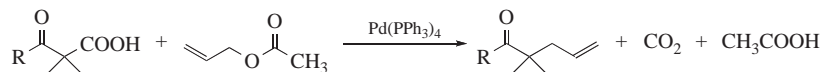
Vinyl carboxylic acids (conjugated acids) were shown to react with NBS and lithium acetate in aq acetonitrile, to give the corresponding vinyl bromide ($\text{C}=\text{C}-\text{CO}_2\text{H} \rightarrow \text{C}=\text{C}-\text{Br}$), using microwave irradiation.⁴⁸¹ A similar reaction was reported using Na_2MoO_4 , KBr and aq H_2O_2 .⁴⁸²

A related reaction reacts the sodium salt of an alkylsulfonic acid with thionyl chloride at 100 °C, to give the alkyl chloride.⁴⁸³

OS **III**, 578; **V**, 126; **VI**, 179; **75**, 124; **X**, 237. See also, OS **VI**, 403.

14-31 Decarboxylative Allylation

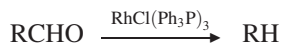
Allyl-de-carboxylation



The COOH group of a β -keto acid is replaced by an allylic group when the acid is treated with an allylic acetate and a Pd catalyst at room temperature.⁴⁸⁴ The reaction is successful for various substituted allylic groups. The less highly substituted end of the allylic group forms the new bond. Thus, both $\text{CH}_2=\text{CHCHMeOAc}$ and $\text{MeCH}=\text{CH}-\text{CH}_2\text{OAc}$ gave $\text{O}=\text{C}(\text{R})-\text{C}-\text{CH}_2\text{CH}-\text{CHMe}$ as the product.

14-32 Decarbonylation of Aldehydes and Acyl Halides

Carbonyl-extrusion



Aldehydes, both aliphatic and aromatic, can be decarbonylated⁴⁸⁵ by heating with a Rh catalyst⁴⁸⁶ or other catalysts (e.g., Pd).⁴⁸⁷ The compound $\text{RhCl}(\text{Ph}_3\text{P})_3$ is often called

⁴⁷⁹ When Br_2 reacts with aryl R, at low temperature in inert solvents, it is possible to isolate a complex containing both Br_2 and the silver carboxylate: see Bryce-Smith, D.; Isaacs, N.S.; Tumi, S.O. *Chem. Lett.* **1984**, 1471.

⁴⁸⁰ Bunce, N.J.; Murray, N.G. *Tetrahedron* **1971**, 27, 5323.

⁴⁸¹ Kuang, C.; Senboku, H.; Tokuda, M. *Synlett* **2000**, 1439.

⁴⁸² Sinha, J.; Layek, S.; Bhattacharjee, M.; Mandal, G.C. *Chem. Commun.* **2001**, 1916.

⁴⁸³ Carlsen, P.H.J.; Rist, Ø.; Lund, T.; Helland, I. *Acta Chem. Scand. B* **1995**, 49, 701.

⁴⁸⁴ Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* **1986**, 51, 421.

⁴⁸⁵ See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA **1987**, pp. 768–775; Baird, M.C. in Patai, S. *The Chemistry of Functional Groups, Supplement B* pt. 2, Wiley, NY, **1979**, pp. 825–857; Tsuji, J. in Wender, I.; Pino, P. *Organic Syntheses Via Metal Carbonyls*, Vol. 2, Wiley, NY, **1977**, pp. 595–654; Tsuji, J.; Ohno, K. *Synthesis* **1969**, 157; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, **1967**, pp. 239–247.

⁴⁸⁶ Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, 90, 99; Baird, C.W.; Nyman, C.J.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 348.

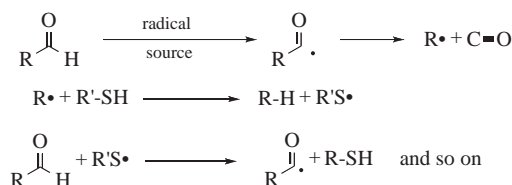
⁴⁸⁷ Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, **1973**, pp. 260–267.

Wilkinson's catalyst.⁴⁸⁸ In an older reaction aliphatic (but not aromatic) aldehydes are decarbonylated by heating with di-*tert*-butyl peroxide or other peroxides,⁴⁸⁹ usually in a solution containing a hydrogen donor, such as a thiol. The reaction has also been initiated with light, and thermally (without an initiator) by heating at $\sim 500^\circ\text{C}$.

Wilkinson's catalyst has also been reported to decarbonylate aromatic acyl halides at 180°C ($\text{ArCOX} \rightarrow \text{ArX}$).⁴⁹⁰ This reaction has been carried out with acyl iodides,⁴⁹¹ bromides, and chlorides. Aliphatic acyl halides that lack a hydrogen also give this reaction,⁴⁹² but if an α hydrogen is present, elimination takes place instead (Reaction 17-17). Aromatic acyl cyanides give aryl cyanides ($\text{ArCOCN} \rightarrow \text{ArCN}$).⁴⁹³ Aromatic acyl chlorides and cyanides can also be decarbonylated with Pd catalysts.⁴⁹⁴

It is possible to decarbonylate acyl halides in another way, to give alkanes ($\text{RCOCl} \rightarrow \text{RH}$). This is done by heating the substrate with tripropylsilane (Pr_3SiH) in the presence of *tert*-butyl peroxide.⁴⁹⁵ Yields are good for R = primary or secondary alkyl and poor for R = tertiary alkyl or benzylic. There is no reaction when R = aryl. (See also, the decarbonylation $\text{ArCOCl} \rightarrow \text{Ar}-\text{Ar}$ mentioned in Reaction 14-29.)

The mechanism of the peroxide- or light-induced reaction seems to be as follows (in the presence of thiols).⁴⁹⁶



The reaction of aldehydes with *Wilkinson's catalyst* goes through complexes of the form 46 and 47, which have been trapped.⁴⁹⁷ The reaction has been shown to give retention of configuration at a chiral R ,⁴⁹⁸ and deuterium labeling demonstrates that the reaction is

⁴⁸⁸ For a review of this catalyst, see Jardine, F.H. *Prog. Inorg. Chem.* **1981**, 28, 63.

⁴⁸⁹ See Vinogradov, M.G.; Nikishin, G.I. *Russ. Chem. Rev.* **1971**, 40, 916; Schubert, W.M.; Kintner, R.R. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 711–735.

⁴⁹⁰ Kampmeier, J.A.; Rodehorst, R.; Philip Jr., J.B. *J. Am. Chem. Soc.* **1981**, 103, 1847.

⁴⁹¹ Blum, J.; Rosenman, H.; Bergmann, E.D. *J. Org. Chem.* **1968**, 33, 1928.

⁴⁹² Tsuji, J.; Ohno, K. *Tetrahedron Lett.* **1966**, 4713; *J. Am. Chem. Soc.* **1966**, 88, 3452.

⁴⁹³ Blum, J.; Oppenheimer, E.; Bergmann, E.D. *J. Am. Chem. Soc.* **1967**, 89, 2338.

⁴⁹⁴ Murahashi, S.; Naota, T.; Nakajima, N. *J. Org. Chem.* **1986**, 51, 898.

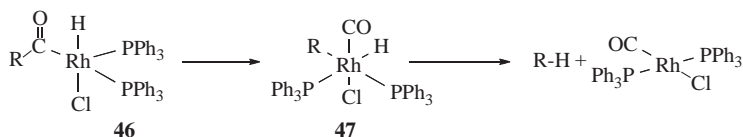
⁴⁹⁵ Billingham, N.C.; Jackson, R.A.; Malek, F. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1137.

⁴⁹⁶ Berman, J.D.; Stanley, J.H.; Sherman, V.W.; Cohen, S.G. *J. Am. Chem. Soc.* **1963**, 85, 4010. See Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, 130, 5206.

⁴⁹⁷ Kampmeier, J.A.; Harris, S.H.; Mergelsberg, I. *J. Org. Chem.* **1984**, 49, 621.

⁴⁹⁸ Walborsky, H.M.; Allen, L.E. *J. Am. Chem. Soc.* **1971**, 93, 5465. See also, Tsuji, J.; Ohno, K. *Tetrahedron Lett.* **1967**, 2173.

intramolecular: RCOD give RD.⁴⁹⁹ Free radicals are not involved.⁵⁰⁰ The mechanism with acyl halides appears to be more complicated.⁵⁰¹



For aldehyde decarbonylation by an electrophilic mechanism, see Reaction **11-34**.

⁴⁹⁹ Walborsky, H.M.; Allen, L.E. *J. Am Chem. Soc.* **1971**, 93, 5465. See, however, Baldwin, J.E.; Bardenm, T.C.; Pugh, R.L.; Widdison, W.C. *J. Org. Chem.* **1987**, 52, 3303.

⁵⁰⁰ Kampmeier, J.A.; Harris, S.H.; Wedegaertner, D.K. *J. Org. Chem.* **1980**, 45, 315.

⁵⁰¹ Kampmeier, J.A.; Liu, T. *Organometallics* **1989**, 8, 2742

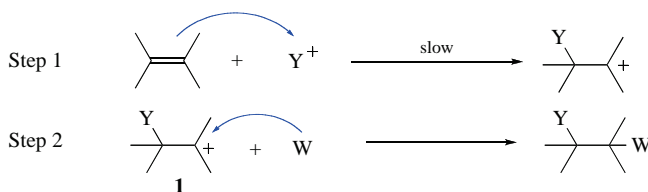
Addition to Carbon–Carbon Multiple Bonds

There are four fundamental ways in which addition to a double or triple bond can take place. Three of these are two-step processes, with initial attack by a nucleophile, or attack upon an electrophile or a free radical. The second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity. In the fourth type of mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous (concerted). Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions. Some of the reactions in this chapter can take place by all four mechanistic types.

15.A. MECHANISMS

15.A.i. Electrophilic Addition¹

In this mechanism, a positive species approaches the double or triple bond and in the first step forms a bond by donation of the π pair of electrons² to the electrophilic species to form a σ bond:

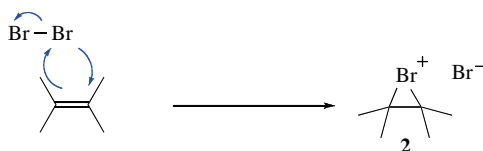


The IUPAC designation for this mechanism is $A_E + A_N$ (or $A_H + A_N$ if $Y^+ = H^+$). As in electrophilic substitution (Sec. 11.A.i), Y need not actually be a positive ion, but can be the

¹ See de la Mare, P.B.D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*, 2nd ed., Elsevier, NY, **1982**. For reviews, see Schmid, G.H. in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, **1989**, pp. 679–731; Schmid, G.H.; Garratt, D.G. in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 1, pt. 2, Wiley, NY, **1977**, pp. 725–912; Freeman, F. *Chem. Rev.* **1975**, 75, 439.

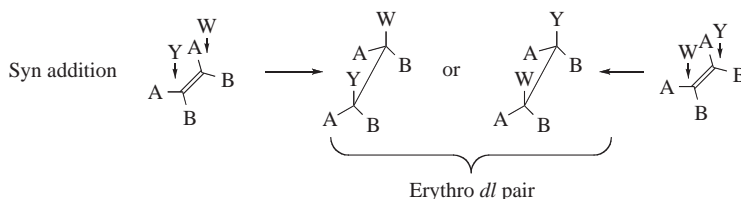
² See Mayr, H.; Kempf, B.; Ofial, A.R. *Acc. Chem. Res.* **2003**, 36, 66.

positive end of a dipole or an induced dipole, with the negative part breaking off either during the first step or shortly after. The second step is a combination of **1** with a species carrying an electron pair and often bearing a negative charge. This step is the same as the second step of the S_N1 mechanism. Not all electrophilic additions follow the simple mechanism given above. In many bromination reactions it is fairly certain that **1**, if formed at all, very rapidly cyclizes to a bromonium ion (**2**):

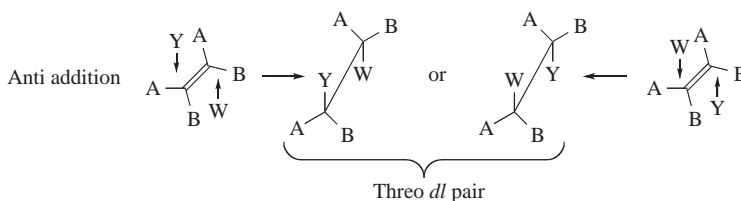


This intermediate is similar to those encountered in the neighboring-group mechanism of nucleophilic substitution (see Sec. 10.C). The attack of W: on an intermediate like **2** is an S_N2 step. Whether the intermediate is **1** or **2**, the mechanism is called Ad_E2 (electrophilic addition, bimolecular).

The most useful type of information for investigating the mechanism of addition to a double bond, is perhaps, the stereochemistry of the reaction.³ The two carbons of the double bond and the four atoms immediately attached to them are all in a plane (Sec. 1.D); there are thus three possibilities. Both Y and W may enter from the same side of the plane, in which case the addition is stereospecific and syn; they may enter from opposite sides for stereospecific anti addition; or the reaction may be nonstereospecific. In order to determine which of these possibilities is occurring in a given reaction, the following type of experiment is often done: YW is added to the *cis* and *trans* isomers of an alkene of the form $ABC=CBA$. Using the *cis*-alkene as an example, if the addition is syn, the product will be the erythro *dl* pair, because each carbon has a 50% chance of being attacked by Y:



On the other hand, if the addition is anti, the threo *dl* pair will be formed:

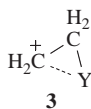


Of course, the *trans* isomer will give the opposite results: the threo pair if the addition is syn and the erythro pair if it is anti. These diastereomers have different physical properties. In the special case, where $Y = W$ (as in the addition of Br_2), the “erythro pair” is a meso

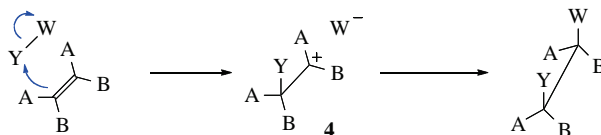
³ See Fahey, R.C. *Top. Stereochem.* **1968**, 3, 237; Bartlett, P.A. *Tetrahedron* **1980**, 36, 2, pp. 3–15.

compound. In addition to triple-bond compounds of the type $AC\equiv CA$, syn addition results in a *cis*-alkene and anti addition in a *trans*-alkene. By the definition given in Section 4.N, addition to triple bonds cannot be stereospecific, although it can be, and often is, stereoselective.

It is easily seen that in reactions involving cyclic intermediates like **2**, addition must be anti, since the second step is an S_N2 step and must occur from the rear. It is not so easy to predict the stereochemistry for reactions involving **1**. If **1** has a relatively long life, the addition should be nonstereospecific, since there will be free rotation about the single bond. In addition, the carbocation is planar, so there is no facial bias for nucleophilic attack. On the other hand, if there is some factor that maintains the configuration, the group W may come in from the same *or* the opposite side, depending on the circumstances. For example, the positive charge might be stabilized by an attraction for Y that does not involve a full bond (see **3**). In such a case, Y is said to stabilize the positive center via back-donation.

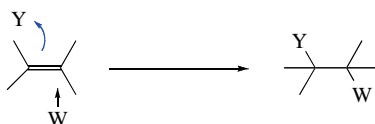


Such stabilization usually leads to anti attack of the second group. This contrasts with a circumstance that would favor syn addition: Formation of an ion pair (**4**) after the addition of Y^4 :



Since W is already on the same side of the plane as Y, collapse of the ion pair leads to syn addition.

Another possibility is that anti addition might, at least in some cases, be caused by the operation of a mechanism in which attack by W and Y are essentially *simultaneous*, but from opposite sides:

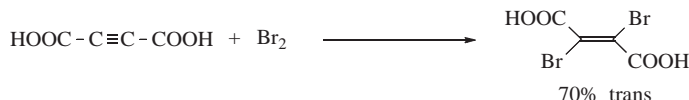


This mechanism, called the Ad_E3 mechanism (*termolecular addition*, IUPAC A_NA_E),⁵ has the disadvantage that three molecules must come together in the transition state. Note that it is the reverse of the $E2$ mechanism for elimination, for which the transition state is known to possess this geometry (Sec. 17.A.i).

⁴ Heasley, G.E.; Bower, T.R.; Dougherty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* **1980**, *45*, 5150.

⁵ See Roberts, R.M.G. *J. Chem. Soc. Perkin Trans. 2*, **1976**, 1374; Pasto, D.J.; Gadberry, J.F. *J. Am. Chem. Soc.* **1978**, *100*, 1469; Naab, P.; Staab, H.A. *Chem. Ber.* **1978**, *111*, 2982.

There is much evidence that when an alkene attacks Br^+ (or a carrier of it), bromonium ion **2** is usually the intermediate and the addition is anti, so the reaction is diastereospecific. Such ions have also been isolated in reactions involving addition of a Br^+ species to a double bond.⁶ Treatment of maleic acid with bromine gave the *dl* pair of 2,3-dibromosuccinic acid, for example, while fumaric acid (the *trans* isomer) gave the meso compound.⁷ Many similar experiments have been performed with similar results. Bromination of dicarboxyacetylene gave 70% of the *trans* isomer.⁸



There is other evidence for mechanisms involving **2**. As seen in Section 10.C, bromonium ions have been isolated in stable solutions in nucleophilic substitution reactions involving bromine as a neighboring group. The following is further evidence. If the two bromines approach the double bond from opposite sides, it is very unlikely that they could come from the same bromine molecule. This means that if the reaction is performed in the presence of nucleophiles, some of these will compete in the second step with the bromide liberated from the bromine. It has been found, indeed, that treatment of ethylene with bromine in the presence of chloride ions gives some 1-chloro-2-bromoethane along with the dibromoethane.⁹ Similar results are found when the reaction is carried out in the presence of water (Reaction **15-40**) or of other nucleophiles.¹⁰ *Ab initio* MO studies show that **2** is more stable than its open isomer **1** ($\text{Y} = \text{Br}$).¹¹ There is evidence that formation of **2** is reversible.¹²

However, a number of examples have been found where addition of bromine is not stereospecifically anti. For example, the addition of Br_2 to *cis*- and *trans*-1-phenylpropenes in CCl_4 was nonstereospecific.¹³ Furthermore, the stereospecificity of bromine addition to stilbene depends on the dielectric constant of the solvent. In solvents of low dielectric constant, the addition was 90–100% anti, but with an increase in dielectric constant, the reaction became less stereospecific, until at a dielectric constant of ~ 35 , the addition was completely nonstereospecific.¹⁴ Likewise in the case of triple bonds, stereoselective anti addition was found in bromination of 3-hexyne, but both *cis* and *trans* products were obtained in bromination of phenylacetylene.¹⁵ These results indicate that a bromonium ion

⁶ Slebocka-Tilk, H.; Ball, R.G.; Brown, R.S. *J. Am. Chem. Soc.* **1985**, *107*, 4504.

⁷ Fischer, E. *Liebigs Ann. Chem.* **1911**, 386, 374; McKenzie, A. *Proc. Chem. Soc.* **1911**, 150; *J. Chem. Soc.* **1912**, 101, 1196.

⁸ Michael, A. *J. Prakt. Chem.* **1892**, 46, 209.

⁹ Francis, A.W. *J. Am. Chem. Soc.* **1925**, 47, 2340.

¹⁰ See Zefirov, N.S.; Koz'min, A.S.; Dan'kov, Yu.V.; Zhdankin, V.V.; Kirin, V.N. *J. Org. Chem. USSR* **1984**, 20, 205.

¹¹ Hamilton, T.P.; Schaefer, III, H.F. *J. Am. Chem. Soc.* **1990**, 112, 8260.

¹² Ruasse, M.; Motallebi, S.; Galland, B. *J. Am. Chem. Soc.* **1991**, 113, 3440; Bellucci, G.; Bianchini, R.; Chiappe, C.; Brown, R.S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* **1991**, 113, 8012; Bennet, A.J.; Brown, R.S.; McClung, R.E.D.; Klobukowski, M.; Aarts, G.H.M.; Santarsiero, B.D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.* **1991**, 113, 8532.

¹³ Fahey, R.C.; Schneider, H. *J. Am. Chem. Soc.* **1968**, 90, 4429. See also, Rolston, J.H.; Yates, K. *J. Am. Chem. Soc.* **1969**, 91, 1469, 1477, 1483.

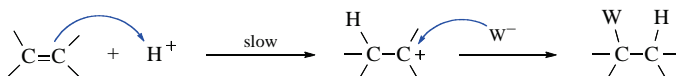
¹⁴ Ruasse, M.; Dubois, J.E. *J. Am. Chem. Soc.* **1975**, 97, 1977; Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F. *J. Org. Chem.* **1990**, 55, 4094.

¹⁵ Pincock, J.A.; Yates, K. *Can. J. Chem.* **1970**, 48, 3332.

is not formed where the open cation can be stabilized in other ways (e.g., addition of Br^+ to 1-phenylpropene gives the ion $\text{PhC}^+\text{HCHBrCH}_3$, which is a relatively stable benzylic cation). In addition, there is probably a spectrum of mechanisms between complete bromonium ion (**2**, no rotation) formation and completely open-cation (**1**, free rotation) formation, with partially bridged bromonium ions (**3**, restricted rotation) in between.¹⁶ Previously seen cases (Sec. 10.C.i, category 4) showed that cations require more stabilization from outside sources as they become intrinsically less stable themselves.¹⁷ Further evidence for the open cation mechanism where aryl stabilization is present was reported in an isotope effect study of Br_2 addition to $\text{ArCH}=\text{CHCHAr}'$ ($\text{Ar} = p$ -nitrophenyl, $\text{Ar}' = p$ -tolyl). The ^{14}C isotope effect for one of the double-bond carbons (the one closer to the NO_2 group) was considerably larger than for the other one.¹⁸

When the π bond of an alkene attacks Cl^+ ,¹⁹ I^+ ,²⁰ or RS^+ ,²¹ the result is similar to that when the electrophile is Br^+ ; there is a spectrum of mechanisms between cyclic intermediates and open cations. As might be expected from the discussion in Section 10.C, iodonium ions compete with open carbocations more effectively than bromonium ions, while chloronium ions compete less effectively. There is kinetic and spectral evidence that at least in some cases (e.g., in the addition of Br_2 or ICl), the electrophile forms a π complex with the alkene before a covalent bond is formed.²² There is evidence for β -chloro and β -bromocarbenium ions in some reactions.²³

When the electrophile is a proton,²⁴ a cyclic intermediate is not possible, and the mechanism is the simple $\text{A}_\text{H} + \text{A}_\text{N}$ process shown before



This is an $\text{A-S}_\text{E}2$ mechanism (see Reaction 10-6). There is a great deal of evidence²⁵ for it, including:

1. The reaction is general acid, not specific acid catalyzed, implying rate-determining proton transfer from the acid to the double bond.²⁶

¹⁶ Cadogan, J.I.G.; Cameron D.K.; Gosney, I.; Highcock, R.M.; Newlands, S.F. *J. Chem. Soc., Chem. Commun.* **1985**, 1751. For a review, see Ruasse, M. *Acc. Chem. Res.* **1990**, 23, 87.

¹⁷ See Naae, D.G. *J. Org. Chem.* **1980**, 45, 1394.

¹⁸ Kokil, P.B.; Fry, A. *Tetrahedron Lett.* **1986**, 27, 5051.

¹⁹ Fahey, R.C. *Top. Stereochem.* **1968**, 3, 237, pp. 273–277.

²⁰ Hassner, A.; Boerwinkle, F.; Levy, A.B. *J. Am. Chem. Soc.* **1970**, 92, 4879.

²¹ Capozzi, G.; Modena, G. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, **1985**, pp. 246–298; Dittmer, D.C.; Patwardhan, B.H. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, **1981**, pp. 387–412; Capozzi, G.; Lucchini, V.; Modena, G.; *Rev. Chem. Intermed.* **1979**, 2, 347; Schmid, G.H. *Top. Sulfur Chem.* **1977**, 3, 102; Mueller, W.H. *Angew. Chem. Int. Ed.* **1969**, 8, 482. The specific nature of the three-membered sulfur-containing ring is in dispute; see Smit, W.A.; Zefirov, N.S.; Bodrikov, I.V.; Krimer, M.Z. *Acc. Chem. Res.* **1979**, 12, 282; Schmid, G.H.; Garratt, D.G.; Dean, C.L. *Can. J. Chem.* **1987**, 65, 1172; Schmid, G.H.; Strukelj, M.; Dalipi, S. *Can. J. Chem.* **1987**, 65, 1945.

²² See Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F.; Ambrosetti, R.; Brown, R.S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* **1989**, 111, 2640.

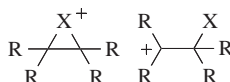
²³ Ohta, B.K.; Hough, R.E.; Jeffrey W.; Schubert, J.W. *Org. Lett.* **2007**, 9, 2317.

²⁴ See Sergeev, G.B.; Smirnov, V.V.; Rostovshchikova, T.N. *Russ. Chem. Rev.* **1983**, 52, 259.

²⁵ Also see Hampel, M.; Just, G.; Pisanenko, D.A.; Pritzkow, W. *J. Prakt. Chem.* **1976**, 318, 930; Allen, A.D.; Tidwell, T.T. *J. Am. Chem. Soc.* **1983**, 104, 3145.

²⁶ Schubert, W.M.; Keeffe, J.R. *J. Am. Chem. Soc.* **1972**, 94, 559; Chiang, Y.; Kresge, A.J. *J. Am. Chem. Soc.* **1985**, 107, 6363.

2. The existence of open carbocation intermediates is supported by the contrast in the pattern of alkyl substituent effects²⁷ with that found in brominations, where cyclic intermediates are involved. In the latter case, substitution of alkyl groups on $\text{H}_2\text{C}=\text{CH}_2$ causes a cumulative rate acceleration

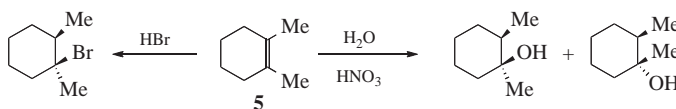


until all four hydrogen atoms have been replaced by alkyl groups, because each group helps to stabilize the positive charge.²⁸ In addition of HX, the effect is not cumulative. Replacement of the two hydrogen atoms on one carbon causes great rate increases (primary \rightarrow secondary \rightarrow tertiary carbocation), but additional substitution on the other carbon produces little or no acceleration.²⁹ This is evidence for open cations when a proton is the electrophile.³⁰

3. Open carbocations are prone to rearrange (Chapter 18). Many rearrangements have been found to accompany additions of HX and H_2O .³¹

It may also be recalled that vinylic ethers react with proton donors in a similar manner (see Reaction 10-6).

The stereochemistry of HX addition is varied. Examples are known of predominant syn, anti, and nonstereoselective addition. It was found that treatment of 1,2-dimethylcyclohexene (**5**) with HBr gave predominant anti addition,³² while addition of water to **5** gave equal amounts of the cis and trans alcohols:³³



On the other hand, addition of DBr to acenaphthylene and to indene and 1-phenylpropene gave predominant syn addition, as shown:³⁴



In fact, it has been shown that changing the reaction conditions can control the stereoselectivity of HCl addition. Addition of HCl to **5** in CH_2Cl_2 at -98°C

²⁷ Schmid, G.H.; Garratt, D.G. *Can. J. Chem.* **1973**, *51*, 2463.

²⁸ See Anantakrishnan, S.V.; Ingold, C.K. *J. Chem. Soc.* **1935**, 1396; Swern, D. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, **1971**, pp. 451–454; Nowlan, V.J.; Tidwell, T.T. *Acc. Chem. Res.* **1977**, *10*, 252.

²⁹ See Bartlett, P.D.; Sargent, G.D. *J. Am. Chem. Soc.* **1965**, *87*, 1297 and are references cited therein.

³⁰ See Mayr, H.; Pock, R. *Chem. Ber.* **1986**, *119*, 2473.

³¹ See Stammann, G.; Griesbaum, K. *Chem. Ber.* **1980**, *113*, 598.

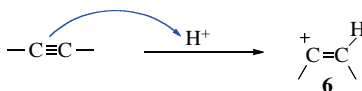
³² Hammond, G.S.; Nevitt, T.D. *J. Am. Chem. Soc.* **1954**, *76*, 4121; See also, Pasto, D.J.; Meyer, G.R.; Lepeska, B. *J. Am. Chem. Soc.* **1974**, *96*, 1858.

³³ Collins, C.H.; Hammond, G.S. *J. Org. Chem.* **1960**, *25*, 911.

³⁴ See Heasley, G.E.; Bower, T.R.; Dougherty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* **1980**, *45*, 5150.

gave predominantly syn addition, while in ethyl ether at 0°C, the addition was mostly anti.³⁵

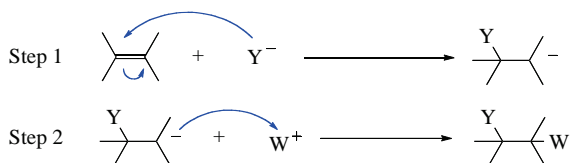
Addition of HX to triple bonds has the same mechanism, although the intermediate in this case is a vinylic cation (**6**).³⁶



In all these cases (except for the Ad_E3 mechanism), it was assumed that formation of the intermediate (**1**, **2**, or **3**) is the slow step and attack by the nucleophile on the intermediate is rapid. This finding is probably true in most cases. However, some additions have been found in which the second step is rate determining.³⁷

15.A.ii. Nucleophilic Addition³⁸

In the first step of nucleophilic addition, a nucleophile donates a pair of electrons to one carbon atom of the double or triple bond, creating a carbanion, which reacts with a positive species in the second step:



This mechanism is the same as the simple electrophilic one shown in Section 15.A.i except that the charges are reversed (IUPAC A_N + A_E or A_N + A_H). When the alkene contains a good leaving group (as defined for nucleophilic substitution), substitution is a side reaction (this is nucleophilic substitution at a vinylic substrate, see Sec. 10.F).

In the special case of addition of HY to a substrate of the form —C=C—Z, where Z = CHO, COR³⁹ (including quinones⁴⁰), CO₂R, CONH₂, CN, NO₂, SOR, 2R,⁴¹ and so on, addition nearly always follows a nucleophilic mechanism,⁴² with Y[−] bonding with the carbon *away* from the Z group, for example,

³⁵ Becker, K.B.; Grob, C.A. *Synthesis* **1973**, 789. See also, Marcuzzi, F.; Melloni, G.; Modena, G. *Tetrahedron Lett.* **1974**, 413; Naab, P.; Staab, H.A. *Chem. Ber.* **1978**, *111*, 2982.

³⁶ See Rappoport, Z. *React. Intermed. (Plenum)* **1983**, *3*, 427, pp. 428–440; Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, **1979**, pp. 24–151; Stang, P.J. *Prog. Phys. Org. Chem.* **1973**, *10*, 205; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* **1971**, *9*, 185, pp. 187–231.

³⁷ See Bellucci, G.; Berti, G.; Ingrosso, G.; Mastroilli, E. *Tetrahedron Lett.* **1973**, 3911.

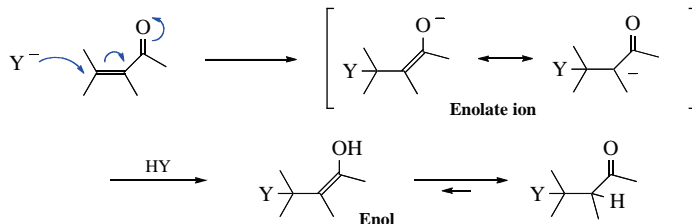
³⁸ Patai, S.; Rappoport, Z. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, **1964**, pp. 469–584.

³⁹ See in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, **1989**, the articles by Boyd, G.V. pp. 281–315; Duval, D.; Gèribaldi, S. pp. 355–469.

⁴⁰ See Kuttyrev, A.A.; Moskva, V.V. *Russ. Chem. Rev.* **1991**, *60*, 72; Finley, K.T. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, **1988**, pp. 537–717, see pp. 539–589; Finley, K.T. in Patai, S. *The Chemistry of the Quinonoid Compounds*, pt. 2, Wiley, NY, **1974**, pp. 877–1144.

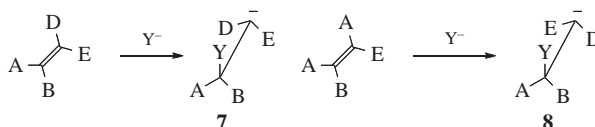
⁴¹ See Simpkins, N.S. *Tetrahedron* **1990**, *46*, 6951; Fuchs, P.L.; Braish, T.F. *Chem. Rev.* **1986**, *86*, 903.

⁴² See Bernasconi, C.F. *Tetrahedron* **1989**, *45*, 4017.



After the reaction with HY, the product is a resonance-stabilized enolate anion. Subsequent protonation of the enolate ion is probably at the oxygen to give an enol, which tautomerizes to the ketone (Sec. 2.N.i). Although the net result of the reaction is addition to a carbon-carbon double bond, the *mechanism* is 1,4-nucleophilic addition to the $\text{C}=\text{C}-\text{C}=\text{O}$ (or similar) system and is thus very similar to the mechanism of addition to carbon-oxygen double and similar bonds (see Chapter 16). This mechanism is essentially that of the *Michael reaction* discussed in Reaction 15-24, and such reactions are often called *Michael reactions* or *Michael-type reactions*. When Z is CN or a $\text{C}=\text{O}$ group, it is also possible for Y^- to attack C of the cyano or carbonyl, which sometimes competes. When it happens, it is called 1,2-addition (see nucleophilic acyl addition in Chapter 16). 1,4-Addition to these substrates is also known as *conjugate addition*. Attack of the Y^- ion at the 3 position is very difficult, since the resulting carbanion would have no resonance stabilization.⁴³ Systems of the type $\text{C}=\text{C}-\text{C}=\text{C}-\text{Z}$ can give 1,2-, 1,4-, or 1,6-addition.⁴⁴ *Michael-type reactions* are reversible, and compounds of the type $\text{YCH}_2\text{CH}_2\text{Z}$ can often be decomposed to YH and $\text{CH}_2=\text{CHZ}$ by heating, either with or without alkali.

If the mechanism for nucleophilic addition is the simple carbanion mechanism outlined above for an alkene, the addition should be nonstereospecific, although it might well be stereoselective (see Sec. 4.N for the distinction). For example, the (*E*) and (*Z*) forms of an alkene $\text{ABC}=\text{CDE}$ would give **7** and **8**. If the carbanion has



even a short lifetime, **7** and **8** will assume the most favorable conformation before the reaction with W. This is of course the same for both, and reaction with W will give the same product. This will be one of two possible diastereomers, so the reaction will be diastereoselective; but since the *cis* and *trans* isomers do not give rise to different isomers, it will not be diastereospecific. Unfortunately, this prediction has not been tested on open-chain alkenes. Except for *Michael-type substrates*, the stereochemistry of nucleophilic addition to double bonds has been studied only in cyclic systems, where only the *cis* isomer exists. In these cases, the reaction has been shown to be stereoselective, with *syn* addition reported in some cases⁴⁵ and *anti* addition in others.⁴⁶ When the reaction is performed on a *Michael-type substrate* ($\text{C}=\text{C}-\text{Z}$) the hydrogen does not arrive at the carbon directly, but only

⁴³ See Barbot, F.; Kadib-Elban, A.; Miginiac, P. *J. Organomet. Chem.* **1988**, 345, 239.

⁴⁴ See, however, Klumpp, G.W.; Mierop, A.J.C.; Vrielink, J.J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* **1985**, 107, 6740.

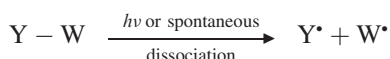
⁴⁵ Truce, W.E.; Levy, A.J. *J. Org. Chem.* **1963**, 28, 679.

⁴⁶ Truce, W.E.; Levy, A.J. *J. Am. Chem. Soc.* **1961**, 83, 4641; Zefirov, N.S.; Yur'ev, Yu.K.; Prikazchikova, L.P.; Bykhovskaya, M.Sh. *J. Gen. Chem. USSR* **1963**, 33, 2100.

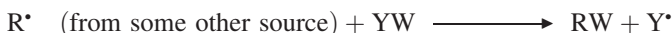
through a tautomeric equilibrium. The product naturally assumes the most thermodynamically stable configuration, without relation to the direction of original attack of Y. In one such case (the addition of EtOD and of Me₃CSD to *trans*-MeCH=CHCOOEt), predominant anti addition was found. There is evidence that the stereoselectivity here results from the final protonation of the enolate, and not from the initial attack.⁴⁷ For obvious reasons, additions to triple bonds cannot be stereospecific. As with electrophilic additions, nucleophilic additions to triple bonds are usually stereoselective and anti,⁴⁸ although syn addition⁴⁹ and nonstereoselective addition⁵⁰ have also been reported.

15.A.iii. Free Radical Addition

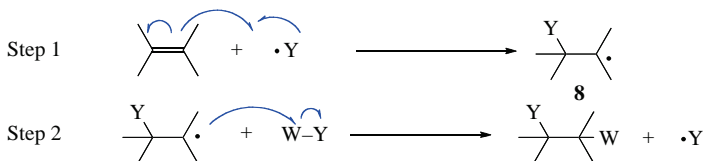
The mechanism of free radical addition⁵¹ follows the pattern discussed in Section 14.A.i. The method of principal component analysis has been used to analyze polar and enthalpic effects in radical addition reactions.⁵² A radical is generated by



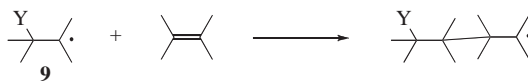
or



For subsequent reaction with an alkene, propagation occurs by



Step 2 is an abstraction (an atom transfer), so W is nearly always univalent, either hydrogen or halogen (Sec. 14.B.i). Termination of the chain can occur in any of the ways discussed in Section 14.A.i. If **9** adds to another alkene molecule, a dimer is formed. This can add to still another alkene unit, and chains, long or short, may be built up. This is the mechanism of free radical polymerization. Short polymeric molecules (called *telomers*), formed in this manner, are often troublesome side products in free radical addition reactions.



⁴⁷ Mohrig, J.R.; Fu, S.S.; King, R.W.; Warnet, R.; Gustafson, G. *J. Am. Chem. Soc.* **1990**, *112*, 3665.

⁴⁸ See Truce, W.E.; Tichenor, G.J.W. *J. Org. Chem.* **1972**, *37*, 2391.

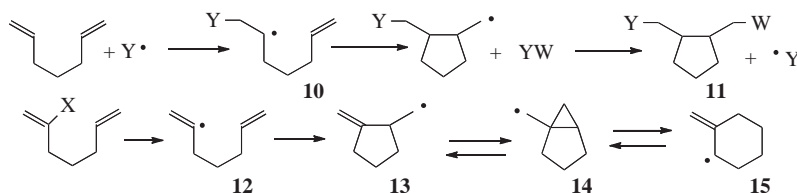
⁴⁹ Hayakawa, K.; Kamikawaji, Y.; Wakita, A.; Kanematsu, K. *J. Org. Chem.* **1984**, *49*, 1985.

⁵⁰ Truce, W.E.; Brady, D.G. *J. Org. Chem.* **1966**, *31*, 3543; Prilezhaeva, E.N.; Vasil'ev, G.S.; Mikhaleshvili, I.L.; Bogdanov, V.S. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1970**, 1820.

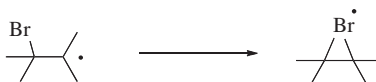
⁵¹ Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, **1970**; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry* Cambridge University Press, London, **1974**; Pyor, W.A. *Free Radicals* McGraw-Hill, NY, **1965**. See Giese, B. *Rev. Chem. Intermed.* **1986**, *7*, 3; *Angew. Chem. Int. Ed.* **1983**, *22*, 753; Abell, P.I. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, **1973**, pp. 63–112; Minisci, F. *Acc. Chem. Res.* **1975**, *8*, 165.

⁵² Héberger, K.; Lopata, A. *J. Chem. Soc. Perkin Trans. 2*, **1995**, 91.

When free radicals are added to 1,5- or 1,6-dienes, the initially formed radical (**10**) can add intramolecularly to the other bond, leading to a cyclic product (**11**).⁵³ When the radical is generated from a precursor that gives vinyl radical **12**, however, cyclization leads to **13**, which is in equilibrium with cyclopropylcarbinyl radical **14** via a 5-exo-trig reaction.⁵⁴ A 6-endo-trig reaction (Sec. 6.E) leads to **15**, but unless there are perturbing substituent effects, cyclopropanation should be the major process. Radicals of type **10**, generated in other ways, also undergo these cyclizations. Both five- and six-membered rings can be formed (Sec. 15.B.i).



The free radical addition mechanism just outlined predicts that the addition should be nonstereospecific, at least if **9** has any, but an extremely short lifetime. However, the reactions may be stereoselective, for reasons similar to those discussed above for nucleophilic addition to alkenes. A few free radical additions are selective. For example, addition of HBr to 1-bromocyclohexene is regioselective in that it gave only *cis*-1,2-dibromocyclohexane and none of the *trans* isomer (anti addition),⁵⁵ and propyne (at -78 to -60°C) gave only *cis*-1-bromopropene (anti addition), making it stereoselective.⁵⁶ Selectivity was observed in radical cyclization reactions of functionalized alkenes, which proceeded via a *trans*-ring closure.⁵⁷ The most important case is probably addition of HBr to 2-bromo-2-butene under free radical conditions at -80°C . Under these conditions, the *cis* isomer gave 92% of the *meso* product, while the *trans* isomer gave mostly the *dl* pair.⁵⁸ This stereospecificity disappeared at room temperature, where both alkenes gave the same mixture of products ($\sim 78\%$ of the *dl* pair and 22% of the *meso* compound), so the addition was still stereoselective, but no longer stereospecific. The stereospecificity at low temperatures is probably caused by a stabilization of the intermediate radical through the formation of a bridged bromine radical, of the type mentioned in Section 14.A.iv:



This species is similar to the bromonium ion (**2**) that is responsible for stereospecific anti addition in the electrophilic mechanism. Further evidence for the existence of such bridged

⁵³ RajanBabu, T.V. *Acc. Chem. Res.* **1991**, 24, 139; Beckwith, A.L.J. *Rev. Chem. Intermed.* **1986**, 7, 143; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, **1986**, pp. 141–209; Surzur, J. *React. Intermed. (Plenum)* **1982**, 2, 121–295; Julia, M. *Acc. Chem. Res.* **1972**, 4, 386; *Pure Appl. Chem.* **1974**, 40, 553; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, 46, 1385.

⁵⁴ Denis, R.C.; Rancourt, J.; Ghiro, E.; Boutonnet, F.; Gravel, D. *Tetrahedron Lett.* **1993**, 34, 2091.

⁵⁵ Goering, H.L.; Abell, P.I.; Aycock, B.F. *J. Am. Chem. Soc.* **1952**, 74, 3588. See also, LeBel, N.A.; Czaja, R.F.; DeBoer, A. *J. Org. Chem.* **1969**, 34, 3112.

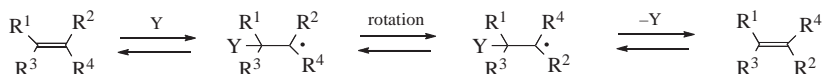
⁵⁶ Skell, P.S.; Allen, R.G. *J. Am. Chem. Soc.* **1958**, 80, 5997.

⁵⁷ Ogura, K.; Kayano, A.; Fujino, T.; Sumitani, N.; Fujita, M. *Tetrahedron Lett.* **1993**, 34, 8313.

⁵⁸ Goering, H.L.; Larsen, D.W. *J. Am. Chem. Soc.* **1959**, 81, 5937. Also see, Skell, P.S.; Freeman, P.K. *J. Org. Chem.* **1964**, 29, 2524.

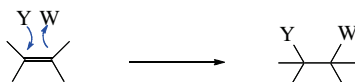
radicals was obtained by addition of Br^\bullet to alkenes at 77 K. The ESR spectra of the resulting species were consistent with bridged structures.⁵⁹

For many radicals, step 1 ($\text{C}=\text{C} + \text{Y}^\bullet \rightarrow \bullet\text{C}-\text{C}-\text{Y}$) is reversible. In such cases free radicals can cause *cis* \rightarrow *trans* isomerization of a double bond by the pathway⁶⁰



15.A.iv. Cyclic Mechanisms

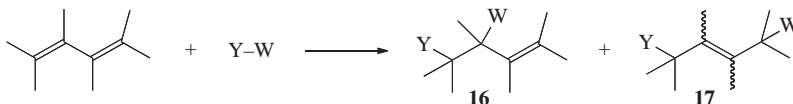
There are some addition reactions where the initial reaction is not at one carbon of the double bond, but both carbons react simultaneously. Some of these are four-center mechanisms, which follow the following pattern:



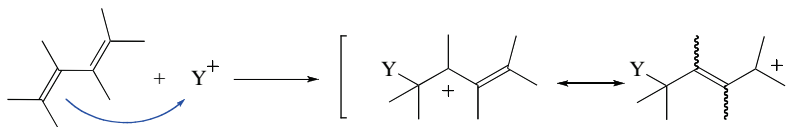
In others, there is a five- or a six-membered transition state. In these cases the addition to the double or triple bond must be *syn*. The most important reaction of this type is the *Diels-Alder reaction* (15-60).

15.A.v. Addition to Conjugated Systems

When electrophilic addition is carried out on a compound with two double bonds in conjugation, a 1,2-addition product (16) is often obtained, but in most cases there is also a 1,4-addition product (17), often in larger yield:⁶¹



If the diene is unsymmetrical, there may be two 1,2-addition products. The competition between two types of addition product comes about because the carbocation resulting from attack on Y^+ is a resonance hybrid, with partial positive charges at the 2 and 4 positions:



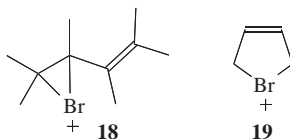
W^- may then be attacked by either position. The original reaction with Y^+ is always at the end of the conjugated system because reaction at a middle carbon would give a cation unstabilized by resonance. In the case of electrophiles like Br^+ , which can form cyclic intermediates, both 1,2- and 1,4-addition products can be rationalized as stemming from an

⁵⁹ Abell, P.I.; Piette, L.H. *J. Am. Chem. Soc.* **1962**, 84, 916. See also, Leggett, T.L.; Kennerly, R.E.; Kohl, D.A. *J. Chem. Phys.* **1974**, 60, 3264.

⁶⁰ Golden, D.M.; Furuyama, S.; Benson, S.W. *Int. J. Chem. Kinet.* **1969**, 1, 57.

⁶¹ Khristov, V.Kh.; Angelov, Kh.M.; Petrov, A.A. *Russ. Chem. Rev.* **1991**, 60, 39.

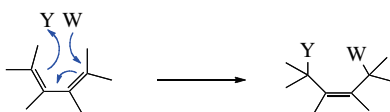
intermediate like **18**. Direct nucleophilic attack by W^- would give the 1,2-product, while the 1,4-product could be formed by attack at the 4 position, by an S_N2' -type mechanism (see Sec. 10.E). Intermediates like **19** have been postulated, but ruled out for Br and Cl by the observation that chlorination or bromination of butadiene gives trans 1,4-products.⁶² If an ion like **19** were the intermediate, the 1,4-products would have to have the cis configuration.



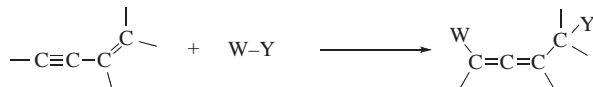
In most cases, more 1,4- than 1,2-addition product is obtained. This may be a consequence of thermodynamic control of products, as against kinetic, and usually temperature dependent. In most cases, under the reaction conditions, **16** is converted to a mixture of **16** and **17** that is richer in **17**. That is, either isomer gives the same mixture of both, which contains more **17**. It was found that at low temperatures, butadiene and HCl gave only 20–25% 1,4-adduct, while at high temperatures, where attainment of equilibrium is more likely, the mixture contained 75% 1,4-product.⁶³ 1,2-Addition predominated over 1,4- in the reaction between DCl and 1,3-pentadiene, where the intermediate was symmetrical (except for the D label).⁶⁴ Ion pairs were invoked to explain this result, since Cl^- would attack a free ion equally well at both positions, except for the very small isotope effect.



Addition to conjugated systems can also be accomplished by any of the other three mechanisms. In each case, there is competition between 1,2- and 1,4-addition. In the case of nucleophilic or free radical attack,⁶⁵ the intermediates are resonance hybrids and behave like the intermediate from electrophilic attack. Dienes can similarly give 1,4-addition by a cyclic mechanism:



Other conjugated systems, including trienes, enynes, diynes, and so on, have been studied much less but behave similarly. 1,4-Addition to enynes is an important way of making allenes:



Radical addition to conjugated systems is an important part of chain-propagation reactions. The rate constants for addition of cyclohexyl radical to conjugated amides

⁶² Mislow, K. *J. Am. Chem. Soc.* **1953**, 75, 2512.

⁶³ Kharasch, M.S.; Kritchevsky, J.; Mayo, F.R. *J. Org. Chem.* **1938**, 2, 489.

⁶⁴ Nordlander, J.E.; Owuor, P.O.; Haky, J.E. *J. Am. Chem. Soc.* **1979**, 101, 1288.

⁶⁵ Afanas'ev, I.B.; Samokhvalov, G.I. *Russ. Chem. Rev.* **1969**, 38, 318.

have been measured, and shown to be faster than addition to styrene.⁶⁶ In additions to $\text{RCH}=\text{C}(\text{CN})_2$ systems, where the R group has a stereogenic center, the *Felkin-Anh model* (Sec. 4.H, category 1) applies and the reaction proceeds with high selectivity.⁶⁷ Addition of some radicals [e.g., $(\text{Me}_3\text{Si})_3\text{Si}^\bullet$], is reversible and this can lead to poor selectivity or isomerization.⁶⁸

15.B. ORIENTATION AND REACTIVITY

15.B.i. Reactivity

As with electrophilic aromatic substitution (Chapter 11), electron-donating groups increase the reactivity of a double bond toward electrophilic addition and electron-withdrawing groups decrease it. This is illustrated in Tables 15.1 and 15.2.⁶⁹ As a further illustration, the reactivity toward electrophilic addition of a group of alkenes increased in the order $\text{CCl}_3\text{CH}=\text{CH}_2 < \text{Cl}_2\text{CHCH}=\text{CH}_2 < \text{ClCH}_2\text{CH}=\text{CH}_2 < \text{CH}_3\text{CH}_2=\text{CH}_2$.⁷⁰ For nucleophilic addition, the situation is reversed. These reactions are best carried out on substrates containing three or four electron-withdrawing groups, two of the most common being $\text{F}_2\text{C}=\text{CF}_2$ ⁷¹ and $(\text{NC})_2\text{C}=\text{C}(\text{CN})_2$.⁷² The effect of substituents is so great that it is possible to make the statement that *simple alkenes do not react by the nucleophilic mechanism, and polyhalo or polycyano alkenes do not generally react by the electrophilic mechanism*.⁷³ There are some reagents that attack only as nucleophiles (e.g., ammonia) and these add only to substrates susceptible to nucleophilic attack. Other reagents attack only as electrophiles, and, for example, $\text{F}_2\text{C}=\text{CF}_2$ does not react with these. In still other cases, the same reagent reacts with a simple alkene by the electrophilic mechanism and with a polyhalo alkene by a nucleophilic mechanism. For example, Cl_2 and HF are normally electrophilic reagents, but it has been shown that Cl_2 adds to $(\text{N}\equiv\text{C})_2\text{C}=\text{CHC}\equiv\text{N}$ with initial attack by Cl^- ⁷⁴ and that HF adds to $\text{F}_2\text{C}=\text{CClF}$ with initial attack by F^- .⁷⁵ Compounds that have a double bond conjugated with a Z group (as defined in Sec. 15.A.ii) nearly always react by a nucleophilic mechanism.⁷⁶ These are actually 1,4-additions, also discussed in Section 15.A.ii. A number of studies have been made of the relative activating abilities of various Z groups.⁷⁷ On the basis of these studies,

⁶⁶ Curran, D.P.; Qi, H.; Porter, N.A.; Su, Q.; Wu, W.-X. *Tetrahedron Lett.* **1993**, 34, 4489.

⁶⁷ Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* **1992**, 441.

⁶⁸ Ferreri, C.; Ballestri, M.; Chatgililoglu, C. *Tetrahedron Lett.* **1993**, 34, 5147.

⁶⁹ Table 15.1 is from de la Mare, P.B.D. *Q. Rev. Chem. Soc.* **1949**, 3, 126, p. 145. Table 15.2 is from Dubois, J.E.; Mouvier, G. *Tetrahedron Lett.* **1963**, 1325. See also, Grosjean, D.; Mouvier, G.; Dubois, J.E. *J. Org. Chem.* **1976**, 41, 3869, 3872.

⁷⁰ Shelton, J.R.; Lee, L. *J. Org. Chem.* **1960**, 25, 428.

⁷¹ See Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* **1965**, 4, 51.

⁷² See Fatiadi, A.J. *Synthesis* **1987**, 249, 749; Dhar, D.N. *Chem. Rev.* **1967**, 67, 611.

⁷³ See Olah, G.A.; Mo, Y.K. *J. Org. Chem.* **1972**, 37, 1028; Belen'kii, G.G.; German, L.S. *Sov. Sci. Rev. Sect. B* **1984**, 5, 183; Dyatkin, B.L.; Mochalina, E.P.; Knunyants, I.L. *Fluorine Chem. Rev.* **1969**, 3, 45.

⁷⁴ Dickinson, C.L.; Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* **1960**, 82, 6132. For another example, see Atkinson, R.C.; de la Mare, P.B.D.; Larsen, D.S. *J. Chem. Soc. Perkin Trans. 2*, **1983**, 271.

⁷⁵ Miller, Jr., W.T.; Fried, J.H.; Goldwhite, H. *J. Am. Chem. Soc.* **1960**, 82, 3091.

⁷⁶ Müllen, K.; Wolf, P. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, **1989**, pp. 513–558.

⁷⁷ See Ring, R.N.; Tesoro, G.C.; Moore, D.R. *J. Org. Chem.* **1967**, 32, 1091.

TABLE 15.1 Relative Reactivity of Some Alkenes Toward Bromine in Acetic Acid at 24 °C^a

Alkene	Relative Rate
PhCH=CH ₂	Very fast
PhCH=CHPh	18
CH ₂ =CHCH ₂ Cl	1.6
CH ₂ =CHCH ₂ Br	1.0
PhCH=CHBr	0.11
CH ₂ =CHBr	0.0011

Reproduced from de la Mare, P.B.D. *Q. Rev. Chem. Soc.* **1949**, 3, 126 with permission from the Royal Society of Chemistry.

^aSee Ref. 69.

TABLE 15.2 Relative Reactivity of Some Alkenes Toward Bromine in Methanol^a

Alkene	Relative Rate
CH ₂ =CH ₂	3.0×10^1
CH ₃ CH ₂ CH=CH ₂	$2/9 \times 10^3$
<i>cis</i> -CH ₃ CH ₂ CH=CHCH ₃	1.3×10^5
(CH ₃) ₂ C=C(CH ₃) ₂	2.8×10^7

[Reprinted with permission from Dubois, J.E. Mouvier, G. *Tetrahedron Lett.* **1963**, 1325, Copyright © 1963, with permission from Elsevier Science].

^aSee Ref. 69.

the following order of decreasing activating ability has been suggested: Z = NO₂, COAr, CHO, COR, SO₂Ar, CN, CO₂R, SOAr, CONH₂, and CONHR.⁷⁸

It seems obvious that electron-withdrawing groups enhance nucleophilic addition and inhibit electrophilic addition because they lower the electron density of the double bond. Addition of electrophilic radicals to electron-rich alkenes has been reported,⁷⁹ so the reaction is possible in some cases. This is probably true, and yet similar reasoning does not always apply to a comparison between double and triple bonds.⁸⁰ There is a higher concentration of electrons between the carbons of a triple bond than in a double bond, and

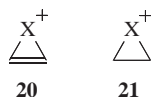
⁷⁸ Shenhav, H.; Rappoport, Z.; Patai, S. *J. Chem. Soc. B* **1970**, 469.

⁷⁹ Curran, D.P.; Ko, S.-B. *Tetrahedron Lett.* **1998**, 39, 6629.

⁸⁰ See in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, **1978**, the articles by Schmid, G.H. pt. 1, pp. 275–341, and by Dickstein, J.I.; Miller, S.I. pt. 2, pp. 813–955; Miller, S.I.; Winterfeldt, E. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 267–334. For comparisons of double and triple bond reactivity, see Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* **1981**, 14, 227; Allen, A.D.; Chiang, Y.; Kresge, A.J.; Tidwell, T.T. *J. Org. Chem.* **1982**, 47, 775.

yet triple bonds are *less* subject to attack at an electrophilic site and *more* subject to nucleophilic attack than double bonds.⁸¹ This statement is not universally true, but it does hold in most cases. In compounds containing both double and triple bonds (nonconjugated), bromine, an electrophilic reagent, always adds to the double bond.⁸² In fact, all reagents that form bridged intermediates like **2** react faster with double than with triple bonds. On the other hand, addition of electrophilic H^+ (acid-catalyzed hydration, Reaction **15-3**; addition of hydrogen halides, Reaction **15-2**) takes place at about the same rates for alkenes as for corresponding alkynes.⁸³ Furthermore, the presence of electron-withdrawing groups lowers the alkene/alkyne rate ratio. For example, while styrene ($PhCH=CH_2$) was brominated 3000 times faster than $PhC\equiv CH$, the addition of a second phenyl group ($PhCH=CHPh$ versus $PhC\equiv CPh$) lowered the rate ratio to ~ 250 .⁸⁴ In the case of *trans*- $MeOOCCH=CHCOOMe$ versus $MeOOC\equiv CCOOMe$, the triple-bond compound was actually brominated faster.⁸⁵

As mentioned earlier, it is true that in general triple bonds are more susceptible to nucleophilic and less prone to reaction at an electrophilic site than double bonds, in spite of their higher electron density. One explanation is that the electrons in the triple bond are held more tightly because of the smaller carbon-carbon distance. Thus it is harder to donate an electron pair to an electrophile. There is evidence from far-UV spectra to support this conclusion.⁸⁶ Another possible explanation has to do with the availability of the unfilled orbital in the alkyne. It has been shown that a π^* orbital of bent alkynes (e.g., cyclooctyne) has a lower energy than the π^* orbital of alkenes, and it has been suggested⁸⁷ that linear alkynes can achieve a bent structure in their transition states when reacting with an electrophile. Where electrophilic addition involves bridged-ion intermediates, those arising from triple bonds (**20**) are more strained than the corresponding **21**. This may be a reason why electrophilic addition by such electrophiles as Br, I, SR, and so on, is slower for triple than for double bonds.⁸⁸ As might be expected, triple bonds connected to a Z group ($C\equiv C-Z$) undergo nucleophilic addition especially well.⁸⁹



Although alkyl groups in general increase the rates of electrophilic addition, as mentioned in Section 15.A.i, category 1, there is a different pattern depending on whether the intermediate is a bridged ion or an open carbocation. For brominations and other electrophilic additions in which the first step of the mechanism is rate determining, the rates for substituted alkenes correlate well with the ionization potentials of the alkenes, which means that steric effects are not important.⁹⁰ Where the second step is rate

⁸¹ See Strozier, R.W.; Caramella, P.; Houk, K.N. *J. Am. Chem. Soc.* **1979**, *101*, 1340.

⁸² Petrov, A.A. *Russ. Chem. Rev.* **1960**, *29*, 489.

⁸³ Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* **1981**, *14*, 227, p. 228.

⁸⁴ Robertson, P.W.; Dasent, W.E.; Milburn, R.M.; Oliver, W.H. *J. Chem. Soc.* **1950**, 1628.

⁸⁵ Wolf, S.A.; Ganguly, S.; Berliner, E. *J. Am. Chem. Soc.* **1985**, *50*, 1053.

⁸⁶ Walsh, A.D. *Q. Rev. Chem. Soc.* **1948**, *2*, 73.

⁸⁷ Ng, L.; Jordan, K.D.; Krebs, A.; Rüger, W. *J. Am. Chem. Soc.* **1982**, *104*, 7414.

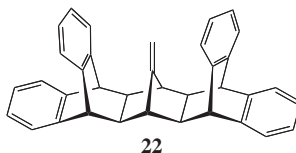
⁸⁸ See Schmid, G.H.; Modro, A.; Lenz, F.; Garratt, D.G.; Yates, K. *J. Org. Chem.* **1976**, *41*, 2331.

⁸⁹ See Winterfeldt, E. *Angew. Chem. Int. Ed.* **1967**, *6*, 423; *Newer Methods Prep. Org. Chem.* **1971**, *6*, 243.

⁹⁰ Nelson, D.J.; Cooper, P.J.; Soundararajan, R. *J. Am. Chem. Soc.* **1989**, *111*, 1414.

determining [e.g., oxymercuration Reaction (15-3), hydroboration Reaction (15-17)], steric effects are important.⁸⁹

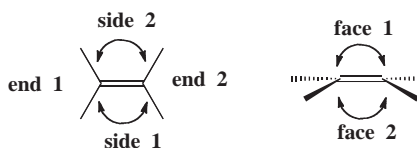
Free radical additions can occur with any type of substrate. The determining factor is the presence of a reactive free radical species. Some reagents (e.g., HBr, RSH) attack by ionic mechanisms if no initiator is present, but in the presence of a free radical initiator, the mechanism changes and the addition is of the free radical type. Nucleophilic radicals (Sec. 14.A.ii) behave like nucleophiles in that the rate is increased by the presence of electron-withdrawing groups in the substrate. The reverse is true for electrophilic radicals.⁹¹ However, nucleophilic radicals react with alkynes more slowly than with the corresponding alkenes,⁹² which is contrary to what might have been expected.⁹³



Steric influences are important in some cases. In catalytic hydrogenation, where the substrate must be adsorbed onto the catalyst surface, the reaction becomes more difficult with increasing substitution. The hydrocarbon (22), in which the double bond is entombed between the benzene rings, does not react with Br₂, H₂SO₄, O₃, BH₃, :CBr₂, or other reagents that react with most double bonds.⁹⁴ A similarly inactive compound is tetra-*tert*-butyllallene (*t*-Bu)₂C=C=C(*t*-Bu)₂, which is inert to Br₂, Cl₂, O₃, and catalytic hydrogenation.⁹⁵

15.B.ii. Orientation

When an unsymmetrical reagent is added to an unsymmetrical substrate, the question arises: Which side of the reagent goes to which side of the double or triple bond? In other words, what is the *regioselectivity* of the reaction? *Regioselectivity is defined as one direction of bond making or breaking that occurs preferentially over all other possible directions.* The terms side and face are arbitrary, and a simple guide is shown to help understand



the arguments used here. For reaction with an electrophile, the traditional answer is given by *Markovnikov's rule*: *The positive portion of the reagent goes to the side of the double or triple bond that has more hydrogen atoms.*⁹⁶ Mechanistically, regioselectivity is predicted by attack of the π bond on Y^+ , forming a bond to the carbon that will give the

⁹¹ See Tedder, J.M. *Angew. Chem. Int. Ed.* **1982**, 21, 401.

⁹² Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* **1982**, 21, 768.

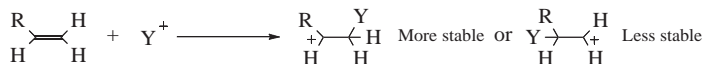
⁹³ See Volovik, S.V.; Dyadyusha, G.G.; Staninets, V.I. *J. Org. Chem. USSR* **1986**, 22, 1224.

⁹⁴ Butler, D.N.; Gupta, I.; Ng, W.W.; Nyburg, S.C. *J. Chem. Soc., Chem. Commun.* **1980**, 596.

⁹⁵ Bolze, R.; Eierdanz, H.; Schlüter, K.; Massa, W.; Grahn, W.; Berndt, A. *Angew. Chem. Int. Ed.* **1982**, 21, 924.

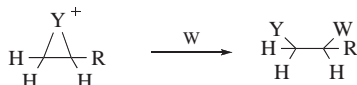
⁹⁶ See Isenberg, N.; Grdinic, M. *J. Chem. Educ.* **1969**, 46, 601; Grdinic, M.; Isenberg, N. *Intra-Sci. Chem. Rep.*, **1970**, 4, 145–162.

more stable carbocation. For example, secondary carbocations are more stable than primary:



This mechanism is supported by evidence from core electron spectroscopy and by theoretical analysis.⁹⁷ The *Hammond postulate* is invoked to say that the lower energy carbocation is preceded by the lower energy transition state. *Markovnikov's rule* also applies for halogen substituents, and the mechanistic rationale is that the halogen stabilizes the carbocation by resonance, so the intermediate with the positive charge on the Cl bearing carbon is more stable.

Markovnikov's rule is also followed where bromonium ions or other three-membered rings are intermediates formed in protic solvents (e.g., methanol).⁹⁸ In such a medium, attack by the nucleophile W on the three-membered ring must resemble the S_N1 (see Sec. 10.A.ii) rather than the S_N2 mechanism (and see Sec. 10.G.viii), although the overall stereospecific anti addition in these reactions means that the nucleophilic substitution step is taking place with inversion of configuration. This result suggests a tight ion pair rather than a free carbocation.



Alkenes containing strong electron-withdrawing groups may violate *Markovnikov's rule*, but formation of the more stable carbocation still controls the reaction. For example, attack at the *Markovnikov* position of Me₃N⁺—CH=CH₂ would give an ion with positive charges on adjacent atoms. The compound CF₃CH=CH₂ has been reported to give electrophilic addition with acids in an *anti-Markovnikov* direction, but it has been shown⁹⁹ that, when treated with acids, this compound does not give simple electrophilic addition at all; the apparently *anti-Markovnikov* products are formed by other pathways. Molecular electrostatic potentials for the π-region of substituted alkenes were studied, with electron donating and withdrawing substituents (based on the increase or decrease in the negative character of V_{min} - most negative-valued point), and plots of V_{min} shows a good linear correlation with the *Hammett* σ_ρ constants, suggesting similar substituent electronic effects for substituted ethylenes and substituted benzenes.¹⁰⁰

In free radical addition¹⁰¹ the main effect seems to be steric.¹⁰² All substrates CH₂=CHX preferentially react at the CH₂, regardless of the identity of X or of the radical. With a reagent, such as HBr, which generates Br• *in situ* via hydrogen-atom exchange, this means that the addition is *anti-Markovnikov*:

⁹⁷ Sæthre, L.J.; Thomas, T.D.; Svensson, S. *J. Chem. Soc. Perkin Trans. 2*, **1997**, 749.

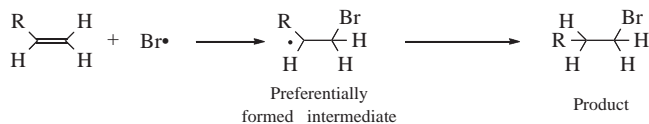
⁹⁸ See Dubois, J.E.; Chrétien, J.R. *J. Am. Chem. Soc.* **1978**, *100*, 3506.

⁹⁹ Myhre, P.C.; Andrews, G.D. *J. Am. Chem. Soc.* **1970**, *92*, 7595, 7596. See also, Newton, T.A. *J. Chem. Educ.* **1987**, *64*, 531.

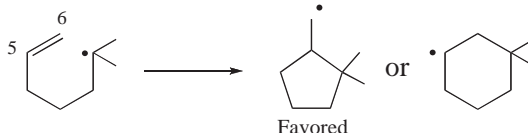
¹⁰⁰ Suresh, C.H.; Koga, N.; Gadre, S.R. *J. Org. Chem.* **2001**, *66*, 6883.

¹⁰¹ Tedder, J.M.; Walton, J.C. *Tetrahedron* **1980**, *36*, 701; *Acc. Chem. Res.* **1976**, *9*, 183. See also, Giese, B. *Rev. Chem. Intermed.* **1986**, *7*, 3; Tedder, J.M. *J. Chem. Educ.* **1984**, *61*, 237.

¹⁰² See, however, Gleicher, G.J.; Mahiou, B.; Aretakis, A.J. *J. Org. Chem.* **1989**, *54*, 308.

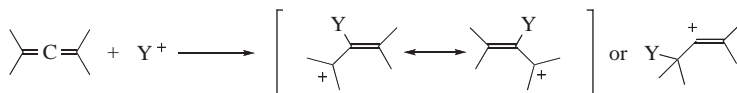


Thus the observed orientation in both kinds of HBr addition (*Markovnikov* electrophilic and *anti-Markovnikov* free radical) is caused by formation of the more stable secondary intermediate.



In *intramolecular* additions (radical cyclization, see Reaction **15-30**) of radicals containing a 5,6 double bond,⁵³ both five- and six-membered rings can be formed, but in most cases¹⁰³ the five-membered rings are greatly preferred kinetically, even (as in the case shown) where five-membered ring closure means generating a primary radical and six-membered ring closure a secondary radical. This phenomenon may be caused by more favorable entropy factors leading to a five-membered ring, as well as by stereoelectronic factors, but other explanations have also been offered.¹⁰⁴ Similar behavior is found when the double bond is in other positions (from the 3,4 to the 7,8 position). In each case, the smaller ring (*exo-trig* addition) is preferred to the larger (*endo-trig* addition)¹⁰⁵ (see *Baldwin rules*, Sec. 6.E). However, when a radical that is unsaturated in the 5,6 position contains an alkyl group in the 5 position, formation of the six-membered ring is generally favored, presumably due to unfavorable steric interactions.¹⁰⁶

For conjugated dienes, attack at a positive ion, by a negative ion, or reaction with a free radical is almost always at the *end* of the conjugated system, since in each case this gives an intermediate stabilized by resonance. In the case of an unsymmetrical diene, the more stable ion is formed. For example, isoprene ($\text{CH}_2=\text{CMeCH}=\text{CH}_2$) treated with HCl gives only $\text{Me}_2\text{CClCH}=\text{CH}_2$ and $\text{Me}_2\text{C}=\text{CHCH}_2\text{Cl}$, with none of the product arising from attack at the other end. The compound $\text{PhCH}=\text{CHCH}=\text{CH}_2$ gives only $\text{PhCH}=\text{CHCHClCH}_3$ since it is the only one of the eight possible products that has a double bond in conjugation with the ring and that results from attack that places the proton at an end of the conjugated system.



When allenes attack electrophilic reagents,¹⁰⁷ *Markovnikov's rule* would predict that formation of the new bond should be at the end of the system, since there are no hydrogen

¹⁰³ For an exception, see Wilt, J.W. *Tetrahedron* **1985**, 41, 3979.

¹⁰⁴ See Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron* **1985**, 41, 3925; Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* **1987**, 52, 959.

¹⁰⁵ See Beckwith, A.L.J.; Easton, C.J.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* **1980**, 482.

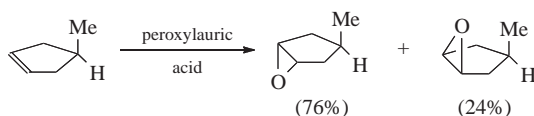
¹⁰⁶ See Chuang, C.; Gallucci, J.C.; Hart, D.J.; Hoffman, C. *J. Org. Chem.* **1988**, 53, 3218.

¹⁰⁷ See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis* Wiley, NY, **1984**; Pasto, D.J. *Tetrahedron* **1984**, 40, 2805; Smadja, W. *Chem. Rev.* **1983**, 83, 263; in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, **1982**, articles by Landor, S.R., Jacobs, T.L.; Hopf, H. pp. 351–577; Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, **1979**, pp. 152–167; Richey, Jr., H.G.; Richey, J.M. in Olah, G. A.; Schleyer, P.v.R. *Carbocation Ions*, Vol. 2, Wiley, NY, **1970**, pp. 917–922; Taylor, D.R. *Chem. Rev.* **1967**, 67, 317, pp. 338–346; Griesbaum, K. *Angew. Chem. Int. Ed.* **1966**, 5, 933. See Ma, S. *Pure Appl. Chem.* **2006**, 78, 197.

atoms in the middle. Reaction at the center gives a carbocation stabilized by resonance, but not immediately. In order for such stabilization to be in effect, the three p orbitals must be parallel, and it requires a rotation about the C—C bond.¹⁰⁸ Therefore, the stability of the allylic cation has no effect on the transition state, which still has a geometry similar to that of the original allene (Sec. 4.C, category 5). Probably because of this, reaction of the unsubstituted $\text{CH}_2=\text{C}=\text{CH}_2$ is most often at the end carbon, to give a vinylic cation, although reaction at the center carbon has also been reported. However, as alkyl or aryl groups are substituted on the allene carbons, reaction at the middle carbon becomes more favorable because the resulting cation is stabilized by the alkyl or aryl groups (it is now a secondary, tertiary, or benzylic cation). For example, allenes of the form $\text{RCH}=\text{C}=\text{CH}_2$ react most often at the end, but $\text{RCH}=\text{C}=\text{CHR}'$ usually gives reaction at the center carbon.¹⁰⁹ Free radicals¹¹⁰ react with allenes most often at the end,¹¹¹ although reaction at the middle carbon has also been reported.¹¹² As with reactions that proceed via electrophilic intermediates and for the same reason, the stability of the allylic radical has no effect on the transition state of the reaction between a free radical and an allene. Again, the presence of alkyl groups increases the extent of reaction by a radical at the middle carbon.¹¹³

15.B.iii. Stereochemical Orientation

It has already been pointed out that some additions are syn, with both groups approaching from the same side, and that others are anti, with the groups approaching from opposite sides of the double or triple bond. For cyclic compounds steric orientation must be considered. In syn addition to an unsymmetrical cyclic alkene, the two groups can come in from the more- or from the less-hindered face of the double bond. The rule is that syn addition is usually, although not always, from the less-hindered face. For example, epoxidation of 4-methylcyclopentene gave 76% addition from the less-hindered and 24% from the more-hindered face.¹¹⁴



In anti addition to a cyclic substrate, the initial reaction with the electrophile is also from the less-hindered face. However, many (although not all) electrophilic additions to norbornene and similar strained bicycloalkenes are syn additions.¹¹⁵ In these cases reaction

¹⁰⁸ See Okuyama, T.; Izawa, K.; Fueno, T. *J. Am. Chem. Soc.* **1973**, *95*, 6749.

¹⁰⁹ Also see Poutsma, M.L.; Ibarbia, P.A. *J. Am. Chem. Soc.* **1971**, *93*, 440.

¹¹⁰ Jacobs, T.L. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, **1982**, pp. 399–415.

¹¹¹ Griesbaum, K.; Oswald, A.A.; Quiram, E.R.; Naegle, W. *J. Org. Chem.* **1963**, *28*, 1952.

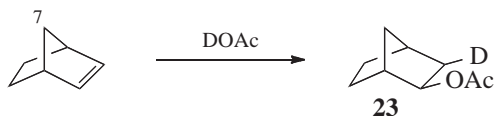
¹¹² See Pasto, D.J.; L'Hermine, G. *J. Org. Chem.* **1990**, *55*, 685.

¹¹³ See Pasto, D.J.; Warren, S.E.; Morrison, M.A. *J. Org. Chem.* **1981**, *46*, 2837. See, however, Bartels, H.M.; Boldt, P. *Liebigs Ann. Chem.* **1981**, 40.

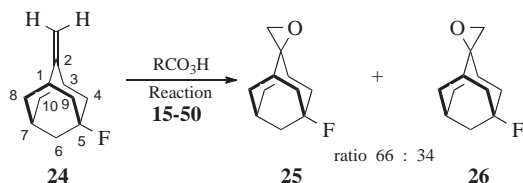
¹¹⁴ Henbest, H.B.; McCullough, J.J. *Proc. Chem. Soc.* **1962**, 74.

¹¹⁵ See Traylor, T.G. *Acc. Chem. Res.* **1969**, *2*, 152.

is always from the exo side, as in formation of **23**,¹¹⁶ unless the exo



side is blocked by substituents in the 7 position, in which case endo attack may predominate [e.g., 7,7-dimethylnorbornene undergoes syn–endo epoxidation (Reaction **15-50**) and hydroboration¹¹⁷ (Reaction **15-16**)]. However, addition of DCl and F₃CCO₂D to, and oxymercuration (Reaction **15-2**) of, 7,7-dimethylnorbornene proceeds syn–exo in spite of the methyl groups in the 7 position.¹¹⁸ Similarly, free radical additions to norbornene and similar molecules are often syn–exo, although anti additions and endo attacks are also known.¹¹⁹



Electronic effects can also play a part in determining which face reacts preferentially with the electrophilic species. In the adamantane derivative (**24**), steric effects are about the same for each face of the double bond. Yet epoxidation, dibromocarbene reactions (**15-64**), and hydroboration (**15-16**) all take place predominantly from the face that is syn to the electron-withdrawing fluorine.¹²⁰ In the case shown, about twice as much **25** was formed, compared to **26**. Similar results have been obtained on other substrates:¹²¹ groups that are electron withdrawing by the field effect ($-I$) direct attack from the syn face; $+I$ groups from the anti face, for both electrophilic and nucleophilic attack. These results are attributed¹²² to hyperconjugation (Sec. 2.M): For the adamantane case, there is overlap between the σ^* orbital of the newly forming bond (between the attacking species and C-2 in **24**) and the filled σ orbitals of the C $_{\alpha}$ –C $_{\beta}$ bonds on the opposite side. This is called the *Cieplak effect*. The LiAlH₄ reduction of 2-axial methyl or methoxy cyclohexanones supports Cieplak's proposal.¹²³ In addition reactions of methanol to norbornanones, however, little evidence was found to support the Cieplak effect.¹²⁴ The four possible bonds are C-3–C-4 and C-1–C-9 on the syn side and C-3–C-10 and C-1–C-8 on the anti side. The preferred pathway is the one where the incoming group has the more electron-rich bonds on the side *opposite* to it (these are the ones it overlaps with). Since the electron-withdrawing F has its greatest effect on the bonds closest to it, the C-1–C-8 and C-3–C-10 bonds are more electron rich, and the group comes in on the face syn to the F.

¹¹⁶ Koga, N.; Ozawa, T.; Morokuma, K. *J. Phys. Org. Chem.* **1990**, 3, 519.

¹¹⁷ Brown, H.C.; Kawakami, J.H.; Liu, K. *J. Am. Chem. Soc.* **1973**, 95, 2209.

¹¹⁸ Brown, H.C.; Liu, K. *J. Am. Chem. Soc.* **1975**, 97, 600, 2469.

¹¹⁹ See Azovskaya, V.A.; Prilezhaeva, E.N. *Russ. Chem. Rev.* **1972**, 41, 516.

¹²⁰ Srivastava, S.; le Noble, W.J. *J. Am. Chem. Soc.* **1987**, 109, 5874. See also, Bodepudi, V.R.; le Noble, W.J. *J. Org. Chem.* **1991**, 56, 2001.

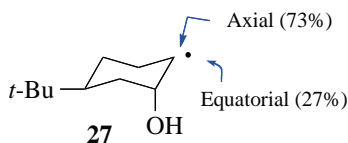
¹²¹ Cieplak, A.S.; Tait, B.D.; Johnson, C.R. *J. Am. Chem. Soc.* **1989**, 111, 8447.

¹²² Cieplak, A.S. *J. Am. Chem. Soc.* **1981**, 103, 4540. See also, Jorgensen, W.L. *Chemtracts: Org. Chem.* **1988**, 1, 71.

¹²³ Senda, Y.; Nakano, S.; Kunii, H.; Itoh, H. *J. Chem. Soc. Perkin Trans. 2*, **1993**, 1009.

¹²⁴ Coxon, J.M.; McDonald, D.Q. *Tetrahedron* **1992**, 48, 3353.

It has been mentioned that additions of Br_2 and HOBr are often anti because of formation of bromonium ions and that free radical addition of HBr is also anti. When the substrate in any of these additions is a cyclohexene, the addition is not only anti but the initially formed product is conformationally specific too, being mostly diaxial.¹²⁵ This is so because diaxial opening of the three-membered ring preserves a maximum coplanarity of the participating centers in the transition state; indeed, on opening, epoxides also give diaxial products.¹²⁶ However, the initial diaxial product may then pass over to the diequatorial conformer unless other groups on the ring render the latter less stable than the former. In free radical additions to cyclohexenes in which cyclic intermediates are not involved, the initial reaction with the radical is also usually from the axial direction,¹²⁷ resulting in a diaxial initial product if the overall addition is anti. The direction from which unsymmetrical radicals react has also been studied.¹²⁸ For example, when the radical (**27**) adds to a double bond it preferentially does so anti to the OH group, leading to a diaxial trans product.¹²⁶

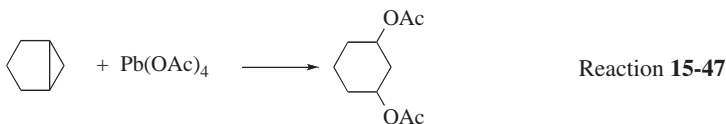


15.B.iv. Addition to Cyclopropane Rings¹²⁹

Section 4.Q.iv showed that cyclopropane rings resemble double bonds in some aspects of their reactivity.¹³⁰ It is not surprising, therefore, that cyclopropanes undergo addition reactions analogous to those undergone by double-bond compounds, resulting in the opening of the three-membered rings, as in the two examples shown, where Reactions **15-2** and **15-47** describe the reaction to alkene chemistry.

Reaction **15-2**

Ref. 131

Reaction **15-47**

Other examples are discussed at Reaction **15-3**, **15-15**, and **15-63**.

Additions to cyclopropanes can take place by any of the four mechanisms already discussed in this chapter, but the most important type involves attack on an electrophile.¹³²

¹²⁵ Readio, P.D.; Skell, P.S. *J. Org. Chem.* **1966**, *31*, 753, 759.

¹²⁶ See Anselmi, C.; Berti, G.; Catelani, G.; Lecce, L.; Monti, L. *Tetrahedron* **1977**, *33*, 2771.

¹²⁷ LeBel, N.A.; Czaja, R.F.; DeBoer, A. *J. Org. Chem.* **1969**, *34*, 3112.

¹²⁸ See Giese, B. *Angew. Chem. Int. Ed.* **1989**, *28*, 969.

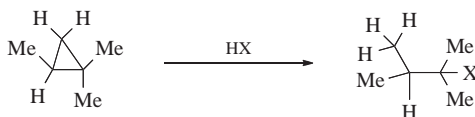
¹²⁹ Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, vol 2., Wiley, NY, **1970**, pp. 569–592; Reissig, H. *Top. Curr. Chem.* **1988**, *144*, 73; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

¹³⁰ See, however, Gordon, A.J. *J. Chem. Educ.* **1967**, *44*, 461.

¹³¹ Moon, S. *J. Org. Chem.* **1964**, *39*, 3456.

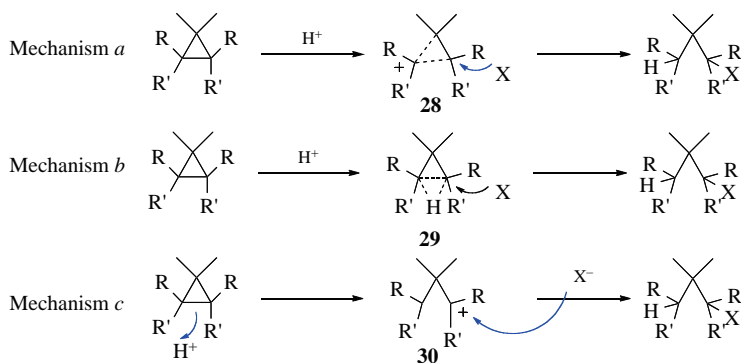
¹³² See DePuy, C.H. *Top. Curr. Chem.* **1973**, *40*, 73–101. For a list of references to pertinent mechanistic studies, see Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* **1985**, *107*, 988.

For substituted cyclopropanes, these reactions usually follow *Markovnikov's rule*, although exceptions are known and the degree of regioselectivity is often small. The application of *Markovnikov's rule* to these substrates can be illustrated by the reaction of 1,1,2-trimethylcyclopropane with HX.¹³³ The rule predicts that the electrophile (in this case H⁺) goes to the



carbon with the most hydrogen atoms and the nucleophile goes to the carbon that can best stabilize a positive charge (in this case the tertiary rather than the secondary carbon). The stereochemistry of the reaction can be investigated at two positions: the one that becomes connected to the electrophile and the one that becomes connected to the nucleophile. The results at the former position are mixed. Additions have been found to take place with 100% retention,¹³⁴ 100% inversion,¹³⁵ and with mixtures of retention and inversion.¹³⁶ At the carbon that becomes connected to the nucleophile, the result is usually inversion, although retention has also been found,¹³⁷ and elimination, rearrangement, and racemization processes often compete, indicating that in many cases a positively charged carbon is generated at this position.

At least three mechanisms have been proposed for electrophilic addition (these mechanisms are shown for reaction with HX, but analogous mechanisms can be written for other electrophiles).



Mechanism *a* involves a corner-protonated cyclopropane¹³⁸ (**28**). Examples of such ions were seen in the 2-norbornyl and 7-norbornenyl cations (Sec. 10.C.i). Mechanism *b* involves an edge-protonated cyclopropane (**29**). Mechanism *c* consists of a one-step S_E2 type attack on H⁺ to give the classical cation **30**, which then reacts with the nucleophile. Although the three mechanisms as drawn show retention of configuration at the carbon that

¹³³ Kramer, G.M. *J. Am. Chem. Soc.* **1970**, 92, 4344.

¹³⁴ See Hendrickson, J.B.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* **1969**, 91, 3269.

¹³⁵ See Hogeveen, H.; Roobeek, C.F.; Volger, H.C. *Tetrahedron Lett.* **1972**, 221; Battiste, M.A.; Mackiernan, J. *Tetrahedron Lett.* **1972**, 4095. See also, Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* **1990**, 55, 4136.

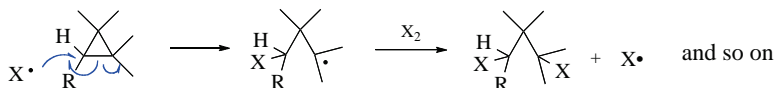
¹³⁶ DePuy, C.H.; Fünfschilling, P.C.; Andrist, A.H.; Olson, J.M. *J. Am. Chem. Soc.* **1977**, 99, 6297.

¹³⁷ Hendrickson, J.B.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* **1971**, 93, 4491.

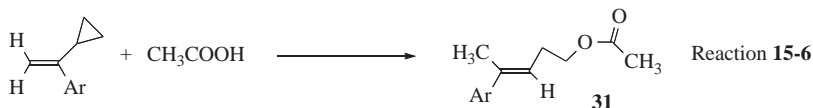
¹³⁸ Collins, C.J. *Chem. Rev.* **1969**, 69, 543; Lee, C.C. *Prog. Phys. Org. Chem.* **1970**, 7, 129.

becomes attached to the proton, mechanisms *a* and *c* at least can also result in inversion at this carbon. Unfortunately, the evidence on hand at present does not allow us unequivocally to select any of these as the exclusive mechanism in all cases. Matters are complicated by the possibility that more than one edge-protonated cyclopropane is involved, at least in some cases. There is strong evidence for mechanism *b* with the electrophiles Br^+ and Cl^+ ¹³⁹; and for mechanism *a* with D^+ and Hg^{2+} .¹⁴⁰ *Ab initio* studies show that the corner-protonated **28** is slightly more stable ($\sim 1.4 \text{ kcal mol}^{-1}$, 6 kJ mol^{-1}) than the edge-protonated **29**.¹⁴¹ There is some evidence against mechanism *c*.¹⁴²

Free radical additions to cyclopropanes have been studied much less, but it is known that Br_2 and Cl_2 add to cyclopropanes by a free radical mechanism in the presence of UV light. The addition follows *Markovnikov's rule*, with the initial radical reacting at the least-substituted carbon and the second group going to the most-substituted position. Several investigations have shown that the reaction is stereospecific at one carbon, taking place with inversion there, but nonstereospecific at the other carbon.¹⁴³ A mechanism that accounts for this behavior is¹⁴⁴



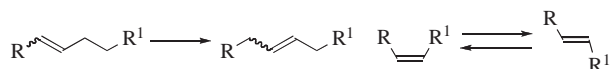
In some cases, conjugate addition has been performed on systems where a double bond is “conjugated” with a cyclopropyl ring. An example is the formation of **31**.¹⁴⁵



15.C. REACTIONS

15.C.i. Isomerization of Double and Triple Bonds

15-1 Isomerization



Without a transition metal catalyst, there is usually a rather high-energy barrier for the excited state required for (*E/Z*) isomerization.¹⁴⁶ The transition metal catalyzed

¹³⁹ Coxon, J.M.; Steel, P.J.; Whittington, B.I.; Battiste, M.A. *J. Org. Chem.* **1989**, *54*, 1383; Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* **1989**, *54*, 3702.

¹⁴⁰ Lambert, J.B.; Chelius, E.C.; Bible, Jr., R.H.; Hadju, E. *J. Am. Chem. Soc.* **1991**, *113*, 1331.

¹⁴¹ Koch, W.; Liu, B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1989**, *111*, 3479, and references cited therein.

¹⁴² Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* **1985**, *107*, 988.

¹⁴³ Maynes, G.G.; Applequist, D.E. *J. Am. Chem. Soc.* **1973**, *95*, 856; Incremona, J.H.; Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* **1973**, *95*, 6728; Upton, C.J.; Incremona, J.H. *J. Org. Chem.* **1976**, *41*, 523.

¹⁴⁴ See Wiberg, K.B.; Waddell, S.T.; Laidig, K. *Tetrahedron Lett.* **1986**, *27*, 1553.

¹⁴⁵ Sarel, S.; Ben-Shoshan, B. *Tetrahedron Lett.* **1965**, 1053. See also, Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

¹⁴⁶ Arai, T.; Takahashi, O. *J. Chem. Soc., Chem. Commun.* **1995**, 1837.

isomerization of an alkene from (*E*) to (*Z*) or (*Z*) to (*E*) is a well-studied reaction.¹⁴⁷ Among the metals used, Pt is widely used, and rather selective.¹⁴⁸ The Pd catalyzed isomerization of (*Z*)-alkenes to (*E*)-alkenes required the presence of Bu₃SnH.¹⁴⁹ However, a 1:1 mixture of *cis*/*trans*-styrene derivatives was isomerized to a 90% yield of the *trans*-styrene derivatives reported using a Pd catalyst.¹⁵⁰ Isomerization of cyclic alkenes is difficult for rings of seven members and less, but *cis*/*trans* isomerization of cyclooctene is induced photochemically.¹⁵¹ Radical-induced (*E*/*Z*) isomerization is known.¹⁵² Isomerization of the C=C units in dienes is also induced photochemically.¹⁵³

In a different type of reaction, isomerization of alkynes to 1,3-dienes is possible using Rh or Pd catalysts.¹⁵⁴

There are several reagents that lead to isomerization of a double bond to form a new alkene. In general, there is an energetic preference of an α,β - versus β,γ -double bond.¹⁵⁵ Allylic arenes (Ar—CH₂CH=CH₂) have been converted to the corresponding (*Z*)-1-propenyl arene (Ar—CH=CHMe) using an Ru catalyst¹⁵⁶ or a polymer-supported Ir catalyst.¹⁵⁷ In the presence of a Rh catalyst, certain allylic amines are converted to an enamine with high selectivity for the (*Z*) isomer.¹⁵⁸ Double-bond migration has been observed in sulfide photoirradiation, induced by singlet oxygen.¹⁵⁹ Many of these reactions were discussed in Reaction 12-2.

For conjugated carbonyl compounds that have a hydrogen atom at the γ -position (C-4), it is possible to move a double bond *out* of conjugation. Photolysis of conjugated esters, at -40 °C in the presence of *N,N*-dimethylaminoethanol, gave the nonconjugated ester.¹⁶⁰ Heating an *N*-allylic amide (N—C—C=C) with Fe(CO)₅, neat, gave the enamide (N—C=C—C).¹⁶¹ Conjugated aldehydes have been isomerized using thiourea in DMF.¹⁶²

Double bonds of atoms other than carbon are subject to isomerization. Azobenzenes (Ar—N=N—Ar) exist as (*E*) and (*Z*) isomers, and photochemical isomerization is possible.¹⁶³

¹⁴⁷ See Dugave, C.; Demange, L. *Chem. Rev.* **2003**, 103, 2475. See Bond, G.C.; Wells, P.B. *Adv. Catal.* **1964**, 15, 91; Anderson, J.R.; Baker, B.G. in *Chemisorption and Reactions on Metallic Films*, Vol. 2 Anderson, J.R., Ed. Academic Press, London, **1971**, p. 63; Zaera, F. *Langmuir* **1996**, 12, 88.

¹⁴⁸ Lee, I.; Zaera, F. *J. Am. Chem. Soc.* **2005**, 127, 12174.

¹⁴⁹ Kim, I.S.; Dong, G.R.; Jung, Y.H. *J. Org. Chem.* **2007**, 72, 5424.

¹⁵⁰ Yu, J.; Gaunt, M.J.; Spencer, J.B. *J. Org. Chem.* **2002**, 67, 4627.

¹⁵¹ Royzen, M.; Yap, G.P.A.; Fox, J.M. *J. Am. Chem. Soc.* **2008**, 130, 3760.

¹⁵² Baag, Md.M.; Kar, A.; Argade, N.P. *Tetrahedron* **2003**, 59, 6489.

¹⁵³ Wakamatsu, K.; Takahashi, Y.; Kikuchi, K.; Miyashi, T. *J. Chem. Soc. Perkin Trans. 2*, **1996**, 2105.

¹⁵⁴ Yasui, H.; Yorimitsu, H.; Oshima, K. *Synlett* **2006**, 1783. For a review, see Kwong, C.K.-W.; Fu, M.Y.; Lam, C. S.-L.; Toy, P.H. *Synthesis* **2008**, 2307.

¹⁵⁵ Lee, P.S.; Du, W.; Boger, D.L.; Jorgensen, W.L. *J. Org. Chem.* **2004**, 69, 5448.

¹⁵⁶ Sato, T.; Komine, N.; Hirano, M.; Komiya, S. *Chem. Lett.* **1999**, 441.

¹⁵⁷ Baxendale, I.R.; Lee, A.-L.; Ley, S.V. *Synlett* **2002**, 516.

¹⁵⁸ Alphonse, F.-A.; Yudin, A.K. *J. Am. Chem. Soc.* **2006**, 128, 11754. See Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* **2004**, 45, 5257.

¹⁵⁹ Clennan, E.L.; Aebischer, D. *J. Org. Chem.* **2002**, 67, 1036.

¹⁶⁰ Bargiggia, F.; Piva, O. *Tetrahedron Asymmetry* **2001**, 12, 1389.

¹⁶¹ Sergeyev, S.; Hesse, M. *Synlett* **2002**, 1313.

¹⁶² Phillips, O.A.; Eby, P.; Maiti, S.N. *Synth. Commun.* **1995**, 25, 87.

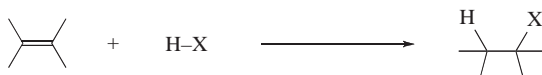
¹⁶³ Carreño, M.C.; García, I.; Ribagorda, M.; Merino, E.; Pieraccini, S.; Spada, G.P. *Org. Lett.* **2005**, 7, 2869.

15.C.ii. Reactions in Which Hydrogen Adds to One Side

A. Halogen on the Other Side

15-2 Addition of Hydrogen Halides

Hydro-halo-addition



Any of the four hydrogen halides can be added to double bonds.¹⁶⁴ Alkenes react as Brønsted–Lowry bases with HI, HBr, and HF¹⁶⁵ at room temperature, but reaction with HCl is more difficult and usually requires heat.²⁴ Hydrogen Chloride adds easily in the presence of silica gel. However,¹⁶⁶ HF is difficult to handle, but a convenient method for the addition of HF involves the use of a polyhydrogen fluoride–pyridine solution in THF.¹⁶⁷

The addition of hydrogen halides to simple alkenes, in the absence of peroxides, takes place by an electrophilic mechanism, and the orientation is in accord with *Markovnikov's rule*.¹⁶⁸ In other words, the π bond of the alkenes donates two electrons to the acidic proton of H—X. The addition follows second-order kinetics.¹⁶⁹ When peroxides are added, the addition of HBr occurs by a free-radical mechanism and the orientation is *anti-Markovnikov* (Sec. 15.B.i).¹⁷⁰ It must be emphasized that this is true *only* for HBr. Free radical addition of HF and HI has never been observed, even in the presence of peroxides; free radical addition of HCl has been observed only rarely. In the rare cases where free radical addition of HCl was noted, the orientation was still *Markovnikov*, presumably because the more stable product was formed.¹⁷¹ Free radical addition of HF, HI, and HCl is energetically unfavorable (see the discussions in Sec. 14.B.i and 14.C.i). It is known that under some conditions *anti-Markovnikov addition* of HBr takes place even when peroxides have not been added. This happens because the substrate alkenes absorb oxygen from the air, forming small amounts of peroxides (Reaction 14-7). *Markovnikov addition* can be ensured by rigorous purification of the substrate, but in practice this is not easy to achieve. It is more common to add inhibitors (e.g., phenols or quinones), which suppress the free radical pathway. The presence of free radical precursors (e.g., peroxides) does not inhibit the ionic mechanism, but does inhibit the more rapid radical reaction, which is a chain process. In most cases, it is possible to control the mechanism (and hence the orientation) by adding peroxides to achieve complete free radical addition, or inhibitors to achieve complete electrophilic addition, although there are some cases where the ionic mechanism is fast enough to compete with the free radical

¹⁶⁴ For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 633–636.

¹⁶⁵ See Sharts, C.M.; Sheppard, W.A. *Org. React.* **1974**, 21, 125, pp. 192–198, 212–214; Hudlicky, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, **1976**, pp. 36–41.

¹⁶⁶ Kropp, P.J.; Daus, K.A.; Tubergen, M.W.; Kepler, K.D.; Wilson, V.P.; Craig, S.L.; Baillargeon, M.M.; Breton, G.W. *J. Am. Chem. Soc.* **1993**, 115, 3071.

¹⁶⁷ Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* **1979**, 44, 3872. For a related method, see Olah, G.A.; Li, X. *Synlett* **1990**, 267.

¹⁶⁸ See Sergeev, G.B.; Smirnov, V.V.; Rostovshchikova, T.N.; *Russ. Chem. Rev.* **1983**, 52, 259; Dewar, M.J.S. *Angew. Chem. Int. Ed.* **1964**, 3, 245.

¹⁶⁹ Boregeaud, R.; Newman, H.; Schelpe, A.; Vasco, V.; Hughes, D.E.P. *J. Chem. Soc., Perkin Trans. 2*, **2002**, 810.

¹⁷⁰ See Thaler, W.A. *Methods Free-Radical Chem.* **1969**, 2, 121, see pp. 182–195.

¹⁷¹ Mayo, F.R. *J. Am. Chem. Soc.* **1962**, 84, 3964.

mechanism and complete control cannot be attained. *Markovnikov addition* of HBr, HCl, and HI has also been accomplished, in high yields, by the use of phase transfer catalysis.¹⁷² For alternative methods of adding HBr (or HI) with *anti-Markovnikov orientation*, see Reaction **12-31**.

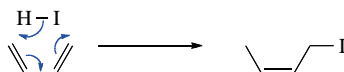
Alkynes also react as bases with acids (e.g., HX). It is possible to add 1¹⁷³ or 2 equiv of any of the four hydrogen halides to triple bonds. *Markovnikov's rule* ensures that *gem*-dihalides and not *vic*-dihalides are the products of the addition of 2 equiv.



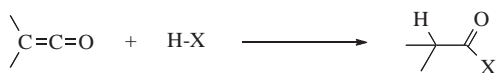
Chlorotrimethylsilane can be added to alkenes to give alkyl chlorides. 1-Hexene reacts with Me₃SiCl in water, for example, to give 2-chlorohexane.¹⁷⁴ Treatment of an alkene with KHF₂ and SiF₄ leads to the alkyl fluoride,¹⁷⁵ and bromotrimethylsilane adds to alkynes to give the vinyl bromide.¹⁷⁶

Brønsted–Lowry acids (e.g., HX) are electrophilic reagents, and many polyhalo or polycyano alkenes do not react with them in the absence of free radical conditions. Vinylcyclopropanes, however, react with opening of the cyclopropane ring to give a homoallylic chloride.¹⁷⁷ When such reactions do occur, however, they take place by a nucleophilic addition mechanism, that is, initial attack is by X[−]. This type of mechanism also occurs with *Michael-type substrates* (C=C—Z),¹⁷⁸ where the orientation is always such that the halogen goes to the carbon that does not bear the Z, so the product is of the form X—C—CH—Z, even in the presence of free radical initiators.

The reaction has been carried out with conjugated dienes, where both 1,2- and 1,4-addition are possible. Hydrogen iodide adds 1,4 to conjugated dienes in the gas phase by a pericyclic mechanism:¹⁷⁹



In a related reaction, HX can be added to ketenes¹⁸⁰ to give acyl halides:



OS I, 166; II, 137, 336; III, 576; IV, 238, 543; VI, 273; VII, 59; **80**, 129.

¹⁷² Landini, D.; Rolla, F. *J. Org. Chem.* **1980**, 45, 3527.

¹⁷³ See Cousseau, J. *Synthesis* **1980**, 805; Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675.

¹⁷⁴ Boudjouk, P.; Kim, B.-K.; Han, B.-H. *Synth. Commun.* **1996**, 26, 3479.

¹⁷⁵ Tamura, M.; Shibakami, M.; Kurosawa, S.; Arimura, T.; Sekiya, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1891.

¹⁷⁶ Su, M.; Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, 42, 3771.

¹⁷⁷ Siriwardana, A.I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, 44, 985.

¹⁷⁸ For an example, see Marx, J.N. *Tetrahedron* **1983**, 39, 1529.

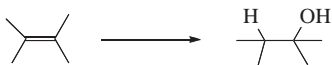
¹⁷⁹ Gorton, P.J.; Walsh, R. *J. Chem. Soc., Chem. Commun.* **1972**, 782. For evidence that a pericyclic mechanism may be possible, even for an isolated double bond, see Sergeev, G.B.; Stepanov, N.F.; Leenson, I.A.; Smirnov, V. V.; Pupyshv, V.I.; Tyurina, L.A.; Mashyanov, M.N. *Tetrahedron* **1982**, 38, 2585.

¹⁸⁰ Tidwell, T.T. *Acc. Chem. Res.* **1990**, 23, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* **1986**, 42, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* **1975**, 4, 231.

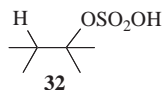
B. Oxygen on the Other Side

15-3 Hydration of Double bonds

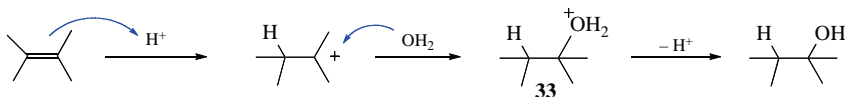
Hydro-hydroxy-addition



Double bonds can be hydrated by treatment with water and an acid catalyst. Sulfuric acid is a common catalyst, but other acids that have relatively non-nucleophilic counterions, such as nitric, perchloric, or more commonly sulfonic acids (*p*-toluenesulfonic acid, methanesulfonic acid, etc.) can also be used. The mechanism is electrophilic and begins with attack of the π bond on an acidic proton (Sec. 15.A.i). The resulting carbocation is then attacked by negative species (e.g., HSO_4^- , or a similar counterion in the case of other acids), to give the initial product (**32**), which can be isolated in some cases. However, such compounds are rather unstable, and



under the conditions of the reaction are usually hydrolyzed to the alcohol (Reaction 10-4). Under some reaction conditions, other nucleophiles are present in the reaction, either from the solvent or from added compounds. In an aqueous medium, water is a competitive nucleophile, and attack by water forms oxonium ion **33**. Products, such as **32**, are not involved when other nucleophiles react with the carbocation, and the mechanism is exactly (by the principle of microscopic reversibility) the reverse of *E1* elimination of alcohols (Reaction 17-1).¹⁸¹ The initial carbocation occasionally rearranges to a more stable one. For example, hydration of $\text{CH}_2=\text{CHCH}(\text{CH}_3)_2$ gives $\text{CH}_3\text{CH}_2\text{COH}(\text{CH}_3)_2$. Hydration of simple alkenes leads to alcohols predicted by *Markovnikov's rule*.



*Oxymercuration*¹⁸² (addition of oxygen and mercury) of alkenes followed by *in situ* treatment with sodium borohydride¹⁸³ (Reaction 12-24), gives an alcohol (see example) under mild conditions, in high yields, and without rearrangement products. For example, treatment of 2-methyl-1-butene with mercuric acetate,¹⁸⁴ followed by NaBH_4 , gave 2-methyl-2-butanol. *Oxymercuration* of alkenes has been reported in water, using cyclodextrins as phase-transfer catalysts.¹⁸⁵

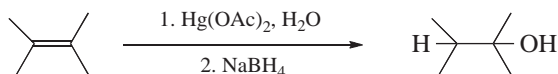
¹⁸¹ See Vinnik, M.I.; Obratsov, P.A. *Russ. Chem. Rev.* **1990**, 59, 63; Liler, M. *Reaction Mechanisms in Sulphuric Acid* Academic Press, NY, **1971**, pp. 210–225.

¹⁸² See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, **1986**; Kitching, W. *Organomet. React.* **1972**, 3, 319; *Organomet. Chem. Rev.* **1968**, 3, 61; Oullette, R.J. in Trahanovsky, W.S. *Oxidation in Organic Chemistry* pt. B, Academic Press, NY, **1973**, pp. 140–166; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 387–396.

¹⁸³ Brown, H.C.; Geoghegan, Jr., P.J. *J. Org. Chem.* **1972**, 37, 1937; Brown, H.C.; Geoghegan Jr., P.J.; Lynch, G.J.; Kurek, J.T. *J. Org. Chem.* **1972**, 37, 1941; Barrelle, M.; Appar, M. *Bull. Soc. Chim. Fr.* **1972**, 2016.

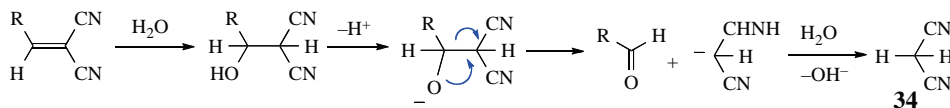
¹⁸⁴ See Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, **1981**, pp. 1–145.

¹⁸⁵ Abreu, A.R.; Costa, I.; Rosa, C.; Ferreira, L.M.; Lourenço, A.; Santos, P.P. *Tetrahedron* **2005**, 61, 11986.



This method, which is applicable to mono-, di-, tri-, and tetraalkyl, as well as phenyl-substituted alkenes, gives almost complete *Markovnikov addition*. Hydroxy, methoxy, acetoxy, halo, and other groups may be present in the substrate, and generally do not cause difficulties.¹⁸⁶ When two double bonds are present in the same molecule, changing the carboxylic acid ligand of the mercuric salt allows oxymercuration of the less-substituted one without affecting the other, with ultrasound.¹⁸⁷ A related reaction treats an alkene with zinc borohydride on silica gel to give a 35:65 mixture of secondary/primary alcohols.¹⁸⁸

With substrates of the type $\text{C}=\text{C}-\text{Z}$ (Z is as defined in Sec.15.A.ii) the product is almost always $\text{HO}-\text{C}-\text{CH}-\text{Z}$ and the mechanism is usually nucleophilic,¹⁸⁹ although electrophilic addition gives the same product¹⁹⁰ since a cation $\text{CH}-\text{C}-\text{Z}$ would be destabilized by the positive charges (full or partial) on two adjacent atoms. However, the α -hydroxy compound $\text{HC}-\text{CH}(\text{OH})\text{Z}$, was obtained by treatment of the substrate with O_2 , PhSiH_3 , and a manganese-complex catalyst.¹⁹¹ Addition of water to $\text{RCH}=\text{CZZ}'$ substrates may result in cleavage of the adduct to give an aldehyde and $\text{CH}_2\text{ZZ}'$ (**34**).¹⁹² The cleavage step is an example of Reaction **12-41**.



For another method of *anti-Markovnikov* hydration, see hydroboration (Reaction **15-16**).

Indirect hydration, with *anti-Markovnikov* orientation, was achieved by treatment of the alkene with a 1:1 mixture of $\text{PhCH}_2\text{NEt}_3^+ \text{BH}_4^-$ and Me_3SiCl , followed by addition of an aqueous solution of K_2CO_3 .¹⁹³ Reaction of alkenes with $\text{Ti}(\text{BH}_4)_3$, and then aq K_2CO_3 also leads to the *anti-Markovnikov* alcohol.¹⁹⁴ Alkenes react with PhO_2BH and a Nb catalyst, followed by oxidation with NaOO^- , to give the alcohol,¹⁹⁵ and Cp_2TiCl_4 can also be used.¹⁹⁶ Conjugated alkenes also react with PhSiH_2 and oxygen, with a Mn catalyst, to give an α -hydroxy ketone.¹⁹⁷ Alkenes react with molecular oxygen in the presence of a Co porphyrin catalyst, and reduction with $\text{P}(\text{OMe})_3$ leads to the secondary alcohol.¹⁹⁸ This procedure has also been used to hydrate conjugated dienes,¹⁹⁹ although conjugated dienes are seldom hydrated.

¹⁸⁶ See the extensive tables in Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, **1986**, pp. 4–71.

¹⁸⁷ Einhorn, J.; Einhorn, C.; Luche, J.L. *J. Org. Chem.* **1989**, *54*, 4479.

¹⁸⁸ Campelo, J.M.; Chakraborty, R.; Marinas, J.M. *Synth. Commun.* **1996**, *26*, 1639.

¹⁸⁹ See Bernasconi, C.F.; Leonarduzzi, G.D. *J. Am. Chem. Soc.* **1982**, *104*, 5133, 5143.

¹⁹⁰ See Noyce, D.S.; DeBruin, K.E. *J. Am. Chem. Soc.* **1968**, *90*, 372.

¹⁹¹ Magnus, P.; Scott, D.A.; Fielding, M.R. *Tetrahedron Lett.* **2001**, *42*, 4127.

¹⁹² Bernasconi, C.F.; Paschalis, P. *J. Am. Chem. Soc.* **1989**, *111*, 5893, and other papers in this series.

¹⁹³ Baskaran, S.; Gupta, V.; Chidambaram, N.; Chandrasekaran, S. *J. Chem. Soc., Chem. Commun.* **1989**, 903.

¹⁹⁴ Kumar, K.S.R.; Baskaran, S.; Chandrasekaran, S. *Tetrahedron Lett.* **1993**, *34*, 171.

¹⁹⁵ Burgess, K.; Jaspars, M. *Tetrahedron Lett.* **1993**, *34*, 6813.

¹⁹⁶ Burgess, K.; van der Donk, W.A. *Tetrahedron Lett.* **1993**, *34*, 6817.

¹⁹⁷ Magnus, P.; Payne, A.H.; Waring, M.J.; Scott, D.A.; Lynch, V. *Tetrahedron Lett.* **2000**, *41*, 9725.

¹⁹⁸ Matsushita, Y.; Sugamoto, K.; Matsui, T. *Chem. Lett.* **1993**, 925.

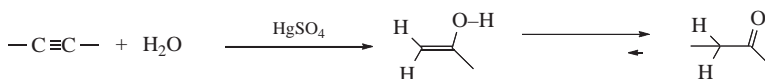
¹⁹⁹ Matshshita, Y.; Sugamoto, K.; Nakama, T.; Sakamoto, T.; Matsui, T.; Nakayama, M. *Tetrahedron Lett.* **1995**, *36*, 1879.

The addition of water to enol ethers causes hydrolysis to aldehydes or ketones (Reaction 10-6). Ketenes add water to give carboxylic acids ($R_2C=C=O \rightarrow R_2CO_2H$) in a reaction catalyzed by acids²⁰⁰:

OS IV, 555, 560; VI, 766. Also see, OS V, 818.

15-4 Hydration of Triple Bonds

Dihydro-oxo-biaddition



The hydration of triple bonds is generally carried out with mercuric ion salts (often the sulfate or acetate or even mercuric oxide) as catalysts.²⁰¹ In contrast to oxymercuration of alkenes, the organomercury intermediate from this reaction is unstable and loss of mercury *in situ* leads to an enol product. The enol tautomerizes to the ketone (see Sec. 2.N.i), so the isolated product is the ketone from either an internal or terminal alkyne (the OH unit will always be on the more substituted carbon via the more stable secondary vinyl carbocation). Only acetylene gives an aldehyde. With alkynes of the form $RC\equiv CR'$ both possible ketone products are usually obtained. The reaction can be conveniently carried out with a catalyst prepared by impregnating mercuric oxide onto Nafion-H (a superacidic perfluorinated resinsulfonic acid; see Sec. 5.A.ii).²⁰² Gold,²⁰³ In,²⁰⁴ and Ru²⁰⁵ catalysts have been used to convert alkynes to the ketone. Gold(I) catalysts have also been used in the hydration of allenes.²⁰⁶ Internal alkynes were treated with 2-aminophenol in refluxing dioxane using a Pd catalyst to produce the corresponding ketone.²⁰⁷ Lactones have been prepared from trimethylsilyl alkenes containing a hydroxyl unit elsewhere in the molecule, when reacted with molecular oxygen, $CuCl_2$, and a Pd catalyst.²⁰⁸ When a carboxylic acid that contains a double bond in the chain is treated with a strong acid, the intramolecular hydration reaction gives a γ - and/or a δ -lactone, regardless of the original position of the double bond in the chain, since strong acids catalyze double-bond shifts (Reaction 15-1; and see 12-2).²⁰⁹ The double bond always migrates to a position favorable for the reaction, whether this has to be toward or away from the carboxyl group. The use of a chiral *Cinchonidine*

²⁰⁰ See Poon, N.L.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1485; Tidwell, T.T. *Acc. Chem. Res.* **1990**, 23, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* **1986**, 42, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* **1975**, 4, 231.

²⁰¹ See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, **1986**, pp. 123–148; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, **1974**, pp. 91–95. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1217–1219.

²⁰² Olah, G.A.; Meidar, D. *Synthesis* **1978**, 671.

²⁰³ Marion, N.; Ramm, R.S.; Nolan, S.P. *J. Am. Chem. Soc.* **2009**, 131, 448; Leyva, A.; Corma, A. *J. Org. Chem.* **2009**, 74, 2067.

²⁰⁴ Hirabayashi, T.; Okimoto, Y.; Saito, A.; Morita, M.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* **2006**, 62, 2231.

²⁰⁵ Alvarez, P.; Basetti, M.; Gimeno, J.; Mancini, G. *Tetrahedron Lett.* **2001**, 42, 8467.

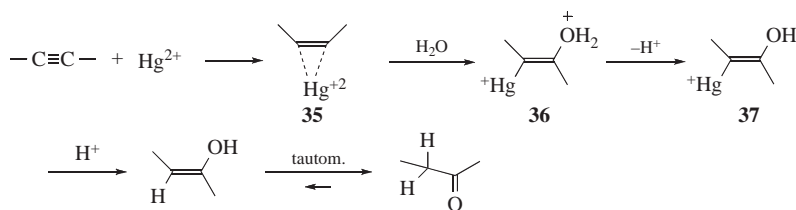
²⁰⁶ Zhang, Z.; Lee, S.D.; Fisher, A.S.; Widenhoefer, R.A. *Tetrahedron* **2009**, 65, 1794.

²⁰⁷ Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, 124, 12670.

²⁰⁸ Compain, P.; Goré, J.; Vatière, J.-M. *Tetrahedron* **1996**, 52, 10405.

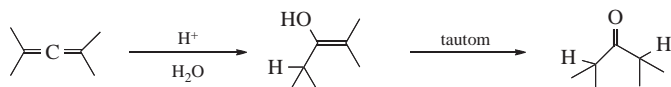
²⁰⁹ See Ansell, M.F.; Palmer, M.H. *Q. Rev. Chem. Soc.* **1964**, 18, 211. For a Rh(I)-catalyzed reaction in ionic liquids, see Oonishi, Y.; Ogura, J.; Sato, Y. *Tetrahedron Lett.* **2007**, 48, 7505.

alkaloid additive leads to lactone formation with modest enantioselectivity.²¹⁰

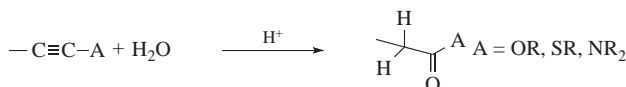


The first step of the mercury-mediated mechanism is formation of a complex (**35**). It is known that ions like Hg^{2+} form complexes with alkynes (Sec. 3.C.i). Water then attacks in an $\text{S}_{\text{N}}2$ type process to give the intermediate **36**, which loses a proton to give **37**. Hydrolysis of **37** (an example of Reaction **12-34**) gives the enol, which tautomerizes to the product. A spectrum of the enol was detected by flash photolysis when phenylacetylene was hydrated photolytically.²¹¹ Note that another possibility for **35** is a mercury-stabilized carbocation rather than a formal three-membered ring complex. In such a carbocation, the carbocation is stabilized by back-donation from the metal, and nucleophilic attack is more like a $\text{S}_{\text{N}}1$ type process.

Metal-free reactions are known, often using strong acids. Phenyl acetylene was converted to acetophenone [e.g., in water at 100°C with a catalytic amount of Tf_2NH (trifluoromethanesulfonimide)], which is a very powerful acid.²¹² Simple alkynes can also be converted to ketones by heating with formic acid, without a catalyst.²¹³ Metal-free hydration of terminal alkynes occurs by reacting water, heated with microwave irradiation, to give the corresponding methyl ketone.²¹⁴ 1-Selenoalkynes (e.g., $\text{PhSe-C}\equiv\text{C-Ph}$) react with tosic acid in dichloromethane to give a seleno ester [$\text{PhSeC(=O)SH}_2\text{Ph}$] after treatment with water.²¹⁵ Allenes can be hydrolyzed to ketones using an acid catalyst.²¹⁶



Carboxylic esters, thiol esters, and amides can be made, respectively, by acid-catalyzed hydration of acetylenic ethers, thioethers,²¹⁷ and ynamines, without a mercuric catalyst.²¹⁸



²¹⁰ Wang, M.; Gao, L.X.; Mai, W.P.; Xia, A.X.; Wang, F.; Zhang, S.B. *J. Org. Chem.* **2004**, 69, 2874.

²¹¹ Chiang, Y.; Kresge, A.J.; Capponi, M.; Wirz, J. *Helv. Chim. Acta* **1986**, 69, 1331.

²¹² Tsuchimoto, T.; Joya, T.; Shirakawa, E.; Kawakami, Y. *Synlett* **2000**, 1777.

²¹³ Menashe, N.; Reshef, D.; Shvo, Y. *J. Org. Chem.* **1991**, 56, 2912.

²¹⁴ Vasudevan, A.; Verzas, M.K. *Synlett* **2004**, 631. An acid catalyst may be added, see Le Bras, G.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2006**, 47, 5497.

²¹⁵ Sheng, S.; Liu, X. *Org. Prep. Proceed. Int.* **2002**, 34, 499.

²¹⁶ See Cramer, P.; Tidwell, T.T. *J. Org. Chem.* **1981**, 46, 2683.

²¹⁷ Braga, A.L.; Martins, T.L.C.; Silveira, C.C.; Rodrigues, O.E.D. *Tetrahedron* **2001**, 57, 3297. Also see Brandsma, L.; Bos, H.J.T.; Arens, J.F. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 751–860.

²¹⁸ Arens, J.F. *Adv. Org. Chem.* **1960**, 2, 163; Brandsma, L.; Bos, H.J.T.; Arens, J.F. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 774–775.

This is ordinary electrophilic addition, with rate-determining protonation as the first step.²¹⁹ Certain other alkynes have also been hydrated to ketones with strong acids in the absence of mercuric salts.²²⁰

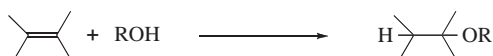
Catalysts have been developed for the *anti-Markovnikov* hydration of alkynes.²²¹ When 1-octyne was heated with water, isopropyl alcohol and a Ru catalyst, for example, the product was octanal.²²² The presence of certain functionality can influence the regioselectivity of hydration.

A Ni catalyzed reaction has been reported between alkynes and allyl phenyl sulfides to give thioallylation.²²³

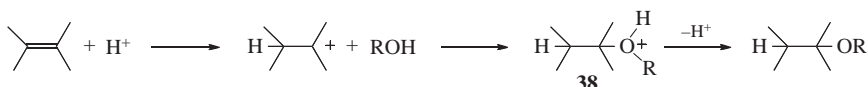
OS **III**, 22; **IV**, 13; **V**, 1024.

15-5 Addition of Alcohols and Phenols

Hydro-alkoxy-addition



Just as water adds to an alkene via hydration to form an alcohol, alcohols can also add to form an ether. Addition of alcohols and phenols to double bonds is catalyzed by acids or bases. When the reactions are acid catalyzed, the mechanism is electrophilic, where H^+ of the acid catalyst, is attacked by the π bond. The more stable carbocation is formed and subsequently attacked by a molecule of alcohol to give an oxonium ion (**38**).



The addition, therefore, follows *Markovnikov's rule*. Primary alcohols give better results than secondary, and tertiary alcohols are relatively inactive. This method is convenient for the preparation of tertiary ethers by the use of a suitable alkene (e.g., $\text{Me}_2\text{C}=\text{CH}_2$). Addition of alcohols to allylic systems can proceed with rearrangement, and the use of chiral additive can lead to asymmetric induction.²²⁴ The uncatalyzed addition of alcohols occurs in supercritical alcohols.²²⁵

Metal-catalyzed addition to alkenes is a useful variation. The Pd catalyzed addition of alcohols to aryl alkenes gives the ether.²²⁶ The Au(III)— CuCl_2 catalyzed reaction of alcohols and alkenes gives the ether.²²⁷ Gold(I) catalyzed intermolecular addition of phenols leads to aryl ethers.²²⁸

²¹⁹ Banait, N.; Hojatti, M.; Findlay, P.; Kresge, A.J. *Can. J. Chem.* **1987**, 65, 441.

²²⁰ Noyce, D.S.; Schiavelli, M.D. *J. Org. Chem.* **1968**, 33, 845; *J. Am. Chem. Soc.* **1968**, 90, 1020, 1023.

²²¹ Labonne, A.; Kribber, T.; Hintermann, L. *Org. Lett.* **2006**, 8, 5853.

²²² Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* **2001**, 3, 735. Also see Grotjahn, D.B.; Lev, D.A. *J. Am. Chem. Soc.* **2004**, 126, 12232.

²²³ Hua, R.; Takeda, H.; Onozawa, S.-y.; Abe, Y.; Tanaka, M. *Org. Lett.* **2007**, 9, 263.

²²⁴ See Nakamura, H.; Ishihara, K.; Yamamoto, H. *J. Org. Chem.* **2002**, 67, 5124.

²²⁵ Kamitanaka, T.; Hikida, T.; Hayashi, S.; Kishida, N.; Matsuda, T.; Harada, T. *Tetrahedron Lett.* **2007**, 48, 8460.

²²⁶ Gligorich, K.M.; Schultz, M.J.; Sigman, M.S. *J. Am. Chem. Soc.* **2006**, 128, 2794.

²²⁷ Zhang, X.; Corma, A. *Chem. Commun.* **2007**, 3080.

²²⁸ Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, 127, 6966.

Alcohols add intramolecularly to alkenes to generate cyclic ethers, and the product often bears a hydroxyl unit,²²⁹ but not always.²³⁰ Cyclization is facilitated by Re,²³¹ Ti,²³² or Pt compounds,²³³ forming functionalized tetrahydrofurans or tetrahydropyans. Intramolecular addition of alcohols to alkenes can be promoted by a Pd catalyst, but migration of the double bond in the final product is sometimes a problem.²³⁴ Furan derivatives are available from alkene–ketones using CuCl₂ and a Pd²³⁵ Cr,²³⁶ Ag(I),²³⁷ or lanthanide catalyst.²³⁸ A gold catalyst was used with conjugated ketones bearing an alkyne substituent to give fused-ring furans.²³⁹ Note that the reaction of an alkene–alcohol and NIS with a chiral Ti catalyst leads to a THF with a pendant iodoalkyl group, with modest enantioselectivity.²⁴⁰

Alcohols add to alkynes under certain conditions to give vinyl ethers. In an excess of alcohol, and in the presence of a Pt²⁴¹ or a Au catalyst,²⁴² internal alkynes are converted to ketals. The alcohol to alkyne addition reaction is quite useful for the preparation of heterocycles. Dihydrofurans,²⁴³ furans,²⁴⁴ benzofurans,²⁴⁵ and pyran derivatives²⁴⁶ have been prepared using this approach. Tetrahydrofurans bearing an exocyclic double bond (vinylidene tetrahydrofurans) were prepared from alkynyl alcohols and a silver carbonate catalyst.²⁴⁷

Allenes that react with alcohols and allenic alcohols have been converted to THF derivatives bearing a vinyl group at the α -position, using diphenyliodonium salts.²⁴⁸ In the presence of allylic bromide and a Pd catalyst, allenic alcohols lead to allylically substituted dihydrofurans.²⁴⁹ The intramolecular Au(I) catalyzed reaction of alcohols and allenes has been reported.²⁵⁰ Intramolecular addition of alcohols to allenes leads to cyclic vinyl ethers.²⁵¹

²²⁹ Gruttadauria, M.; Aprile, C.; Riela, S.; Noto, R. *Tetrahedron Lett.* **2001**, 42, 2213.

²³⁰ Miura, K.; Hondo, T.; Okajima, S.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Org. Chem.* **2002**, 67, 6082; Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* **2002**, 4, 4451.

²³¹ McDonald, F.E.; Towne, T.B. *J. Org. Chem.* **1995**, 60, 5750.

²³² Lattanzi, A.; Della Sala, G.D.; Russo, M.; Screttri, A. *Synlett* **2001**, 1479.

²³³ Qian, H.; Han, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* **2004**, 126, 9536.

²³⁴ Rönn, M.; Bäckvall, J.-E.; Andersson, P.G. *Tetrahedron Lett.* **1995**, 36, 7749. See Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* **1999**, 797.

²³⁵ Han, X.; Widenhoefer, R.A. *J. Org. Chem.* **2004**, 69, 1738.

²³⁶ Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2002**, 124, 5260.

²³⁷ Yang, C.-G.; Reich, N.W.; Shi, Z.; He, C. *Org. Lett.* **2005**, 7, 4553.

²³⁸ Yu, X.; Seo, S.Y.; Marks, T.J. *J. Am. Chem. Soc.* **2007**, 129, 7244.

²³⁹ Yao, T.; Zhang, X.; Larock, R.C. *J. Am. Chem. Soc.* **2004**, 126, 11164.

²⁴⁰ Kang, S.H.; Park, C.M.; Lee, S.B.; Kim, M. *Synlett* **2004**, 1279.

²⁴¹ Hartman, J.W.; Sperry, L. *Tetrahedron Lett.* **2004**, 45, 3787.

²⁴² Antonietti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, 127, 9976; Santos, L.L.; Ruiz, V.R.; Sabater, M.J.; Corma, A. *Tetrahedron* **2008**, 64, 7902.

²⁴³ Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, 64, 7687.

²⁴⁴ Qing, F.L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* **2000**, 65, 2003. See Kel'in, A.V.; Gevorgyan, V. *J. Org. Chem.* **2002**, 67, 95.

²⁴⁵ Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, 2, 297. See also, Arcadi, A.; Cacchi, S.; DiGiuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, 453.

²⁴⁶ Davidson, M.H.; McDonald, F.E. *Org. Lett.* **2004**, 6, 1601.

²⁴⁷ Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019.

²⁴⁸ The phenyl group also added to the allene. Kang, S.-K.; Baik, T.-G.; Kulak, A.N. *Synlett* **1999**, 324.

²⁴⁹ Ma, S.; Gao, W. *J. Org. Chem.* **2002**, 67, 6104.

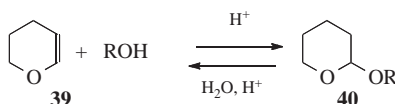
²⁵⁰ Zhang, Z.; Widenhoefer, R.A. *Angew. Chem. Int. Ed.* **2007**, 46, 283.

²⁵¹ Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* **2004**, 69, 6867.

Functionalized ethers can be formed in the presence of other reagents. In methanol with a $R-Se-Br$ reagent, alkenes are converted to selenoalkyl ethers ($MeO-C-C-SeR$).²⁵²

Base-catalyzed reactions are known. For those substrates more susceptible to nucleophilic attack, for example, polyhalo alkenes and alkenes of the type $C=C-Z$, it is better to carry out the reaction in basic solution, where the attacking species is RO^- .²⁵³ The reactions with $C=C-Z$ are of the *Michael type*, and OR goes to the side away from the Z .²⁵⁴

Since triple bonds are more susceptible to nucleophilic attack than double bonds, it might be expected that bases would catalyze addition to triple bonds particularly well. This is the case, and enol ethers and acetals can be produced by this reaction.²⁵⁵ Because enol ethers are more susceptible than triple bonds to electrophilic attack, the addition of alcohols to enol ethers can also be catalyzed by acids.²⁵⁶ One utilization of this reaction



involves the compound dihydropyran (**39**), which is often used to protect the OH groups of primary and secondary alcohols²⁵⁷ and phenols.²⁵⁸ When the desired reactions are completed, **40** is easily cleaved by treatment with dilute acids (Reaction 10-6). In base-catalyzed addition to triple bonds, the rate falls in going from a primary to a tertiary alcohol, and phenols require more severe conditions.

Photochemical addition of alcohols to certain double-bond compounds (cyclohexenes, cycloheptenes) is possible²⁵⁹ in the presence of a photosensitizer (e.g., benzene). The mechanism is electrophilic and *Markovnikov* orientation is found. The alkenes react in their first excited triplet states.²⁶⁰

The oxymercuration–demercuration procedure mentioned in Reaction 15-3 can be adapted to the preparation of ethers in what is known as *alkoxymercuration–demercuration* (*Markovnikov* orientation), if the reaction is carried out in an alcohol (ROH) solvent.²⁶¹ For example, oxymercuration of 2-methyl-1-butene in ethanol gives $EtMe_2COEt$.²⁶² Primary alcohols give good yields when mercuric acetate is used, but for secondary and tertiary alcohols, it is necessary to use mercuric trifluoroacetate.²⁶³ However, even this reagent fails where the product would be a ditertiary ether. It is possible to combine the alcohol reactant with another reagent. The reaction of an alkene with iodine and allyl alcohol, in the presence of HgO , gave the *vic*-iodo ether.²⁶⁴ Alkene-alcohols react with mercuric trifluoroacetate and the aq KBr (with $LiBH_4/BEt_3$) to

²⁵² Back, T.G.; Moussa, Z.; Parvez, M. *J. Org. Chem.* **2002**, 67, 499.

²⁵³ See Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* **1965**, 4, 51, pp. 53–61.

²⁵⁴ See Farnsworth, M.V.; Cross, M.J.; Louie, J. *Tetrahedron Lett.* **2004**, 45, 7441.

²⁵⁵ Shostakovskii, M.F.; Trofimov, B.A.; Atavin, A.S.; Lavrov, V.I. *Russ. Chem. Rev.* **1968**, 37, 907.

²⁵⁶ See Kresge, A.J.; Yin, Y. *J. Phys. Org. Chem.* **1989**, 2, 43.

²⁵⁷ See Bolitt, V.; Mioskowski, C.; Shin, D.; Falck, J.R. *Tetrahedron Lett.* **1988**, 29, 4583.

²⁵⁸ See Johnston, R.D.; Marston, C.R.; Krieger, P.E.; Goem G.L. *Synthesis* **1988**, 393.

²⁵⁹ See Wan, P.; Yates, K. *Rev. Chem. Intermed.* **1984**, 5, 157.

²⁶⁰ Marshall, J.A. *Acc. Chem. Res.* **1969**, 2, 33.

²⁶¹ See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, **1986**, pp. 162–345.

²⁶² Brown, H.C.; Rei, M. *J. Am. Chem. Soc.* **1969**, 91, 5646.

²⁶³ Brown, H.C.; Kurek, J.T.; Rei, M.; Thompson, K.L. *J. Org. Chem.* **1984**, 49, 2551; **1985**, 50, 1171.

²⁶⁴ Talybov, G.M.; Mekhtieva, V.Z.; Karaev, S.F. *Russ. J. Org. Chem.* **2001**, 37, 600.

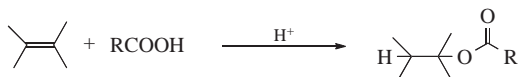
give a THF derivative bearing an iodoalkyl substituent [—O—C—CH(I)R].²⁶⁵ Alkynes generally react under the same conditions to give acetals. If the oxymercuration is carried out in the presence of a hydroperoxide instead of an alcohol, the product (after demercuration with NaBH_4) is an alkyl peroxide (*peroxy-mercuration*).²⁶⁶ This can be done intramolecularly.²⁶⁷

Both alcohols and phenols add to ketenes to give carboxylic esters [$\text{R}_2\text{C}=\text{C}=\text{O} + \text{ROH} \rightarrow \text{R}_2\text{CHCO}_2\text{R}$].²⁶⁸ This has been done intramolecularly (with the ketene end of the molecule generated and used *in situ*) to form medium- and large-ring lactones.²⁶⁹ In the presence of a strong acid, ketene reacts with aldehydes or ketones (in their enol forms) to give enol acetates. 1,4-Asymmetric induction is possible when chiral alcohols add to ketenes.²⁷⁰

OS **III**, 371, 774, 813; **IV**, 184, 558; **VI**, 916; **VII**, 66, 160, 304, 334, 381; **VIII**, 204, 254; **IX**, 472.

15-6 Addition of Carboxylic Acids to Form Esters

Hydro-acyloxy-addition



Carboxylic esters are produced by the addition of carboxylic acids to alkenes, a reaction that is usually acid catalyzed (by Brønsted–Lowry or Lewis acids²⁷¹) and similar in mechanism to Reaction **15-5**. Since *Markovnikov's rule* is followed, hard-to-get esters of tertiary alcohols can be prepared from alkenes of the form $\text{R}_2\text{C}=\text{CHR}$.²⁷² Carboxylic esters have also been prepared by the acyloxymercuration–demercuration of alkenes (similar to the procedures mentioned in Reactions **15-3** and **15-4**).²⁷³ Addition of carboxylic acids to alkenes to form esters or lactones is catalyzed by Pd compounds.²⁷⁴ Thallium acetate also promotes this cyclization reaction.²⁷⁵ Diene carboxylic acids have been cyclized using acetic acid and a Pd catalyst to form lactones that have an allylic acetate moiety elsewhere in the molecule.²⁷⁶

²⁶⁵ Kang, S.H.; Kim, M. *J. Am. Chem. Soc.* **2003**, 125, 4684. For an enantioselective example, see Kang, S.H.; Lee, S.B.; Park, C.M. *J. Am. Chem. Soc.* **2003**, 125, 15748.

²⁶⁶ See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, **1986**, pp. 346–366.

²⁶⁷ Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, F. *Tetrahedron Lett.* **1995**, 36, 463.

²⁶⁸ Quadbeck, G. *Newer Methods Prep. Org. Chem.* **1963**, 2, 133–161. See Tidwell, T.T. *Acc. Chem. Res.* **1990**, 23, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* **1986**, 42, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* **1975**, 4, 231.

²⁶⁹ Boeckman, Jr., R.K.; Pruitt, J.R. *J. Am. Chem. Soc.* **1989**, 111, 8286.

²⁷⁰ Cannizzaro, C.E.; Strassner, T.; Houk, K.N. *J. Am. Chem. Soc.* **2001**, 123, 2668.

²⁷¹ See Ballantine, J.A.; Davies, M.; Purnell, H.; Rayanakorn, M.; Thomas, J.M.; Williams, K.J. *J. Chem. Soc., Chem. Commun.* **1981**, 8.

²⁷² See Peterson, P.E.; Tao, E.V.P. *J. Org. Chem.* **1964**, 29, 2322.

²⁷³ See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis* Springer, NY, **1986**, pp. 367–442.

²⁷⁴ Larock, R.C.; Hightower, T.R. *J. Org. Chem.* **1993**, 58, 5298; Annby, U.; Stenkula, M.; Andersson, C.-M. *Tetrahedron Lett.* **1993**, 34, 8545.

²⁷⁵ Ferraz, H.M.C.; Ribeiro, C.M.R. *Synth. Commun.* **1992**, 22, 399.

²⁷⁶ Verboom, R.C.; Persson, B.A.; Bäckvall, J.-E. *J. Org. Chem.* **2004**, 69, 3102.

Triple bonds can give enol esters²⁷⁷ or acylals when treated with carboxylic acids. Mercuric salts are usually catalysts,²⁷⁸ and vinylmercury compounds ($\text{RO}_2\text{C}-\text{C}=\text{C}-\text{HgX}$) are intermediates,²⁷⁹ but Ru complexes have also been used.²⁸⁰ Terminal alkynes ($\text{RC}\equiv\text{CH}$) react with CO_2 , a secondary amine ($\text{R}'_2\text{NH}$), and a Ru complex catalyst, to give enol carbamates $[\text{RCH}=\text{CHOC}(=\text{O})\text{NR}]$.²⁸¹ This reaction has also been performed intramolecularly, to produce unsaturated lactones.²⁸² Cyclic unsaturated lactones (internal vinyl esters) have been generated from alkyne-carboxylic acids using a Pd²⁸³ or a Ru catalyst.²⁸⁴ Carboxylic esters can also be obtained by the addition to alkenes of diacyl peroxides.²⁸⁵ These reactions are catalyzed by Cu and are free radical processes.

Allene carboxylic acids have been cyclized to butenolides with copper(II) chloride.²⁸⁶ Allene esters were converted to butenolides by treatment with acetic acid and LiBr.²⁸⁷ Cyclic carbonates can be prepared from allene alcohols using carbon dioxide and a Pd catalyst.²⁸⁸ Carboxylic acids react with ketenes to give anhydrides²⁸⁹ and acetic anhydride is prepared industrially in this manner $[\text{CH}_2=\text{C}=\text{O} + \text{MeCO}_2\text{H} \rightarrow (\text{MeC}=\text{O})_2\text{O}]$.

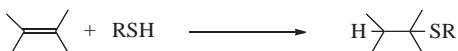
Sulfonic acids add to alkenes and alkynes. The reaction of an alkyne with *p*-toluenesulfonic acid and treatment with silica gives the vinyl sulfonate ($\text{C}=\text{C}-\text{OSO}_2\text{ToI}$).²⁹⁰ Cyclic sulfonates can be generated by the reaction of an allylic sulfonate salt ($\text{C}=\text{C}-\text{C}-\text{OSO}_3^-$) with silver nitrate in acetonitrile containing an excess of bromine and a catalytic amount of water.²⁹¹ Sultones are formed when alkenes react with PhIO and 2 equiv of $\text{Me}_2\text{SiSO}_3\text{Cl}$.²⁹²

OS III, 853; IV, 261, 417, 444; V, 852, 863; VII, 30, 411. Also see, OS I, 317.

C. Sulfur on the Other Side

15-7 Addition of H_2S and Thiols

Hydro-alkylthio-addition



²⁷⁷ Goossen, L.J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706. See Hua, R.; Tian, X. *J. Org. Chem.* **2004**, 69, 5782.

²⁷⁸ See Bianchini, C.; Meli, A.; Peruzzini, M.; Zanolini, F.; Bruneau, C.; Dixneuf, P.H. *Organometallics* **1990**, 9, 1155.

²⁷⁹ Bassetti, M.; Floris, B. *J. Chem. Soc. Perkin Trans. 2*, **1988**, 227; Grishin, Yu.K.; Bazhenov, D.V.; Ustynyuk, Yu.A.; Zefirov, N.S.; Kartashov, V.R.; Sokolova, T.N.; Skorobogatova, E.V.; Chernov, A.N. *Tetrahedron Lett.* **1988**, 29, 4631.

²⁸⁰ Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, 52, 2230.

²⁸¹ Mahé, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P.H. *J. Org. Chem.* **1989**, 54, 1518.

²⁸² See Sofia, M.J.; Katzenellenbogen, J.A. *J. Org. Chem.* **1985**, 50, 2331. For a list of other examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, p. 1895.

²⁸³ Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, 60, 3711.

²⁸⁴ Jiménez-Tenorio, M.; Puerta, M.C.; Valerga, P.; Moreno-Dorado, F.J.; Guerra, F.M.; Massanet, G.M. *Chem. Commun.* **2001**, 2324.

²⁸⁵ Kharasch, M.S.; Fono, A. *J. Org. Chem.* **1959**, 24, 606; Kochi, J.K. *J. Am. Chem. Soc.* **1962**, 84, 1572.

²⁸⁶ Ma, S.; Wu, S. *J. Org. Chem.* **1999**, 64, 9314.

²⁸⁷ Ma, S.; Li, L.; Wei, Q.; Xie, H.; Wang, G.; Shi, Z.; Zhang, J. *Pure Appl. Chem.* **2000**, 72, 1739.

²⁸⁸ Uemura, K.; Shiraishi, D.; Noziri, M.; Inoue, Y. *Bull. Chem. Soc. Jpn.* **1999**, 72, 1063.

²⁸⁹ See Blake, P.G.; Vayjooee, M.H.B. *J. Chem. Soc. Perkin Trans. 2*, **1976**, 1533.

²⁹⁰ Braga, A.L.; Emmerich, D.J.; Silveira, C.C.; Martins, T.L.C.; Rodrigues, O.E.D. *Synlett* **2001**, 371.

²⁹¹ Steinmann, J.E.; Phillips, J.H.; Sanders, W.J.; Kiessling, L.L. *Org. Lett.* **2001**, 3, 3557.

²⁹² Bassindale, A.R.; Katampe, I.; Maesano, M.G.; Patel, P.; Taylor, P.G. *Tetrahedron Lett.* **199**, 40, 7417.

Hydrogen sulfide (H_2S) and thiols add to alkenes to give alkyl thiols or sulfides by electrophilic, nucleophilic, or free radical mechanisms.²⁹³ In the absence of initiators, the addition to simple alkenes is by an electrophilic mechanism, similar to that in Reaction 15-5, and *Markovnikov's rule* is followed. However, this reaction is usually very slow and often cannot be done or requires very severe conditions unless a Brønsted–Lowry or Lewis acid catalyst is used. For example, the reaction can be performed in concentrated H_2SO_4 ²⁹⁴ or with the addition of AlCl_3 .²⁹⁵ In the presence of free radical initiators, H_2S and thiols add to double and triple bonds by a free radical mechanism and the orientation is *anti-Markovnikov*.²⁹⁶ *Anti-Markovnikov* addition of thiols to vinyl ethers occurs under solvent- and catalyst-free conditions,²⁹⁷ and is promoted by water.²⁹⁸

Additives can influence the regioselectivity. Styrene reacts with thiophenol to give primarily the *anti-Markovnikov* product, whereas addition of thiophenol in the presence of Montmorillonite K-10 clay gives primarily the *Markovnikov addition* product.²⁹⁹ The addition of thiophenol to an alkene with a zeolite, however, leads to the *anti-Markovnikov* sulfide.³⁰⁰ In fact, the orientation can be used as a diagnostic tool to indicate which mechanism is operating. Free radical addition can be done with H_2S , RSH (R may be primary, secondary, or tertiary), ArSH , or RCOSH .³⁰¹ The R group may contain various functional groups. The alkenes may be terminal, internal, contain branching, be cyclic, and have various functional groups including OH, CO_2H , CO_2R , NO_2 , RSO_2 , and so on. Addition of Ph_3SiSH to terminal alkenes under radical conditions also leads to the primary thiol.³⁰²

Alkynes react with thiols to give vinyl sulfides. With alkynes it is possible to add 1 or 2 molar equivalents of RSH , giving a vinyl sulfide³⁰³ or a dithioacetal, respectively. Thiols also add to alkynes with a Pd catalyst to give vinyl sulfides.³⁰⁴ Thiols add to alkenes under photochemical conditions to form thioethers, and the reaction can be done intramolecularly to give cyclic thioethers.³⁰⁵ Thiocarbonates function as thiol surrogates, converting alkenes to alkyl thiols in the presence of TiCl_4 and CuO .³⁰⁶ Sulfonic acids add to alkynes to give vinyl sulfonates in the presence of a Au catalyst.³⁰⁷ A cesium carbonate catalyzed reaction

²⁹³ See Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, **1974**, pp. 169–178.

²⁹⁴ Shostakovskii, M.F.; Kul'bovskaia, N.K.; Gracheva, E.P.; Laba, V.I.; Yakushina, L.M. *J. Gen. Chem. USSR* **1962**, 32, 707.

²⁹⁵ Belley, M.; Zamboni, R. *J. Org. Chem.* **1989**, 54, 1230.

²⁹⁶ See Voronkov, M.G.; Martynov, A.V.; Mirskova, A.N. *Sulfur Rep.*, **1986**, 6, 77; Griesbaum, K. *Angew. Chem. Int. Ed.* **1970**, 9, 273; Oswald, A.A.; Griesbaum, K. in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, **1966**, pp. 233–256; Stacey, F.W.; Harris, Jr., J.F. *Org. React.* **1963**, 13, 150, pp. 165–196, 247–324.

²⁹⁷ Lou, F.-W.; Xu, J.-M.; Liu, B.-K.; Wu, Q.; Pan, Q.; Lin, X.-F. *Tetrahedron Lett.* **2007**, 48, 8815. For a solvent free, Ce(III)-promoted reaction, see Silveira, C.C.; Mendes, S.R.; Líbero, F.M. *Synlett* **2010**, 790.

²⁹⁸ Ranu, B.C.; Mandal, T. *Synlett* **2007**, 925; Ranu, B.C. *Can. J. Chem.* **2009**, 87, 1605.

²⁹⁹ Kanagasabapathy, S.; Sudalai, A.; Benicewicz, B.C. *Tetrahedron Lett.* **2001**, 42, 3791.

³⁰⁰ Kumar, P.; Pandey, R.K.; Hegde, V.R. *Synlett* **1999**, 1921.

³⁰¹ Janssen, M.J. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, **1969**, pp. 720–723.

³⁰² Haché, B.; Gareau, Y. *Tetrahedron Lett.* **1994**, 35, 1837.

³⁰³ See Arjona, O.; Medel, R.; Rojas, J.; Costa, A.M.; Vilarrasa, J. *Tetrahedron Lett.* **2003**, 44, 6369.

³⁰⁴ Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, 114, 5902.

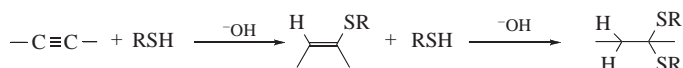
³⁰⁵ Kirpichenko, S.V.; Tolstikova, L.L.; Suslova, E.N.; Voronkov, M.G. *Tetrahedron Lett.* **1993**, 34, 3889.

³⁰⁶ Mukaiyama, T.; Saitoh, T.; Jona, H. *Chem. Lett.* **2001**, 638.

³⁰⁷ Cui, D.-M.; Meng, Q.; Zheng, J.-Z.; Zhang, C. *Chem. Commun.* **2009**, 1577.

gives the vinyl sulfide with good (*Z*)-selectivity.³⁰⁸ The $\text{Rh}^{-309}\text{In}^{-}$,³¹⁰ organoactinide³¹¹, organozirconium-,³¹² or Pt catalyzed³¹³ reaction of alkynes with thiols gives the corresponding vinyl sulfide. Similar results were obtained under solvent-free conditions using an alumina-KF system.³¹⁴ Alternative preparations are available, as in the reaction of a terminal alkyne with $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ followed by PhSCl to give the vinyl sulfide with the SPh unit at the less substituted position ($\text{PhCH}=\text{CHSPh}$).³¹⁵ The intramolecular addition of a thiol to an ene-yne, with a Pd catalyst, leads to substituted thiophene derivatives.³¹⁶ Alkenes react with diphenyl disulfide in the presence of GaCl_3 to give the product with two phenylthio units ($\text{PhS}-\text{C}-\text{C}-\text{SPh}$).³¹⁷ The reaction of an alkyne with diphenyl disulfide and a Pd catalyst leads to the bis(vinyl) sulfide ($\text{PhS}-\text{C}=\text{C}-\text{SPh}$).³¹⁸

When thiols are added to substrates susceptible to nucleophilic attack, bases catalyze the reaction and the mechanism is nucleophilic. These substrates may be of the *Michael type*³¹⁹ or may be polyhalo alkenes or alkynes.²⁵⁵ As with the free-radical mechanism, alkynes can give either vinylic thioethers or dithioacetals:



By any mechanism, the initial product of addition of H_2S to a double bond is a thiol, which is capable of adding to a second molecule of alkene, so that sulfides are often produced: $\text{C}=\text{C} \rightarrow \text{H}-\text{C}-\text{C}-\text{S}-\text{C}-\text{C}-\text{H}$. As with alcohols, ketenes add thiols to give thiol esters $[\text{R}_2\text{C}=\text{C}=\text{O} + \text{RSH} \rightarrow \text{R}_2\text{CHCOSR}]$.³²⁰

Selenium compounds (RSeH) add in a similar manner to thiols.³²¹ Vinyl selenides can be prepared from alkynes using diphenyl diselenide and sodium borohydride.³²² A Pd(II) catalyzed reaction of PhSeH with alkynes, in pyridine, also gives the corresponding vinyl selenide.³²³

The conjugate addition of thiols to α,β -unsaturated carbonyl derivatives is discussed in Reaction 15-31.

OS III, 458; IV, 669; VIII, 302. See also, OS VIII, 458.

³⁰⁸ Kondoh, A.; Takami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2005**, 70, 6468.

³⁰⁹ Cao, C.; Fraser, L.R.; Love, J.A. *J. Am. Chem. Soc.* **2005**, 127, 17614; Yang, J.; Sabarre, A.; Fraser, L.R.; Patrick, B.O.; Love, J.A. *J. Org. Chem.* **2009**, 74, 182.

³¹⁰ Yadav, J.S.; Subba Reddy, B.V.; Raju, A.; Ravindar, K.; Baishya, G. *Chem. Lett.* **2007**, 36, 1474

³¹¹ Weiss, C.J.; Wobser, S.D.; Marks, T.J. *J. Am. Chem. Soc.* **2009**, 131, 2062.

³¹² Weiss, C.J.; Marks, T.J. *J. Am. Chem. Soc.* **2010**, 132, 10533.

³¹³ Yamashita, F.; Kuniyasu, H.; Terao, J.; Kambe, N. *Org. Lett.* **2008**, 10, 101.

³¹⁴ Silva, M.S.; Lara, R.G.; Marczewski, J.M.; Jacob, R.G.; Lenardão, E.J.; Perin, G. *Tetrahedron Lett.* **2008**, 49, 1927.

³¹⁵ Huang, X.; Zhong, P.; Guo, W.-r. *Org. Prep. Proceed. Int.* **1999**, 31, 201.

³¹⁶ Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, 2, 351.

³¹⁷ Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, 6, 601.

³¹⁸ Ananikov, V.P.; Beletskaya, I.P. *Org. Biomol. Chem.* **2004**, 2, 284.

³¹⁹ See Gassman, P.G.; Gilbert, D.P.; Cole, S.M. *J. Org. Chem.* **1977**, 42, 3233.

³²⁰ See Blake, A.J.; Friend, C.L.; Outram, R.J.; Simpkins, N.S.; Whitehead, A.J. *Tetrahedron Lett.* **2001**, 42, 2877.

³²¹ Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Sonoda, N. *Tetrahedron Lett.* **1992**, 33, 5525.

³²² Dabdoub, M.J.; Baroni, A.C.M.; Lenardão, E.J.; Gianeti, T.R.; Hurtado, G.R. *Tetrahedron* **2001**, 57, 4271.

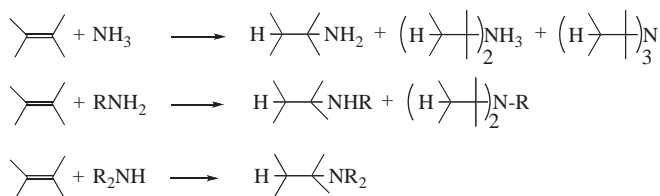
³²³ Kamiya, I.; Nishinaka, E.; Ogawa, A. *J. Org. Chem.* **2005**, 70, 696.

D. Nitrogen or Phosphorus on the Other Side

15-8 Addition of Ammonia and Amines, Phosphines, and Related Compounds³²⁴

Hydro-amino-addition

Hydro-phosphino-addition



Ammonia and primary and secondary amines add to alkenes *in some cases*.³²⁵ Ammonia and amines are much weaker acids than water, alcohols, and thiols (see Reactions **15-3**, **15-5**, and **15-7**) and since acids turn NH_3 into the weak acid, the ammonium ion (NH_4^+), this reaction does not occur by an electrophilic mechanism. The reaction tends to give very low yields, if any, with ordinary alkenes, unless extreme conditions are used (e.g., 178–200 °C, 800–1000 atm, and the presence of metallic Na, for the reaction between NH_3 and ethylene³²⁶). There is, however, a proton-catalyzed hydroamination reaction in which aniline derivatives add to alkenes in the presence of anilinium salts, in 20–90% yield depending on the alkene.³²⁷

There are many examples of transition-catalyzed addition of nitrogen compounds to alkenes, alkynes,³²⁸ and so on. Amines can be added to certain nonactivated alkenes using Pd,³²⁹ Rh,³³⁰ In,³³¹ Ti,³³² Fe,³³³ Ta,³³⁴ Au,³³⁵ Y,³³⁶ Mo,³³⁷ and various lanthanide catalysts.³³⁸ 1,3-Dienes,³³⁹ and also allenes,³⁴⁰ undergo hydroamination in the presence

³²⁴ Müller, T.E.; Hultsch, K.C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

³²⁵ See Gasc, M.B.; Lattes, A.; Périé, J.J. *Tetrahedron* **1983**, *39*, 703; Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds* Academic Press, NY, **1977**, pp. 423–454; Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C.G.; Seayad, J.; Thiel, O.R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579. For selectivity, see Tillack, A.; Khedkar, V.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 8875.

³²⁶ Howk, B.W.; Little, E.L.; Scott, S.L.; Whitman, G.M. *J. Am. Chem. Soc.* **1954**, *76*, 1899.

³²⁷ Anderson, L.L.; Arnold, J.; Bergman, R.G. *J. Am. Chem. Soc.* **2005**, *127*, 14542.

³²⁸ For a review, see Doye, S. *Synlett* **2004**, 1653.

³²⁹ See Gasc, M.B.; Lattes, A.; Périé, J.J. *Tetrahedron* **1983**, *39*, 703; Bäckvall, J. *Adv. Met.-Org. Chem.* **1989**, *1*, 135. Also see Rogers, M.M.; Kotov, V.; Chatwichien, J.; Stahl, S.S. *Org. Lett.* **2007**, *9*, 4331. See also Singer, R.A.; Doré, M.; Sieser, J.E.; Berliner, M.A. *Tetrahedron Lett.* **2006**, *47*, 3727.

³³⁰ The anti-Markovnikov amine is produced: Utsonomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* **2004**, *126*, 2702; Routaboul, L.; Buch, C.; Klein, H.; Jackstell, R.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 7401. For mechanistic studies, see Takaya, J.; Hartwig, J.F. *J. Am. Chem. Soc.* **2005**, *127*, 5756.

³³¹ Huang, J.-M.; Wong, C.-M.; Xu, F.-X.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 3375.

³³² Kaspar, L.T.; Fingerhut, B.; Ackermann, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 5972.

³³³ Michaux, J.; Terrasson, V.; Marque, S.; Wehbe, J.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 2601.

³³⁴ Herzon, S.B.; Hartwig, J.F. *J. Am. Chem. Soc.* **2007**, *129*, 6690.

³³⁵ Hesp, K.D.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 18026.

³³⁶ O'Shaughnessy, P.N.; Scott, P. *Tetrahedron Asymmetry* **2003**, *14*, 1979.

³³⁷ Srivastava, R.S.; Nicholas, K.M. *Chem. Commun.* **1996**, 2335.

³³⁸ Hultsch, K.C. *Org. Biomol. Chem.* **2005**, *3*, 1819; Yin, P.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 3791. See Reznichenko, A.L.; Nguyen, H.N.; Hultsch, K.C. *Angew. Chem. Int. Ed.* **2010**, *49*, 8984.

³³⁹ Brouwer, C.; He, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1744.

³⁴⁰ Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3314.

of an Au catalyst. Complexation with the metal lowers the electron density of the double bond, facilitating nucleophilic attack.³⁴¹ *Markovnikov* orientation is observed and the addition is anti.³⁴² Aniline reacts with dienes and a Pd catalyst to give allylic amines.³⁴³ Diene amines react with Sm catalysts to give 2-alkenyl pyrrolidines.³⁴⁴ The mechanism of the Au(I) catalyzed hydroamination reaction of alkenes has been studied.³⁴⁵ It is believed to involve a ligand substitution reaction in the active Au species followed by nucleophile attack of the N-nucleophile on the activated double bond, which is followed by proton transfer from the NH₂ group to the unsaturated carbon atom.

Cyclization reactions are useful variations of this reaction. An intramolecular addition of an amine unit to an alkene to form a pyrrolidine was reported using a Pd³⁴⁶ Rh,³⁴⁷ Sc,³⁴⁸ Sm,³⁴⁹ Ti,³⁵⁰ Zr,³⁵¹ or a Lu catalyst.³⁵² as well as a lanthanide reagent,³⁵³ or a Y reagent.³⁵⁴ An intramolecular Ca mediated reaction of amino alkenes leads to cyclic amines.³⁵⁵ Alkenyl amines give cyclic amines as the major product, in good yield, when treated with *n*-butyllithium.³⁵⁶ Reaction of a secondary amine with butyllithium generates an amide base, which reacts with alkenes to give alkyl amines,³⁵⁷ and can add intramolecularly to an alkene to form a pyrrolidine.³⁵⁸ Pyrroles can be generated in this manner.³⁵⁹

Other nitrogen compounds, among them hydroxylamine and hydroxylamines,³⁶⁰ hydrazines, and amides (Reaction 15-9), also add to alkenes. Tertiary amines (except those that are too bulky) add to *Michael-type* substrates (C=C—Z) in a reaction that is catalyzed by acids like HCl or HNO₃ to give the corresponding quaternary ammonium salts (R₃N⁺—C—C—Z).³⁶¹ The tertiary amine can be aliphatic, cycloalkyl, or heterocyclic (including pyridine). The reaction of NaOH with an amine containing two distal alkene units, followed by addition of a neodymium catalyst, leads to a bicyclic amine.³⁶²

³⁴¹ See Hegedus, L.S.; Åkermarck, B.; Zetterberg, K.; Olsson, L.F. *J. Am. Chem. Soc.* **1984**, *106*, 7122.

³⁴² See Utsunomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* **2003**, *125*, 14286.

³⁴³ Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshifuji, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4501.

³⁴⁴ Hong, S.; Marks, T.J. *J. Am. Chem. Soc.* **2002**, *124*, 7886.

³⁴⁵ Kovács, G.; Ujaque, G.; Lledós, A. *J. Am. Chem. Soc.* **2008**, *130*, 853.

³⁴⁶ Ney, J.E.; Wolfe, J.P. *J. Am. Chem. Soc.* **2005**, *127*, 8644. See also, Sakai, N.; Ridder, A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2006**, *128*, 8134; Rogers, M.M.; Wendlandt, J.E.; Guzei, I.A.; Stahl, S.S. *Org. Lett.* **2006**, *8*, 2257.

³⁴⁷ Takemiya, A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2006**, *128*, 6042; Liu, Z.; Hartwig, J.F. *J. Am. Chem. Soc.* **2008**, *130*, 1570.

³⁴⁸ Kim, J.Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 4391.

³⁴⁹ Quinet, C.; Ates, A.; Markó, I.E. *Tetrahedron Lett.* **2008**, *49*, 5032.

³⁵⁰ Müller, C.; Loos, C.; Schulenberg, N.; Doye, S. *Eur. J. Org. Chem.* **2006**, 2499.

³⁵¹ Kim, H.; Lee, P.H.; Livinghouse, T. *Chem. Commun.* **2005**, 5205; Yang, L.; Xu, L.-W.; Zhou, W.; Gao, Y.-H.; Sun, W.; Xia, C.-G. *Synlett* **2009**, 1167.

³⁵² Gribkov, D.V.; Hultzsich, K.C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.

³⁵³ Ryu, J.-S.; Marks, T.J.; McDonald, F.E. *Org. Lett.* **2001**, *3*, 3091. See Hong, S.; Tian, S.; Metz, M.V.; Marks, T. *J. Am. Chem. Soc.* **2003**, *125*, 14768.

³⁵⁴ Kim, Y.K.; Livinghouse, T.; Bercaw, J.E. *Tetrahedron Lett.* **2001**, *42*, 2933.

³⁵⁵ Crimmin, M.R.; Casely, I.J.; Hill, M.S. *J. Am. Chem. Soc.* **2005**, *127*, 2042.

³⁵⁶ Ates, A.; Quinet, C. *Eur. J. Org. Chem.* **2003**, 1623.

³⁵⁷ Hartung, C.G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* **2000**, *56*, 5157.

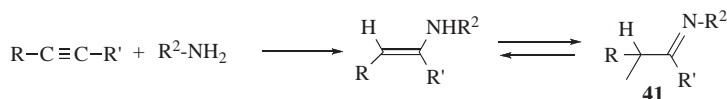
³⁵⁸ Fujita, H.; Tokuda, M.; Nitta, M.; Sugimoto, H. *Tetrahedron Lett.* **1992**, *33*, 6359.

³⁵⁹ Dieter, R.K.; Yu, H. *Org. Lett.* **2000**, *2*, 2283.

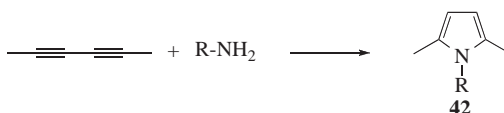
³⁶⁰ Singh, S.; Nicholas, K.M. *Synth. Commun.* **2001**, *31*, 3087.

³⁶¹ Le Berre, A.; Delacroix, A. *Bull. Soc. Chim. Fr.* **1973**, 640, 647. See also, Vogel, D.E.; Büchi, G. *Org. Synth.*, **66**, 29.

³⁶² Molander, G.A.; Pack, S.K. *J. Org. Chem.* **2003**, *68*, 9214.



Primary amines add to triple bonds³⁶³ to give enamines that have a hydrogen on the nitrogen and (analogously to enols) tautomerize (Sec. 2.N.ii, category 4) to the more stable imines (**41**).³⁶⁴ The reaction has been done with a Pd,³⁶⁵ a Ti,³⁶⁶ a Ta,³⁶⁷ a Cu,³⁶⁸ or an Au catalyst.³⁶⁹ An intramolecular addition of amines to an alkyne unit in the presence of a Pd catalyst generated heterocyclic or cyclic amine compounds.³⁷⁰ A variation treats an alkynyl imine with CuI to form pyrroles.³⁷¹ *N,N*-Diphenylhydrazine reacts with diphenyl acetylene and a Ti catalyst to give indole derivatives.³⁷² Treatment of an imine of 2-alkynyl benzaldehyde with iodide gave a functionalized isoquinoline.³⁷³ When ammonia is used instead of a primary amine, the corresponding $\text{R}_2\text{C}=\text{NH}$ imine product is not stable enough for isolation, but polymerizes. Ammonia and primary amines (aliphatic and aromatic) add to conjugated diynes to give pyrroles (**42**).³⁷⁴ *Anti-Markovnikov* addition of alkynes is possible using a Cu catalyst.³⁷⁵



A related reaction of amines and alkynes, in supercritical CO_2 , leads to amides.³⁷⁶

Allenes are reaction partners,³⁷⁷ and amines add to allenes in the presence of a catalytic amount of CuBr,³⁷⁸ Au,³⁷⁹ or Pd compounds.³⁸⁰ Intramolecular reaction of allene amines leads to dihydropyrroles, using a Au catalyst.³⁸¹ Cyclic imines can be prepared from allene amines using a Ti catalyst.³⁸²

³⁶³ See Chekulaeva, I.A.; Kondrat'eva, L.V. *Russ. Chem. Rev.* **1965**, *34*, 669; Hartung, C.G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* **2001**, *66*, 6339.

³⁶⁴ See Kruse, C.W.; Kleinschmidt, R.F. *J. Am. Chem. Soc.* **1961**, *83*, 213, 216.

³⁶⁵ Patil, N.T.; Lutete, L.M.; Wu, H.; Pahadi, N.K.; Gridnev, I.D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270.

³⁶⁶ Khedkar, V.; Tillack, A.; Beller, M. *Org. Lett.* **2003**, *5*, 4767; Tillack, A.; Castro, I.G.; Hartung, C.G.; Beller, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2541; Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2001**, 4411.

³⁶⁷ Anderson, L.L.; Arnold, J.; Bergman R.G. *Org. Lett.* **2004**, *6*, 2519; Cao, C.; Li, Y.; Shi, Y.; Odom, A.L. *Chem. Commun.*, **2004**, 2002.

³⁶⁸ Shanbhag, G.V.; Kumbhar, S.M.; Joseph, T.; Halligudi, S.B. *Tetrahedron Lett.* **2006**, *47*, 141.

³⁶⁹ Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349.

³⁷⁰ MülHiroya, K.; Matsumoto, S.; Sakamoto, T. *Org. Lett.* **2004**, *6*, 2953; Lutete, L.M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622. See also, Karur, S.; Kotti, S.R.S.S.; Xu, X.; Cannon, J.F.; Headley, A.; Li, G. *J. Am. Chem. Soc.* **2003**, *125*, 13340.

³⁷¹ Kel'in, A.; Sromek, A.W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074.

³⁷² Ackermann, L.; Born, R. *Tetrahedron Lett.* **2004**, *45*, 9541. For a different approach using hypervalent iodine, see Barluenga, J.; Trincado, M.; Rubio, E.; González, J.M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2406.

³⁷³ Huang, Q.; Hunter, J.A.; Larock, R.C. *J. Org. Chem.* **2002**, *67*, 3437.

³⁷⁴ Schult, K.E.; Reisch, J.; Walker, H. *Chem. Ber.* **1965**, *98*, 98.

³⁷⁵ Zhou, L.; Bohle, D.S.; Jiang, H.-F.; Li, C.-J. *Synlett* **2009**, 937.

³⁷⁶ Mak, X.Y.; Ciccolini, R.P.; Robinson, J.M.; Tester, J.W.; Danheiser, R.L. *J. Org. Chem.* **2009**, *74*, 9381.

³⁷⁷ Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421.

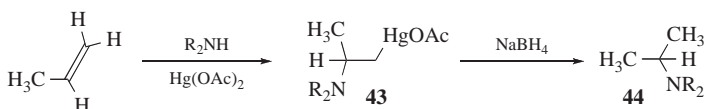
³⁷⁸ Geri, R.; Polizzi, C.; Lardicci, L.; Caporusso, A.M. *Gazz. Chim. Ital.*, **1994**, *124*, 241.

³⁷⁹ Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* **2009**, *11*, 3166.

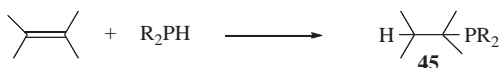
³⁸⁰ Davies, I.W.; Scopes, D.I.C.; Gallagher, T. *Synlett* **1993**, 85.

³⁸¹ Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121.

³⁸² Ackermann, L.; Bergman, R.G.; Loy, R.N. *J. Am. Chem. Soc.* **2003**, *125*, 11956.



A NH_2 or NR_2 unit can be added to double bonds (even ordinary double bonds) in an indirect manner by the use of hydroboration (Reaction 15-16) followed by treatment with NH_2Cl or $\text{NH}_2\text{OSO}_2\text{OH}$ (Reaction 12-32). This produces a primary amine with *anti-Markovnikov* orientation. An indirect way of adding a primary or secondary amine to a double bond consists of aminomercuration to give **43**, followed by reduction (see Reaction 15-3 for the analogous *oxymmercuration-demercuration* procedure) to give amine **44**.³⁸³ The addition of a secondary amine produces a tertiary amine, while addition of a primary amine gives a secondary amine. The overall orientation follows *Markovnikov's rule*. For conversion of **43** to other products, see Reaction 15-53.



Phosphines add to alkenes to give alkyl phosphines (**45**) and to alkynes to give vinyl phosphines. A Pd catalyzed reaction of alkenes and triarylphosphines gives alkyltrialkylphosphonium salts.³⁸⁴ Alkenes also react with diarylphosphines and a Ni catalyst to give the alkyl phosphine.³⁸⁵ Silylphosphines ($\text{R}_3\text{Si}-\text{PAR}_2$) react with alkenes and Bu_4NF to give the *anti-Markovnikov* allyl phosphine.³⁸⁶ Phosphine oxides can be prepared by the reaction of an aryl substituted alkene and diphenylphosphine oxide, $\text{Ph}_2\text{P}(=\text{O})\text{H}$.³⁸⁷ Phosphonate esters were similarly prepared from alkenes and diethyl phosphite $[(\text{EtO})_2\text{P}(=\text{O})\text{H}]$ and an Mn catalyst in a reaction exposed to oxygen.³⁸⁸ Similar addition was observed in the reaction of an alkene with NaH_2PO_2 to give the phosphinate $[\text{RCH}=\text{CH}_2 \rightarrow \text{RCH}_2\text{CH}_2\text{P}(=\text{O})\text{ONa}]$.³⁸⁹ Palladium catalysts were used for the preparation of similar compounds from alkenes³⁹⁰ and the reaction of terminal alkynes with dimethyl phosphite and a Ni catalyst gave the *Markovnikov* vinyl phosphonate ester.³⁹¹

In the presence of an Yb catalyst, diphenylphosphine added to diphenyl acetylene to give the corresponding vinyl phosphine.³⁹² A Pd catalyst was used for the addition of diphenylphosphine to terminal alkynes, giving the *anti-Markovnikov* vinyl phosphine, but a Ni catalyst led to the *Markovnikov* vinyl phosphine.³⁹³ A Co catalyst has also been used.³⁹⁴ Diphenylphosphine oxide also reacted with terminal alkynes to give the

³⁸³ See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, **1986**, pp. 443–504. See also, Barluenga, J.; Perez-Prieto, J.; Asensio, G. *Tetrahedron* **1990**, *46*, 2453.

³⁸⁴ Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2006**, *128*, 50. See Kawaguchi, S.-i.; Nagata, S.; Nomoto, A.; Sonoda, M.; Ogawa, A. *J. Org. Chem.* **2008**, *73*, 7928.

³⁸⁵ Shulyupin, M.O.; Kazankova, M.A.; Beletskaya, I.P. *Org. Lett.* **2002**, *4*, 761.

³⁸⁶ Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* **2004**, *45*, 9167.

³⁸⁷ Bunlaksanansorn, T.; Knochel, P. *J. Org. Chem.* **2004**, *69*, 4595.

³⁸⁸ Tayama, O.; Nakano, A.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 5494.

³⁸⁹ Deprère, S.; Montchamp, J.-L. *J. Org. Chem.* **2001**, *66*, 6745.

³⁹⁰ Deprère, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9386.

³⁹¹ Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* **2004**, *126*, 5080.

³⁹² Takaki, K.; Koshiji, G.; Komeyama, K.; Takeda, M.; Shishido, T.; Kitani, A.; Takehira, K. *J. Org. Chem.* **2003**, *68*, 6554.

³⁹³ Kazankova, M.A.; Efimova, I.V.; Kochetkov, A.N.; Atanas'ev, V.V.; Beletskaya, I.P.; Dixneuf, P.H. *Synlett* **2001**, 497.

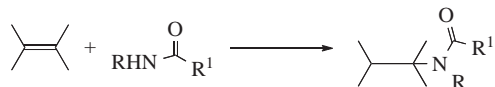
³⁹⁴ Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 2368.

anti-Markovnikov vinyl phosphine oxide using an Rh catalyst.³⁹⁵ Other phosphites were added to dienes to give an allylic phosphonate ester using a Pd catalyst.³⁹⁶ Diarylphosphines react with vinyl ethers and a Ni catalyst to give α -alkoxy phosphonate esters.³⁹⁷

OS I, 196; III, 91, 93, 244, 258; IV, 146, 205; V, 39, 575, 929; VI, 75, 943; VIII, 188, 190, 536; 80, 75. See also, OS VI, 932.

15-9 Addition of Amides

Hydro-amido-addition



Under certain conditions, primary and secondary amides can add directly to alkenes to form *N*-alkylated amides. Sulfonamides react in a similar manner. Alkenes react with amides and related compounds in the presence of certain transition metals. The Ti catalyzed reaction of alkenyl *N*-tosylamines gives *N*-tosyl cyclic amines.³⁹⁸

The reaction can be done intramolecularly. 3-Pentenamide cyclized to 5-methyl-2-pyrrolidinone by treatment with trifluorosulfonic acid.³⁹⁹ *N*-Benzyl pent-4-ynamide reacted with tetrabutylammonium fluoride to an alkylidene lactam.⁴⁰⁰ Acyl hydrazine derivatives also cyclize in the presence of hypervalent iodine reagents to give lactams.⁴⁰¹ Treatment of triflamide alkenes with triflic acid gives the corresponding *N*-triflyl cyclic amine.⁴⁰² Intramolecular cyclization of sulfamate esters, catalyzed by a Rh complex, leads to cyclic sulfamates.⁴⁰³

Alkynes and allenes also react with amides. A Ru/In catalyzed addition of sulfonamides to alkynes leads to cyclic *N*-sulfonyl derivatives.⁴⁰⁴ Palladium-catalyzed reactions give similar results,⁴⁰⁵ and Bi and Hf have been used as catalysts.⁴⁰⁶ Phenylthiomethyl alkynes were converted to *N*-Boc-*N*-phenylthio allenes with Boc azide and an iron catalyst.⁴⁰⁷ Enamides are prepared by the Re⁴⁰⁸ or Ru catalyzed⁴⁰⁹ hydroamidation of terminal alkynes with amides. The Pd catalyzed reaction of an allene amide, with iodobenzene, leads to *N*-sulfonyl aziridines having an allylic group at C-1.⁴¹⁰ Other allene *N*-tosylamines similarly give *N*-tosyl tetrahydropyridines.⁴¹¹

³⁹⁵ Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* **2001**, 66, 5929.

³⁹⁶ Mirzaei, F.; Han, L.-B.; Tanaka, M. *Tetrahedron Lett.* **2001**, 42, 297.

³⁹⁷ Kazankova, M.A.; Shulyupin, M.O.; Beletskaya, I.P. *Synlett* **2003**, 2155.

³⁹⁸ Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* **2000**, 2, 385.

³⁹⁹ Marson, C.M.; Fallah, A. *Tetrahedron Lett.* **1994**, 35, 293.

⁴⁰⁰ Jacobi, P.A.; Briellmann, H.L.; Hauck, S.I. *J. Org. Chem.* **1996**, 61, 5013.

⁴⁰¹ Scartozzi, M.; Grondin, R.; Leblanc, Y. *Tetrahedron Lett.* **1992**, 33, 5717.

⁴⁰² Schlummer, B.; Hartwig, J.F. *Org. Lett.* **2002**, 4, 1471; Haskins, C.M.; Knight, D.W. *Chem. Commun.* **2002**, 2724.

⁴⁰³ Zalatan, D.N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, 130, 9220.

⁴⁰⁴ Trost, B.M.; Maulide, N.; Livingston, R.C. *J. Am. Chem. Soc.* **2008**, 130, 16502.

⁴⁰⁵ Bajracharya, G.B.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2005**, 70, 4883; Patil, N.T.; Huo, Z.; Bajracharya, G.B.; Yamamoto, Y. *J. Org. Chem.* **2006**, 71, 3612; Narsireddy, M.; Yamamoto, Y. *J. Org. Chem.* **2008**, 73, 9698.

⁴⁰⁶ Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chemistry: Asian J.* **2007**, 2, 150.

⁴⁰⁷ Bacci, J.P.; Greenman, K.L.; van Vranken, D.L. *J. Org. Chem.* **2003**, 68, 4955.

⁴⁰⁸ Yudha S., S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, 9, 5609.

⁴⁰⁹ Gooßen, L.J.; Salih, K.S.M.; Blanchot, M. *Angew. Chem. Int. Ed.* **2008**, 47, 8492.

⁴¹⁰ Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, 64, 2992.

⁴¹¹ Na, S.; Yu, F.; Gao, W. *J. Org. Chem.* **2003**, 68, 5943; Ma, S.; Gao, W. *Org. Lett.* **2002**, 4, 2989.

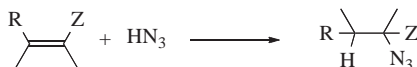
N-Bromocarbamates also add to alkenes, in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give a *vic*-bromo *N*-Boc amine.⁴¹² When a carbamate was treated with Bu_3SnH , and AIBN, addition to an alkene led to a bicyclic lactam.⁴¹³ Alkenyl amides and carbamates react with transition metal catalysts to form lactams or cyclic carbamates. Similar addition of a tosylamide–alkene, with a Pd catalyst, led to a vinyl *N*-tosyl pyrrolidine.⁴¹⁴ Both Pd⁴¹⁵ and Au⁴¹⁶ catalyzed cyclization reactions of carbamates are known, and Os compounds have been used.⁴¹⁷ Ionic liquids have been used to catalyze these reactions.⁴¹⁸

Imides can also add to alkenes or alkynes. Phthalimide reacts with an alkene in the presence of a Pd catalyst.⁴¹⁹ Ethyl 2-propynoate reacted with phthalimide, in the presence of a Pd catalyst, to give ethyl 2-phthalimido-2-propenoate.⁴²⁰

Nickel-catalyzed hydrophosphinylation reactions are known, such as the reaction of an alkyne with an alkyl phosphinate to give a vinyl phosphinate ester.⁴²¹ Both H-phosphinates and secondary phosphine oxides add to alkenes in an *anti*-Markovnikov manner, induced by air in what is likely a radical reaction.⁴²²

15-10 Addition of Hydrazoic Acid

Hydro-azido-addition



Hydrazoic acid (HN_3) can be added to certain Michael-type substrates (Z is as defined in Sec. 15.A.ii) to give β -azido compounds.⁴²³ The reaction apparently fails if R is phenyl. Hydrazoic acid also adds to enol ethers $\text{CH}_2=\text{CHOR}$ to give $\text{CH}_3-\text{CH}(\text{OR})\text{N}_3$, and to silyl enol ethers,⁴²⁴ but it does not add to ordinary alkenes unless a Lewis acid catalyst (e.g., TiCl_4) is used, in which case good yields of azide can be obtained.⁴²⁴

⁴¹² Sliwiska, A.; Zwierzak, A. *Tetrahedron* **2003**, 59, 5927.

⁴¹³ Callier, A.-C.; Quiclet-Sire, B.; Zard, S.Z. *Tetrahedron Lett.* **1994**, 35, 6109.

⁴¹⁴ Larock, R.C.; Hightower, T.R.; Hasvold, L.A.; Peterson, K.P. *J. Org. Chem.* **1996**, 61, 3584. See also, Pinho, P.; Minnaard, A.J.; Feringa, B.L. *Org. Lett.* **2003**, 5, 259. For an electrochemical variation, see Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2008**, 130, 13542.

⁴¹⁵ Alexanian, E.J.; Lee, C.; Sorensen, E.J. *J. Am. Chem. Soc.* **2005**, 127, 7690; Michael, F.E.; Cochran, B.M. *J. Am. Chem. Soc.* **2006**, 128, 4246. For a related reaction, see Zabawa, T.P.; Kasi, D.; Chemler, S.R. *J. Am. Chem. Soc.* **2005**, 127, 11250.

⁴¹⁶ Zhang, Z.; Liu, C.; Kinder, R.E.; Han, X.; Qian, H.; Widenhoefer, R.A. *J. Am. Chem. Soc.* **2006**, 128, 9066; LaLonde, R.L.; Sherry, B.D.; Kang, E.J.; Toste, F.D. *J. Am. Chem. Soc.* **2007**, 129, 2452; Han, X.; Widenhoefer, R.A. *Angew. Chem. Int. Ed.* **2006**, 45, 1747.

⁴¹⁷ Donohoe, T.J.; Chughtai, M.J.; Klauber, D.J.; Griffin, D.; Campbell, A.D. *J. Am. Chem. Soc.* **2006**, 128, 2514.

⁴¹⁸ Yang, L.; Xu, L.-W.; Xia, C.-G. *Synthesis* **2009**, 1969.

⁴¹⁹ Brice, J.L.; Harang, J.E.; Timokhin, V.I.; Anastasi, N.R.; Stahl, S.S. *J. Am. Chem. Soc.* **2005**, 127, 2868; Liu, G.; Stahl, S.S. *J. Am. Chem. Soc.* **2006**, 128, 7179; Qian, H.; Widenhoefer, R.A. *Org. Lett.* **2005**, 7, 2635.

⁴²⁰ Trost, B.M.; Dake, G.R. *J. Am. Chem. Soc.* **1997**, 119, 7595.

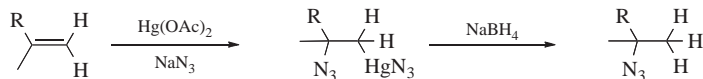
⁴²¹ Ribière, P.; Bravo-Altamirano, K.; Antczak, M.I.; Hawkins, J.D.; Montchamp, J.-L. *J. Org. Chem.* **2005**, 70, 4064.

⁴²² Hirai, T.; Han, L.-B. *Org. Lett.* **2007**, 9, 53.

⁴²³ Harvey, G.R.; Ratts, K.W. *J. Org. Chem.* **1966**, 31, 3907. See Biffin, M.E.C.; Miller, J.; Paul, D.B. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, **1971**, pp. 120–136.

⁴²⁴ Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, 49, 4237.

Hydrazoic acid can also be added indirectly to ordinary alkenes by azidomercuration, followed by demercuration,⁴²⁵ analogous to the

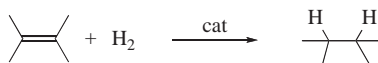


similar procedures mentioned in Reactions **15-3**, **15-5**, **15-6**, and **15-8**. The method can be applied to terminal alkenes or strained cycloalkenes (e.g., norbornene), but fails for unstrained internal alkenes. A variation is the hydroazidation reaction of alkenes using a Co catalyst and *tert*-BuOOH to give the alkyl azide.⁴²⁶

E. Hydrogen on Both Sides

15-11 Hydrogenation of Double and Triple Bonds⁴²⁷

Dihydro-addition



Most carbon–carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents, can be catalytically hydrogenated, usually in quantitative or near-quantitative yields.⁴²⁸ However, a transition metal catalyst is required to break apart H₂ into metal-bound hydrogen atoms before reaction can occur with the alkene. Almost all known alkenes added hydrogen at temperatures between 0 and 275 °C. The catalysts used can be divided into two broad classes, both of which mainly consist of transition metals and their compounds: (1) Catalysts insoluble in the reaction medium (*heterogeneous catalysts*). Among the most effective are Raney nickel,⁴²⁹ Pd-on-charcoal (perhaps the most common),⁴³⁰ NaBH₄ reduced nickel⁴³¹ (also called nickel boride), Pt metal or its oxide, Rh, Ru, and zinc oxide,⁴³² (2) Catalysts soluble in the reaction medium

⁴²⁵ Heathcock, C.H. *Angew. Chem. Int. Ed.* **1969**, 8, 134. See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, **1986**, pp. 522–527.

⁴²⁶ Waser, J.; Nambu, H.; Carreira, E.M. *J. Am. Chem. Soc.* **2005**, 127, 8294.

⁴²⁷ See Mitsui, S.; Kasahara, A. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, **1970**, pp. 175–214. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 422–438.

⁴²⁸ See Rylander, P.N. *Hydrogenation Methods* Academic Press, NY, **1985**; *Catalytic Hydrogenation in Organic Synthesis* Academic Press, NY, **1979**; Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis* Wiley, NY, **1978**; *Practical Catalytic Hydrogenation* Wiley, NY, **1971**; Augustine, R.L. *Catalytic Hydrogenation* Marcel Dekker, NY, **1965**; Parker, D. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 979–1047.

⁴²⁹ Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, **1974**, pp. 175–311; Pojer, P.M. *Chem. Ind. (London)* **1986**, 177.

⁴³⁰ See Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* **2004**, 45, 2421.

⁴³¹ See Ganem, B.; Osby, J.O. *Chem. Rev.* **1986**, 86, 763.

⁴³² See Minachev, Kh.M.; Khodakov, Yu.S.; Nakhshunov, V.S. *Russ. Chem. Rev.* **1976**, 45, 142.

(homogeneous catalysts).⁴³³ An important example is chlorotris(triphenylphosphine)rhodium [RhCl(Ph₃P)₃],⁴³⁴ **46**, *Wilkinson's catalyst*,⁴³⁵ which catalyzes the hydrogenation of many alkenyl compounds without disturbing such groups as CO₂R, NO₂, CN, or COR present in the same molecule.⁴³⁶ Even unsaturated aldehydes can be reduced to saturated aldehydes,⁴³⁷ although in this case decarbonylation (Reaction **14-32**) may be a side reaction. In general, for catalytic hydrogenation many functional groups may be present in the molecule, for example, OH, COOH, NR₂ (including NH₂), and N(R)COR' (including carbamates),⁴³⁸ CHO, COR, CO₂R, or CN. Vinyl esters can be hydrogenated using homogeneous Rh catalyst.⁴³⁹ Some of these groups are also susceptible to catalytic reduction, but it is usually possible to find conditions under which double bonds can be reduced selectively⁴⁴⁰ (see Table 19.2). Controlling the solvent allows catalytic hydrogenation of an alkene in the presence of an aromatic nitro group.⁴⁴¹

Modification of the catalyst includes a polymer bound Ru catalyst,⁴⁴² and a polymer incarcerated Pd catalyst.⁴⁴³ A nanoparticulate Pd catalyst in an ionic liquid has been used for the hydrogenation of alkenes.⁴⁴⁴

Homogeneous catalysts have the advantages of better catalyst reproducibility and better selectivity. Apart from *Wilkinson's catalyst* (**46**), chlorotris(triphenylphosphine)hydridoruthenium(II) [(Ph₃P)₃RuClH]⁴⁴⁵ is an important homogeneous catalyst that is specific for terminal double bonds (other double bonds are hydrogenated slowly or not at all). Homogeneous catalysts are also less susceptible to catalyst poisoning.⁴⁴⁶ Heterogeneous catalysts are usually poisoned by small amounts of sulfur, often found in rubber stoppers, or by thiols and sulfides.⁴⁴⁷ Note that heterogeneous catalysts are usually easier to separate from a reaction mixture.

Using soluble, homogeneous catalysts, unfunctionalized alkenes are hydrogenated with good diastereoselectivity and enantioselectivity⁴⁴⁸ using various metal catalysts

⁴³³ James, B.R. *Homogeneous Hydrogenation* Wiley, NY, **1973**; Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry* University Science Books, Mill Valley, CA **1987**, pp. 523–564; Birch, A.J.; Williamson, D.H. *Org. React.* **1976**, *24*, 1; James, B.R. *Adv. Organomet. Chem.* **1979**, *17*, 319; Harmon, R.E.; Gupta, S.K.; Brown, D.J. *Chem. Rev.* **1973**, *73*, 21; Rylander, P.N. *Organic Syntheses with Noble Metal Catalysts* Academic Press, NY, **1973**, pp. 60–76.

⁴³⁴ See van Bekkum, H.; van Rantwijk, F.; van de Putte, T. *Tetrahedron Lett.* **1969**, 1.

⁴³⁵ See Jardine, F.H. *Prog. Inorg. Chem.* **1981**, *28*, 63–202.

⁴³⁶ Harmon, R.E.; Parsons, J.L.; Cooke, D.W.; Gupta, S.K.; Schoonenberg, J. *J. Org. Chem.* **1969**, *34*, 3684. See also, Mohrig, J.R.; Dabora, S.L.; Foster, T.F.; Schultz, S.C. *J. Org. Chem.* **1984**, *49*, 5179.

⁴³⁷ Jardine, F.H.; Wilkinson, G. *J. Chem. Soc. C* **1967**, 270.

⁴³⁸ Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2000**, *56*, 8433.

⁴³⁹ Tang, W.; Liu, D.; Zhang, X. *Org. Lett.* **2003**, *5*, 205.

⁴⁴⁰ See Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, **1967**, pp. 59–120. Also see, Hudlicky, M. *Reductions in Organic Chemistry* Ellis Horwood Ltd., Chichester **1984**.

⁴⁴¹ Jourdan, A.; González-Zamora, E.; Zhu, J. *J. Org. Chem.* **2002**, *67*, 3163.

⁴⁴² Taylor, R.A.; Santora, B.P.; Gagné, M.R. *Org. Lett.* **2000**, *2*, 1781.

⁴⁴³ Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 2871. See also, Bremeyer, N.; Ley, S.V.; Ramarao, C.; Shirley, I.M.; Smith, S.C. *Synlett* **2002**, 1843.

⁴⁴⁴ Huang, J.; Jiang, T.; Han, B.; Gao, H.; Chang, Y.; Zhao, G.; Wu, W. *Chem. Commun.* **2003**, 1654.

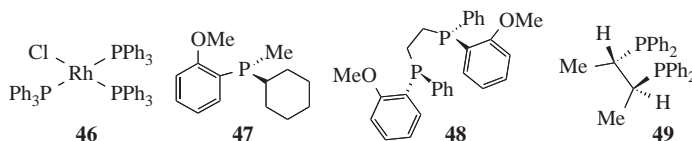
⁴⁴⁵ Hallman, P.S.; McGarvey, B.R.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 3143; Jardine, F.H.; McQuillin, F.J. *Tetrahedron Lett.* **1968**, 5189.

⁴⁴⁶ Birch, A.J.; Walker, K.A.M. *Tetrahedron Lett.* **1967**, 1935.

⁴⁴⁷ Barbier, J.; Lamy-Pitara, E.; Marecot, P.; Boitiaux, J.P.; Cosyns, J.; Verna, F. *Adv. Catal.* **1990**, *37*, 279–318.

⁴⁴⁸ Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.

(e.g., Ir,⁴⁴⁹ Pd,⁴⁵⁰ or Zr,⁴⁵¹ and chiral ligands).⁴⁵² The chiral transition metal catalyst (Rh and Ru are probably the most common) is usually prepared with suitable chiral ligands prior to addition to the reaction. Alternatively, an achiral catalyst (e.g., *Wilkinson's catalyst*, **46**), is simply added along with a chiral ligand. With monophosphine chiral ligands,⁴⁵³ the phosphorous may be chiral, as in **47** (called R-camp)⁴⁵⁴ or bis(phosphine) **48** (called dipamp),⁴⁵⁵ but pyramidal inversion at elevated temperatures (see Sec. 4.C) limits the utility of such ligands. The alternative is to prepare phosphines that contain a chiral carbon, as in **49** (known as Chiraphos),⁴⁵⁶ but there are many variations of chiral bis(phosphine) ligands.⁴⁵⁷ Chiral poisoning has been used as a strategy for asymmetric catalysis.⁴⁵⁸



Hydrogenations are carried out at room temperature and just above atmospheric pressure, in most cases, but some double bonds are more resistant and require higher temperatures and pressures. The poor reactivity is usually a function of increasing substitution and is presumably caused by steric factors. Trisubstituted double bonds require, say, 25 °C and 100 atm, while tetrasubstituted double bonds may require 275 °C and 1000 atm. Among the double bonds most difficult to hydrogenate or which cannot be hydrogenated at all are those common to two rings, as in steroid **49**. Hydrogenations, even at about atmospheric pressure, are often performed in a special hydrogenator, but this is not always necessary. Indeed, placing a hydrogen-filled balloon over the reaction flask is common for small-scale hydrogenations that do not require heat or

⁴⁴⁹ Roseblade, S.J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402; Källström, K.; Andersson, P.G. *Tetrahedron Lett.* **2006**, *47*, 7477; Li, X.; Kong, L.; Gao, Y.; Wang, X. *Tetrahedron Lett.* **2007**, *48*, 3915; Özkar, S.; Finke, R.G. *J. Am. Chem. Soc.* **2005**, *127*, 4800; Schrems, M.G.; Neumann, E.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8274; Källström, K.; Munslow, I.; Andersson, P.G. *Chemistry: European J.* **2006**, *12*, 3194.

⁴⁵⁰ Callis, N.M.; Thierry, E.; Le Bras, J.; Muzart, J. *Tetrahedron Lett.* **2007**, *48*, 8128. See Brunel, J.M. *Tetrahedron* **2007**, *63*, 3899.

⁴⁵¹ Troutman, M.V.; Appella, D.H.; Buchwald, S.L. *J. Am. Chem. Soc.* **1999**, *121*, 4916.

⁴⁵² Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934; Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L.K.; Andersson, P.G. *J. Am. Chem. Soc.* **2006**, *128*, 2995. See McIntosh, A.I.; Watson, D.J.; Burton, J.W.; Lambert, R.M. *J. Am. Chem. Soc.* **2006**, *128*, 7329; Diguez, M.; Mazuela, J.; Pmies, O.; Verendel, J.J.; Andersson, P.G. *J. Am. Chem. Soc.* **2008**, *130*, 7208; Chen, W.; Roberts, S.M.; Whittall, J. *Tetrahedron Lett.* **2006**, *47*, 4263; Tang, W.-J.; Huang, Y.-Y.; He, Y.-M.; Fan, Q.-H. *Tetrahedron Asymmetry* **2006**, *17*, 536; Tang, W.; Qu, B.; Capacci, A.G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N.K.; Krishnamurthy, D.; Chris H.; Senanayake, C.H. *Org. Lett.* **2010**, *12*, 176; Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 6421.

⁴⁵³ Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *J. Org. Chem.* **2004**, *69*, 2355; Hua, Z.; Vassar, V.C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831. For a review, see Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron Asymmetry* **2004**, *15*, 2101.

⁴⁵⁴ Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D. *Adv. Chem. Ser.* **1974**, *132*, 274.

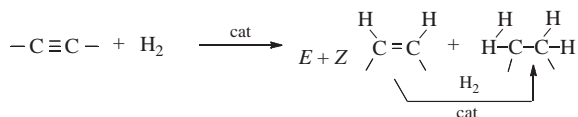
⁴⁵⁵ Brown, J.M.; Chaloner, P.A. *J. Chem. Soc., Chem. Commun.* **1980**, 344; **1978**, 321; *J. Am. Chem. Soc.* **1980**, *102*, 3040.

⁴⁵⁶ See Chan, A.S.C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838; Chua, P.S.; Roberts, N.K.; Bosnich, B.; Okrasinski, S.J.; Halpern, J. *J. Chem. Soc. Chem. Commun.* **1981**, 1278.

⁴⁵⁷ See Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

⁴⁵⁸ Faller, J.W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804.

pressure. The great variety of catalysts available often allows an investigator to find one that is highly selective. For example, the catalyst Pd(salen) encapsulated in zeolites permitted the catalytic hydrogenation of 1-hexene in the presence of cyclohexene.⁴⁵⁹ It has been shown that the pressure of the reaction can influence enantioselectivity in asymmetric catalytic hydrogenations.⁴⁶⁰



Triple bonds can be reduced, either by catalytic hydrogenation or by the other methods mentioned in the following two sections. The comparative reactivity of triple and double bonds depends on the catalyst. *With most catalysts (e.g., Pd), triple bonds are hydrogenated more easily*, and therefore it is usually possible to add just 1 equiv of hydrogen and reduce a triple to a double bond or to reduce a triple bond without affecting a double bond present in the same molecule.⁴⁶¹ A particularly good catalyst for this purpose is the *Lindlar catalyst* (Pd—CaCO₂—PbO),⁴⁶² which gives rather lean syn addition, and a (Z)-alkene. An alternative catalyst used for selective hydrogenation to *cis*-alkenes is the Pd on a barium sulfate (BaSO₄) catalyst, poisoned with quinoline⁴⁶³ (sometimes called the *Rosenmund catalyst*). Palladium on calcium carbonate in PEG has also been used as a recyclable catalyst system.⁴⁶⁴ Catalytic hydrogenation of alkynes leads to *cis*-alkenes with a Pd catalyst and DMF/KOH was found to be an efficient transfer-hydrogen source.⁴⁶⁵ Hydrogenation of a C≡C unit occurs in the presence of other functional groups, including NR₂ including NH₂,⁴⁶⁶ and sulfonyl.⁴⁶⁷

Conjugated dienes can add hydrogen by 1,2- or 1,4-addition. Selective 1,4-addition can be achieved by hydrogenation in the presence of CO, with bis(cyclopentadienyl)chromium as catalyst.⁴⁶⁸ With allenes,⁴⁶⁹ catalytic hydrogenation usually reduces both double bonds. Hydrogenation of functionalized alkenes is possible. The Rh catalyzed hydrogenation of enamines leads to amines,⁴⁷⁰ for example. Hydrogenation of fluorinated alkenes has been reported using an Ir catalyst.⁴⁷¹ The hydrogenation of conjugated alkenes is discussed in Reaction 15-14.

⁴⁵⁹ Kowalak, S.; Weiss, R.C.; Balkus Jr., K.J. *J. Chem. Soc., Chem. Commun.* **1991**, 57.

⁴⁶⁰ Sun, Y.; Landau, R.N.; Wang, J.; LeBlond, C.; Blackmond, D.G. *J. Am. Chem. Soc.* **1996**, *118*, 1348.

⁴⁶¹ See Hutchins, R.O.; Hutchins, M.G.K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, **1983**, pp. 571–601; Marvell, E.N.; Li, T. *Synthesis* **1973**, 457; Gutmann, H.; Lindlar, H. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 355–363.

⁴⁶² Lindlar, H.; Dubuis, R. *Org. Synth.* **V**, 880. See also, Rajaram, J.; Narula, A.P.S.; Chawla, H.P.S.; Dev, S. *Tetrahedron* **1983**, *39*, 2315; McEwen, A.B.; Guttieri, M.J.; Maier, W.F.; Laine, R.M.; Shvo, Y. *J. Org. Chem.* **1983**, *48*, 4436.

⁴⁶³ Cram, D.J.; Allinger, N.L. *J. Am. Chem. Soc.* **1956**, *78*, 2518; Rosenmund, K.W. *Ber.* **1918**, *51*, 585; Mosettig, E.; Mozingo, R. *Org. React.* **1948**, *4*, 362.

⁴⁶⁴ Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* **2004**, *45*, 2421.

⁴⁶⁵ Li, J.; Hua, R.; Liu, T. *J. Org. Chem.* **2010**, *75*, 2966.

⁴⁶⁶ Campos, K.R.; Cai, D.; Journet, M.; Kowal, J.J.; Larsen, R.D.; Reider, P.J. *J. Org. Chem.* **2001**, *66*, 3634.

⁴⁶⁷ Zhong, P.; Huang, X.; Ping-Guo, M. *Tetrahedron* **2000**, *56*, 8921.

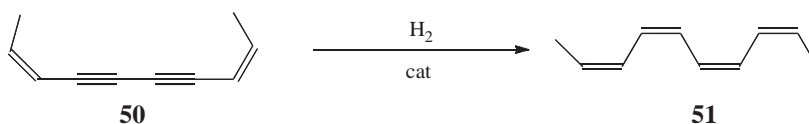
⁴⁶⁸ Miyake, A.; Kondo, H. *Angew. Chem. Int. Ed.* **1968**, *7*, 631. For other methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 403–404.

⁴⁶⁹ See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis* Wiley, NY, **1984**, pp. 57–61.

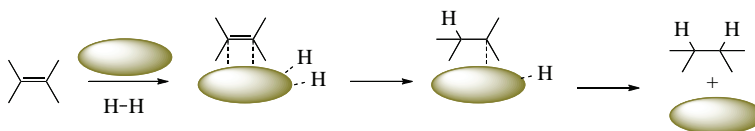
⁴⁷⁰ Hou, G.-H.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 11774.

⁴⁷¹ Engman, M.; Diesen, J.S.; Paptchikhine, A.; Andersson, P.G. *J. Am. Chem. Soc.* **2007**, *129*, 4536.

Most catalytic reductions of double or triple bonds, whether heterogeneous or homogeneous, have been shown to be mostly *syn*, with the hydrogen atoms incorporated from the less-hindered side of the molecule.⁴⁷² This selectivity depends in large part of how well the reactive intermediates are bound to the metal, and isomerization of the double bond is possible. Stereospecificity can be investigated only for tetrasubstituted alkenes (except when the reagent is D₂), which are the hardest to hydrogenate, but the results of these investigations show that the addition is usually 80–100% *syn*, although some of the anti-addition product is normally also found and in some cases predominates. Catalytic hydrogenation of alkynes is nearly always stereoselective, giving the *cis*-alkene (usually at least 80%), even when it is thermodynamically less stable. For example, **50** gave **51**, even though the steric hindrance is such that a planar molecule is impossible.⁴⁷³ This is



thus a useful method for preparing *cis*-alkenes.⁴⁷⁴ However, when steric hindrance is too great, the *trans*-alkene may be formed. One factor that complicates the study of the stereochemistry of heterogeneous catalytic hydrogenation is that exchange of hydrogen atoms takes place, as can be shown by hydrogenation with deuterium.⁴⁷⁵ Thus deuteration of ethylene produced all the possible deuterated ethylenes and ethanes (even C₂H₆), as well as HD.⁴⁷⁶ With 2-butene, it was found that double-bond migration, *cis*–*trans* isomerization, and even exchange of hydrogen with groups not on the double bond could occur (e.g., C₄H₂D₈ and C₄HD₉ were detected on treatment of *cis*-2-butene with deuterium and a catalyst).⁴⁷⁷ Indeed, *alkanes* have been found to exchange with deuterium over a catalyst,⁴⁷⁸ and even without deuterium (e.g., CH₄ + CD₄ → CHD₃ + CH₃D in the gas phase), with a catalyst. All this makes it difficult to investigate the stereochemistry of heterogeneous catalytic hydrogenation.



The mechanism of the heterogeneous catalytic hydrogenation of double bonds is not thoroughly understood because it is a very difficult reaction to study.⁴⁷⁹ Because the reaction is heterogeneous, kinetic data, although easy to obtain (measurement of decreasing hydrogen pressure), are difficult to interpret. Furthermore, there are the difficulties

⁴⁷² See Brown, J.M. *Angew. Chem. Int. Ed.* **1987**, 26, 190.

⁴⁷³ Holme, D.; Jones, E.R.H.; Whiting, M.C. *Chem. Ind. (London)* **1956**, 928.

⁴⁷⁴ See Burch, R.R.; Muettterties, E.L.; Teller, R.G.; Williams, J.M. *J. Am. Chem. Soc.* **1982**, 104, 4257.


⁴⁷⁵ See Gudkov, B.S. *Russ. Chem. Rev.* **1986**, 55, 259.

⁴⁷⁶ Turkevich, J.; Schissler, D.O.; Irsa, P. *J. Phys. Chem.* **1951**, 55, 1078.

⁴⁷⁷ Wilson, J.N.; Otvos, J.W.; Stevenson, D.P.; Wagner, C.D. *Ind. Eng. Chem.* **1953**, 45, 1480.

⁴⁷⁸ See Gudkov, B.S.; Balandin, A.A. *Russ. Chem. Rev.* **1966**, 35, 756. For an intramolecular exchange, see Lebrilla, C.B.; Maier, W.F. *Tetrahedron Lett.* **1983**, 24, 1119. See also, Poretti, M.; Gäumann, T. *Helv. Chim. Acta* **1985**, 68, 1160.

⁴⁷⁹ See Webb, G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20; Elsevier, NY, **1978**, pp. 1–121; Clarke, J.K.A.; Rooney, J.J. *Adv. Catal.* **1976**, 25, 125–183.

caused by the aforementioned hydrogen exchange. The currently accepted mechanism for the common two-phase reaction was originally proposed in 1934.⁴⁸⁰ According to this, the alkene is adsorbed onto the surface of the metal, although the nature of the actual bonding is unknown,⁴⁸¹ despite many attempts to elucidate it.⁴⁸² In the 1934 work, the metallic site was indicated by an asterisk, but here  is used. For steric reasons it is apparent that adsorption of the alkene takes place with its less-hindered side attached to the catalyst surface, probably as an η^2 complex (Sec. 3.C.i). The fact that addition of hydrogen is generally also from the less-hindered side indicates that the hydrogen too is probably adsorbed on the catalyst surface before it reacts with the alkene. It is likely that as the H_2 molecule is adsorbed on (coordinated to) the metal catalyst, cleavage occurs to give η^1 -coordinated hydrogen atoms (Sec. 3.C.i). Note that this model suggests a single metal particle for coordination of the alkene and the hydrogen atoms, but the hydrogen atoms and the alkene could be coordinated to different metal particles. It has been shown that Pt catalyzes homolytic cleavage of hydrogen molecules.⁴⁸³ In the second step, one of the adsorbed (η^1 -coordinated) hydrogen atoms becomes attached to a carbon atom, creating in effect, an alkyl radical, which is still bound to the catalyst although only by one bond, probably η^1 -coordination. Transfer of a hydrogen atom to carbon opens a site on the metal catalyst for coordination to additional hydrogen atoms. Finally, another hydrogen atom (not necessarily the one originally connected to the first hydrogen) combines with the radical to give the reaction product, freed from the catalyst surface, and the metal catalyst that is now available for coordination of additional hydrogen atoms and/or alkenes. All the various side reactions, including hydrogen exchange and isomerism, can be explained by this type of process.⁴⁸⁴ Although this mechanism is satisfactory as far as it goes,⁴⁸⁵ there are still questions it does not answer, among them questions⁴⁸⁶ that involve the nature of the asterisk, the nature of the bonding, and the differences caused by the differing nature of each catalyst.⁴⁸⁷

Another problem with any study of heterogeneous catalysis is that it occurs at the surface, and different types of metal particles are exposed to the medium and reactants. Maier⁴⁸⁸ suggested the presence of **terrace**-, **step**-, and **kink**-type atoms (in Fig. 15.1)⁴⁸⁸ on the surface of a heterogeneous catalyst. These terms refer to different atom types, characterized by the number of nearest neighbors, which correspond to different transition metal fragments, as well as to different coordination states of that metal.⁴⁸⁹ A terrace-type atom (A in Fig. 15.1) typically has eight or nine neighbors and corresponds to a geometry shown for the ML_5 particle. The step type of atom (B) usually has seven neighbors and can

⁴⁸⁰ Horiuti, I.; Polanyi, M. *Trans. Faraday Soc.* **1934**, 30, 1164.

⁴⁸¹ See Burwell, Jr., R.L.; Schrage, K. *J. Am. Chem. Soc.* **1965**, 87, 5234.

⁴⁸² See Bautista, F.M.; Campelo, J.M.; Garcia, A.; Guardño, R.; Luna, D.; Marinas, J.M. *J. Chem. Soc. Perkin Trans. 2*, **1989**, 493.

⁴⁸³ Krasna, A.I. *J. Am. Chem. Soc.* **1961**, 83, 289.

⁴⁸⁴ Smith, G.V.; Burwell, Jr., R.L. *J. Am. Chem. Soc.* **1962**, 84, 925.

⁴⁸⁵ A different mechanism has been proposed by Zaera, F.; Somorjai, G.A. *J. Am. Chem. Soc.* **1984**, 106, 2288, but there is evidence against it: Beebe, Jr., T.P.; Yates, Jr., J.T. *J. Am. Chem. Soc.* **1986**, 108, 663. See also, Thomson, S.J.; Webb, G. *J. Chem. Soc., Chem. Commun.* **1976**, 526.

⁴⁸⁶ See Augustine, R.L.; Yaghmaie, F.; Van Peppen, J.F. *J. Org. Chem.* **1984**, 49, 1865; Maier, W.F. *Angew. Chem. Int. Ed.* **1989**, 28, 135.

⁴⁸⁷ See Schlögl, R.; Noack, K.; Zbinden, H.; Reller, A. *Helv. Chim. Acta* **1987**, 70, 627.

⁴⁸⁸ Maier, W.F. *Angew. Chem. Int. Ed.* **1989**, 28, 135.

⁴⁸⁹ Maier, W.F. in Rylander, P.N.; Greenfield, H.; Augustine, R.L. *Catalysis of Organic Reactions*, Marcel Dekker, NY, **1988**, pp 211–231, Cf. p. 220.

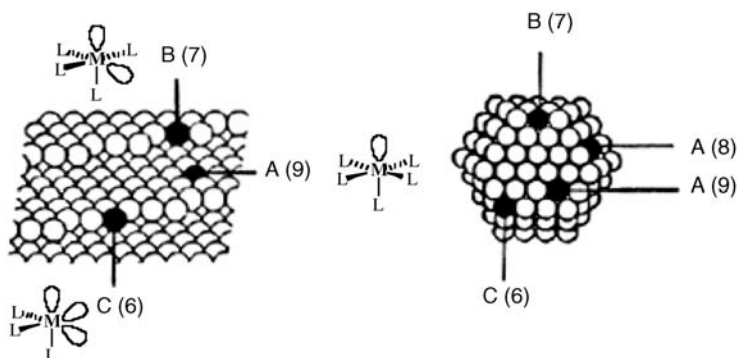
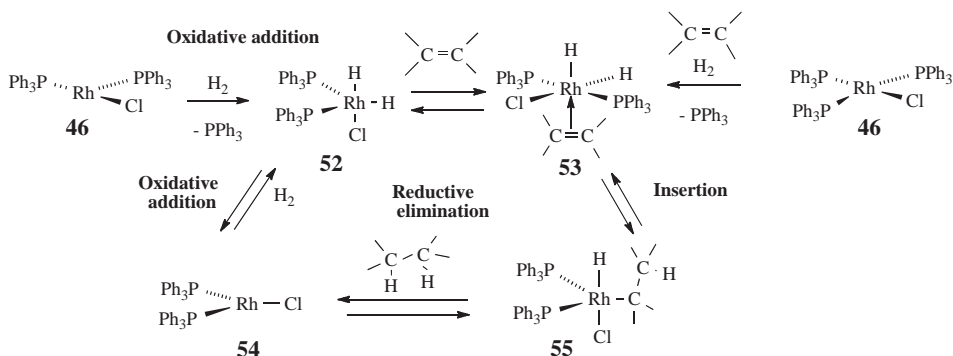


FIG. 15.1. The principal surface and particle sites for heterogeneous catalysts. [Reprinted with permission from Maier, W.F. *Angew. Chem. Int. Ed.* **1989**, 135, Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © **1989** by Wiley–VCH Verlag]

be correlated with the geometry shown for the ML_4 particle. Finally, the kink-type atom (C) has six neighbors and corresponds to geometry shown for the ML_3 particle. In general, as the particle size increases, the relative concentration of terrace atoms will increase, whereas small particle size favors the kink type of surface atoms.



The mechanism of homogeneous hydrogenation⁴⁹⁰ catalyzed by $RhCl(Ph_3P)_3$ (**46**, *Wilkinson's catalyst*)⁴⁹¹ involves reaction of the catalyst with hydrogen to form a metal hydride $(PPh_3)_2RhH_2Cl$ (**52**).⁴⁹² Replacement of a triphenylphosphine ligand with two atoms of hydrogen constitutes an oxidative addition. After coordination of the alkene to form **53**, transfer of hydrogen to carbon is an insertion process, presumably generating **55**, and a second insertion liberates the hydrogenated compound, and Rh species **54**, which adds hydrogen by oxidative addition to give **55**. In a different study of Pd catalyzed hydrogenations, a palladium hydride species was detected.⁴⁹³ Alternatively, replacement of triphenylphosphine can lead to **53**, with two hydrogen atoms and a η^2 alkene complex. If a mixture of H_2 and D_2 is used, the product contains only dideuterated and nondeuterated

⁴⁹⁰ See Crabtree, R.H. *Organometallic Chemistry of the Transition Metals*, Wiley, NY, **1988**, pp. 190–200; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 1049–1071.

⁴⁹¹ Koga, N.; Daniel, C.; Han, J.; Fu, X.Y.; Morokuma, K. *J. Am. Chem. Soc.* **1987**, 109, 3455.

⁴⁹² Tolman, C.A.; Meakin, P.Z.; Lindner, D.L.; Jesson, J.P. *J. Am. Chem. Soc.* **1976**, 96, 2762.

⁴⁹³ López-Serrano, J.; Duckett, S.B.; Lledós, A. *J. Am. Chem. Soc.* **2006**, 128, 9596.

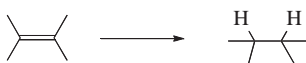
compounds; no monodeuterated products are found, indicating that (unlike the case of heterogeneous catalysis) H_2 or D_2 has been added to one alkene molecule and that no exchange takes place.⁴⁹¹ Although conversion of **53** to the products takes place in two steps,⁴⁹⁴ the addition of H_2 to the double bond is syn, although bond rotation in **55** can lead to stereochemical mixtures.

The occurrence of hydrogen exchange and double-bond migration in heterogeneous catalytic hydrogenation means that the hydrogenation does not necessarily take place by straightforward addition of two hydrogen atoms at the site of the original double bond. Consequently, this method is not synthetically useful for adding D_2 to a double or triple bond in a regioselective or stereospecific manner. However, this objective can be achieved (with syn addition) by a homogeneous catalytic hydrogenation, which usually adds D_2 without scrambling⁴⁹⁵ or by the use of one of the diimide methods (Reaction **15-12**). Deuterium can also be regioselectively added by the hydroboration–reduction procedure previously mentioned.

Reductions of double and triple bonds are found at OS **I**, 101, 311; **II**, 191, 491; **III**, 385, 794; **IV**, 298, 304, 408; **V**, 16, 96, 277; **VI**, 68, 459; **VII**, 226, 287; **VIII**, 420, 609; **IX**, 169, 533.

Catalysts and apparatus for hydrogenation are found at OS **I**, 61, 463; **II**, 142; **III**, 176, 181, 685; **V**, 880; **VI**, 1007.

15-12 Other Reductions of Double and Triple Bonds



Although catalytic hydrogenation is the method most often used, double or triple bonds can be reduced by other reagents as well. These include sodium in ethanol, sodium and *tert*-butyl alcohol in HMPA,⁴⁹⁶ lithium in aliphatic amines⁴⁹⁷ (see also, Reaction **15-13**), zinc and acids, and $(\text{EtO})_3\text{SiH}-\text{Pd}(\text{OAc})_2$.⁴⁹⁸ Trialkylsilanes (R_3SiH) in conjunction with an acid will reduce double bonds.⁴⁹⁹ When double bonds are reduced by lithium in ammonia or amines, the mechanism is similar to that of the *Birch reduction* (Reaction **15-13**).⁵⁰⁰ The reduction with trifluoroacetic acid and Et_3SiH has an ionic mechanism, with H^+ coming in from the acid and H^- from the silane.²⁸⁹ In accord with this mechanism, the reaction can be applied only to those alkenes that when protonated can form a tertiary carbocation or one stabilized in some other way (e.g., by a OR substitution).⁵⁰¹ It has been

⁴⁹⁴ Smith, G.V.; Shuford, R.J. *Tetrahedron Lett.* **1970**, 525; Atkinson, J.G.; Luke, M.O. *Can. J. Chem.* **1970**, *48*, 3580.

⁴⁹⁵ Morandi, J.R.; Jensen, H.B. *J. Org. Chem.* **1969**, *34*, 1889. See, however, Atkinson, J.G.; Luke, M.O. *Can. J. Chem.* **1970**, *48*, 3580.

⁴⁹⁶ Whitesides, G.M.; Ehmann, W.J. *J. Org. Chem.* **1970**, *35*, 3565.

⁴⁹⁷ Benkeser, R.A.; Schroll, G.; Sauve, D.M. *J. Am. Chem. Soc.* **1955**, *77*, 3378.

⁴⁹⁸ Tour, J.M.; Pandalwar, S.L. *Tetrahedron Lett.* **1990**, *31*, 4719.

⁴⁹⁹ Masuno, M.N.; Molinski, T.F. *Tetrahedron Lett.* **2001**, *42*, 8263; Kursanov, D.N.; Parnes, Z.N.; Kalinkin, M.I.; Loim, N.M. *Ionic Hydrogenation and Related Reactions* Harwood Academic Publishers, Chur, Switzerland, **1985**.

⁵⁰⁰ See Toromanoff, E. *Bull. Soc. Chim. Fr.* **1987**, 893–901; Russell, G.A. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, **1989**, pp. 471–512.

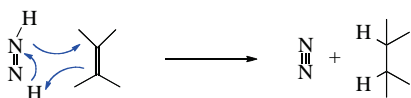
⁵⁰¹ Parnes, Z.N.; Bolestova, G.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1972**, *21*, 1927.

shown, by the detection of CIDNP, that reduction of α -methylstyrene by hydridopentacarbonylmanganese(I), $[\text{HMn}(\text{CO})_5]$, involves free radical addition.⁵⁰²

Triethylamine reduces alkynes in the presence of a Pd catalyst.⁵⁰³ Samarium iodide in water and a triamine additive led to reduction of alkenes.⁵⁰⁴ Similar reduction was reported using $\text{Co}_2(\text{CO})_8$ and an excess of water in dimethoxyethane.⁵⁰⁵

Another hydrogenation method is called *transfer hydrogenation*.⁵⁰⁶ In this method, the hydrogen atom comes from another organic molecule, and that molecule is oxidized. A transition metal catalyst, heterogeneous or homogeneous, is frequently employed. A common reducing agent is cyclohexene, which, when a Pd catalyst is used, is oxidized to benzene, losing 2 molar equivalents of hydrogen. Nickel nanoparticles reduce alkenes by transfer hydrogenation using 2-propanol.⁵⁰⁷

Diimide ($\text{NH}=\text{NH}$) is a reducing agent for simple alkenes, formed *in situ* from N_2H_4 from the reaction of a mixture of hydrazine and hydroxylamine.⁵⁰⁸ The rate of this reaction has been studied.⁵⁰⁹ Diimide is also generated from hydrazine using a flavin catalyst in an oxygen atmosphere.⁵¹⁰ Although both the syn and anti forms of diimide are produced, only the syn form reduces the double bond,⁵¹¹ at least in part by a cyclic mechanism.⁵¹²



The addition is stereospecifically syn⁵¹³ and, like catalytic hydrogenation, generally takes place from the less-hindered side of a double bond, although not much discrimination in this respect is observed where the difference in bulk effects is small.⁵¹⁴ Diimide reductions are most successful with symmetrical multiple bonds ($\text{C}=\text{C}$, $\text{C}\equiv\text{C}$, $\text{N}=\text{N}$) and are not useful for those inherently polar ($\text{C}\equiv\text{N}$, $\text{C}=\text{N}$, $\text{C}=\text{O}$, etc.). Diimide is not stable enough for isolation at ordinary temperatures, although it has been prepared⁵¹⁵ as a yellow solid at -196°C .

An indirect method⁵¹⁶ of double-bond reduction involves formation of an alkylborane from an alkene, followed by hydrolysis of the borane (prepared by Reaction **15-16**).

⁵⁰² Sweany, R.L.; Halpern, J. *J. Am. Chem. Soc.* **1977**, 99, 8335. See also, Bullock, R.M.; Samsel, E.G. *J. Am. Chem. Soc.* **1987**, 109, 6542.

⁵⁰³ Luo, F.; Pan, C.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron* **2010**, 66, 1399. See Han, J.W.; Hayashi, T. *Tetrahedron Asymm.* **2010**, 21, 2193.

⁵⁰⁴ Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2003**, 44, 2661.

⁵⁰⁵ Lee, H.-Y.; An, M. *Tetrahedron Lett.* **2003**, 44, 2775.

⁵⁰⁶ Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. *Chem. Rev.* **1985**, 85, 129; Brieger, G.; Nestrick, T.J. *Chem. Rev.* **1974**, 74, 567.

⁵⁰⁷ Alonso, F.; Riente, P.; Yus, M. *Tetrahedron* **2009**, 65, 10637.

⁵⁰⁸ See Pasto, D.J.; Taylor, R.T. *Org. React.* **1991**, 40, 91; Hünig, S.; Müller, H.R.; Thier, W. *Angew. Chem. Int. Ed.* **1965**, 4, 271.

⁵⁰⁹ Nelson, D.J.; Henley, R.L.; Yao, Z.; Smith, T.D. *Tetrahedron Lett.* **1993**, 34, 5835.

⁵¹⁰ Imada, Y.; Iida, H.; Naota, T. *J. Am. Chem. Soc.* **2005**, 127, 14544.

⁵¹¹ Aylward, F.; Sawistowska, M.H. *J. Chem. Soc.* **1964**, 1435.

⁵¹² Willis, C.; Back, R.A.; Parsons, J.A.; Purdon, J.G. *J. Am. Chem. Soc.* **1977**, 99, 4451.

⁵¹³ Corey, E.J.; Pasto, D.J.; Mock, W.L. *J. Am. Chem. Soc.* **1961**, 83, 2957.

⁵¹⁴ van Tamelen, E.E.; Timmons, R.J. *J. Am. Chem. Soc.* **1962**, 84, 1067.

⁵¹⁵ Wiberg, N.; Fischer, G.; Bachhuber, H. *Angew. Chem. Int. Ed.* **1977**, 16, 780. See also, Craig, N.C.; Kliewer, M.A.; Shih, N.C. *J. Am. Chem. Soc.* **1979**, 101, 2480.

⁵¹⁶ See Zweifel, G. *Intra-Sci. Chem. Rep.* **1973**, 7(2), 181–189.

Trialkylboranes can be hydrolyzed by heating to reflux with carboxylic acids,⁵¹⁷ while monoalkylboranes (RBH₂) can be hydrolyzed with base.⁵¹⁸ A mild procedure involves treatment of the alkene with 2 molar equivalents of catecholborane, a catalytic amount of MeCONMe₂, followed by reduction of the organoborane with 4 molar equivalents of MeOH and then treatment with air.⁵¹⁹ Triple bonds can be similarly reduced to *cis*-alkenes.⁵²⁰ Further reduction is also possible. When an alkyne was treated with decaborane and Pd/C in methanol, 2 equiv of hydrogen are transferred to give the alkane.⁵²¹ Reduction of alkenes occurs with *tert*-butylamine•borane complex in methanol with 10% Pd/C.⁵²² In a related reaction, reduction occurs *in situ* when an alkene is treated with NaBH₄, NiCl₂•6 H₂O with moist alumina.⁵²³ Hydrogenation with Ni₂B on borohydride-exchange resin (BER) has also been used.⁵²⁴

Metallic hydrides (e.g., lithium aluminum hydride and sodium borohydride) do not typically reduce carbon–carbon double bonds, although in special cases where the double bond is polar, as in 1,1-diarylethenes⁵²⁵ and in enamines,⁵²⁶ reduction can occur. Note that both LiAlH₄ and NaBH₄, as well as NaH, reduce ordinary alkenes and alkynes when complexed with transition metal salts (e.g., FeCl₂ or CoBr₂).⁵²⁷ Lithium aluminum hydride reduces cyclopropenes with a pendant alcohol in the allylic position to the corresponding cyclopropane.⁵²⁸ Transition metals catalyze the reduction of alkenes using NaBH₄. Among the metals used for this purpose are Pd,⁵²⁹ and Ru.⁵³⁰ A mixture of NaBH₄ and BiCl₃ also reduced certain alkenes.⁵³¹ Zinc metal catalyzes the reduction of alkenes in water in the presence of a Rh complex.⁵³²

The fact that ordinary double bonds are inert toward metallic hydrides is quite useful, since it permits reduction of, say, a carbonyl or nitro group, without disturbing a double bond in the same molecule (see Chap 19 for a discussion of selectivity in reduction reactions). Sodium in liquid ammonia also does not reduce ordinary double bonds,⁵³³ although it does reduce alkynes, allenes, conjugated dienes,⁵³⁴ and aromatic rings (Reaction 15-13).

⁵¹⁷ Brown, H.C.; Murray, K.J. *Tetrahedron* **1986**, *42*, 5497; Kabalka, G.W.; Newton Jr., R.J.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 4185.

⁵¹⁸ Weinheimer, A.J.; Marisco, W.E. *J. Org. Chem.* **1962**, *27*, 1926.

⁵¹⁹ Pozzi, D.; Scanlan, E.M.; Renaud, P. *J. Am. Chem. Soc.* **2005**, *127*, 14204.

⁵²⁰ Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* **1959**, *81*, 1512.

⁵²¹ Lee, S.H.; Park, Y.J.; Yoon, C.M. *Tetrahedron Lett.* **2000**, *41*, 887.

⁵²² Couturier, M.; Andresen, B.M.; Tucker, J.L.; Dubé, P.; Brenek, S.J.; Negri, J.J. *Tetrahedron Lett.* **2001**, *42*, 2763.

⁵²³ Yakabe, S.; Hirano, M.; Morimoto, T. *Tetrahedron Lett.* **2000**, *41*, 6795.

⁵²⁴ Choi, J.; Yoon, N.M. *Synthesis* **1996**, 597.

⁵²⁵ See Granoth, I.; Segall, Y.; Leader, H.; Alkabetz, R. *J. Org. Chem.* **1976**, *41*, 3682.

⁵²⁶ Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* **1985**, *17*, 317; Nilsson, A.; Carlson, R. *Acta Chem. Scand. Sect. B* **1985**, *39*, 187.

⁵²⁷ See Ashby, E.C.; Lin, J.J. *J. Org. Chem.* **1978**, *43*, 2567; Chung, S. *J. Org. Chem.* **1979**, *44*, 1014. See also, Osby, J.O.; Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* **1986**, *108*, 67.

⁵²⁸ Zohar, E.; Marek, I. *Org. Lett.* **2004**, *6*, 341.

⁵²⁹ Tran, A.T.; Huynh, V.A.; Friz, E.M.; Whitney, S.K.; Cordes, D.B. *Tetrahedron Lett.* **2009**, *50*, 1817.

⁵³⁰ Adair, G.R.A.; Kapoor, K.K.; Scolan, A.L.B.; Williams, J.M.J. *Tetrahedron Lett.* **2006**, *47*, 8943.

⁵³¹ Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Synth. Commun.* **1996**, *26*, 763.

⁵³² Sato, T.; Watanabe, S.; Kiuchi, H.; Oi, S.; Inoue, Y. *Tetrahedron Lett.* **2006**, *47*, 7703.

⁵³³ There are some exceptions. Butler, D.N. *Synth. Commun.* **1977**, *7*, 441, and references cited therein.

⁵³⁴ See Caine, D. *Org. React.* **1976**, *23*, 1–258.

Enantioselective reduction of certain alkenes has also been achieved by reducing with baker's yeast.⁵³⁵

Catalytic hydrogenation of triple bonds and the reaction with Dibal-H (diisobutylaluminum hydride) usually give the *cis*-alkene (Reaction 15-11). Most of the other methods of triple-bond reduction lead to the more thermodynamically stable *trans*-alkene. However, this is not the case with the method involving hydrolysis of boranes or with the reductions with activated zinc, hydrazine, or $\text{NH}_2\text{OSO}_3\text{H}$, which also give the *cis* products.

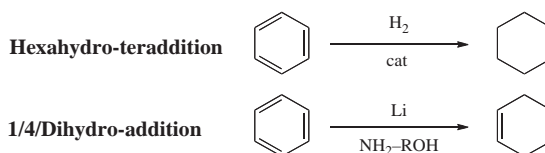
Triple bonds can also be selectively reduced to double bonds with Dibal-H,⁵³⁶ with activated zinc (see Reaction 12-38),⁵³⁷ or (internal triple bonds only) with alkali metals (Na, Li) in liquid ammonia or a low-molecular-weight amine.⁵³⁸ Terminal alkynes are not reduced by the $\text{Na}-\text{NH}_3$ procedure because they are converted to acetylide ions under these conditions. However, terminal triple bonds can be reduced to double bonds by the addition to the $\text{Na}-\text{NH}_2$ solution of $(\text{NH}_4)_2\text{SO}_4$, which liberates the free ethynyl group.⁵³⁹ The reaction of a terminal alkyne with lithium naphthalenide and NiCl_2 effectively reduced the alkyne unit.⁵⁴⁰ This reagent is also effective for the reduction of simple alkenes.⁵⁴¹

Alkynes are converted to *trans*-alkenes with siloxanes $[(\text{RO})_3\text{SiH}]$ ⁵⁴² and a Ru catalyst, followed by treatment with AgF , or silanes⁵⁴³ and a Ru catalyst, followed by treatment with CuI and Bu_4NF . Reduction of an alkyne to an alkene can be done via an organometallic, by heating the alkyne with In metal in aq ethanol.⁵⁴⁴ Alkynes are reduced with palladium acetate and sodium ethoxide. In methanol, the product is the alkane, whereas in THF the product is the *cis*-alkene.⁵⁴⁵

Reduction of just one double bond of an allene, to give an alkene, has been accomplished by treatment with $\text{Na}-\text{NH}_3$ ⁵⁴⁶ or with Dibal-H,⁵⁴⁷ and by hydrogenation with $\text{RhCl}(\text{PPh}_3)_3$ as catalyst.⁵⁴⁸

Reductions of double and triple bonds are found at OS **III**, 586, 742; **IV**, 136, 302, 887; **V**, 281, 993; **VII**, 524; **80**, 120.

15-13 Hydrogenation of Aromatic Rings



⁵³⁵ See Ferraboschi, P.; Reza-Elahi, S.; Verza, E.; Santaniello, E. *Tetrahedron Asymmetry* **1999**, 10, 2639. For reviews of baker's yeast, see Csuk, R.; Glänzer, B.I. *Chem. Rev.* **1991**, 91, 49; Servi, S. *Synthesis* **1990**, 1.

⁵³⁶ Ulan, J.G.; Maier, W.F.; Smith, D.A. *J. Org. Chem.* **1987**, 52, 3132.

⁵³⁷ Chou, W.; Clark, D.L.; White, J.B. *Tetrahedron Lett.* **1991**, 32, 299. See Kaufman, D.; Johnson, E.; Mosher, M.D. *Tetrahedron Lett.* **2005**, 46, 5613.

⁵³⁸ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 405–410.

⁵³⁹ Henne, A.L.; Greenlee, K.W. *J. Am. Chem. Soc.* **1943**, 65, 2020.

⁵⁴⁰ Alonso, F.; Yus, M. *Tetrahedron Lett.* **1997**, 38, 149.

⁵⁴¹ Alonso, F.; Yus, M. *Tetrahedron Lett.* **1996**, 37, 6925.

⁵⁴² Fürstner, A.; Radkowski, K. *Chem. Commun.* **2002**, 2182.

⁵⁴³ Trost, B.M.; Ball, Z.T.; Jöge, T. *J. Am. Chem. Soc.* **2002**, 124, 7922.

⁵⁴⁴ Ranu, B.C.; Dutta, J.; Guchhait, S.K. *J. Org. Chem.* **2001**, 66, 5624.

⁵⁴⁵ Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Leou, S.-P.; Wu, M.-J. *Tetrahedron Lett.* **2003**, 44, 1979.

⁵⁴⁶ Vaidyanathaswamy, R.; Joshi, G.C.; Devaprabhakara, D. *Tetrahedron Lett.* **1971**, 2075.

⁵⁴⁷ Montury, M.; Goré, J. *Tetrahedron Lett.* **1980**, 21, 51.

⁵⁴⁸ Bhagwat, M.M.; Devaprabhakara, D. *Tetrahedron Lett.* **1972**, 1391.

Aromatic rings can be reduced by catalytic hydrogenation,⁵⁴⁹ but higher temperatures (100–200 °C) are required than for double bonds in alkenes.⁵⁵⁰ Although the reaction is usually carried out with heterogeneous catalysts, homogeneous catalysts have also been used; conditions are much milder with these.⁵⁵¹ Hydrogenations using phase transfer catalysts often proceed under mild conditions.⁵⁵² Hydrogenation in ionic liquids is known,⁵⁵³ and also hydrogenation in supercritical ethane containing water.⁵⁵⁴ Many functional groups (e.g., OH, O[−], CO₂H, CO₂R, NH₂) do not interfere with the reaction, but some groups may be preferentially reduced. Among these are CH₂OH groups, which undergo hydrogenolysis to CH₃ (Reaction 19-54). Phenols may be reduced to cyclohexanones, presumably through the enol. A computational study of the mechanism of hydrogenation of aromatic compounds has been reported, and it was shown that the barrier for uncatalyzed 1,4-hydrogenation is substantially lower than that for 1,2-hydrogenation, despite similar reaction enthalpies.⁵⁵⁵

It is usually impossible to stop the reduction of benzene rings after only one or two bonds have been reduced, since alkenes are more easily reduced than aromatic rings.⁵⁵⁶ Thus, 1 molar equivalent of benzene, treated with 1 molar equivalent of hydrogen, gives no cyclohexadiene or cyclohexene, but one-third equivalent of cyclohexane and two-thirds equivalent of recovered benzene. This is not true for all aromatic systems. With anthracene, for example, it is easy to stop after only the 9,10-bond has been reduced (Sec. 2.I.i). Hydrogenation of phenol derivatives can lead to conjugated cyclohexenones.⁵⁵⁷ Hydrogenation of toluene in an ionic liquid using a Ru catalyst gave methylcyclohexane.⁵⁵⁸

Heterocyclic compounds are often reduced by hydrogenation.⁵⁵⁹ Furan gives THF, pyrroles⁵⁶⁰ give pyrrolidines, and pyridines⁵⁶¹ give piperidines. The nitrogen-containing ring of quinolines is reduced by hydrogenation using iodine and an Ir catalyst.⁵⁶² Catalytic hydrogenation of the five-membered ring in indole derivatives using a chiral Rh catalyst gave hydroindoles with excellent enantioselectivity.⁵⁶³

When aromatic rings are reduced by Li (or K or Na) in liquid ammonia (such reductions are known as *dissolving metal reductions*), usually in the presence of an alcohol (often ethyl, isopropyl, or *tert*-butyl alcohol), 1,4-addition of hydrogen takes place and

⁵⁴⁹ See Karakhanov, E.A.; Dedov, A.G.; Loktev, A.S. *Russ. Chem. Rev.* **1985**, *54*, 171.

⁵⁵⁰ See Timmer, K.; Thewissen, D.H.M.W.; Meinema, H.A.; Bulten, E.J. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 87.

⁵⁵¹ Muetterties, E.L.; Bleeke, J.R. *Acc. Chem. Res.* **1979**, *12*, 324. See also, Tsukinoki, T.; Kanda, T.; Liu, G.-B.; Tsuzuki, H.; Tashiro, M. *Tetrahedron Lett.* **2000**, *41*, 5865.

⁵⁵² Januszkiewicz, K.R.; Alper, H. *Organometallics* **1983**, *2*, 1055.

⁵⁵³ Dyson, P.J.; Ellis, D.J.; Parker, D.G.; Welton, T. *Chem. Commun.* **1999**, 25. Rhodium nanoparticles are used as a catalyst: Mu, X.-d.; Meng, J.-q.; Li, Z.-C.; Kou, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9694.

⁵⁵⁴ Bonilla, R.J.; James, B.R.; Jessop, P.G. *Chem. Commun.* **2000**, 941.

⁵⁵⁵ Zhong, G.; Chan, B.; Radom, L. *J. Am. Chem. Soc.* **2007**, *129*, 924.

⁵⁵⁶ For an indirect method of hydrogenating benzene to cyclohexene, see Harman, W.D.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 7906.

⁵⁵⁷ Higashijima, M.; Nishimura, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 824.

⁵⁵⁸ Boxwell, C.J.; Dyson, P.J.; Ellis, D.J.; Welton, T. *J. Am. Chem. Soc.* **2002**, *124*, 9334.

⁵⁵⁹ Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357.

⁵⁶⁰ Kuwano, R.; Kashiwabara, M.; Ohsumi, M.; Kusano, H. *J. Am. Chem. Soc.* **2008**, *130*, 808.

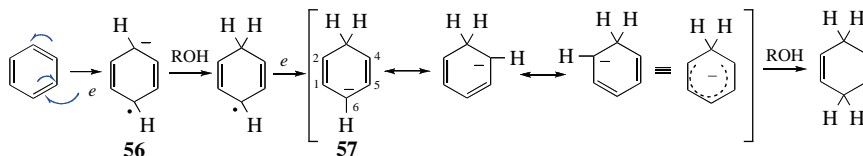
⁵⁶¹ Piras, L.; Genesio, E.; Ghiron, C.; Taddei, M. *Synlett* **2008**, 1125.

⁵⁶² Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536.

⁵⁶³ Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213. See Kim, J.T.; Gevorgyan, V. *J. Org. Chem.* **2005**, *70*, 2054.

nonconjugated cyclohexadienes are produced.⁵⁶⁴ This reaction is called the *Birch reduction*.⁵⁶⁵ Heterocycles (e.g., pyrroles,⁵⁶⁶ furans,⁵⁶⁷ pyridines,⁵⁶⁸ and indolones⁵⁶⁹) can be reduced using *Birch reduction*. Ammonia obtained commercially often has iron salts as impurities that lower the yield in the *Birch reduction*. Therefore it is often necessary to distill the ammonia. When substituted aromatic compounds are subjected to the *Birch reduction*, electron-donating groups (e.g., alkyl or alkoxy) decrease the rate of the reaction and are generally found on the nonreduced positions of the product. For example, anisole gives 1-methoxy-1,4-cyclohexadiene, not 3-methoxy-1,4-cyclohexadiene. On the other hand, electron-withdrawing groups (e.g., COOH or CONH₂) increase the reaction rate and are found on the reduced positions of the product.⁵⁷⁰ The regioselectivity of the reaction has been examined.⁵⁷¹ The mechanism involves solvated electrons,⁵⁷² which are transferred from the metal to the solvent, and hence to the ring.⁵⁷³

The sodium becomes oxidized to Na⁺ and creates a radical ion (**56**).⁵⁷⁴ There is a great deal of evidence from ESR spectra for these species.⁵⁷⁵ The radical ion accepts a proton from the alcohol to give a radical, which is reduced to a carbanion by another sodium atom. Finally, **57** accepts another proton. Thus the function of the alcohol is to supply protons, since with most substrates ammonia is not acidic enough for this purpose. In the absence of the alcohol, products arising from dimerization of **56** are frequently obtained. There is evidence⁵⁷⁶ at least with some substrates (e.g., biphenyl) that the radical ion corresponding to **56** is converted to the carbanion corresponding to **56** by a different pathway, in which the order of the steps is reversed: First a second electron is gained to give a dianion,⁵⁷³ which then acquires a proton, producing the intermediate (e.g., **56**).



Ordinary alkenes are usually unaffected by *Birch-reduction* conditions, and double bonds may be present in the molecule if they are not conjugated with the ring. However,

⁵⁶⁴ See Brandsma, L.; van Soolingen, J.; Andringa, H. *Synth. Commun.* **1990**, 20, 2165. Also see, Weitz, I.S.; Rabinovitz, M. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 117.

⁵⁶⁵ Akhrem, A.A.; Reshotova, I.G.; Titov, Yu.A. *Birch Reduction of Aromatic Compounds* Plenum, NY, **1972**; Birch, A.J. *Pure Appl. Chem.* **1996**, 68, 553; Rabideau, P.W. *Tetrahedron* **1989**, 45, 1579; Birch, A.J.; Subba Rao, G. *Adv. Org. Chem.* **1972**, 8, 1; Kaiser, E.M. *Synthesis* **1972**, 391.

⁵⁶⁶ Donohoe, T.J.; House, D. *J. Org. Chem.* **2002**, 67, 5015.

⁵⁶⁷ Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocyclic Chem.* **1996**, 33, 1313.

⁵⁶⁸ Donohoe, T.J.; McRiner, A.J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1435.

⁵⁶⁹ Guo, Z.; Schultz, A.G. *J. Org. Chem.* **2001**, 66, 2154.

⁵⁷⁰ See Zimmerman, H.E.; Wang, P.A. *J. Am. Chem. Soc.* **1990**, 112, 1280; Rabideau, P.W.; Karrick, G.L. *Tetrahedron Lett.* **1987**, 28, 2481.

⁵⁷¹ Zimmerman, H.E.; Wang, P.A. *J. Am. Chem. Soc.* **1993**, 115, 2205.

⁵⁷² For reviews of solvated electrons and related topics, see Dye, J.L. *Prog. Inorg. Chem.* **1984**, 32, 327–441; Alpatova, N.M.; Krishtalik, L.I.; Pleskov, Y.V. *Top. Curr. Chem.* **1987**, 138, 149–219.

⁵⁷³ Birch, A.J.; Nasipuri, D. *Tetrahedron* **1959**, 6, 148.

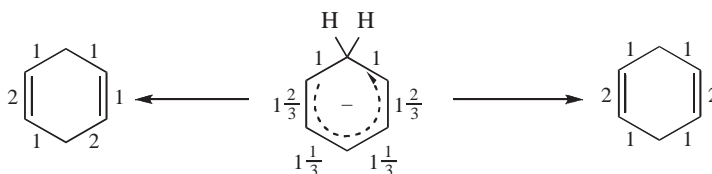
⁵⁷⁴ See Holy, N.L. *Chem. Rev.* **1974**, 74, 243.

⁵⁷⁵ See Jones, M.T. in Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, **1968**, pp. 245–274; Bowers, K.W. *Adv. Magn. Reson.*, **1965**, 1, 317; Carrington, A. *Q. Rev. Chem. Soc.* **1963**, 17, 67.

⁵⁷⁶ Rabideau, P.W.; Peters, N.K.; Huser, D.L. *J. Org. Chem.* **1981**, 46, 1593.

phenylated alkenes, internal alkynes (Reaction 15-12),⁵⁷⁷ and conjugated alkenes (with C=C or C=O) are reduced under these conditions.

Note that **56** is a resonance hybrid; that is, two additional canonical forms can be written. The question therefore arises: Why does the carbanion pick up a proton at the 6 position to give the 1,4-diene? Why not at the 2 position to give the 1,3-diene?⁵⁷⁸ An answer to this question has been proposed by Hine,⁵⁷⁹ who suggested that this case is an illustration of the operation of the *principle of least motion*. According to this principle, “those elementary reactions will be favored that involve the least change in atomic position and electronic configuration.”⁵⁷⁸ The principle can be applied to the case at hand in the following manner (simplified): The valence bond bond orders (Sec. 2.A) for the six carbon–carbon bonds (on the assumption that each of the three forms contributes equally) are (going around the ring) $1\frac{2}{3}$, 1, 1, $1\frac{2}{3}$, $1\frac{1}{3}$, and $1\frac{1}{3}$. When the carbanion is converted to the diene, these bond orders change as follows:



It can be seen that the two bonds whose bond order is 1 are unchanged in the two products, but for the other four bonds there is a change. If the 1,4-diene is formed, the change is $\frac{1}{3} + \frac{1}{3} + \frac{1}{3} + \frac{1}{3}$, while formation of the 1,3-diene requires a change of $\frac{1}{3} + \frac{2}{3} + \frac{2}{3} + \frac{1}{3}$. Since a greater change is required to form the 1,3-diene, the principle of least motion predicts formation of the 1,4-diene. This may not be the only factor, because the ^{13}C NMR spectrum of **111** shows that the 6 position has a somewhat greater electron density than the 2 position, which presumably would make the former more attractive to a proton.⁵⁸⁰

Reduction of aromatic rings with Li ⁵⁸¹ or Ca ⁵⁸² in amines (instead of ammonia: called *Benkeser reduction*) proceeds further and cyclohexenes are obtained. It is thus possible to reduce a benzene ring, by proper choice of reagent, so that one, two, or all three double bonds are reduced.⁵⁸³ Lithium triethylborohydride (LiBET_3H) has also been used, to reduce pyridine derivatives to piperidine derivatives.⁵⁸⁴

Transition metals and metal compounds can reduce aromatic rings in the proper medium. Indium metal reduces the pyridine ring in quinoline in aq ethanol solution,⁵⁸⁵ as well as the C=C unit in the five-membered ring of indole derivatives.⁵⁸⁶ Samarium

⁵⁷⁷ See Brandsma, L.; Nieuwenhuizen, W.F.; Zwikker, J.W.; Mäeorg, U. *Eur. J. Org. Chem.* **1999**, 775.

⁵⁷⁸ See Rabideau, P.W.; Huser, D.L. *J. Org. Chem.* **1983**, 48, 4266.

⁵⁷⁹ Hine, J. *J. Org. Chem.* **1966**, 31, 1236; Hine, J. *Adv. Phys. Org. Chem.* **1977**, 15, 1. See also, Jochum, C.; Gasteiger, J.; Ugi, I. *Angew. Chem. Int. Ed.* **1980**, 19, 495.

⁵⁸⁰ Bates, R.B.; Brenner, S.; Cole, C.M.; Davidson, E.W.; Forsythe, G.D.; McCombs, D.A.; Roth, A.S. *J. Am. Chem. Soc.* **1973**, 95, 926.

⁵⁸¹ Benkeser, R.A.; Agnihotri, R.K.; Burrous, M.L.; Kaiser, E.M.; Mallan, J.M.; Ryan, P.W. *J. Org. Chem.* **1964**, 29, 1313; Kwart, H.; Conley, R.A. *J. Org. Chem.* **1973**, 38, 2011.

⁵⁸² Benkeser, R.A.; Belmonte, F.G.; Kang, J. *J. Org. Chem.* **1983**, 48, 2796. See also, Benkeser, R.A.; Laugal, J.A.; Rappa, A. *Tetrahedron Lett.* **1984**, 25, 2089.

⁵⁸³ See Keay, J.G. *Adv. Heterocycl. Chem.* **1986**, 39, 1.

⁵⁸⁴ Blough, B.E.; Carroll, F.I. *Tetrahedron Lett.* **1993**, 34, 7239.

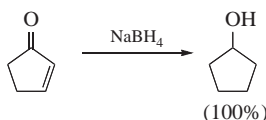
⁵⁸⁵ Moody, C.J.; Pitts, M.R. *Synlett* **1998**, 1029.

⁵⁸⁶ Pitts, M.R.; Harrison, J.R.; Moody, C.J. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 955.

iodide (SmI_2) reduces pyridine in aq THF⁵⁸⁷ and phenol in MeOH/KOH.⁵⁸⁸ Ammonium formate and a Pd—C catalyst reduces pyridine *N*-oxide to piperidine in methanol.⁵⁸⁹ The nitrogen-containing ring of quinolines is reduced with an In catalyst in isopropyl alcohol.⁵⁹⁰

OS **I**, 99, 499; **II**, 566; **III**, 278, 742; **IV**, 313, 887, 903; **V**, 398, 400, 467, 591, 670, 743, 989; **VI**, 371, 395, 461, 731, 852, 856, 996; **VII**, 249.

15-14 Reduction of the Double or Triple Bonds Conjugated to Carbonyls, Cyano, Nitro, and so on



Reduction of only the C=C bond of conjugated $\text{C}=\text{C}-\text{C}=\text{O}$ and $\text{C}=\text{C}-\text{C}\equiv\text{N}$ systems⁵⁹¹ has been achieved by many reducing agents,⁵⁹² including catalytic hydrogenation with a Rh,⁵⁹³ a Ru,⁵⁹⁴ a Pd,⁵⁹⁵ or an Ir catalyst,⁵⁹⁶ and with Raney nickel alone.⁵⁹⁷ Reagents, such as SmI_2 ⁵⁹⁸ and catecholborane,⁵⁹⁹ are effective. Conjugated ketones react with 2 equiv of Cp_2TiCl in THF/MeOH to give the corresponding saturated ketone.⁶⁰⁰ Zinc and acetic acid has been used for the conjugate reduction of dihydropyridin-4-ones.⁶⁰¹ Formic acid with a Pd catalyst reduced conjugated carboxylic acids.⁶⁰² A zinc–titanocene protocol has been developed for conjugate reductions.⁶⁰³ Both NaBH_4 in MeOH—THF⁶⁰⁴ and NaCNBH_3 on a zeolite⁶⁰⁵ reduce α,β -unsaturated nitro compounds to nitroalkanes.

In certain cases,⁶⁰⁶ metallic hydride reagents may selectively reduce double bonds that are in conjugation with C=O bonds,⁶⁰⁷ although the C=O bonds are also reduced in many

⁵⁸⁷ Kamochi, Y.; Kudo, T. *Heterocycles* **1993**, 36, 2383.

⁵⁸⁸ Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* **1994**, 35, 4169.

⁵⁸⁹ Zacharie, B.; Moreau, N.; Dockendorff, C. *J. Org. Chem.* **2001**, 66, 5264.

⁵⁹⁰ Fujita, K.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. *Tetrahedron Lett.* **2004**, 45, 3215.

⁵⁹¹ See Keinan, E.; Greenspoon, N. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, **1989**, pp. 923–1022.; Augustine, R.L. *Adv. Catal.* **1976**, 25, 56.

⁵⁹² See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 13–27.

⁵⁹³ Cabello, J.A.; Campelo, J.M.; Garcia, A.; Luna, D.; Marinas, J.M. *J. Org. Chem.* **1986**, 51, 1786.

⁵⁹⁴ Wang, C.-J.; Tao, H.; Zhang, X. *Tetrahedron Lett.* **2006**, 47, 1901.

⁵⁹⁵ Nagano, H.; Yokota, M.; Iwazaki, Y. *Tetrahedron Lett.* **2004**, 45, 3035.

⁵⁹⁶ Yue, T.-Y.; Nugent, W.A. *J. Am. Chem. Soc.* **2002**, 124, 13692;

⁵⁹⁷ Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* **1999**, 1663; Wang, H.; Lian, H.; Chen, J.; Pan, Y.; Shi, Y. *Synth. Commun.* **1999**, 29, 129.

⁵⁹⁸ Cabrera, A.; Alper, H. *Tetrahedron Lett.* **1992**, 33, 5007. See also, Tarnopolsky, A.; Hoz, S. *J. Am. Chem. Soc.* **2007**, 129, 3402.

⁵⁹⁹ Evans, D.A.; Fu, G.C. *J. Org. Chem.* **1990**, 55, 5678.

⁶⁰⁰ Moisan, L.; Hardouin, C.; Rousseau, B.; Doris, E. *Tetrahedron Lett.* **2002**, 43, 2013.

⁶⁰¹ Comins, D.L.; Brooks, C.A.; Ingalls, C.L. *J. Org. Chem.* **2001**, 66, 2181.

⁶⁰² Arterburn, J.B.; Pannala, M.; Gonzalez, A.M.; Chamberlin, R.M. *Tetrahedron Lett.* **2000**, 41, 7847.

⁶⁰³ Kosal, A.D.; Ashfeld, B.L. *Org. Lett.* **2010**, 12, 44.

⁶⁰⁴ Varma, R.S.; Kabalka, G.W. *Synth. Commun.* **1985**, 15, 151.

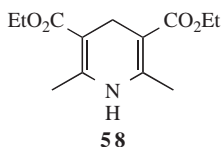
⁶⁰⁵ Gupta, A.; Haque, A.; Vankar, Y.D. *Chem. Commun.* **1996**, 1653.

⁶⁰⁶ See Meyer, G.R. *J. Chem. Educ.* **1981**, 58, 628.

⁶⁰⁷ For a discussion of hydride affinity with respect to hydride reducing agents, see Zhu, X.-Q.; Zhang, M.; Liu, Q.-Y.; Wang, X.-X.; Zhang, J.-Y.; Cheng, J.-P. *Angew. Chem. Int. Ed.* **2006**, 45, 3954; Vianello, R.; Peran, N.; Maksić, Z.B. *Eur. J. Org. Chem.* **2007**, 5296.

cases, as in the conversion of cyclopentenone to cyclopentanol.⁶⁰⁸ The reagent NaBH_4 has a greater tendency than LiAlH_4 to effect this double reduction, although even with NaBH_4 the product of 1,2-reduction (of the $\text{C}=\text{O}$ bond) is usually formed in larger amount than the doubly reduced product. The $\text{C}=\text{C}$ unit proximal to the carbonyl in dienyl amides is selectively reduced with NaBH_4/I_2 .⁶⁰⁹ Mixed hydride reducing agents (e.g., $\text{NaBH}_4\text{—BiCl}_3$,⁶¹⁰ $\text{NaBH}_4\text{—InCl}_3$,⁶¹¹ and $\text{Dibal-H—Co(acac)}_2$)⁶¹² have been used. The $\text{InCl}_3\text{—NaBH}_4$ reagent was used to covert conjugated diene ketones ($\text{C}=\text{C—C}=\text{C—C}=\text{O}$) selectively to the nonconjugated alkenyl ketone ($\text{C}=\text{C—CH}_2\text{CH}_2\text{—C}=\text{O}$).⁶¹³ Lithium aluminum hydride also reduces the double bonds of allylic alcohols.⁶¹⁴

Transfer hydrogenation can be applied to the reduction of conjugated alkenes. Reduction of the $\text{C}=\text{C}$ unit of conjugated aldehydes is accomplished with an imidazolidinone catalyst⁶¹⁵ or an amino ester⁶¹⁶ in the presence of a *Hantzsch ester* (e.g., **58**). Nitroalkenes are hydrogenated using a thiourea catalyst in the presence of **58**.⁶¹⁷ Palladium/carbon with microwave heating is used for the transfer hydrogenation of conjugated carboxylic acids, using 1,4-cyclohexadiene as the hydrogen-transfer agent.⁶¹⁸ Solvent-free transfer hydrogenation is possible using a Ru complex, with formic acid or water⁶¹⁹ as the hydrogen donor.⁶²⁰ Palladium— $\text{P}(t\text{-Bu})_3$ has been used as a mild catalyst for transfer hydrogenation.⁶²¹ Titanium-catalyzed reductions are also known.⁶²²



Silanes reduce the $\text{C}=\text{C}$ unit in conjugated systems in the presence of Cu species.⁶²³ An asymmetric CuH catalyzed hydrosilation reaction is known.⁶²⁴ Phenylsilane (PhSiH_3) and

⁶⁰⁸ Brown, H.C.; Hess, H.M. *J. Org. Chem.* **1969**, *34*, 2206. For other methods of reducing both double bonds, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, p. 1096.

⁶⁰⁹ Das, B.; Kashinatham, A.; Madhusudhan, P. *Tetrahedron Lett.* **1998**, *39*, 677.

⁶¹⁰ Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Synth. Commun.* **1995**, *25*, 3395.

⁶¹¹ Ranu, B.C.; Samanta, S. *Tetrahedron Lett.* **2002**, *43*, 7405.

⁶¹² Ikeno, T.; Kimura, T.; Ohtsuka, Y.; Yamada, T. *Synlett* **1999**, 96.

⁶¹³ Ranu, B.C.; Samanta, S. *J. Org. Chem.* **2003**, *68*, 7130.

⁶¹⁴ See Blunt, J.W.; Hartshorn, M.P.; Soong, L.T.; Munro, M.H.G. *Aust. J. Chem.* **1982**, *35*, 2519; Vincens, M.; Fadel, R.; Vidal, M. *Bull. Soc. Chim. Fr.* **1987**, 462.

⁶¹⁵ Ouellet, S.G.; Tuttle, J.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2005**, *127*, 32; Tuttle, J.B.; Ouellet, S.G.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2006**, *128*, 12662; Adolfsson, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 3340.

⁶¹⁶ Martin, N.J.A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.

⁶¹⁷ Martin, N.J.A.; Ozoires, L.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 8976.

⁶¹⁸ Quinn, J.F.; Razzano, D.A.; Golden, K.C.; Gregg, B.T. *Tetrahedron Lett.* **2008**, *49*, 6137.

⁶¹⁹ Li, X.; Li, L.; Tang, Y.; Zhong, L.; Cun, L.; Zhu, J.; Liao, J.; Deng, J. *J. Org. Chem.* **2010**, *75*, 2981.

⁶²⁰ Naskar, S.; Bhattacharjee, M. *Tetrahedron Lett.* **2007**, *48*, 465.

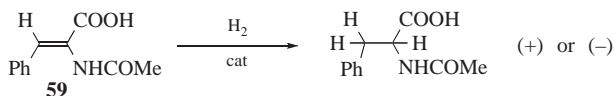
⁶²¹ Brunel, J.M. *Synlett* **2007**, 330.

⁶²² Che, J.; Lam, Y. *Synlett* **2010**, 2415.

⁶²³ Mori, A.; Fujita, A.; Nishihara, Y.; Hiyama, R. *Chem. Commun.* **1997**, 2159; Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573.

⁶²⁴ Huang, S.; Voigttritter, K.R.; Unger, J.B.; Lipshutz, B.H. *Synlett* **2010**, 2041.

a Ni catalyst,⁶²⁵ CuCl,⁶²⁶ a Mn catalyst⁶²⁷ or a Mo⁶²⁸ catalyst have been used for hydrosilation reactions. Triphenylsilane was also used for the asymmetric reduction of nitro alkenes (C=C–NO₂).⁶²⁹ Poly(methylhydrosiloxane) with a chiral Cu catalyst gave conjugate reduction of conjugated esters to give the saturated derivative with high enantioselectivity.⁶³⁰ Polymethylhydrosiloxane, in the presence of a Co-catalyst reduces conjugated nitriles.⁶³¹ A β-bromo conjugated lactone was reduced to the β-bromolactone with modest enantioselectivity using an excess of Ph₃SiH and a CuCl catalyst with a chiral ligand.⁶³² Tributyltin hydride, in the presence of MgBr₂•OEt₂ gave 1,4-reduction of conjugated esters.⁶³³



Optically active homogeneous hydrogenation catalysts have been used to achieve the enantioselective hydrogenation⁶³⁴ of many prochiral conjugated substrates.⁶³⁵ For example,⁶³⁶ hydrogenation of **59** with a suitable catalyst gives the (+) or (–) amino ester (depending on which enantiomer of the catalyst is used) with an ee as high as 96%.⁶³⁷ Prochiral substrates that give such high optical yields generally contain functional groups (e.g., a carbonyl group,⁶³⁸ amide groups, cyano groups) or combinations of such groups as in **58**.⁶³⁹ The catalyst in such cases⁶⁴⁰ is usually a Ru⁶⁴¹ or Rh complex⁶⁴² with chiral

⁶²⁵ Boudjouk, P.; Choi, S.-B.; Hauck, B.J.; Rajkumar, A.B. *Tetrahedron Lett.* **1998**, 39, 3951.

⁶²⁶ Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* **1997**, 38, 8887.

⁶²⁷ Magnus, P.; Waring, M.J.; Scott, D.A. *Tetrahedron Lett.* **2000**, 41, 9731.

⁶²⁸ Keinan, E.; Perez, D. *J. Org. Chem.* **1987**, 52, 2576.

⁶²⁹ Czekelius, C.; Carreira, E.M. *Org. Lett.* **2004**, 6, 4575.

⁶³⁰ See Jurkauskas, V.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, 124, 2892; Lipshutz, B.H.; Servosko, J.M.; Taft, B.R. *J. Am. Chem. Soc.* **2004**, 126, 8352.

⁶³¹ Kim, D.; Park, B.-M.; Yun, J. *Chem. Commun.* **2005**, 1755.

⁶³² Hughes, G.; Kimura, M.; Buchwald, S.L. *J. Am. Chem. Soc.* **2003**, 125, 11253.

⁶³³ Hirasawa, S.; Nagano, H.; Kameda, Y. *Tetrahedron Lett.* **2004**, 45, 2207.

⁶³⁴ See Gridnev, I.D.; Imamoto, T. *Acc. Chem. Res.* **2004**, 37, 633.

⁶³⁵ Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, 45, 6901, pp. 6902–6916; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis* VCH, NY, **1986**, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* **1983**, 16, 106; Brunner, H. *Angew. Chem. Int. Ed.* **1983**, 22, 897; Caplar, V.; Comisso, G.; Sunjic, V. *Synthesis* **1981**, 85. See also, Wroblewski, A. E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J. G. *J. Am. Chem. Soc.* **1988**, 110, 4144; Knowles, W.S. *Angew. Chem. Int. Ed.* **2002**, 41, 1999.

⁶³⁶ See Ashby, M.T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, 113, 589; Heiser, B.; Broger, E.A.; Cramer, Y. *Tetrahedron: Asymmetry* **1991**, 2, 51; Burk, M.J. *J. Am. Chem. Soc.* **1991**, 113, 8518.

⁶³⁷ Koenig, K.E. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, **1985**, p. 74.

⁶³⁸ Reetz, M.T.; Mehler, G. *Angew. Chem. Int. Ed.* **2000**, 39, 3889.

⁶³⁹ Koenig, K.E. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, **1985**, pp. 83–101.

⁶⁴⁰ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 8–12. See Izumi, Y. *Adv. Catal.* **1983**, 32, 215; Mortreux, A.; Petit, F.; Buono, G.; Peiffer, G. *Bull. Soc. Chim. Fr.* **1987**, 631.

⁶⁴¹ Wu, H.-P.; Hoge, G. *Org. Lett.* **2004**, 6, 3645; Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, 125, 9570.

⁶⁴² Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Itoh, J.-i.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. *Chemistry: European J.* **2006**, 12, 63.

phosphine ligands.⁶⁴³ Good asymmetric induction⁶⁴⁴ has been achieved using chiral Rh complexes with other chiral additives.⁶⁴⁵ Iridium complexes have been used with excellent enantioselectivity.⁶⁴⁶ The role of solvent has been examined.⁶⁴⁷ A pressure-dependent enantioselective hydrogenation has been reported.⁶⁴⁸ Asymmetric catalytic hydrogenation has been reported for conjugated carboxylic acids⁶⁴⁹ and conjugated ketones.⁶⁵⁰ Asymmetric hydrogenation of conjugated carboxylic acids in an ionic liquid is known using a chiral Ru complex⁶⁵¹

See Reaction **19-36** for methods of reducing C=O bonds in the presence of conjugated C=C bonds.

The C=C unit of conjugated aldehydes has been reduced using AlMe₃ with a catalytic amount of CuBr⁶⁵² and with ammonium formate/Pd—C.⁶⁵³ Polymer-supported formate has been used for the 1,4-reduction of conjugated ketones⁶⁵⁴ and for conjugated acids using an Rh catalyst and microwave irradiation.⁶⁵⁵ Isopropyl alcohol and an Ir catalyst gives conjugate reduction of conjugated ketones.⁶⁵⁶ The reaction of conjugated ketones with aluminum chlorides, followed by treatment with water generates the saturated ketone.⁶⁵⁷

Enzymatic reduction of conjugated systems requires the reactivity with certain purified or whole cell enzymes. Baker's yeast reduces conjugated nitro compounds to nitroalkanes⁶⁵⁸ and also the C=C unit of conjugated ketones.⁶⁵⁹ Other enzymatic reductions are possible. A reductase from *Nicotiana tabacum* reduced a conjugated ketone to the

⁶⁴³ Pagenkopf, B.L. *J. Org. Chem.* **2004**, 69, 4177; Fu, Y.; Guo, X.-X.; Zhu, S.-F.; Hu, A.-G.; Xie, J.-H.; Zhou, Q.-L. *J. Org. Chem.* **2004**, 69, 4648; Yi, B.; Fan, Q.-H.; Deng, G.-J.; Li, Y.-M.; Qiu, L.-Q.; Chan, A.S.C. *Org. Lett.* **2004**, 6, 1361; Hoen, R.; van den Berg, M.; Bernsmann, H.; Minnaard, A.J.; de Vries, J.G.; Feringa, B.L. *Org. Lett.* **2004**, 6, 1433; Fu, Y.; Hou, G.-H.; Xie, J.-H.; Xing, L.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2004**, 69, 8157; Hoge, G.; Wu, H.-P.; Kissel, W.S.; Pflum, D.A.; Greene, D.J.; Bao, J. *J. Am. Chem. Soc.* **2004**, 126, 5966; Ikeda, S.-i.; Sanuki, R.; Miyachi, H.; Miyashita, H.; Taniguchi, M.; Odashima, K. *J. Am. Chem. Soc.* **2004**, 126, 10331; Huang, H.; Liu, X.; Chen, S.; Chen, H.; Zheng, Z. *Tetrahedron Asymmetry* **2004**, 15, 2011; Hattori, G.; Hori, T.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, 129, 12930.

⁶⁴⁴ Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, 63, 9590; Burk, M.J.; Casy, G.; Johnson, N.B. *J. Org. Chem.* **1998**, 63, 6084; Burk, M.J.; Allen, J.G.; Kiesman, W.F. *J. Am. Chem. Soc.* **1998**, 120, 657.

⁶⁴⁵ Noyori, R.; Hashiguchi, S. *Accs. Chem. Res.* **1997**, 30, 97.

⁶⁴⁶ Li, S.; Zhu, S.-F.; Zhang, C.-M.; Song, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2008**, 130, 8584; Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Angew. Chem. Int. Ed.* **2008**, 47, 10133.

⁶⁴⁷ Heller, D.; Drexler, H.-J.; Spannenberg, A.; Heller, B.; You, J.; Baumann, W. *Angew. Chem. Int. Ed.* **2002**, 41, 777.

⁶⁴⁸ Heller, D.; Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Börner, A. *J. Org. Chem.* **2001**, 66, 6816.

⁶⁴⁹ Suárez, A.; Pizzano, A. *Tetrahedron Asymmetry* **2001**, 12, 2501. See Okano, T.; Kaji, M.; Isotani, S.; Kiji, J. *Tetrahedron Lett.* **1992**, 33, 5547 for the influence of water on the regioselectivity of this reduction.

⁶⁵⁰ Yamaguchi, M.; Nitta, A.; Reddy, R.S.; Hiram, M. *Synlett* **1997**, 117.

⁶⁵¹ Brown, R.A.; Pollet, P.; McKoon, E.; Eckert, C.A.; Liotta, C.L.; Jessop, P.G. *J. Am. Chem. Soc.* **2001**, 123, 1254.

⁶⁵² Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Synlett* **1994**, 679.

⁶⁵³ Ranu, B.C.; Sarkar, A. *Tetrahedron Lett.* **1994**, 35, 8649.

⁶⁵⁴ Basu, B.; Bhuiyan, Md.M.H.; Das, P.; Hossain, I. *Tetrahedron Lett.* **2003**, 44, 8931.

⁶⁵⁵ Desai, B.; Danks, T.N. *Tetrahedron Lett.* **2001**, 42, 5963.

⁶⁵⁶ Sakaguchi, S.; Yamaga, T.; Ishii, Y. *J. Org. Chem.* **2001**, 66, 4710.

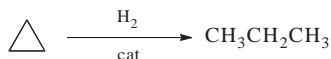
⁶⁵⁷ Koltunov, K.Yu.; Repinskaya, I.B.; Borodkin, G.I. *Russ. J. Org. Chem.* **2001**, 37, 1534.

⁶⁵⁸ Kawai, Y.; Inaba, Y.; Tokitoh, N. *Tetrahedron Asymmetry* **2001**, 12, 309.

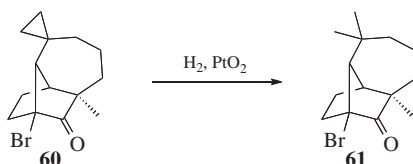
⁶⁵⁹ Filho, E.P.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron Asymmetry* **2001**, 12, 847; Kawai, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Asymmetry* **2001**, 12, 3007.

saturated ketone, with excellent enantioselectivity.⁶⁶⁰ Enzyme YNAR-I and NADP-H reduces conjugated nitro compounds to nitroalkanes.⁶⁶¹ Conjugated nitro compounds are reduced in the presence of *Clostridium sporogenes*.⁶⁶²

15-15 Reductive Cleavage of Cyclopropanes

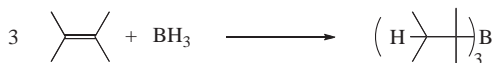


Cyclopropanes can be cleaved by catalytic hydrogenolysis.⁶⁶³ Among the catalysts used have been Ni, Pd, Rh,⁶⁶⁴ and Pt. The reaction can often be run under mild conditions.⁶⁶⁵ Certain cyclopropane rings, especially cyclopropyl ketones and aryl-substituted cyclopropanes,⁶⁶⁶ can be reductively cleaved by an alkali metal (generally Na or Li) in liquid ammonia.⁶⁶⁷ Similar reduction has been accomplished photochemically in the presence of LiClO₄.⁶⁶⁸ This reaction is an excellent way to introduce a *gem*-dimethyl unit into a molecule. Hydrogenation of the cyclopropane ring in **60**, for example, gave the *gem*-dimethyl unit in **61** using PtO₂ (*Adam's catalyst*).⁶⁶⁹



F. A Metal on the Other Side

15-16 Hydroboration



When alkenes are treated with borane⁶⁷⁰ in ether solvents, BH₃ adds across the double bond.⁶⁷¹ The alkene reacts as a base with the boron essentially reacting as a Lewis acid. Borane cannot be prepared as a stable pure compound⁶⁷² (it dimerizes to diborane, B₂H₆),

⁶⁶⁰ Shimoda, K.; Kubota, N.; Hamada, H. *Tetrahedron Asymmetry* **2004**, 15, 2443.

⁶⁶¹ Kawai, Y.; Inaba, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Lett.* **2001**, 42, 3367.

⁶⁶² Fryszkowska, A.; Fisher, K.; Gardiner, J.M.; Stephens, G.M. *J. Org. Chem.* **2008**, 73, 4295.

⁶⁶³ See Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, **1970**, pp. 588–592; Newham, J. *Chem. Rev.* **1963**, 63, 123; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals* Academic Press, NY, **1967**, pp. 469–474.

⁶⁶⁴ Bart, S.C.; Chirik, P.J. *J. Am. Chem. Soc.* **2003**, 125, 886.

⁶⁶⁵ See Woodworth, C.W.; Buss, V.; Schleyer, P.v.R. *Chem. Commun.* **1968**, 569.

⁶⁶⁶ See Walborsky, H.M.; Aronoff, M.S.; Schulman, M.F. *J. Org. Chem.* **1970**, 36, 1036.

⁶⁶⁷ For a review, see Staley, S.W. *Sel. Org. Transform.* **1972**, 2, 309.

⁶⁶⁸ Cossy, J.; Furet, N. *Tetrahedron Lett.* **1993**, 34, 8107.

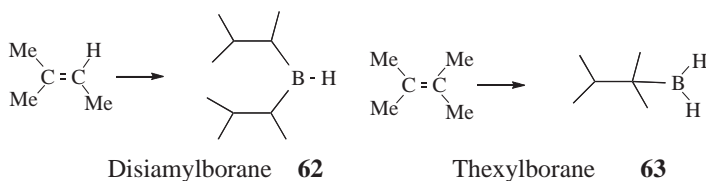
⁶⁶⁹ Karimi, S.; Tavares, P. *J. Nat. Prod.* **2003**, 66, 520.

⁶⁷⁰ See Lane, C.F. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, **1977**, pp. 1–191.

⁶⁷¹ See Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**; *Organic Syntheses Via Boranes* Wiley, NY, **1975**; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, **1973**; Matteson, D.S. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 307–409, pp. 315–337; Suzuki, A.; Dhillon, R.S. *Top. Curr. Chem.* **1986**, 130, 23.

⁶⁷² Fehlner, T.P. *J. Am. Chem. Soc.* **1971**, 93, 6366.

but it is commercially available in the form of “ate” complexes with THF, Me_2S ,⁶⁷³ phosphines, or tertiary amines. The alkenes can be treated with a solution of one of these complexes. Tetrahydrofuran– BH_3 reacts at 0°C and is the most convenient to use and $\text{R}_3\text{N}–\text{BH}_3$ generally require temperatures of $\sim 100^\circ\text{C}$. The latter can be prepared as air-stable liquids or solids, while the former can only be used as relatively dilute solutions in THF and are decomposed by moisture (in air) or with a mixture of NaBH_4 and BF_3 etherate, which generates borane *in situ*.⁶⁷⁴ Pyridine–borane can be used for the hydroboration of alkenes at room temperature.⁶⁷⁵ With relatively unhindered alkenes, the process cannot be stopped with the addition of one molecule of BH_3 because the resulting RBH_2 adds to another molecule of alkene to give R_2BH , which in turn adds to a third alkene molecule, so that the isolated product is a trialkylborane (R_3B). The reaction can be performed on alkenes with one to four substituents, including cyclic alkenes, but when the alkene is moderately hindered, the product is the dialkylborane (R_2BH) or even the monoalkylborane (RBH_2).⁶⁷⁶ For example, **62** (*disiamylborane*) and **63** (*thexylborane*)⁶⁷⁷ have been prepared in this manner. Monoalkylboranes (RBH_2), which can be prepared from hindered alkenes, (as above) and dialkylboranes (R_2BH) also add to alkenes, to give the mixed trialkylboranes ($\text{RR}'_2\text{B}$ and $\text{R}_2\text{R}'\text{B}$), respectively. Surprisingly, when methylborane (MeBH_2),⁶⁷⁸ which is not a bulky molecule, adds to alkenes in the solvent THF, the reaction can be stopped with one addition to give dialkylboranes (RMeBH).⁶⁷⁹ Reaction of this with a second alkene produces the trialkylborane ($\text{RR}'\text{MeB}$).⁶⁸⁰ Other monoalkylboranes (*i*- PrBH_2 , *n*- BuBH_2 , *s*- BuBH_2 , and *t*- BuBH_2), behave similarly with internal alkenes, but not with alkenes of the type $\text{RCH}=\text{CH}_2$.⁶⁸¹



In all cases, the boron goes to the side of the double bond that has more hydrogen atoms (less substituted), whether the substituents are aryl or alkyl.⁶⁸² Technically, this follows *Markovnikov's rule*, since boron is more positive than hydrogen. The regioselectivity is caused mostly by steric factors, although electronic factors also play a part. Studies of the effect of ring substituents on rates and on the direction of attack in hydroboration of

⁶⁷³ See Hutchins, R.O.; Cistone, F. *Org. Prep. Proced. Int.* **1981**, 13, 225; Cadot, C.; Dalko, P.I.; Cossy, J. *Tetrahedron Lett.* **2001**, 42, 1661.

⁶⁷⁴ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1005–1009.

⁶⁷⁵ Clay, J.M.; Vedejs, E. *J. Am. Chem. Soc.* **2005**, 127, 5766.

⁶⁷⁶ Unless coordinated with a strong Lewis base, such as a tertiary amine, mono- and dialkylboranes actually exist as hydrogen-bridged dimers: Brown, H.C.; Klender, G.J. *Inorg. Chem.* **1962**, 1, 204.

⁶⁷⁷ See Negishi, E.; Brown, H.C. *Synthesis* **1974**, 77.

⁶⁷⁸ See Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* **1986**, 51, 4925.

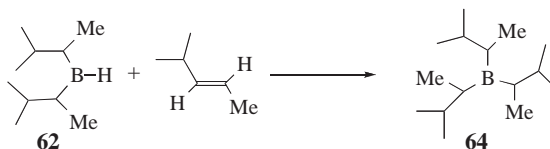
⁶⁷⁹ Srebnik, M.; Cole, T.E.; Brown, H.C. *J. Org. Chem.* **1990**, 55, 5051.

⁶⁸⁰ See Kulkarni, S.U.; Basavaiah, D.; Zaidlewicz, M.; Brown, H.C. *Organometallics* **1982**, 1, 212.

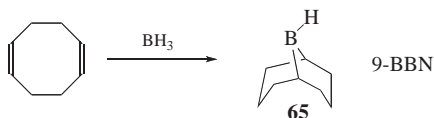
⁶⁸¹ Srebnik, M.; Cole, T.E.; Ramachandran, P.V.; Brown, H.C. *J. Org. Chem.* **1989**, 54, 6085.

⁶⁸² Cragg, G.M.L. *Organoboranes in Organic Synthesis* Marcel Dekker, NY, **1973**, pp. 63–84, 137–197; Brown, H.C.; Vara Prasad, J.V.N.; Zee, S. *J. Org. Chem.* **1986**, 51, 439.

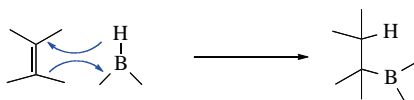
substituted styrenes showed that the reaction with boron and the alkene has electrophilic character.⁶⁸³ When both sides of the double bond are monosubstituted or disubstituted, about equal amounts of each isomer are obtained. However, it is possible in such cases to make the addition regioselective by the use of a large borane molecule. For example, treatment of $i\text{PrCH}=\text{CHMe}$ with borane gave 57% of product with boron on the methyl-bearing carbon and 43% of the other, while treatment with **62** gave 95% **64** and only 5% of the other isomer.⁶⁸⁴



Another reagent with high regioselectivity is 9-borabicyclo[3.3.1]nonane (9-BBN, **65**), which is prepared by hydroboration of 1,5-cyclooctadiene,⁶⁸⁵ and has the advantage that it is stable in air. Borane is quite unselective and attacks all sorts of double bonds. Disiamylborane, 9-BBN, and similar molecules are far more selective and preferentially react at the less-hindered bonds, so it is often possible to hydroborate one double bond in a molecule and leave others unaffected or to hydroborate one alkene in the presence of a less reactive alkene.⁶⁸⁶ For example, 1-pentene can be removed from a mixture of 1- and 2-pentenes, and a *cis*-alkene can be selectively hydroborated in a mixture of the *cis* and *trans* isomers.



For most substrates, the addition in hydroboration is stereospecific and syn, with attack taking place from the less-hindered side.⁶⁸⁷ Note that organoboranes can be analyzed using ¹¹B NMR.⁶⁸⁸ The mechanism⁶⁸⁹ may be a cyclic four-center one:⁶⁹⁰



⁶⁸³ Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* **1966**, 88, 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* **1967**, 7, 377. See also, Marshall, P.A.; Prager, R.H. *Aust. J. Chem.* **1979**, 32, 1251; Mo, Y.; Jiao, H.; Schleyer, P.v.R. *J. Org. Chem.* **2004**, 69, 3493.

⁶⁸⁴ Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, 83, 1241.

⁶⁸⁵ See Brown, H.C.; Chen, J.C. *J. Org. Chem.* **1981**, 46, 3978; Soderquist, J.A.; Brown, H.C. *J. Org. Chem.* **1981**, 46, 4599.

⁶⁸⁶ Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* **1966**, 88, 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* **1967**, 7, 377.

⁶⁸⁷ Kabalka, G.W.; Newton Jr., R.J.; Jacobus, J. *J. Org. Chem.* **1978**, 43, 1567.

⁶⁸⁸ Medina, J.R.; Cruz, G.; Cabrera, C.R.; Soderquist, J.A. *J. Org. Chem.* **2003**, 68, 4631.

⁶⁸⁹ See Nelson, D.J.; Cooper, P.J. *Tetrahedron Lett.* **1986**, 27, 4693; Brown, H.C.; Chandrasekharan, J. *J. Org. Chem.* **1988**, 53, 4811.

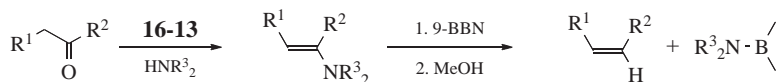
⁶⁹⁰ Narayana, C.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1857. See, however, Jones, P.R. *J. Org. Chem.* **1972**, 37, 1886.

When the substrate is an allylic alcohol or amine, the addition is generally anti,⁶⁹¹ although the stereoselectivity can be changed to syn by the use of catecholborane and Rh complexes.⁶⁹² Because the mechanism is different, use of this procedure can result in a change in regioselectivity as well (e.g., styrene, $\text{PhCH}=\text{CH}_2$, gave $\text{PhCH}(\text{OH})\text{CH}_3$).⁶⁹³

Monochloroborane⁶⁹⁴ (BH_2Cl) coordinated with DMS shows greater regioselectivity than BH_3 for terminal alkenes or those of the form $\text{R}_2\text{C}=\text{CHR}$, and the hydroboration product is a dialkylchloroborane (R_2BCl).⁶⁹⁵ For example, 1-hexene gave 94% of the *anti-Markovnikov* product (the boron is on the less substituted carbon) with BH_3 —THF, but 99.2% with $\text{BH}_2\text{Cl}^-\text{SMe}_2$. Treatment of alkenes with dichloroborane—DMS (BHCl_2 — SMe_2) in the presence of BF_3 ⁶⁹⁶ or with BCl_3 and Me_3SiH ⁶⁹⁷ gives alkylidichloroboranes (RBCl_2). Extensions of this basic approach are possible with dihalo alkylboranes. The reaction of an alkene with allyl dibromoborane, incorporated an allyl group and the boron on adjacent carbons.⁶⁹⁸

An important use of the hydroboration reaction is oxidation of an organoborane to alcohols with H_2O_2 and NaOH (see Reaction 12-27). The synthetic result is an indirect way of adding H_2O across a double bond in an *anti-Markovnikov* manner. However, boranes undergo many other reactions as well. Among other things, they react with α -halo carbonyl compounds to give alkylated products (Reaction 10-73), with α,β -unsaturated carbonyl compounds to give *Michael-type* addition of R and H (Reaction 15-27), with CO to give alcohols and ketones (Reactions 18-23–18-24); they can be reduced with carboxylic acids (Reaction 15-11), or they can be oxidized with chromic acid or pyridinium chlorochromate to give ketones⁶⁹⁹ or aldehydes (from terminal alkenes),⁷⁰⁰ dimerized with silver nitrate and NaOH (Reaction 14-26), isomerized (Reaction 18-11), or converted to amines (Reaction 12-32), halides (Reaction 12-31), or carboxylic acids.⁷⁰¹ They are thus useful intermediates for the preparation of a wide variety of compounds. Intramolecular hydroboration reactions are possible.⁷⁰²

Such functional groups as OR, OH, NH_2 , SMe, halogen, and CO_2R may be present in the molecule,⁷⁰³ but not groups that are reducible by borane (e.g., COOH). Hydroboration of enamines with 9-BBN provides an indirect method for reducing an aldehyde or ketone to an alkene, for example,⁷⁰⁴



⁶⁹¹ See Still, W.C.; Barrish, J.C. *J. Am. Chem. Soc.* **1983**, 105, 2487.

⁶⁹² See Burgess, K.; Cassidy, J.; Ohlmeyer, M.J. *J. Org. Chem.* **1991**, 56, 1020; Burgess, K.; Ohlmeyer, M.J. *J. Org. Chem.* **1991**, 56, 1027.

⁶⁹³ Zhang, J.; Lou, B.; Guo, G.; Dai, L. *J. Org. Chem.* **1991**, 56, 1670.

⁶⁹⁴ See Brown, H.C.; Kulkarni, S.U. *J. Organomet. Chem.* **1982**, 239, 23.

⁶⁹⁵ Brown, H.C.; Ravindran, N.; Kulkarni, S.U. *J. Org. Chem.* **1979**, 44, 2417.

⁶⁹⁶ Brown, H.C.; Racherla, U.S. *J. Org. Chem.* **1986**, 51, 895.

⁶⁹⁷ Soundararajan, R.; Matteson, D.S. *J. Org. Chem.* **1990**, 55, 2274.

⁶⁹⁸ Frantz, D.E.; Singleton, D.A. *Org. Lett.* **1999**, 1, 485.

⁶⁹⁹ Parish, E.J.; Parish, S.; Honda, H. *Synth. Commun.* **1990**, 20, 3265.

⁷⁰⁰ Brown, H.C.; Kulkarni, S.U.; Rao, C.G.; Patil, V.D. *Tetrahedron* **1986**, 42, 5515.

⁷⁰¹ Soderquist, J.A.; Martinez, J.; Oyola, Y.; Kock, I. *Tetrahedron Lett.* **2004**, 45, 5541.

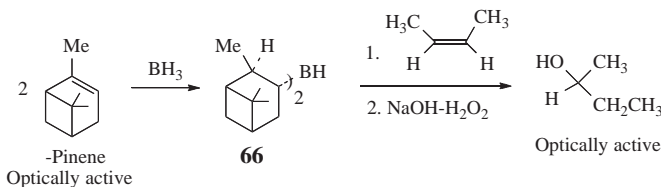
⁷⁰² See Shapland, P.; Vedejs, E. *J. Org. Chem.* **2004**, 69, 4094.

⁷⁰³ See Brown, H.C.; Unni, M.K. *J. Am. Chem. Soc.* **1968**, 90, 2902; Brown, H.C.; Gallivan, Jr., R.M. *J. Am. Chem. Soc.* **1968**, 90, 2906; Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* **1968**, 90, 2915.

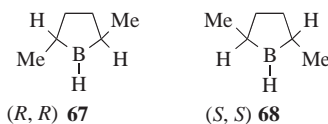
⁷⁰⁴ Singaram, B.; Rangaishenvi, M.V.; Brown, H.C.; Goralski, C.T.; Hasha, D.L. *J. Org. Chem.* **1991**, 56, 1543.

The presence of certain functional groups has directing effects on hydroboration reactions. Amides direct hydroboration reactions in alkenyl amides, for example.⁷⁰⁵ Intramolecular hydroboration is directed by amine groups in alkenyl amines.⁷⁰⁶ Alkenyl alcohols or ethers also undergo hydroboration, where delivery of boron is directed by the oxygen.⁷⁰⁷

Use of the reagent diisopinocampheylborane (**66**, prepared by treating optically active α -pinene with BH_3) results in enantioselective hydroboration–oxidation.⁷⁰⁸ Since both (+) and (–) α -pinene are readily available, both enantiomers can be prepared. Alcohols with moderate-to-excellent enantioselectivities have been obtained



in this way.⁷⁰⁹ However, **66** does not give good results with even moderately hindered alkenes; a better reagent for these compounds is isopinocampheylborane⁷¹⁰ although optical yields are lower. Limonylborane,⁷¹¹ 2- and 4-dicaranylboranes,⁷¹² a myrtanylborane,⁷¹³ and dilongifolylborane⁷¹⁴ have also been used. Other new asymmetric boranes have also been developed. The chiral cyclic boranes *trans*-2,15-dimethylborolanes (**67** and **68**) also add enantioselectively to alkenes (except alkenes of the form $\text{RR}'\text{C}=\text{CH}_2$) to give boranes of high optical purity.⁷¹⁵ When chiral boranes are added to trisubstituted alkenes of the form $\text{RR}'\text{C}=\text{CHR}''$, two new chiral centers are created, and, with **67** or **68**, only one of the four possible diastereomers is predominantly produced, in yields $>90\%$.⁷¹⁵ This has been called *double-asymmetric synthesis*.⁷¹⁶ An alternative asymmetric synthesis of alcohols involves the reaction of catechol borane with an alkene in the presence of a chiral Rh catalyst, giving the alcohol enantioselectivity after the usual oxidation.⁷¹⁷



⁷⁰⁵ Smith, S.M.; Thacker, N.C.; Takacs, J.M. *J. Am. Chem. Soc.* **2008**, *130*, 3734.

⁷⁰⁶ Scheideman, M.; Wang, G.; Vedejs, E. *J. Am. Chem. Soc.* **2008**, *130*, 8669.

⁷⁰⁷ Rarig, R.-A.F.; Scheideman, M.; Vedejs, E. *J. Am. Chem. Soc.* **2008**, *130*, 9182.

⁷⁰⁸ Brown, H.C.; Vara Prasad, J.V.N. *J. Am. Chem. Soc.* **1986**, *108*, 2049.

⁷⁰⁹ Brown, H.C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287; Srebnik, M.; Ramachandran, P.V. *Aldrichimica Acta* **1987**, *20*, 9; Brown, H.C.; Jadhav, P.K. in Morrison, J.D. *Asymmetric Synthesis* Vol. 2, Academic Press, NY, **1983**, pp. 1–43. For a study of electronic effects, see Garner, C.M.; Chiang, S.; Nething, M.; Monestel, R. *Tetrahedron Lett.* **2002**, *43*, 8339.

⁷¹⁰ Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *J. Org. Chem.* **1982**, *47*, 5074. See also, Brown, H.C.; Weissman, S. A.; Perumal, P.T.; Dhokte, U.P. *J. Org. Chem.* **1990**, *55*, 1217. For the crystal structure of this adduct, see Soderquist, J.A.; Hwang-Lee, S.; Barnes, C.L. *Tetrahedron Lett.* **1988**, *29*, 3385.

⁷¹¹ Jadhav, P.K.; Kulkarni, S.U. *Heterocycles* **1982**, *18*, 169.

⁷¹² Brown, H.C.; Vara Prasad, J.V.N.; Zaidlewicz, M. *J. Org. Chem.* **1988**, *53*, 2911.

⁷¹³ Kiesgen de Richter, R.; Bonato, M.; Follet, M.; Kamenka, J. *J. Org. Chem.* **1990**, *55*, 2855.

⁷¹⁴ Jadhav, P.K.; Brown, H.C. *J. Org. Chem.* **1981**, *46*, 2988.

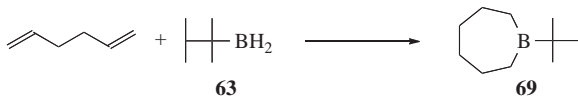
⁷¹⁵ Masamune, S.; Kim, B.M.; Petersen, J.S.; Sato, T.; Veenstra, J.S.; Imai, T. *J. Am. Chem. Soc.* **1985**, *107*, 4549.

See Thomas, S.P.; Aggarwal, V.K. *Angew. Chem. Int. Ed.* **2009**, *48*, 1896.

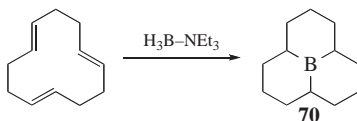
⁷¹⁶ For another enantioselective hydroboration method, see Reaction 15-16.

⁷¹⁷ Demay, S.; Volant, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2001**, *40*, 1235.

The double bonds in a conjugated diene are hydroborated separately; that is, there is no 1,4-addition. However, it is not easy to hydroborate just one of a conjugated system, since conjugated double bonds are less reactive than isolated ones. Thexylborane⁶⁷⁷ (**63**) is particularly useful for achieving the cyclic hydroboration of dienes, conjugated or non-conjugated, as in the formation of **69**.⁷¹⁸



Rings of five, six, or seven members can be formed in this way. Similar cyclization can also be accomplished with other monoalkylboranes and, in some instances, with BH_3 itself.⁷¹⁹ One example is the formation of 9-BBN, shown above. Another is conversion of 1,5,9-cyclododecatriene to perhydro-9*b*-boraphenalene (**70**).⁷²⁰



Boronate esters are prepared from alkenes. The reaction of an alkene with pyridine iodoborane, followed by treatment with pinacol and NaOH, for example, leads to the pinacol boronate ester.⁷²¹

Triple bonds⁷²² can be monohydroborated to give vinylic boranes, which can be reduced with carboxylic acids to *cis*-alkenes or oxidized and hydrolyzed to aldehydes or ketones. Terminal alkynes give aldehydes by this method, in contrast to the mercuric or acid-catalyzed addition of water discussed in Reaction 15-4. However, terminal alkynes give vinylic boranes⁷²³ (and hence aldehydes) only when treated with a hindered borane (e.g., **62**, **63**, or catecholborane, Reaction 12-31 and Sec. 14.A.i),⁷²⁴ or with $\text{BHBr}_2-\text{SMe}_2$.⁷²⁵ The reaction between terminal alkynes and BH_3 produces 1,1-dibora compounds, which can be oxidized either to primary alcohols (with $\text{NaOH}-\text{H}_2\text{O}_2$) or to carboxylic acids (with *m*-chloroperoxybenzoic acid).⁷²⁶ Double bonds can be hydroborated in the presence of triple bonds if the reagent is 9-BBN.⁷²⁷ On the other hand, dimesitylborane selectively hydroborates triple bonds in the presence of double bonds.⁷²⁸ Furthermore, it is often

⁷¹⁸ Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* **1972**, *94*, 3567.

⁷¹⁹ Cyclic hydroboration: see Brown, H.C.; Negishi, E. *Tetrahedron* **1977**, *33*, 2331. See also, Brown, H.C.; Pai, G.G.; Naik, R.G. *J. Org. Chem.* **1984**, *49*, 1072.

⁷²⁰ Brown, H.C.; Negishi, E.; Dickason, W.C. *J. Org. Chem.* **1985**, *50*, 520.

⁷²¹ Karatjas, A.G.; Vedejs, E. *J. Org. Chem.* **2008**, *73*, 9508.

⁷²² See Hudrlik, P.F.; Hudrlik, A.M. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, **1978**, pp. 203–219.

⁷²³ Brown, H.C.; Campbell, Jr., J.B. *Aldrichimica Acta* **1981**, *14*, 1.

⁷²⁴ Brown, H.C.; Gupta, S.K. *J. Am. Chem. Soc.* **1975**, *97*, 5249. See Garrett, C.E.; Fu, G.C. *J. Org. Chem.* **1996**, *61*, 3224.

⁷²⁵ Brown, H.C.; Campbell Jr., J.B. *J. Org. Chem.* **1980**, *45*, 389.

⁷²⁶ Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* **1967**, *89*, 291.

⁷²⁷ Brown, H.C.; Coleman, R.A. *J. Org. Chem.* **1979**, *44*, 2328.

⁷²⁸ Pelter, A.; Singaram, S.; Brown, H.C. *Tetrahedron Lett.* **1983**, *24*, 1433.

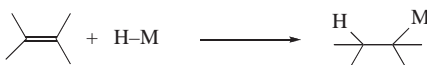
possible to hydroborate selectively one particular double bond of a nonconjugated diene.⁷²⁹ A triple bond can be hydroborated in the presence of a ketone, and treatment with acetic acid reduces the $\text{C}\equiv\text{C}$ unit to a *cis*-alkene (see Reaction 15-12).⁷³⁰ When the reagent is catecholborane, hydroboration is catalyzed by Rh complexes,⁷³¹ (e.g., *Wilkinson's catalyst*, **46**,⁷³² by SmI_2 ,⁷³³ or lanthanide reagents).⁷³⁴ Enantioselective hydroboration–oxidation has been achieved by the use of optically active Rh complexes.⁷³⁵

A chain extension variation involved the reaction of styrene with catecholborane and then $\text{Me}_3\text{SiCHN}_2$.⁷³⁶ Subsequent oxidation with $\text{NaOH}/\text{H}_2\text{O}_2$ and the reaction with Bu_4NF gave 3-phenyl-1-propanol.

OS VI, 719, 852, 919, 943; VII, 164, 339, 402, 427; VIII, 532.

15-17 Other Hydrometalation

Hydro-metallo-addition



Metal hydrides of Groups 13 and 14 of the periodic table (e.g., AlH_3 , GaH_3), as well as many of their alkyl and aryl derivatives (e.g., R_2AlH and Ar_3SnH) add to double bonds to give organometallic compounds.⁷³⁷ In each case, the alkene reacts with the Lewis acid. The hydroboration reaction (15-16) is the most important example but, as mentioned, other important metals in this reaction are Al,⁷³⁸ Sn,⁷³⁹ and Zr⁷⁴⁰ (a Group 4 metal). Some of these reactions are uncatalyzed, but in other cases various types of catalyst have been used.⁷⁴¹ Hydrozirconation is most commonly carried out with Cp_2ZrHCl (Cp = cyclopentadienyl),⁷⁴² known as *Schwartz's reagent*. The mechanism with Group 13 hydrides seems to be electrophilic (or four-centered pericyclic with some electrophilic characteristics) while with Group 14 hydrides a mechanism involving free radicals seems more likely. Dialkylmagnesium reagents have been obtained by adding MgH_2 to double bonds.⁷⁴³

⁷²⁹ See Gautam, V.K.; Singh, J.; Dhillon, R.S. *J. Org. Chem.* **1988**, 53, 187. See also, Suzuki, A.; Dhillon, R.S. *Top. Curr. Chem.* **1986**, 130, 23.

⁷³⁰ Kabalka, G.W.; Yu, S.; Li, N.-S. *Tetrahedron Lett.* **1997**, 38, 7681.

⁷³¹ Burgess, K.; van der Donk, W.A.; Westcott, S.A.; Marder, T.B.; Baker, R.T.; Calabrese, J.C. *J. Am. Chem. Soc.* **1992**, 114, 9350; Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1992**, 114, 6671.

⁷³² Burgess, K.; Ohlmeyer, M.J. *Chem. Rev.* **1991**, 91, 1179.

⁷³³ Evans, D.A.; Muci, A.R.; Stürmer, R. *J. Org. Chem.* **1993**, 58, 5307.

⁷³⁴ Harrison, K.N.; Marks, T.J. *J. Am. Chem. Soc.* **1992**, 114, 9220.

⁷³⁵ Sato, M.; Miyaara, N.; Suzuki, A. *Tetrahedron Lett.* **1990**, 31, 231; Brown, J.M.; Lloyd-Jones, G.C. *Tetrahedron: Asymmetry* **1990**, 1, 869.

⁷³⁶ Goddard, J.-P.; LeGall, T.; Mioskowski, C. *Org. Lett.* **2000**, 2, 1455.

⁷³⁷ Negishi, E. *Adv. Met.-Org. Chem.* **1989**, 1, 177; Eisch, J.J. *The Chemistry of Organometallic Compounds*; Macmillan, NY, **1967**, pp. 107–111; Eisch, J.J.; Fichter, K.C. *J. Organomet. Chem.* **1983**, 250, 63.

⁷³⁸ See Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *Russ. Chem. Rev.* **1990**, 59, 1157; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1988**, 44, 5001.

⁷³⁹ See Negishi, E. *Organometallics in Organic Synthesis* Vol. 1, Wiley, NY, **1980**, pp. 45–48, 357–363, 406–412; Speier, J.L. *Adv. Organomet. Chem.* **1979**, 17, 407; Andrianov, K.A.; Soucek, J.; Khananashvili, L.M. *Russ. Chem. Rev.* **1979**, 48, 657.

⁷⁴⁰ Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1; Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *J. Organomet. Chem.* **1986**, 304, 17. Also see, Hoveyda, A.H.; Morken, J.P. *J. Org. Chem.* **1993**, 58, 4237.

⁷⁴¹ Doyle, M.P.; High, K.G.; Nesloney, C.L.; Clayton, Jr., T.W.; Lin, J. *Organometallics* **1991**, 10, 1225.

⁷⁴² Lipshutz, B.H.; Keil, R.; Ellsworth, E.L. *Tetrahedron Lett.* **1990**, 31, 7257.

⁷⁴³ See Bogdanovic, B. *Angew. Chem. Int. Ed.* **1985**, 24, 262.

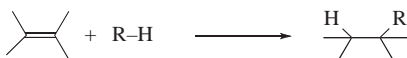
With some reagents triple bonds⁷⁴⁴ can add 1 or 2 equiv.⁷⁴⁵ When 2 molar equivalents are added, electrophilic addition generally gives 1,1-dimetallic products (as with hydro-boration), while free radical addition usually gives the 1,2-dimetallic products.

OS VII, 456; VIII, 268, 295, 507; 80, 104. See also, OS VIII, 277, 381.

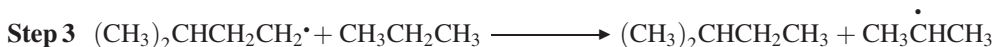
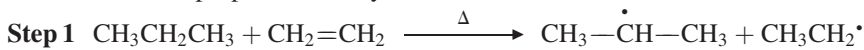
G. Carbon or Silicon on the Other Side

15-18 Addition of Alkanes

Hydro-alkyl-addition

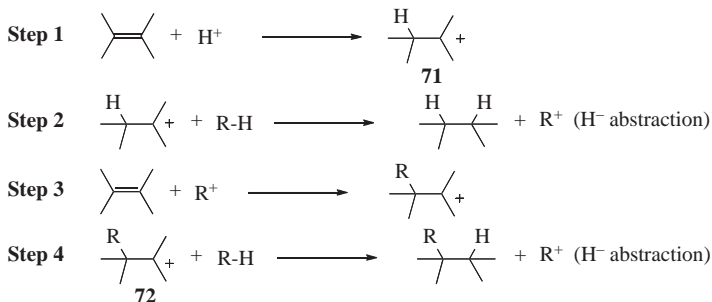


There are two important ways of adding alkanes to alkenes: direct heating, and acid catalysis.⁷⁴⁶ Both give mixtures, and neither is useful for the preparation of relatively pure compounds in reasonable yields. However, both are useful industrially. In the thermal method, the reactants are heated to high temperatures ($\sim 500^\circ\text{C}$) at high pressures (150–300 atm) without a catalyst. As an example, propane and ethylene gave 55.5% isopentane, 7.3% hexanes, 10.1% heptanes, and 7.4% alkenes.⁷⁴⁷ The mechanism is undoubtedly of a free radical type and can be illustrated by one possible sequence in the reaction between propane and ethylene:



There is kinetic evidence that the initiation takes place primarily by steps like 1, which are called *symproportionation* steps⁷⁴⁸ (the opposite of disproportionation, see Sec. 5.C.ii).

In the acid-catalysis method, a protonic or Lewis acid is used as the catalyst and the reaction is carried out at temperatures between -30 and 100°C . This is a *Friedel-Crafts* process that proceeds via a carbocation mechanism⁷⁴⁹ (illustrated for a proton acid catalyst):



⁷⁴⁴ See Hudrlik, P.F.; Hudrlik, A.M. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, **1978**, pp. 219–232.

⁷⁴⁵ Eisch, J.J.; Kaska, W.C. *J. Am. Chem. Soc.* **1966**, 88, 2213; Eisch, J.J.; Rhee, S. *Liebigs Ann. Chem.* **1975**, 565.

⁷⁴⁶ See Shuikin, N.I.; Lebedev, B.L. *Russ. Chem. Rev.* **1966**, 35, 448; Schmerling, L. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 2, Wiley, NY, **1964**, pp. 1075–1111, 1121–1122.

⁷⁴⁷ Frey, E.J.; Hepp, H.J. *Ind. Eng. Chem.* **1936**, 28, 1439.

⁷⁴⁸ Metzger, J.O. *Angew. Chem. Int. Ed.* **1983**, 22, 889; Hartmanns, J.; Klenke, K.; Metzger, J.O. *Chem. Ber.* **1986**, 119, 488.

⁷⁴⁹ See Mayr, H. *Angew. Chem. Int. Ed.* **1990**, 29, 1371.

Carbocation **72** often rearranges before a hydride is transferred, explaining, for example, why the principal product from the reaction between isobutane and ethylene is 2,3-dimethylbutane. Instead of abstracting a hydride, it is also possible for **71** (or **72**) to add to another molar equivalent of alkene, so that not only rearrangement products, but also dimeric and polymeric products, are frequent. If the tri- or tetrasubstituted alkenes are treated with Me_4Si , HCl , and AlCl_3 , protonation gives a tertiary carbocation, which reacts with the Me_4Si to give a product that is the result of addition of H and Me to the original alkene.⁷⁵⁰ (For a free radical hydro-methyl addition, see Reaction **15-28**.) An intramolecular cyclization of 1-dodecene to cyclododecane was reported using aluminum chloride in an ionic liquid.⁷⁵¹

Alkanes add to alkynes under photolysis conditions to give an alkene.⁷⁵² Tetrahydrofuran adds to alkynes to give the alkene with microwave irradiation.⁷⁵³

The reaction can also be base catalyzed, in which case there is nucleophilic addition and a carbanion mechanism.⁷⁵⁴ Carbanions most often used are those stabilized by one or more α -aryl groups. For example, toluene adds to styrene in the presence of sodium to give 1,3-diphenylpropane.⁷⁵⁵



Conjugated dienes give 1,4-addition.⁷⁵⁶ This reaction has also been performed with salts of carboxylic acids in what amounts to a method of alkylation of carboxylic acids⁷⁵⁷ (see also, Reaction **10-59**).

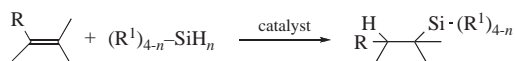


There are transition metal catalyzed addition reactions of alkyl units to alkenes,⁷⁵⁸ often proceeding with metal hydride elimination to form an alkene. An intramolecular cyclization reaction of an *N*-pyrrolidino amide alkene was reported using an iridium catalyst for addition of the carbon α to nitrogen at the alkene unit.⁷⁵⁹

OS **I**, 229; **IV**, 665; **VII**, 479.

15-19 Addition of Silanes (Hydrosilation)

Silyl-hydro-addition



⁷⁵⁰ Bolestova, G.I.; Parnes, Z.N.; Kursanov, D.N. *J. Org. Chem. USSR* **1983**, 19, 2175.

⁷⁵¹ Qiao, K.; Deng, Y. *Tetrahedron Lett.* **2003**, 44, 2191.

⁷⁵² Geraghty, N.W.A.; Hannan, J.J. *Tetrahedron Lett.* **2001**, 42, 3211.

⁷⁵³ Zhang, Y.; Li, C.-J. *Tetrahedron Lett.* **2004**, 45, 7581.

⁷⁵⁴ See Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, **1977**, pp. 240–422; Pines, H. *Acc. Chem. Res.* **1974**, 7, 155.

⁷⁵⁵ Pines, H.; Wunderlich, D. *J. Am. Chem. Soc.* **1958**, 80, 6001.

⁷⁵⁶ Eberhardt, G.G.; Peterson, H.J. *J. Org. Chem.* **1965**, 30, 82; Pines, H.; Stalick, W.M. *Tetrahedron Lett.* **1968**, 3723.

⁷⁵⁷ Schmerling, L.; Toekelt, W.G. *J. Am. Chem. Soc.* **1962**, 84, 3694.

⁷⁵⁸ Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, 35, 826.

⁷⁵⁹ DeBoef, B.; Pastine, S.J.; Sames, D. *J. Am. Chem. Soc.* **2004**, 126, 6556.

Although silanes bearing at least one Si—H unit do not generally react with alkenes or alkynes, addition occurs to give the corresponding alkyl or vinyl silane in the presence of transition metal catalysts.⁷⁶⁰ This reaction is known as hydrosilation. The reaction of an alkylsilane and an alkene with a Ru,⁷⁶¹ Rh,⁷⁶² Pd,⁷⁶³ Re,⁷⁶⁴ La,⁷⁶⁵ Y,⁷⁶⁶ Pt⁷⁶⁷ Cu,⁷⁶⁸ or Sm⁷⁶⁹ catalyst leads to addition with high *anti-Markovnikov* selectivity. Silanes add to dienes with a Pd catalyst, and asymmetric induction is achieved by using a chiral binaphthyl additive.⁷⁷⁰ Alkenes react with Li metal and *t*-Bu₂SiCl₂ to give a three-membered ring silane.⁷⁷¹

Dienes react with zirconium compounds and silanes to produce cyclic compounds in which the silyl group has also added to one C=C unit.⁷⁷² With an Y catalyst, PhSiH₃ reacts with nonconjugated dienes to give cyclic alkenes with a pendant CH₂SiH₂Ph group.⁷⁷³ Rhodium compounds allow silanes to add to enamides to give the α -silylamide.⁷⁷⁴ Formation of silanes via reaction with alkenes can be followed by reaction with fluoride ion and then oxidation to give an alcohol⁷⁷⁵ (see Reaction 10-16; *Tamao–Fleming oxidation*). A variation of this reaction generated allylic silanes from terminal alkenes and a dianion-type zincate using a Ti catalyst.⁷⁷⁶

In the presence of BEt₃, silanes add to alkenes to give the alkylsilane with *anti-Markovnikov* selectivity,⁷⁷⁷ or to alkynes to give the corresponding vinyl silane.⁷⁷⁸ Similar selectivity was observed when a silylated zinc reagent was added to a terminal alkyne.⁷⁷⁹ Hydrosilation of alkynes is accomplished using transition metal catalysts (e.g., Ru⁷⁸⁰ Pt,⁷⁸¹ Ti,⁷⁸² or Ir).⁷⁸³ Organocatalysts have been used as well.⁷⁸⁴ Siloxanes [e.g., (RO)₃SiH] add to alkynes with a Ru catalyst to give the corresponding vinyl silane.⁷⁸⁵ The reaction of Cl₂MeSiH and terminal alkynes, in ethanol–triethylamine with a Ru catalyst, to give

⁷⁶⁰ Buch, F.; Brettar, J.; Harder, S. *Angew. Chem. Int. Ed.* **2006**, 45, 2741.

⁷⁶¹ Glaser, P.B.; Tilley, T.D. *J. Am. Chem. Soc.* **2003**, 125, 13640.

⁷⁶² See Tsuchiya, Y.; Uchimura, H.; Kobayashi, K.; Nishiyama, H. *Synlett* **2004**, 2099.

⁷⁶³ Motoda, D.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 1529.

⁷⁶⁴ Zhao, W.-G.; Hua, R. *Eur. J. Org. Chem.* **2006**, 5495.

⁷⁶⁵ Takaki, K.; Sonoda, K.; Kousaka, T.; Koshiji, G.; Shishido, T.; Takehira, K. *Tetrahedron Lett.* **2001**, 42, 9211.

⁷⁶⁶ Molander, G.A.; Julius, M. *J. Org. Chem.* **1992**, 57, 6347.

⁷⁶⁷ See Sabourault, N.; Mignani, G.; Wagner, A.; Mioskowski, C. *Org. Lett.* **2002**, 4, 2117.

⁷⁶⁸ Nakamura, S.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, 129, 28; Lipshutz, B.H.; Lower, A.; Kucejko, R.J.;

Noson, K. *Org. Lett.* **2006**, 8, 2969.

⁷⁶⁹ Hou, Z.; Zhang, Y.; Tardif, O.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, 123, 9216.

⁷⁷⁰ Hatanaka, Y.; Goda, K.; Yamashita, F.; Hiyama, T. *Tetrahedron Lett.* **1994**, 35, 7981.

⁷⁷¹ Driver, T.G.; Franz, A.K.; Woerpel, K.A. *J. Am. Chem. Soc.* **2002**, 124, 6524.

⁷⁷² Molander, G.A.; Corrette, C.P. *Tetrahedron Lett.* **1998**, 39, 5011.

⁷⁷³ Muci, A.R.; Bercaw, J.E. *Tetrahedron Lett.* **2000**, 41, 7609.

⁷⁷⁴ Murai, T.; Oda, T.; Kimura, F.; Onishi, H.; Kanda, T.; Kato, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2143.

⁷⁷⁵ Jensen, J.F.; Svendsen, B.H.; la Cour, T.V.; Pedersen, H.L.; Johannsen, M. *J. Am. Chem. Soc.* **2002**, 124, 4558.

⁷⁷⁶ Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2005**, 127, 13116.

⁷⁷⁷ Rubin, M.; Schwier, T.; Gevorgyan, V. *J. Org. Chem.* **2002**, 67, 1936.

⁷⁷⁸ Miura, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1993**, 66, 2356.

⁷⁷⁹ Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2004**, 126, 11146.

⁷⁸⁰ Trost, B.M.; Ball, Z.T. *J. Am. Chem. Soc.* **2005**, 127, 17644; Maifeld, S.V.; Tran, M.N.; Lee, D. *Tetrahedron Lett.* **2005**, 46, 105.

⁷⁸¹ Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *Synthesis* **2007**, 2025.

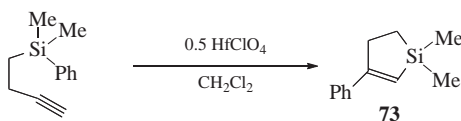
⁷⁸² Takahashi, T.; Bao, F.; Gao, G.; Ogasawara, M. *Org. Lett.* **2003**, 5, 3479.

⁷⁸³ Miyake, Y.; Isomura, E.; Iyoda, M. *Chem. Lett.* **2006**, 35, 836.

⁷⁸⁴ Berthon-Gelloz, G.; Schumers, J.-M.; De Bo, G.; Markó, I.E. *J. Org. Chem.* **2008**, 73, 4190.

⁷⁸⁵ Trost, B.M.; Ball, Z.T. *J. Am. Chem. Soc.* **2001**, 123, 12726.

primarily the *Markovnikov* vinyl silane.⁷⁸⁶ However, Et₃SiH adds to terminal alkynes with a Rh⁷⁸⁷ or a Pt⁷⁸⁸ catalyst to give the *anti-Markovnikov* vinyl silane. Using a 0.5 molar equivalent of HfClO₄ with alkynes bearing a dimethylphenylsilyl unit gave a cyclic vinyl silane with transfer of the phenyl group to carbon (see **73**).⁷⁸⁹



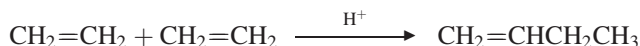
Silanes add to alkenes under radical conditions (using AIBN) with high *anti-Markovnikov* selectivity.⁷⁹⁰ An alternative route to alkylsilanes reacted an alkene with Li metal in the presence of 3 equiv of chlorotrimethylsilane, giving bis-1,2-trimethylsilyl compounds after treatment with water.⁷⁹¹ Silanes also add to alkenes to form the *anti-Markovnikov* alkylsilane (R₃Si—C—C—R') in the presence of a hyponitrite.⁷⁹²

In a reaction more related to those in Reaction **15-24**, vinyl silanes add to conjugated carbonyl compounds in the presence of a Ru catalyst,⁷⁹³ or to acrylonitriles with a Co catalyst.⁷⁹⁴ Silyl phosphines react with conjugated ynones directly to give an enone with an α -trimethylsilyl and a β -phosphine group.⁷⁹⁵ Siloxanes of the type (RO)₃SiH add to the α -carbon of enamines in the presence of a dirhodium catalyst.⁷⁹⁶ The uncatalyzed reaction of trimethylsilyl cyanide and ynamines, however, gave an enamine with a β -trimethylsilyl and an α -cyano group.⁷⁹⁷

bis(Silanes) add to alkylidene malonate derivatives (see Reaction **15-24**) in the presence of a Cu catalyst to give β -silyl malonates [RCH(SiR₃)CH(CO₂Me)₂].⁷⁹⁸ Alkylsilane units add using bis(trialkylsilyl)zinc reagents with a CuCN catalyst.⁷⁹⁹ Trimethylsilyl cyanide (Me₃SiCN) adds a cyano group to α,β -unsaturated amines with a specialized Al(salen)-Y catalyst.⁸⁰⁰

15-20 Addition of Alkenes and/or Alkynes to Alkenes and/or Alkynes

Hydro-alkenyl-addition



⁷⁸⁶ Kawanami, Y.; Sonoda, Y.; Mori, T.; Yamamoto, K. *Org. Lett.* **2002**, *4*, 2825.

⁷⁸⁷ Sato, A.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 2217.

⁷⁸⁸ Wu, W.; Li, C.-J. *Chem. Commun.* **2003**, 1668.

⁷⁸⁹ Asao, N.; Shimada, T.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10899. See also, Sudo, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 8919.

⁷⁹⁰ Kopping, B.; Chatgililoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* **1992**, *57*, 3994.

⁷⁹¹ Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* **2001**, *57*, 10119.

⁷⁹² Dang, H.-S.; Roberts, B.P. *Tetrahedron Lett.* **1995**, *36*, 2875.

⁷⁹³ Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 679; Trost, B.M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371.

⁷⁹⁴ Tayama, O.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Eur. J. Org. Chem.* **2003**, 2286.

⁷⁹⁵ Reisser, M.; Maier, A.; Maas, G. *Synlett* **2002**, 1459.

⁷⁹⁶ Hewitt, G.W.; Somers, J.J.; Sieburth, S.Mc.N. *Tetrahedron Lett.* **2000**, *41*, 10175.

⁷⁹⁷ Lukashev, N.V.; Kazantsev, A.V.; Borisenko, A.A.; Beletskaya, I.P. *Tetrahedron* **2001**, *57*, 10309.

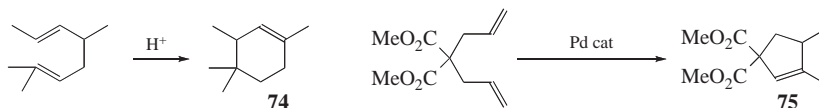
⁷⁹⁸ Clark, C.T.; Lake, J.F.; Scheidt, K.A. *J. Am. Chem. Soc.* **2004**, *126*, 84.

⁷⁹⁹ Oestreich, M.; Weiner, B. *Synlett* **2004**, 2139.

⁸⁰⁰ See Sammis, G.M.; Danjo, H.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2004**, *126*, 9928.

With certain substrates, alkenes can be dimerized by acid catalysts, so that the product is a dimer that contains one double bond.⁸⁰¹ A catalyst comprised of a combination of Zn and a CoCl_2 accomplished this type of coupling.⁸⁰² One alkene adds to another in the presence of a Ni catalyst.⁸⁰³ α -Alkenes add to dienes in a 1,4-manner in the presence of an Fe catalyst.⁸⁰⁴

This reaction is more often carried out internally, as in the formation of cyclohexene (**74**). A Pd catalyzed cyclization is known, in which dienes are converted to cyclopentene derivatives (e.g., **75**).⁸⁰⁵



Ring-forming reactions are possible. A Ru catalyzed version of this reaction gave the five-membered ring with an exocyclic double bond.⁸⁰⁶ Carbocyclization of an alkene unit to another alkene unit was reported using a Y,⁸⁰⁷ or a Ti catalyst.⁸⁰⁸ In some cases, internal coupling of two alkenes can form larger rings.⁸⁰⁹ Carbocyclization was reported using Pd,⁸¹⁰ Rh,⁸¹¹ Ru,⁸¹² Ir,⁸¹³ or a Zr catalyst.⁸¹⁴ Alkene allene substrates were cyclized to form cyclic products with an exocyclic double bond using a Pd catalyst.⁸¹⁵ An interesting variation adds a silyl enol ether to an alkyne using GaCl_3 to give an unconjugated ketone ($\text{O}=\text{C}-\text{C}=\text{C}=\text{C}$).⁸¹⁶ Alkenes and alkynes can also add to each other to give cyclic products in other ways (see Reaction **15-63** and **15-65**).

Processes of this kind are important in the biosynthesis of steroids and tetra- and pentacyclic terpenes. For example, squalene 2,3-oxide is converted by enzymatic catalysis to dammaradienol. The squalene \rightarrow lanosterol biosynthesis, which is a key step in the biosynthesis of cholesterol, is similar. The idea that the biosynthesis of

⁸⁰¹ See Onsager, O.; Johansen, J.E. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, **1985**, pp. 205–257.

⁸⁰² Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *Tetrahedron Lett.* **2004**, *45*, 6203.

⁸⁰³ Ng, S.-S.; Ho, C.-Y.; Schleicher, K.D.; Jamison, T.F. *Pure Appl. Chem.* **2008**, *80*, 929.

⁸⁰⁴ Moreau, B.; Wu, J.Y.; Ritter, T. *Org. Lett.* **2009**, *11*, 337.

⁸⁰⁵ Kisanga, P.; Goj, L.A.; Widenhoefer, R.A. *J. Org. Chem.* **2001**, *66*, 635.

⁸⁰⁶ Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5606; Michaut, M.; Santelli, M.; Parrain, J.-L. *Tetrahedron Lett.* **2003**, *44*, 2157.

⁸⁰⁷ Molander, G.A.; Dowdy, E.D.; Schumann, H. *J. Org. Chem.* **1998**, *63*, 3386.

⁸⁰⁸ Okamoto, S.; Livinghouse, T. *J. Am. Chem. Soc.* **2000**, *122*, 1223. See Hart, D.J.; Bennett, C.E. *Org. Lett.* **2003**, *5*, 1499.

⁸⁰⁹ Toyota, M.; Majo, V.J.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 1555.

⁸¹⁰ Kende, A.S.; Mota Nelson, C.E.; Fuchs, S. *Tetrahedron Lett.* **2005**, *46*, 8149.

⁸¹¹ Wender, P.A.; Dyckman, A.J. *Org. Lett.* **1999**, *1*, 2089; Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490; Cao, P.; Zhang, X. *Angew. Chem. Int. Ed.* **2000**, *39*, 4104.

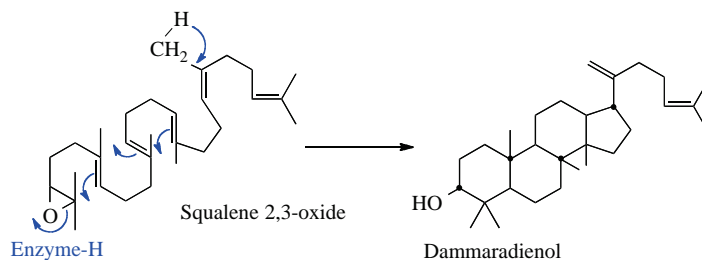
⁸¹² Fernández-Rivas, C.; Méndez, M.; Echavarren, A.M. *J. Am. Chem. Soc.* **2000**, *122*, 1221.

⁸¹³ Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433.

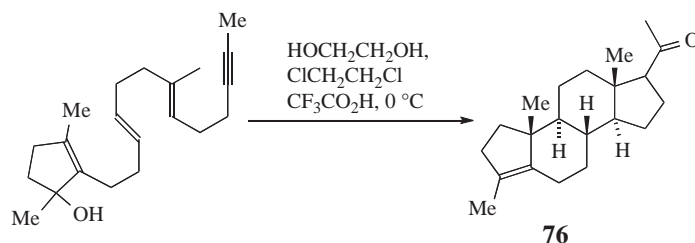
⁸¹⁴ Miura, K.; Funatsu, M.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 9059. Also see, Maye, J.P.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 3359.

⁸¹⁵ See Ohno, H.; Takeoka, Y.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 4541.

⁸¹⁶ Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* **1999**, *121*, 4074.



such compounds involves this type of multiple ring closing was proposed in 1955 and is known as the *Stork–Eschenmoser hypothesis*.⁸¹⁷ Such reactions can also be carried out in the laboratory, without enzymes.⁸¹⁸ By putting cation-stabilizing groups at positions at which positive charges develop, Johnson and co-workers⁸¹⁹ have been able to close as many as four rings stereoselectively and in high yield, in one operation. An example is formation of **76**,⁸²⁰ by what is known as the *Johnson polyene cyclization*.⁸²¹ Lewis acids can be used to initiate this cyclization,⁸²² including EtAlCl_2 used for the coupling of an alkyne and an alkene.⁸²³ A Pd catalyst has been used for a similar cyclization reaction.⁸²⁴ A radical cyclization approach (Reaction 15-30) to polyene cyclization using a seleno-ester anchor gave a tetracyclic system.⁸²⁵



The addition of alkenes to alkenes⁸²⁶ can also be mediated by bases.⁸²⁷ Coupling reactions can occur using transition metal catalyst systems⁸²⁸ (e.g., alkylaluminum

⁸¹⁷ Stork, G.; Burgstahler, A.W. *J. Am. Chem. Soc.* **1955**, *77*, 5068; Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

⁸¹⁸ Gnononfoun, N. *Bull. Soc. Chim. Fr.* **1988**, 862; Johnson, W.S. *Angew. Chem. Int. Ed.* **1976**, *15*, 9; *Acc. Chem. Res.* **1968**, *1*, 1; van Tamelen, E.E. *Acc. Chem. Res.* **1975**, *8*, 152. See Bartlett, P.A. in Morrison, J.D. *Asymmetric Synthesis* Vol. 3, Academic Press, NY, **1985**, pp. 341–409.

⁸¹⁹ Guay, D.; Johnson, W.S.; Schubert, U. *J. Org. Chem.* **1989**, *54*, 4731 and references cited therein.

⁸²⁰ Johnson, W.S.; Gravestock, M.B.; McCarry, B.E. *J. Am. Chem. Soc.* **1971**, *93*, 4332.

⁸²¹ Johnson, W.S. *Acc. Chem. Res.* **1968**, *1*, 1; Kametani T.; Fukumoto, K. *Synthesis* **1972**, 657.

⁸²² Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906.

⁸²³ Asao, N.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3797.

⁸²⁴ Mullen, C.A.; Gagné, M.R. *J. Am. Chem. Soc.* **2007**, *129*, 11880.

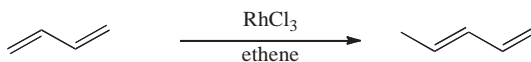
⁸²⁵ Chen, L.; Gill, G.B.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 2593.

⁸²⁶ Fel'dblyum, V.Sh.; Obeshchalova, N.V. *Russ. Chem. Rev.* **1968**, *37*, 789.

⁸²⁷ For a review, see Pines, H. *Synthesis* **1974**, 309.

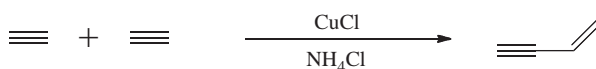
⁸²⁸ Pillai, S.M.; Ravindranathan, M.; Sivaram, S. *Chem. Rev.* **1986**, *86*, 353; Jira, R.; Freiesleben, W. *Organomet. React.* **1972**, *3*, 1, p. 117; Heck, R.F. *Organotransition Metal Chemistry* Academic Press, NY, **1974**, pp. 84–94, 150–157. Also see, Kaur, G.; Manju, K.; Trehan, S. *Chem. Commun.* **1996**, 581.

compounds, known as *Ziegler catalysts*),⁸²⁹ Rh,⁸³⁰ Fe,⁸³¹ or Ni⁸³² catalysts. The 1,4-addition of alkenes to conjugated dienes to give nonconjugated dienes⁸³³ occurs with various transition metal catalysts, as does the dimerization of 1,3-butadienes to octatrienes.⁸³⁴ A



molecule containing two distal conjugated diene units was cyclized to give a bicyclic molecule with an exocyclic double bond using a Pd catalyst.⁸³⁵ A Ni catalyst converted a similar system to a saturated five-membered ring containing an allylic and a vinyl group.⁸³⁶ Ethylene adds to alkenes to form a new alkene in the presence of a Ni⁸³⁷ or a Zr catalyst,⁸³⁸ and to alkynes in the presence of a Ru catalyst⁸³⁹ to form a diene. Allenes add to alkynes to give a diene with a Ti catalyst.⁸⁴⁰

In the presence of cuprous chloride and ammonium chloride, acetylene undergoes self-coupling to give vinylacetylene. Alkynes are coupled to dienes to give enynes in the presence of a Ni catalyst.⁸⁴¹



Another type of alkyne dimerization is the reductive coupling in which two molecules of alkyne, the same or different, give a 1,3-diene, as shown.⁸⁴² In this method, one alkyne is treated with *Schwartz's reagent* (see Reaction 15-17) to produce a vinylic zirconium intermediate. Addition of MeLi or MeMgBr, followed by the second alkyne, gives another intermediate, which, when treated with aq acid, gives the diene in moderate-to-good yields.⁸⁴³ If the second intermediate is treated with I₂ instead of aq acid, the 1,4-diiodo-1,3-diene is obtained, in comparable yield and isomeric purity. The reaction of an alkyne with a *Grignard reagent*, followed by an Fe complex and then an alkene leads to enynes.⁸⁴⁴ A Rh catalyzed coupling reaction of alkenes and electron-deficient internal alkynes leads to 1,3-dienes.⁸⁴⁵ A combination of Zr and Cr reagents allows the coupling of alkynes to form

⁸²⁹ See Fischer, K.; Jonas, K.; Misbach, P.; Stabba, R.; Wilke, G. *Angew. Chem. Int. Ed.* **1973**, 12, 943.

⁸³⁰ Takahashi, N.; Okura, I.; Keii, T. *J. Am. Chem. Soc.* **1975**, 97, 7489.

⁸³¹ Takacs, J.M.; Myoung, Y.C. *Tetrahedron Lett.* **1992**, 33, 317.

⁸³² Zhang, A.; RajanBabu, T.V. *J. Am. Chem. Soc.* **2006**, 128, 54.

⁸³³ Hilt, G.; du Mesnil, F.-X.; Lüers, S. *Angew. Chem. Int. Ed.* **2001**, 40, 387. For a review see Su, A.C.L. *Adv. Organomet. Chem.* **1979**, 17, 269.

⁸³⁴ See Denis, P.; Jean, A.; Croizy, J.F.; Mortreux, A.; Petit, F. *J. Am. Chem. Soc.* **1990**, 112, 1292.

⁸³⁵ Takacs, J.M.; Leonov, A.P. *Org. Lett.* **2003**, 5, 4317.

⁸³⁶ Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* **2004**, 126, 5956.

⁸³⁷ Nomura, N.; Jin, J.; Park, H.; RajanBabu, T.V. *J. Am. Chem. Soc.* **1998**, 120, 459.

⁸³⁸ Takahashi, T.; Xi, Z.; Fischer, R.; Huo, S.; Xi, C.; Nakajima, K. *J. Am. Chem. Soc.* **1997**, 119, 4561.

⁸³⁹ Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, 119, 12388.

⁸⁴⁰ Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* **1997**, 119, 11295.

⁸⁴¹ Shirakura, M.; Sugimoto, M. *J. Am. Chem. Soc.* **2008**, 130, 5410.

⁸⁴² Buchwald, S.L.; Nielsen, R.B. *J. Am. Chem. Soc.* **1989**, 111, 2870.

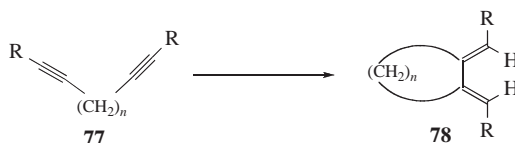
⁸⁴³ Ryan, J.; Micalizio, G.C. *J. Am. Chem. Soc.* **2006**, 128, 2764; Kanno, K.-i.; Igarashi, E.; Zhou, L.; Nakajima, K.; Takahashi, T. *J. Am. Chem. Soc.* **2008**, 130, 5624.

⁸⁴⁴ Hatakeyama, T.; Yoshimoto, Y.; Gabriel, T.; Nakamura, M. *Org. Lett.* **2008**, 10, 5341.

⁸⁴⁵ Shibata, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, 10, 2829; Katagiri, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem. Commun.* **2008**, 3405.

linear polyenes.⁸⁴⁶ Alkynes can also be coupled to allylic silyl ethers with a Ru catalyst to give dienes.⁸⁴⁷ Other alkyne–allylic coupling reactions are known to give dienes.⁸⁴⁸

This reaction can also be done intramolecularly, as in the cyclization of diyne **77** to (*E*, *E*)-exocyclic dienes (**78**) by treatment with a Zr,⁸⁴⁹ Rh,⁸⁵⁰ Ru,⁸⁵¹ Au,⁸⁵² or Pt complex.⁸⁵³ A similar reaction was reported using a Ti catalyst from a diyne amide.⁸⁵⁴ Rings of four, five, and six members were obtained in high yield; seven-membered rings in lower yield. When the reaction is applied to enynes, compounds similar to **78** are formed using various catalysts, but with only one double bond⁸⁵⁵ Larger rings can be formed from the appropriate enyne, including forming cyclohexadiene compounds.⁸⁵⁶ Spirocyclic compounds can be prepared from enynes in this manner using formic acid and a Pd catalyst.⁸⁵⁷



The Rh catalyzed cyclization of 1,6-enynes, triggered by arylboronic acids, leads to rings with an exocyclic alkylidene group.⁸⁵⁸ Alkynes are coupled to give enynes using Ni,⁸⁵⁹ Pd,⁸⁶⁰ Lu,⁸⁶¹ and Ru⁸⁶² catalysts. Similar products are obtained by cross-coupling terminal alkynes with an allene, using a combination of Pd and CuI catalysts.⁸⁶³ The reaction has been carried out internally to convert diynes to large-ring cycloalkynes with an exocyclic double bond.⁸⁶⁴ Dienes have also been cyclized to form cyclic enynes (an endocyclic double bond) using a diruthenium catalyst with ammonium tetrafluoroborate in methanol.⁸⁶⁵ Enynes are similarly cyclized to cyclic alkenes with an endocyclic

⁸⁴⁶ Takahashi, T.; Liu, Y.; Iesato, A.; Chaki, S.; Nakajima, K.; Kanno, K.-i. *J. Am. Chem. Soc.* **2005**, *127*, 11928.

⁸⁴⁷ Trost, B.M.; Surivet, J.-P.; Toste, F.D. *J. Am. Chem. Soc.* **2001**, *123*, 2897.

⁸⁴⁸ Giessert, A.J.; Snyder, L.; Markham, J.; Diver, S.T. *Org. Lett.* **2003**, *5*, 1793.

⁸⁴⁹ Nugent, W.A.; Thorn, D.L.; Harlow, R.L. *J. Am. Chem. Soc.* **1987**, *109*, 2788. See Trost, B.M.; Lee, D.C. *J. Am. Chem. Soc.* **1988**, *110*, 7255; Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478.

⁸⁵⁰ Jang, H.-Y.; Krische, M.J. *J. Am. Chem. Soc.* **2004**, *126*, 7875.

⁸⁵¹ Varela, J.A.; Rubín, S.G.; González-Rodríguez, C.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **2006**, *128*, 9263.

⁸⁵² Zhang, C.; Cui, D.-M.; Yao, L.-Y.; Wang, B.-S.; Hu, Y.-Z.; Hayashi, T. *J. Org. Chem.* **2008**, *73*, 7811.

⁸⁵³ Méndez, M.; Muñoz, M.P.; Nevado, C.; Cárdenas, D.J.; Echavarren, A.M. *J. Am. Chem. Soc.* **2001**, *123*, 10511; Wang, X.; Chakrapani, H.; Madine, J.W.; Keyerleber, M.A.; Widenhoefer, R.A. *J. Org. Chem.* **2002**, *67*, 2778. See also, Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863.

⁸⁵⁴ Urabe, H.; Nakajima, R.; Sato, F. *Org. Lett.* **2000**, *2*, 3481.

⁸⁵⁵ Chakrapani, H.; Liu, C.; Widenhoefer, R.A. *Org. Lett.* **2003**, *5*, 157; Lee, P.H.; Kim, S.; Lee, K.; Seomoon, D.; Kim, H.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Livinghouse, T. *Org. Lett.* **2004**, *6*, 4825.

⁸⁵⁶ Yamamoto, Y.; Kuwabara, S.; Ando, Y.; Nagata, H.; Nishiyama, H.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 6697.

⁸⁵⁷ Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704.

⁸⁵⁸ Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094.

⁸⁵⁹ Ogoshi, S.; Ueta, M.; Oka, M.-a.; Kurosawa, H. *Chem. Commun.* **2004**, 2732.

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⁸⁶¹ Nishiura, M.; Hou, Z.; Wakatsuki, Y.; Yamaki, T.; Miyamoto, T. *J. Am. Chem. Soc.* **2003**, *125*, 1184.

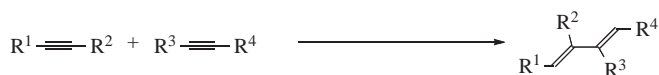
⁸⁶² Bassetti, M.; Pasquini, C.; Raneri, A.; Rosato, D. *J. Org. Chem.* **2007**, *72*, 4558.

⁸⁶³ Bruyere, D.; Grigg, R.; Hinsley, J.; Hussain, R.K.; Korn, S.; Del Cierva, C.O.; Sridharan, V.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 8669.

⁸⁶⁴ Trost, B.M.; Matusbara, S.; Carninji, J.J. *J. Am. Chem. Soc.* **1989**, *111*, 8745.

⁸⁶⁵ Nishibayashi, Y.; Yamanashi, M.; Wakiji, I.; Hidai, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2909.

C=C unit using a dicobalt catalyst.⁸⁶⁶



Enynes can also be converted to cyclic and bicyclic compounds using a Au⁸⁶⁷ Rh,⁸⁶⁸ Fe,⁸⁶⁹ or Pd⁸⁷⁰ catalyst. Enynes having a conjugated alkene unit also undergo this reaction in the presence of ZnBr₂.⁸⁷¹ Using mercury(II) triflate in water, cyclization leads to five-membered rings having an exocyclic double bond, and a pendant alcohol group.⁸⁷² Enynes give cyclic compounds with an endocyclic double bond conjugated to another alkene unit (a conjugated diene) when treated with GaCl₃⁸⁷³ or a Pt catalyst in an ionic liquid.⁸⁷⁴ Allene–alkenes give a similar product with a Pd⁸⁷⁵ or a Ru catalyst,⁸⁷⁶ as do alkyne–allenes with a dirhodium catalyst.⁸⁷⁷

There are many useful variations. Internal coupling of an alkyne with a vinyl halide, using triethylsilane and a Pd catalyst, gave the saturated cyclic compound with two adjacent exocyclic double bonds (a 2,3-disubstituted diene).⁸⁷⁸ Alkynes are added to propargyl acetates using Pd catalyst to give an alkyne–allene.⁸⁷⁹ Alkyne–alkenes were formed by coupling terminal alkynes and allenes in the presence of a Pd catalyst.⁸⁸⁰ An alkyne was coupled internally to give an allene using a Pd catalyst, to give a product that has an exocyclic methylene group and a vinyltin derivative.⁸⁸¹ A similar process occurred with RhCl(PPh₃)₃ to incorporate a vinyl chloride.⁸⁸² Allene–allylic halide systems reacted with phenylboronic acid and a Pd catalyst to give cyclopentane rings with two pendant vinyl groups, one of which contained a phenyl group.⁸⁸³

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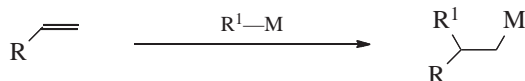
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15-21 Addition of Organometallics to Double and Triple Bonds Not Conjugated to Carbonyls

Hydro-alkyl-addition



Neither *Grignard reagents* nor lithium dialkylcopper reagents generally add to ordinary C=C double bonds in the absence of a transition metal catalyst.⁸⁸⁴ *Grignard reagents* usually add only to double bonds susceptible to nucleophilic attack (e.g., fluoroalkenes and tetracyanoethylene).⁸⁸⁵ However, active *Grignard reagents* (benzylic, allylic) also add to the double bonds of allylic amines,⁸⁸⁶ and of allylic and homoallylic alcohols,⁸⁸⁷ as well as to the triple bonds of propargyl alcohols and certain other alkynols.⁸⁸⁸ Transition metal complexes facilitate the addition of *Grignard reagents* to alkenes. Examples include Ti,⁸⁸⁹ Mn,⁸⁹⁰ Zr,⁸⁹¹ Ni,⁸⁹² Fe,⁸⁹³ and Cu compounds.⁸⁹⁴ Cyclopropenes are an exception, and an excess of a Grignard reagent will add at low temperatures.⁸⁹⁵ Cyclopropene derivatives also react with CuI and then allyl bromide.⁸⁹⁶

Benzylic alkenes react with silylmethyl *Grignard reagents* in the presence of oxygen.⁸⁹⁷ It is likely that cyclic intermediates are involved in these cases, in which the Mg coordinates with the heteroatom. Allylic, benzylic, and tertiary alkyl *Grignard reagents* also add to 1-alkenes and strained internal alkenes (e.g., norbornene), if the reaction is carried out in a hydrocarbon solvent (e.g., pentane) rather than ether, or in the alkene itself as solvent, heated, under pressure if necessary, to 60–130 °C.⁸⁹⁸ Yields are variable.

Intramolecular addition of RMgX to completely unactivated double and triple bonds has been demonstrated.⁸⁹⁹ The reaction of tosylates bearing a remote alkene unit and a *Grignard reagent* leads to cyclization when a Zr catalyst is used.⁹⁰⁰ The intramolecular

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addition of a CH_2Br unit to the $\text{C}=\text{C}$ unit of an allylic ether was accomplished using PhMgBr and a Co catalyst, give a functionalized THF and incorporation of the phenyl group on the $\text{C}=\text{C}$ unit as well.⁹⁰¹

In a useful variation, vinyl epoxides react with *Grignard reagents* and CuBr to give an allylic alcohol via reaction at the $\text{C}=\text{C}$ unit and concomitant opening of the epoxide.⁹⁰² Conjugated dienes react with arylmagnesium halides, Ph_3SiCl , and a Pd catalyst to give a coupling product involving the reaction of 2 equiv of the diene and incorporation of two SiPh_3 units.⁹⁰³ The Cr catalyzed formation of arylmagnesium compounds⁹⁰⁴ and the Rh catalyzed hydroarylation⁹⁰⁵ of alkynes are also known. The Pd catalyzed hydroarylation⁹⁰⁶ of alkynes is possible using arenediazonium salts⁹⁰⁷ as substrates or hydroarylation of 1,3-dienes with boronic acids.⁹⁰⁸

Organolithium reagents (primary, secondary, and tertiary alkyl and in some cases aryl) add to the double and triple bonds of allylic and propargylic alcohols,⁹⁰⁹ (tetramethylethylenediamine is a catalyst) and also to certain other alkenes containing hetero groups (e.g., OR, NR_2 , or SR). Mixing an organolithium reagent with transition metal compounds [e.g., CeCl_3 ⁹¹⁰ or $\text{Fe}(\text{acac})_3$]⁹¹¹ leads to addition of the alkyl group. Cyclopropane derivatives have been formed in this manner.⁹¹² The organolithium reagents can contain heteroatoms (e.g., nitrogen) elsewhere in the molecule, and the organolithium species can be generated from an intermediate organotin derivative.⁹¹³ Organolithium reagents add to the less substituted $\text{C}=\text{C}$ unit of conjugated dienes.⁹¹⁴ Addition of butyllithium to alkenes has been observed with good enantioselectivity when sparteine was added.⁹¹⁵

The intramolecular addition of RLi and R_2CuLi has been reported.⁹¹⁶ Organolithium reagents containing an alkene⁹¹⁷ or alkyne⁹¹⁸ unit cyclize⁹¹⁹ at low temperatures and

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quenching with methanol replaces the new C—Li bond with C—H. Tandem cyclization is possible with dienes and enynes to form more than one ring,⁹²⁰ including bicyclic compounds.⁹²¹ Tandem cyclization is possible with alkyne iodides⁹²² or alkynes with a homoallylic CH₂Li unit.⁹²³ The organolithium compound can be generated *in situ* by reaction of an organotin compound with butyllithium, allowing cyclization to occur upon treatment with an excess of LiCl.⁹²⁴

Unactivated alkenes or alkynes⁹²⁵ react with other organometallic compounds under certain conditions. The Pt catalyzed addition to alkynes leads to functionalized alkenes.⁹²⁶ Phenylboronic acids add to alkynes in the presence of a Co⁹²⁷ or a Pd catalyst.⁹²⁸ Trimethylaluminum reacts with 4-methyl-1-pentene, in the presence of Cl₂ZrCp₂, for example, and subsequent reaction with molecular oxygen leads to (2*R*),4-dimethyl-1-pentanol in good yield and 74% ee.⁹²⁹ These reagents also add to alkynes.⁹³⁰ Ruthenium catalysts have been used to mediate the addition of allylic alcohols to alkynes.⁹³¹ Samarium iodide (SmI₂) induces cyclization of a halide moiety to an alkyne unit⁹³² or an alkene unit⁹³³ to form cyclized products. Copper complexes can catalyze similar cyclization to alkenes, even when an ester unit is present in the molecule.⁹³⁴ Allyl manganese compounds add to allenes to give nonconjugated dienes.⁹³⁵

Organomanganese reagents add to alkenes.⁹³⁶ Manganese triacetate [Mn(OAc)₃], in the presence of cupric acetate, facilitates intramolecular cyclization of a halide unit to an alkene.⁹³⁷ Alkynes react with In reagents [e.g., (allyl)₃In₂I₃] to form dienes (allyl substituted alkenes from the alkyne).⁹³⁸ Allylic halides add to propargyl alcohols using In metal to form the aryl organometallic *in situ*.⁹³⁹ Allyltin reagents add to alkynes in a similar manner in the presence of ZrCl₄.⁹⁴⁰ Alkylzinc reagents add to alkynes to give substituted alkenes in the presence of a Pd catalyst.⁹⁴¹ Allylzinc reagents add to alkynes in

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the presence of a Co catalyst.⁹⁴² A vinyltellurium reagent adds to alkynes in the presence of CuI/PdCl₂.⁹⁴³

Ketones with an α -hydrogen add to alkenes intramolecularly when heated in a sealed tube with CuCl₂ and a Pd catalyst.⁹⁴⁴ A similar reaction was reported using Yb(OTf)₃ and a Pd catalyst⁹⁴⁵ or an In catalyst.⁹⁴⁶ Keto esters add to alkynes using 10% benzoic acid and a Pd catalyst,⁹⁴⁷ or an In catalyst.⁹⁴⁸ 1,3-Diketones add to dienes (1,4-addition) using a Pd catalyst,⁹⁴⁹ a AuCl₃/AgOTf catalyst,⁹⁵⁰ and this addition has been done intramolecularly using 2.4 molar equivalents of CuCl₂ and a Pd catalyst.⁹⁵¹ The intermolecular addition of diesters (e.g., malonates) to alkynes was accomplished in acetic acid and a Pd catalyst under microwave irradiation.⁹⁵² The enolate anion derived from the reaction of a nitrile with potassium *tert*-butoxide added to the less substituted carbon of the C=C unit of styrene in DMSO.⁹⁵³ Silyl enol ethers add to alkynes using a W catalyst.⁹⁵⁴ Malonate derivatives add to alkenes in the presence of an Al(OR)₃ catalyst.⁹⁵⁵ 1,3-Dicarbonyl compounds add to allenes in the presence of a Pd catalyst.⁹⁵⁶

Aryl iodides add to alkynes using a Pt complex in conjunction with a Pd catalyst.⁹⁵⁷ A Pd catalyst has been used alone for the same purpose,⁹⁵⁸ and the intramolecular addition of a arene to an alkene was accomplished with a Pd⁹⁵⁹ or a GaCl₃ catalyst.⁹⁶⁰ Alkyl iodides add intramolecularly to alkenes with a Ti catalyst,⁹⁶¹ or to alkynes using In metal and additives.⁹⁶² The latter cyclization of aryl iodides to alkenes was accomplished with In and I₂⁹⁶³ or with SmI₂.⁹⁶⁴

Aromatic hydrocarbons (e.g., benzene) add to alkenes using a Ru catalyst⁹⁶⁵ a catalytic mixture of AuCl₃/AgSbF₆,⁹⁶⁶ or a Rh catalyst,⁹⁶⁷ and Ru complexes catalyze the addition

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⁹⁶⁷ Thalji, R.K.; Ellman, J.A.; Bergman, R.G. *J. Am. Chem. Soc.* **2004**, *126*, 7192.

of heteroaromatic compounds (e.g., pyridine) to alkynes.⁹⁶⁸ Such alkylation reactions are clearly reminiscent of the *Friedel–Crafts* reaction (**11-11**). Palladium catalysts can also be used for the addition of aromatic compounds to alkynes,⁹⁶⁹ and Rh catalysts for addition to alkenes (with microwave irradiation).⁹⁷⁰ Note that vinylidene cyclopropanes react with furans and a Pd catalyst to give allylically substituted furans.⁹⁷¹

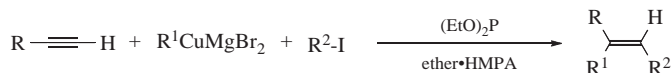
Arylboronic acids (see Reaction **13-13**) add to alkynes to give the substituted alkene using a Rh catalyst.⁹⁷² Allenes react with phenylboronic acid and an aryl iodide, in the presence of a Pd catalyst, to give a substituted alkene.⁹⁷³ 2-Bromo-1,6-dienes react with phenylboronic acid with a Pd catalyst to give a cyclopentane with an exocyclic double bond and a benzyl substituent.⁹⁷⁴

An indirect addition converts alkynes to an organozinc compound using a Pd catalyst, which then reacts with allylic halides.⁹⁷⁵ Similarly, the reaction of an alkyne with $\text{Ti}(\text{O}i\text{Pr})_4/2$ $i\text{PrMgCl}$ followed by addition of an alkyne leads to a conjugated diene.⁹⁷⁶

OS 81, 121.

15-22 The Addition of Two Alkyl Groups to an Alkyne

Dialkyl-addition



Two different alkyl groups can be added to a terminal alkyne⁹⁷⁷ in one laboratory step by treatment with an alkylcopper–magnesium bromide reagent (called *Normant reagents*)⁹⁷⁸ and an alkyl iodide in ether–HMPA containing triethylphosphite.⁹⁷⁹ The groups add stereoselectively syn. The reaction, which has been applied to primary⁹⁸⁰ R^1 and to primary, allylic, benzylic, vinylic, and α -alkoxyalkyl R^1 , involves initial addition of an intermediate alkylcopper reagent,⁹⁸¹ followed by a coupling reaction (**10-57**):

⁹⁶⁸ See Alonso, F.; Beletskaya, I.P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

⁹⁶⁹ Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102.

⁹⁷⁰ Vo-Thanh, G.; Lahrache, H.; Loupy, A.; Kim, I.-J.; Chang, D.-H.; Jun, C.-H. *Tetrahedron* **2004**, *60*, 5539.

⁹⁷¹ Nakamura, I.; Siriwardana, A.I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3445.

⁹⁷² Lautens, M.; Yoshida, M. *J. Org. Chem.* **2003**, *68*, 762; Genin, E.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4157.

⁹⁷³ Yoshida, M.; Gotou, T.; Ihara, M. *Chem. Commun.* **2004**, 1124.

⁹⁷⁴ Oh, C.H.; Sung, H.R.; Park, S.J.; Ahn, K.H. *J. Org. Chem.* **2002**, *67*, 7155.

⁹⁷⁵ Matsubara, S.; Ukai, K.; Toda, N.; Utimoto, K.; Oshima, K. *Synlett* **2000**, 995.

⁹⁷⁶ Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67.

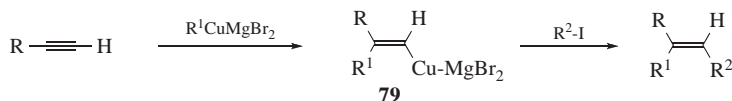
⁹⁷⁷ Raston, C.L.; Salem, G. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 159–306, 233–248; Normant, J.F.; Alexakis, A. *Synthesis* **1981**, 841; Hudrlik, P.F.; Hudrlik, A.M. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, **1978**, pp. 233–238. See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 452–460.

⁹⁷⁸ See Ashby, E.C.; Goel, A.B. *J. Org. Chem.* **1983**, *48*, 2125.

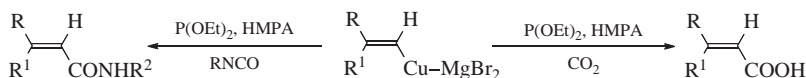
⁹⁷⁹ Gardette, M.; Alexakis, A.; Normant, J.F. *Tetrahedron* **1985**, *41*, 5887 and references cited therein. For an extensive list of references, see Marfat, A.; McGuirk, P.R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888.

⁹⁸⁰ See Rao, S.A.; Periasamy, M. *Tetrahedron Lett.* **1988**, *29*, 4313.

⁹⁸¹ See Westmijze, H.; Kleijn, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 98, and references cited therein.



Acetylene itself ($\text{R}=\text{H}$) undergoes the reaction with R_2CuLi instead of the *Normant reagent*.⁹⁸² The use of R' containing functional groups has been reported.⁹⁸³ If the alkyl iodide is omitted, the vinylic copper intermediate (**79**) can be converted to a carboxylic acid by the addition of CO_2 (see Reaction **16-30**) or to an amide by the addition of an isocyanate, in either case in the presence of HMPA and a catalytic amount of triethyl phosphite.⁹⁸⁴ The use of I_2 results in a vinylic iodide.⁹⁸⁵



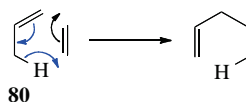
Similar reactions, in which two alkyl groups are added to a triple bond, have been carried out with trialkylalanes (R_3Al) and zirconium complexes as catalysts.⁹⁸⁶ Internal alkynes undergo bis(allylation) using a Ni catalysts and triallylindium.⁹⁸⁷ Allyl ethers and iodobenzene have also been added using a Zr complex.⁹⁸⁸ Similarly, allyl ethers and allyl chlorides have been added.⁹⁸⁹

Arylboronic acids (see Reaction **13-13**) react with alkynes and 1 equiv of an aryl iodide, with a Pd catalyst, to add two aryl groups across the triple bond.⁹⁹⁰

OS VII, 236, 245, 290.

15-23 The Ene Reaction

Hydro-allyl-addition



An interesting addition of RH to a double bond involves the reaction of alkenes with an alkene having an allylic hydrogen (**80**), and is called the *ene reaction* or the *ene synthesis*.⁹⁹¹ The reaction proceeds without a catalyst, but one of the components must

⁹⁸² Furber, M.; Taylor, R.J.K.; Burford, S.C. *J. Chem. Soc. Perkin Trans. 1*, **1986**, 1809.

⁹⁸³ Rao, S.A.; Knochel, P. *J. Am. Chem. Soc.* **1991**, 113, 5735.

⁹⁸⁴ Normant, J.F.; Cahiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* **1973**, 54, C53.

⁹⁸⁵ Alexakis, A.; Cahiez, G.; Normant, J.F. *Org. Synth.* **VII**, 290.

⁹⁸⁶ See Negishi, E. *Acc. Chem. Res.* **1987**, 20, 65; *Pure Appl. Chem.* **1981**, 53, 2333; Negishi, E.; Takahashi, T. *Aldrichimica Acta* **1985**, 18, 31.

⁹⁸⁷ Hirashita, T.; Akutagawa, K.; Kamei, T.; Araki, S. *Chem. Commun.* **2006**, 2598.

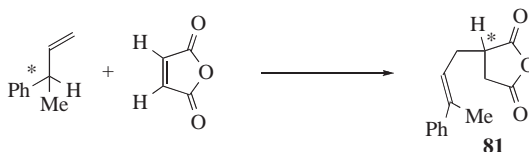
⁹⁸⁸ Hara, R.; Nishihara, Y.; Landré, P.D.; Takahashi, T. *Tetrahedron Lett.* **1997**, 38, 447.

⁹⁸⁹ Takahashi, T.; Kotori, M.; Kasai, K.; Suzuki, N. *Tetrahedron Lett.* **1994**, 35, 5685.

⁹⁹⁰ Zhou, C.; Emrich, D.E.; Larock, R.C. *Org. Lett.* **2003**, 5, 1579; Zhou, C.; Larock, R.C. *J. Org. Chem.* **2005**, 70, 3765; Zhou, C.; Larock, R.C. *Org. Lett.* **2005**, 7, 259.

⁹⁹¹ Carruthers, W. *Cycloaddition Reactions in Organic Synthesis* Pergamon, Elmsford, NY, **1990**; Boyd, G.V. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, **1989**, pp. 477–525; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* **1969**, 8, 556. For reviews of intramolecular ene reactions see Taber, D.F. *Intramolecular Diels–Alder and Alder Ene Reactions* Springer, NY, **1984**; pp. 61–94; Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed.* **1978**, 17, 476–486; Conia, J.M.; Le Perche, P. *Synthesis* **1975**, 1. See Desimoni, G.; Faita, G.; Righetti, P.P.; Sfulcini, A.; Tsyganov, D. *Tetrahedron* **1994**, 50, 1821 for solvent effects in the ene reaction.

be a reactive dienophile (reacts with a diene; see Reaction **15-60** for a definition of this word), such as maleic anhydride, but the other (which supplies the hydrogen) may be a simple alkene (e.g., propene) as long as there is an allylic hydrogen atom. Rather high reaction temperatures (250–450 °C) are common unless the substrates are very activated, but steric acceleration of the uncatalyzed ene reaction is known.⁹⁹² The reaction is compatible with a variety of functional groups that can be appended to the ene and dienophile. N,N-Diallyl amides give an ene cyclization, for example.⁹⁹³ There has been much discussion of the mechanism of this reaction, and both concerted pericyclic (as shown above) and stepwise mechanisms have been suggested. The mechanism of the ene reaction of singlet (¹Δ_g) oxygen with simple alkenes was found to involve two steps, with no intermediate.⁹⁹⁴ A retro-ene reaction is known with allylic dithiocarbonate.⁹⁹⁵ An intramolecular ene reaction between oxazolones and enol ethers leads to functionalized oxazolones.⁹⁹⁶ The reaction between maleic anhydride and optically active PhCHMeCH=CH₂ gave an optically active product (**81**),⁹⁹⁷ which is strong evidence for a concerted rather than a stepwise mechanism.⁹⁹⁸ The reaction can be highly stereoselective.⁹⁹⁹



The reaction can be extended to less-reactive enophiles by the use of Lewis acid catalysts, especially alkylaluminum halides.¹⁰⁰⁰ Titanium catalysts,¹⁰⁰¹ Sc,¹⁰⁰² LiClO₄,¹⁰⁰³ Y,¹⁰⁰⁴ In,¹⁰⁰⁵ Pd,¹⁰⁰⁶ Co,¹⁰⁰⁷ Ni catalysts,¹⁰⁰⁸ as well as a combination of Ag and Au catalysts¹⁰⁰⁹ have also been used. A magnesium–ene cyclization stereochemically directed by an allylic oxyanionic group has been reported.¹⁰¹⁰ The Lewis acid catalyzed reaction

⁹⁹² Choony, N.; Kuhnert, N.; Sammes, P.G.; Smith, G.; Ward, R.W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1999.

⁹⁹³ Cossy, J.; Bouzide, A. *Tetrahedron* **1997**, 53, 5775; Oppolzer, W.; Fürstner, A. *Helv. Chim. Acta* **1993**, 76, 2329; Oppolzer, W.; Schröder, F. *Tetrahedron Lett.* **1994**, 35, 7939.

⁹⁹⁴ Singleton, D.A.; Hang, C.; Szymanski, M.J.; Meyer, M.P.; Leach, A.G.; Kuwata, K.T.; Chen, J.S.; Greer, A.; Foote, C.S.; Houk, K.N. *J. Am. Chem. Soc.* **2003**, 125, 1319.

⁹⁹⁵ Eto, M.; Nishimoto, M.; Kubota, S.; Matsuoka, T.; Harano, K. *Tetrahedron Lett.* **1996**, 37, 2445.

⁹⁹⁶ Fisk, J.S.; Tepe, J.J. *J. Am. Chem. Soc.* **2007**, 129, 3058.

⁹⁹⁷ Nahm, S.H.; Cheng, H.N. *J. Org. Chem.* **1986**, 51, 5093.

⁹⁹⁸ See Jenner, G.; Salem, R.B.; El'yanov, B.; Gonikberg, E.M. *J. Chem. Soc. Perkin Trans. 2*, **1989**, 1671; Thomas IV, B.E.; Loncharich, R.J.; Houk, K.N. *J. Org. Chem.* **1992**, 57, 1354.

⁹⁹⁹ Ooi, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1994**, 50, 6505; Thomas IV, B.E.; Houk, K.N. *J. Am. Chem. Soc.* **1993**, 115, 790; Also see, Masaya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1994**, 35, 7965.

¹⁰⁰⁰ See Chaloner, P.A. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 456–460; Snider, B.B. *Acc. Chem. Res.* **1980**, 13, 426.

¹⁰⁰¹ Sturla, S.J.; Kablaoui, N.M.; Buchwald, S.L. *J. Am. Chem. Soc.* **1999**, 121, 1976.

¹⁰⁰² Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. *Tetrahedron Lett.* **1998**, 39, 1997.

¹⁰⁰³ Davies, A.G.; Kintart, W.J. *J. Chem. Soc. Perkin Trans. 2*, **1993**, 2281.

¹⁰⁰⁴ Molander, G.A.; Corrette, C.P. *J. Org. Chem.* **1999**, 64, 9697.

¹⁰⁰⁵ Hatakeyama, S. *Pure Appl. Chem.* **2009**, 81, 217.

¹⁰⁰⁶ Corkey, B.K.; Toste, F.D. *J. Am. Chem. Soc.* **2005**, 127, 17168.

¹⁰⁰⁷ Hilt, G.; Treutwein, J. *Angew. Chem. Int. Ed.* **2007**, 46, 8500.

¹⁰⁰⁸ Michelet, V.; Galland, J.-C.; Charruault, L.; Savignac, M.; Genêt, J.-P. *Org. Lett.* **2001**, 3, 2065.

¹⁰⁰⁹ Kennedy-Smith, J.J.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* **2004**, 126, 4526.

¹⁰¹⁰ Cheng, D.; Zhu, S.; Yu, Z.; Cohen, T. *J. Am. Chem. Soc.* **2001**, 123, 30.

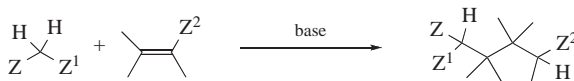
probably has a stepwise mechanism.¹⁰¹¹ An Ir catalyzed ene reaction has been done in an ionic liquid.¹⁰¹² An ene reaction of arynes with alkynes leads to aryl allenes.¹⁰¹³ An *aza-ene reaction*¹⁰¹⁴ has been used in a synthesis of enantioenriched piperidines, using two different imines as starting materials.¹⁰¹⁵ Ene reactions of imines are sometimes called *imino-ene reactions*.¹⁰¹⁶

The *carbonyl-ene reaction*¹⁰¹⁷ is also very useful, and often gives synthetically useful yields of products when catalyzed by Lewis acids.¹⁰¹⁸ Scandium triflate¹⁰¹⁹ and chromium complexes¹⁰²⁰ are useful Lewis acids in this reaction. Asymmetric catalysts¹⁰²¹ for enantioselective carbonyl ene reactions have been reported using chiral Sc catalysts¹⁰²² In,¹⁰²³ or chiral Ni catalysts.¹⁰²⁴ Ketoester ene reactions with silyl enol ethers occurs in the presence of Pd and Ag catalysts.¹⁰²⁵ Carbonyl-ene cyclization has been reported on silica gel at high pressure (15 kbar).¹⁰²⁶ Ene reactions with imines,¹⁰²⁷ nitrile oxides,¹⁰²⁸ as well as nitroso-ene reactions are known.¹⁰²⁹ Vinyl boronates have been prepared via a Ru catalyzed ene reaction.¹⁰³⁰

OS IV, 766; V, 459. See also, OS VIII, 427.

15-24 The Michael Reaction

Hydro-bis(ethoxycarbonyl)methyl-addition,
and so on



Compounds containing electron-withdrawing groups (Z is defined in Sec. 15.A.ii as an electron-withdrawing group) add to alkenes of the form $C=C-Z$ in the presence of bases.¹⁰³¹ This is called the *Michael reaction* and is formally a conjugate addition.¹⁰³² The

¹⁰¹¹ See Snider, B.B.; Ron E. *J. Am. Chem. Soc.* **1985**, 107, 8160.

¹⁰¹² Shibata, T.; Yamasaki, M.; Kadowaki, S.; Takagi, K. *Synlett* **2004**, 2812.

¹⁰¹³ Jayanth, T.T.; Jegannathan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2006**, 128, 2232.

¹⁰¹⁴ See Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2006**, 45, 2254.

¹⁰¹⁵ Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, 129, 10336.

¹⁰¹⁶ See Pandey, M.K.; Bisai, A.; Pandey, A.; Singh, V.K. *Tetrahedron Lett.* **2005**, 46, 5039.

¹⁰¹⁷ For a review, see Clarke, M.L.; France, M.B. *Tetrahedron* **2008**, 64, 9003.

¹⁰¹⁸ See Achmatowicz, O.; Bialek-Florjanczyk, E. *Tetrahedron* **1996**, 52, 8827; Marshall, J.A.; Andersen, M.W. *J. Org. Chem.* **1992**, 57, 5851 for mechanistic discussions of this reaction.

¹⁰¹⁹ See Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. *Tetrahedron Lett.* **1998**, 39, 1997.

¹⁰²⁰ Ruck, R.T.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2002**, 124, 2882.

¹⁰²¹ Grachan, M.L.; Tudge, M.T.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* **2008**, 47, 1469.

¹⁰²² Evans, D.A.; Wu, J. *J. Am. Chem. Soc.* **2005**, 127, 8006.

¹⁰²³ Zhao, J.-F.; Tsui, H.-Y.; Wu, P.-J.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2008**, 130, 16492.

¹⁰²⁴ Zheng, K.; Shi, J.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2008**, 130, 15770.

¹⁰²⁵ Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* **2007**, 129, 12950.

¹⁰²⁶ Dauben, W.G.; Hendricks, R.T. *Tetrahedron Lett.* **1992**, 33, 603.

¹⁰²⁷ Yamanaka, M.; Nishida, A.; Nakagawa, M.; *Org. Lett.* **2000**, 2, 159.

¹⁰²⁸ See Yu, Z.-X.; Houk, K.N. *J. Am. Chem. Soc.* **2003**, 125, 13825.

¹⁰²⁹ Lu, X. *Org. Lett.* **2004**, 6, 2813. See also, Leach, A.G.; Houk, K.N. *J. Am. Chem. Soc.* **2002**, 124, 14820; Adam, W.; Krebs, O. *Chem. Rev.* **2003**, 103, 4131.

¹⁰³⁰ Hansen, E.C.; Lee, D. *J. Am. Chem. Soc.* **2005**, 127, 3252.

¹⁰³¹ See Myers, M.C.; Bharadwaj, A.R.; Milgram, B.C.; Scheidt, K.A. *J. Am. Chem. Soc.* **2005**, 127, 14675.

¹⁰³² See Yanovskaya, L.A.; Kryshnal, G.V.; Kulganek, V.V. *Russ. Chem. Rev.* **1984**, 53, 744; Bergmann, E.D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, 10, 179. For a review of α -substitution versus conjugate addition, see Lewandowska, E. *Tetrahedron* **2007**, 63, 2107.

product formed, RCH_2Z or RCHZZ' , can include aldehydes,¹⁰³³ ketones,¹⁰³⁴ esters,¹⁰³⁵ diesters,¹⁰³⁶ diketones,¹⁰³⁷ keto-esters,¹⁰³⁸ carboxylic acids, dicarboxylic acids,¹⁰³⁹ nitriles,¹⁰⁴⁰ vinyl sulfones,¹⁰⁴¹ nitro compounds (see below),¹⁰⁴² and others of the form ZCH_3 , ZCH_2R , ZCHR_2 , and ZCHRZ' .¹⁰⁴³ In the most common examples, a base removes the acidic proton from the substrate adding to $\text{C}=\text{C}-\text{Z}$ and the mechanism is as outlined in Section 15.A.ii. *Michael addition* is known to be catalyzed by phosphines,¹⁰⁴⁴ as well as other organocatalysts.¹⁰⁴⁵ Catalysts are known that are compatible with an aqueous medium.¹⁰⁴⁶ A double *Michael* process is possible, where conjugate addition to an alkynyl ketone is followed by an intramolecular *Michael reaction* to form a functionalized ring.¹⁰⁴⁷ Vinylogous *Michael* reactions are well known, using a variety of nucleophilic species¹⁰⁴⁸ (see Sec. 6.B for vinylogy). 1,6-Additions are also known.¹⁰⁴⁹ Arylsilanes add to conjugated esters and amides in the presence of a Rh catalyst.¹⁰⁵⁰ Nitro compounds add to conjugated ketones via *Michael addition*.¹⁰⁵¹ Nitroalkenes are *Michael* acceptors¹⁰⁵² for the enolate anions of β -keto esters¹⁰⁵³ or malonate derivatives with a Ni catalyst¹⁰⁵⁴ or

¹⁰³³ Willis, M.C.; McNally, S.J.; Beswick, P.J. *Angew. Chem. Int. Ed.* **2004**, *43*, 340; Chi, Y.; Gellman, S.H. *Org. Lett.* **2005**, *7*, 4253.

¹⁰³⁴ Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559; Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582.

¹⁰³⁵ Kim, S.-G.; Ahn, K.H. *Tetrahedron Lett.* **2001**, *42*, 4175.

¹⁰³⁶ Halland, N.; Aburel, P.S.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* **2003**, *42*, 661.

¹⁰³⁷ da Silva, F.M.; Gomes, A.K.; Jones Jr., J. *Can. J. Chem.* **1999**, *77*, 624.

¹⁰³⁸ Suzuki, T.; Torii, T. *Tetrahedron Asymmetry* **2001**, *12*, 1077; García-Gómez, G.; Moretó, J.M. *Eur. J. Org. Chem.* **2001**, 1359; Kobayashi, S.; Kakumoto, K.; Mori, Y.; Manabe, K. *Isr. J. Chem.* **2001**, *41*, 247.

¹⁰³⁹ Méou, A.; Lamarque, L.; Brun, P. *Tetrahedron Lett.* **2002**, *43*, 5301.

¹⁰⁴⁰ Wolckenhauer, S.A.; Rychnovsky, S.D. *Org. Lett.* **2004**, *6*, 2745; Fleming, F.F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035.

¹⁰⁴¹ Zhu, Q.; Lu, Y. *Org. Lett.* **2008**, *10*, 4803.

¹⁰⁴² Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 11790. See Strzalko, T.; Seyden-Penne, J.; Wartschi, L.; Froment, F.; Corset, J. *Tetrahedron Lett.* **1994**, *35*, 3935.

¹⁰⁴³ Taylor, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2003**, *125*, 11204.

¹⁰⁴⁴ Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R.M.; Vallribera, A. *Tetrahedron* **2005**, *61*, 8598.

¹⁰⁴⁵ Almaşi, D.; Alonso, D.A.; Nájera, C. *Tetrahedron Asymmetry* **2007**, *18*, 299; Vicario, J.L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065.

¹⁰⁴⁶ Chen, X.; She, J.; Shang, Z.; Wu, J.; Zhang, P. *Synthesis* **2008**, 3931.

¹⁰⁴⁷ Holeman, D.S.; Rasne, R.M.; Grossman, R.B. *J. Org. Chem.* **2002**, *67*, 3149.

¹⁰⁴⁸ Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron Lett.* **2001**, *42*, 8471.

¹⁰⁴⁹ Bernardi, L.; López-Cantarero, J.; Niess, B.; Jørgensen, K.A. *J. Am. Chem. Soc.* **2007**, *129*, 5772.

¹⁰⁵⁰ Oi, S.; Taira, A.; Honma, Y.; Sato, T.; Inoue, Y. *Tetrahedron Asymmetry* **2006**, *17*, 598.

¹⁰⁵¹ Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933; Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475; Prieto, A.; Halland, N.; Jørgensen, K.A. *Org. Lett.* **2005**, *7*, 3897.

¹⁰⁵² See Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284; Baer, H.H.; Urbas L. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, **1970**, pp. 130–148. See Thayumanavan, R.; Tanaka, F.; Barbas, III, C.F. *Org. Lett.* **2004**, *6*, 2527; Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558; Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906; Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148.

¹⁰⁵³ Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

¹⁰⁵⁴ Evans, D.A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958; Evans, D.A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583.

an organocatalyst.¹⁰⁵⁵ Other substrates have been added to nitroalkenes via *Michael addition*.¹⁰⁵⁶ Malonate derivatives also add to conjugated ketones,¹⁰⁵⁷ and keto esters add to conjugated esters.¹⁰⁵⁸ Vinyl sulfones undergo *Michael addition*.¹⁰⁵⁹

It is known that 1,2-addition (to the C=O or C≡N group) often competes and sometimes predominates (Reaction **16-38**).¹⁰⁶⁰ In particular, α,β-unsaturated *aldehydes* seldom give 1,4-addition.¹⁰⁶¹ The *Michael reaction* generally gives better yields with fewer side reactions by conversion of the nucleophile to its enolate form (a *preformed enolate*).¹⁰⁶² Phase-transfer catalysts have been used,¹⁰⁶³ and ionic liquids have been used in conjunction with phase-transfer catalysis.¹⁰⁶⁴ Transition metal compounds Ce,¹⁰⁶⁵ Yb,¹⁰⁶⁶ Bi,¹⁰⁶⁷ Fe,¹⁰⁶⁸ Ni,¹⁰⁶⁹ Cu,¹⁰⁷⁰ La,¹⁰⁷¹ Ru,¹⁰⁷² or Sc¹⁰⁷³ also induce the reaction. Conjugate addition has also been promoted by Y-zeolite,¹⁰⁷⁴ and water-promoted *Michael additions* have also been reported.¹⁰⁷⁵ Acylsilanes, when treated with fluoride ion, add to conjugated amides under certain conditions.¹⁰⁷⁶ Addition to the meta-position of phenolic compounds leads to bicyclic ketones.¹⁰⁷⁷ Conjugate addition of nitrones using SmI₂ has

¹⁰⁵⁵ Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454; Xu, D.-Q.; Wang, B.T.; Luo, S.-P.; Yue, H.-D.; Wang, L.-P.; Xu, Z.-Y. *Tetrahedron Asymmetry* **2007**, *18*, 1788; Wu, L.-Y.; Yan, Z.-Y.; Xie, Y.-X.; Niu, Y.-N.; Liang, Y.-M. *Tetrahedron Asymmetry* **2007**, *18*, 2086; Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093.

¹⁰⁵⁶ See Mattson, A.E.; Zuhl, A.M.; Reynolds, T.E.; Scheidt, K.A. *J. Am. Chem. Soc.* **2006**, *128*, 4932; Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C.F. *J. Am. Chem. Soc.* **2006**, *128*, 4966; Huang, H.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2006**, *128*, 7170; Pansare, S.V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624; Chi, Y.; Guo, L.; Kopf, N.A.; Gellman, S.H. *J. Am. Chem. Soc.* **2008**, *130*, 5608; Wiesner, M.; Revell, J.D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc.* **2008**, *130*, 5610; Malerich, J.P.; Hagihara, K.; Rawal, V.H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

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¹⁰⁶⁰ See Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* **1989**, *19*, 227, pp. 232–236.

¹⁰⁶¹ See, however, Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1088.

¹⁰⁶² See Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* **1991**, *20*, 87; **1989**, *19*, 227.

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¹⁰⁶⁵ Bartoli, G.; Bosco, M.; Bellucci, M.C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* **1999**, 617.

¹⁰⁶⁶ Ding, R.; Katebzadeh, K.; Roman, L.; Bergquist, K.-E.; Lindström, U.M. *J. Org. Chem.* **2006**, *71*, 352.

¹⁰⁶⁷ Varala, R.; Alam, M.M.; Adapa, S.R. *Synlett* **2003**, 720.

¹⁰⁶⁸ For a review, see Christoffers, J. *Synlett* **2001**, 723.

¹⁰⁶⁹ For a discussion of *Heck coupling* versus *Michael addition*, see Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chemistry: Asian J.* **2007**, *2*, 1409.

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¹⁰⁷² Watanabe, M.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2003**, *125*, 7508; Wadsworth, K.J.; Wood, F.K.; Chapman, C.J.; Frost, C.G. *Synlett* **2004**, 2022; Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

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¹⁰⁷⁴ Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Tetrahedron Lett.* **1997**, *38*, 6557.

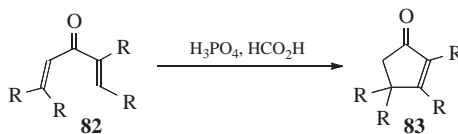
¹⁰⁷⁵ Lubineau, A.; Augé, J. *Tetrahedron Lett.* **1992**, *33*, 8073.

¹⁰⁷⁶ Nahm, M.R.; Potnick, J.R.; White, P.S.; Johnson, J.S. *J. Am. Chem. Soc.* **2006**, *128*, 2751.

¹⁰⁷⁷ Vo, N.T.; Pace, R.D.M.; O'Hara, F.; Gaunt, M.J. *J. Am. Chem. Soc.* **2008**, *130*, 404.

been reported.¹⁰⁷⁸ Cyanide ion adds to *Michael* acceptors, and TMSCN also adds in a *Michael* reaction.¹⁰⁷⁹

Intramolecular versions of *Michael* addition are known.¹⁰⁸⁰ The intramolecular *Michael* addition of an α -chloro ketone enolate anion, formed *in situ* using DABCO, leads to formation of a bicyclo[4.1.0] diketone.¹⁰⁸¹



An important cyclization procedure involves the acid-catalyzed addition of diene-ketones (e.g., **82**), where one conjugated alkene adds to the other conjugated alkene to form cyclopentenones (**83**). This is called the *Nazarov cyclization*.¹⁰⁸² While it may be categorized in Reaction 15-20 because one alkene unit adds to another, the addition is formally a *Michael* addition, and so is placed here. Structural variations are possible that prepare a variety of cyclopentenones. The steric influence of substituents has been discussed,¹⁰⁸³ and the rate-accelerating influence observed in N- and S-heterocycles.¹⁰⁸⁴ Substituents on the C=C units lead to cyclopentenones that bear those substituents. Gold¹⁰⁸⁵ and V catalyzed¹⁰⁸⁶ cyclizations have been reported, as well as a Sc catalyzed cyclization in water.¹⁰⁸⁷ Heating dienones in DME or an ionic liquid has been shown to give the *Nazarov* product without addition of a Lewis acid.¹⁰⁸⁸ Allenes participate in *Nazarov cyclization* reactions.¹⁰⁸⁹ A vinylogous *Nazarov* reaction is involved in the cyclization of cross-conjugated trienes¹⁰⁹⁰ (see Sec. 6.B for vinylogy). The use of a chiral ligand gave the cyclopentenone with modest enantioselectivity.¹⁰⁹¹ Reductive cyclization can also give the nonconjugated five-membered ring.¹⁰⁹² Note that a *retro-Nazarov* is possible with α -bromocyclopentanones.¹⁰⁹³ In one variation using an Al complex, a

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¹⁰⁸¹ Bremeyer, N.; Smith, S.C.; Ley, S.V.; Gaunt, M.J. *Angew. Chem. Int. Ed.* **2004**, 43, 2681.

¹⁰⁸² Nazarov, I.N.; Torgov, I.B.; Terekhova, L.N. *Izv. Akad. Nauk. SSSR otd. Khim. Nauk*, **1942**, 200; Pellissier, H. *Tetrahedron* **2005**, 61, 6479; Frontier, A.J.; Collison, C. *Tetrahedron* **2005**, 61, 7577; Tius, M.A. *Eur. J. Org. Chem.* **2005**, 2193. See Smith, D.A.; Ulmer II, C.W. *J. Org. Chem.* **1993**, 58, 4118 for a discussion of torquoselectivity and hyperconjugation in this reaction.

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¹⁰⁸⁵ Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, 128, 1442.

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¹⁰⁸⁹ Banaag, A.R.; Tius, M.A. *J. Am. Chem. Soc.* **2007**, 129, 5328; Banaag, A.R.; Tius, M.A. *J. Org. Chem.* **2008**, 73, 8133.

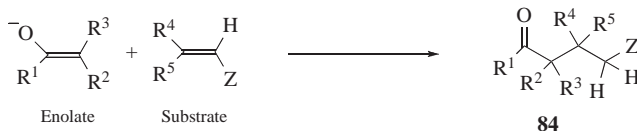
¹⁰⁹⁰ Rieder, C.J.; Winberg, K.J.; West, F.G. *J. Am. Chem. Soc.* **2009**, 131, 7504.

¹⁰⁹¹ Aggarwal, V.K.; Belfield, A.J. *Org. Lett.* **2003**, 5, 5075.

¹⁰⁹² Giese, S.; West, F.G. *Tetrahedron Lett.* **1998**, 39, 8393; Giese, S.; West, F.G. *Tetrahedron* **2000**, 56, 10221.

¹⁰⁹³ Harmata, M.; Lee, D.R. *J. Am. Chem. Soc.* **2002**, 124, 14328. For a discussion of the scope and mechanism of the *retro-Nazarov* reaction, see Harmata, M.; Schreiner, P.R.; Lee, D.R.; Kirchhoefer, P.L. *J. Am. Chem. Soc.* **2004**, 126, 10954. For a torquoselective *retro-Nazarov*, see Harmata, M.; Lee, D.R.; Barnes, C.L. *Org. Lett.* **2005**, 7, 1881.

cyclohexenone was formed.¹⁰⁹⁴ There is a so-called interrupted *Nazarov*, in which an amine is trapped after cyclization to give an α -amino conjugated cyclopentenone.¹⁰⁹⁵ Spirocycles have been prepared via a tandem *Nazarov–Wagner–Meerwein* sequence.¹⁰⁹⁶



In a *Michael reaction* with suitably different R groups, two new stereogenic centers may be created (see **84**). In a diastereoselective process, one of the two pairs is formed exclusively or predominantly as a racemic mixture.¹⁰⁹⁷ When either or both of the reaction components have a chiral substituent, the reaction can be enantioselective (only one of the four diastereomers formed predominantly).¹⁰⁹⁸ There are many examples of catalytic enantioselective Michael additions,¹⁰⁹⁹ often by the use of a chiral catalyst¹¹⁰⁰ or by using optically active enamines instead of enolates.¹¹⁰¹ Common chiral catalysts used with carbonyl substrates include Ru,¹¹⁰² Ni,¹¹⁰³ Sr,¹¹⁰⁴ and Al(salen) complexes.¹¹⁰⁵ Chiral organocatalysts¹¹⁰⁶ (e.g., oxazolidinones)¹¹⁰⁷ have been developed and chiral imines have also been used.¹¹⁰⁸ Certain antibodies have been used to facilitate chiral, intramolecular *Michael addition* reactions.¹¹⁰⁹ Enzymes have been used as for asymmetric *Michael reactions*.¹¹¹⁰ Addition of chiral additives to the reaction (e.g., metal–salen complexes,¹¹¹¹ proline derivatives,¹¹¹² or (–)-sparteine¹¹¹³) lead to product formation with good-to-excellent asymmetric induction. Ultrasound has been used to promote

¹⁰⁹⁴ Magomedev, N.A.; Ruggiero, P.L.; Tang, Y. *Org. Lett.* **2004**, 6, 3373.

¹⁰⁹⁵ Dhoro, F.; Tius, M.A. *J. Am. Chem. Soc.* **2005**, 127, 12472; Dhoro, F.; Kristensen, T.E.; Stockmann, V.; Yap, G.P.A.; Tius, M.A. *J. Am. Chem. Soc.* **2007**, 129, 7256. See also, Grant, T.N.; Rieder, C.J.; West, F.G. *Chem. Commun.* **2009**, 5676.

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¹⁰⁹⁷ See Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* **1989**, 19, pp. 237.

¹⁰⁹⁸ See Töke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* **1995**, 36, 5951; Enders, D.; Demir, A.S.; Rendenbach, B.E.M. *Chem. Ber.* **1987**, 120, 1731; Hawkins, J.M.; Lewis, T.A. *J. Org. Chem.* **1992**, 57, 2114.

¹⁰⁹⁹ See Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.

¹¹⁰⁰ Desimoni, G.; Quadrelli, P.; Righetti, P.P. *Tetrahedron* **1990**, 46, 2927.

¹¹⁰¹ See d'Angelo, J.; Revial, G.; Volpe, T.; Pfau, M. *Tetrahedron Lett.* **1988**, 29, 4427.

¹¹⁰² Guo, R.; Morris, R.H.; Song, D. *J. Am. Chem. Soc.* **2005**, 127, 516.

¹¹⁰³ Evans, D.A.; Thomson, R.J.; Franco, F. *J. Am. Chem. Soc.* **2005**, 127, 10816.

¹¹⁰⁴ Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, 130, 2430.

¹¹⁰⁵ Taylor, M.S.; Zalatan, D.N.; Lerchner, A.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2005**, 127, 1313.

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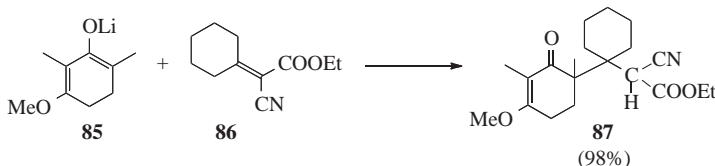
¹¹¹¹ Jha, S.C.; Joshi, N.N. *Tetrahedron Asymmetry* **2001**, 12, 2463.

¹¹¹² Yamaguchi, M.; Shiraishi, T.; Hiram, M. *J. Org. Chem.* **1996**, 61, 3520.

¹¹¹³ Xu, F.; Tillyer, R.D.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Asymmetry* **1998**, 9, 1651.

asymmetric *Michael reactions*.¹¹¹⁴ In reactions of enolate anions, both the enolate anion and substrate can exist as (*Z*) or (*E*) isomers. With enolates derived from ketones or carboxylic esters, the (*E*) enolates gave the syn pair of enantiomers (Sec. 4.G), while (*Z*) enolates gave the anti pair.¹¹¹⁵

When the substrate contains *gem-Z* groups, (e.g., **86**), bulky groups can be added, if the reaction is carried out under aprotic conditions. For example, addition of enolate **85** to **86** gave **87** in which two adjacent quaternary centers have been formed.¹¹¹⁶



In certain cases, *Michael reactions* can take place under acidic conditions.¹¹¹⁷ *Michael-type* addition of radicals to conjugated carbonyl compounds is also known.¹¹¹⁸ Radical addition can be catalyzed by Yb(OTf)₃,¹¹¹⁹ but radicals add under standard conditions as well, even intramolecularly.¹¹²⁰ Electrochemical-initiated *Michael* additions are known.

Alkynes are reactive, and *Michael reactions* are sometimes applied to substrates of the type C≡C–Z, where the coproducts are conjugated systems of the type C=C–Z.¹¹²¹ Terminal alkynes add to conjugated systems.¹¹²² Due to the greater susceptibility of triple bonds to nucleophilic attack, it is even possible for nonactivated alkynes (e.g., acetylene), to be substrates in this reaction.¹¹²³

Silyl enol ethers (e.g., **88**) add to α,β-unsaturated ketones and esters when catalyzed¹¹²⁴ by TiCl₄¹¹²⁵ or InCl₃.¹¹²⁶ Aluminum compounds also catalyze this reaction¹¹²⁷ and the reaction has been done in neat tri-*n*-propylaluminum.¹¹²⁸ A solid-state version of the reaction used alumina•ZnCl₂.¹¹²⁹ Tin-enolates have been used.¹¹³⁰ This reaction has been performed with good diastereoselectivity,¹¹³¹ and silyl enol ethers have been used

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¹¹¹⁵ See Oare, D.A.; Heathcock, C.H. *J. Org. Chem.* **1990**, 55, 157.

¹¹¹⁶ Holton, R.A.; Williams, A.D.; Kennedy, R.M. *J. Org. Chem.* **1986**, 51, 5480.

¹¹¹⁷ See Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* **1974**, 39, 1612; *Org. Synth.* **VII**, 363.

¹¹¹⁸ Bertrand, S.; Glapski, C.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* **1999**, 40, 3169.

¹¹¹⁹ Sibi, M.P.; Jasperse, C.P.; Ji, J. *J. Am. Chem. Soc.* **1995**, 117, 10779. See Wu, J.H.; Radinov, R.; Porter, N.A. *J. Am. Chem. Soc.* **1995**, 117, 11029 for a related reaction.

¹¹²⁰ Enholm, E.J.; Kinter, K.S. *J. Org. Chem.* **1995**, 60, 4850.

¹¹²¹ Rudolf, W.-D.; Schwarz, R. *Synlett* **1993**, 369.

¹¹²² Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, 132, 10275.

¹¹²³ See Makosza, M. *Tetrahedron Lett.* **1966**, 5489.

¹¹²⁴ See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1576–1582; Mukaiyama, T.; Kobayashi, S. *J. Organomet. Chem.* **1990**, 382, 39.

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¹¹²⁶ Loh, T.-P.; Wei, L.-L. *Tetrahedron* **1998**, 54, 7615.

¹¹²⁷ Tucker, J.A.; Clayton, T.L.; Mordas, D.M. *J. Org. Chem.* **1997**, 62, 4370.

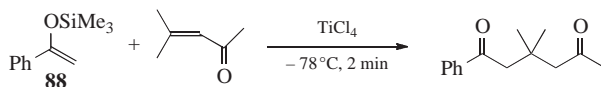
¹¹²⁸ Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron* **1995**, 51, 743.

¹¹²⁹ Ranu, B.C.; Saha, M.; Bhar, S. *Tetrahedron Lett.* **1993**, 34, 1989.

¹¹³⁰ Yasuda, M.; Chiba, K.; Ohigashi, N.; Katoh, Y.; Baba, A. *J. Am. Chem. Soc.* **2003**, 125, 7291.

¹¹³¹ See Heathcock, C.H.; Uehling, D.E. *J. Org. Chem.* **1986**, 51, 279; Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1017, 1817, 1821; **1987**, 743.

in conjunction with chiral additives.¹¹³²

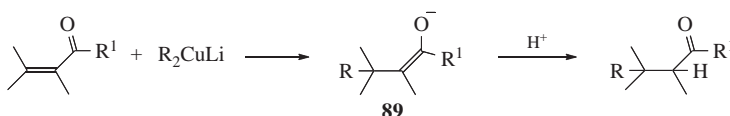


The reaction of $\text{C}=\text{C}-\text{Z}$ compounds with enamines (**10-69**) can also be considered a Michael reaction.

OS **I**, 272; **II**, 200; **III**, 286; **IV**, 630, 652, 662, 776; **V**, 486, 1135; **VI**, 31, 648, 666, 940; **VII**, 50, 363, 368, 414, 443; **VIII**, 87, 210, 219, 444, 467; **IX**, 526. See also, OS **VIII**, 148.

15-25 1,4-Addition of Organocuprates and Other Organometallic Compounds to Activated Double Bonds

Hydro-alkyl-addition



Lithium dialkylcopper reagents (R_2CuLi reagents,¹¹³³ also known as *Gilman reagents*, see Reaction **10-57**) add to α,β -unsaturated aldehydes¹¹³⁴ and ketones ($\text{R}' = \text{H}, \text{R}, \text{Ar}$) and other systems of the form $\text{C}\equiv\text{C}-\text{C}=\text{O}$ ¹¹³⁵ to give conjugate addition products¹¹³⁶ in a reaction closely related to the *Michael reaction*. α,β -Unsaturated esters are less reactive,¹¹³⁷ and the corresponding acids do not react at all. The R group can be primary alkyl, vinylic,¹¹³⁸ or aryl. If Me_3SiCl is present, the reaction takes place much faster and in higher yield; in the example given, the product is the silyl enol ether of **89** (see Reaction **12-17**).¹¹³⁹ The use of Me_3SiCl also permits good yields with allylic R groups.¹¹⁴⁰ Conjugated alkynyl-ketones also react via 1,4-addition to give substituted alkenyl-ketones.¹¹⁴¹ Solvent effects are important for the reactivity of organocuprates,¹¹⁴² which

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¹¹³⁵ For reactions with conjugated enynes, see Miginiac, L. *J. Organomet. Chem.* **1982**, 238, 235.

¹¹³⁶ See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1599–1613, 1814–1824; Posner, G.H. *Org. React.* **1972**, 19, 1; House, H.O. *Acc. Chem. Res.* **1976**, 9, 59; Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, 126, 6287; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, **1980**, pp. 10–67.

¹¹³⁷ See Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, 26, 657.

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¹¹⁴² See also Yangand, J.; Dudley, G.B. *Tetrahedron Lett.* **2007**, 48, 7887.

influence aggregation and aggregation state of the dialkyl cuprate.¹¹⁴³ Organocuprate reactions have been shown to undergo oscillations in complexation.¹¹⁴⁴

An excess of the cuprate reagent relative to the conjugated substrate is often required. In general, only one of the R groups of R_2CuLi adds to the substrate; the other is wasted with respect to the conjugated substrate. This can be a limitation where the precursor (RLi or RCu, see Reaction 12-36) is expensive or available in limited amounts, particularly if an excess of the reagent is required. The difficulty of group transfer can be overcome by using one of the mixed reagents $[R(R'C\equiv C)CuLi]$,¹¹⁴⁵ $R(O-t-Bu)CuLi$,¹¹⁴⁶ $R(PhS)CuLi$ ¹¹⁴⁷ each of which transfers only the R group. Mixed reagents are easily prepared by the reaction of RLi with $R'C\equiv CCu$ ($R' = n-Pr$ or $t-Bu$), $t-BuOCu$, or $PhSCu$, respectively. A further advantage of the mixed reagents is that good yields of addition product are achieved when R is tertiary, so that use of one of them permits the introduction of a tertiary alkyl group. The mixed reagents $R(CN)CuLi$ ¹¹⁴⁸ (prepared from RLi and CuCN) and $R_2Cu(CN)Li_2$ ¹¹⁴⁹ also selectively transfer the R group.¹¹⁵⁰ With mixed cuprates, one of the ligands may be less prone to transfer than the other, as $R(R'Se)Cu(CN)Li_2$, leading to selective transfer of the R group.¹¹⁵¹ This less transferable ligand is sometimes referred to as a “dummy ligand”. The selectivity of ligand transfer depends on two factors, thermodynamics of groups (e.g., alkyl or thioalkyl) and kinetic reactivity of groups (e.g., silylalkyl or vinyl).¹¹⁵² The selectivity arises in the Cu(III) intermediate formed by complexation of the cuprate and the unsaturated carbonyl compound.^{1150,1153} A Cu(III) complex has been detected using rapid injection NMR.¹¹⁵⁴

Various functional groups (e.g., OH and unconjugated C=O groups) may be present in the substrate when organocuprates are employed.¹¹⁵⁵ There is generally little or no competition from 1,2-addition (to the C=O). However, when R is allylic, 1,4-addition is observed with some substrates and 1,2-addition with others.¹¹⁵⁶ The R_2CuLi group also adds to α,β -unsaturated sulfones,¹¹⁵⁷ but not to simple α,β -unsaturated nitriles.¹¹⁵⁸ Organocopper reagents (RCu) as well as certain R_2CuLi add to α,β -unsaturated and acetylenic sulfoxides.¹¹⁵⁹ The reaction has been carried out¹¹⁶⁰ with α,β -acetylenic ketones,¹¹⁶¹ esters, and nitriles. Conjugate addition to α,β -unsaturated and acetylenic

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¹¹⁴⁴ Murphy, M.D.; Ogle, C.A.; Bertz, S.H. *Chem. Commun.* **2005**, 854.

¹¹⁴⁵ Corey, E.J.; Floyd, D.; Lipshutz, B.H. *J. Org. Chem.* **1978**, *43*, 3419.

¹¹⁴⁶ Posner, G.H.; Whitten, C.E. *Tetrahedron Lett.* **1973**, 1815.

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¹¹⁴⁸ See Ledlie, D.B.; Miller, G. *J. Org. Chem.* **1979**, *44*, 1006.

¹¹⁴⁹ See Lipshutz, B.H. *Tetrahedron Lett.* **1983**, *24*, 127.

¹¹⁵⁰ See Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *J. Org. Chem.* **1984**, *49*, 3938.

¹¹⁵¹ Zinn, F.K.; Ramos, E.C.; Comasseto, J.V. *Tetrahedron Lett.* **2001**, *42*, 2415.

¹¹⁵² Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 4697.

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¹¹⁵⁴ Bertz, S.H.; Cope, S.; Murphy, M.; Ogle, C.A.; Taylor, B.J. *J. Am. Chem. Soc.* **2007**, *129*, 7208. See Hu, H.; Snyder, J.P. *J. Am. Chem. Soc.* **2007**, *129*, 7210.

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¹¹⁵⁶ House, H.O.; Fischer Jr., W.F. *J. Org. Chem.* **1969**, *34*, 3615. See also, Daviaud, G.; Miginiac, P. *Tetrahedron Lett.* **1973**, 3345.

¹¹⁵⁷ Domínguez, E.; Carretero, J.C. *Tetrahedron Lett.* **1993**, *34*, 5803.

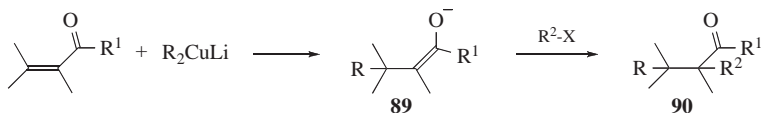
¹¹⁵⁸ House, H.O.; Umen, M.J. *J. Org. Chem.* **1973**, *38*, 3893.

¹¹⁵⁹ Truce, W.E.; Lusch, M.J. *J. Org. Chem.* **1974**, *39*, 3174; **1978**, *43*, 2252.

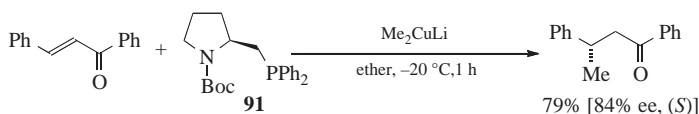
¹¹⁶⁰ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 456–457.

¹¹⁶¹ Lee, P.H.; Park, J.; Lee, K.; Kim, H.-C. *Tetrahedron Lett.* **1999**, *40*, 7109.

acids and esters, as well as ketones, can be achieved by the use of the coordinated reagents $\text{RCu} \cdot \text{BF}_3$ (R = primary).¹¹⁶² Amine units have been transferred using α -lithio amides, CuCN , and various additives, which gave conjugate addition of an amidomethyl unit [$-\text{CH}_2\text{N}(\text{Me})\text{Boc}$].¹¹⁶³ Other amino-cuprates are known to give conjugate addition reactions.¹¹⁶⁴



Conjugate addition of the cuprate to the α,β -unsaturated ketone leads to an enolate ion (**89**), as noted above. It is possible for this enolate anion to react with an electrophilic species (*tandem vicinal difunctionalization*), in some cases at the O and in other cases at the C.¹¹⁶⁵ For example, if an alkyl halide R^2X is present (R^2 = primary alkyl or allylic), the enolate (**89**) can be alkylated directly to give **90**.¹¹⁶⁶ Thus, by this method, both the α and β positions of a ketone are alkylated in one synthetic operation (see also, Reaction **15-22**).



As with the *Michael reaction* (**15-24**) the 1,4-addition of organometallic compounds has been performed diastereoselectively¹¹⁶⁷ and enantioselectively.¹¹⁶⁸ The influence of solvent and additives on yield and selectivity has been examined.¹¹⁶⁹ Addition of chiral ligands to the organocuprate conjugate addition reaction leads to alkylation with good-to-excellent enantioselectivity.¹¹⁷⁰ The conjugate addition of dimethyl cuprate in the presence of a chiral ligand (e.g., **91**) is an example.¹¹⁷¹ Chiral bis(oxazoline) copper catalysts have been used for the conjugate addition of indoles to α,β -unsaturated esters.¹¹⁷² In the presence of a chiral additive and a Cu catalyst, conjugate addition to trisubstituted cyclohexenones leads to the formation of stereogenic quaternary centers.¹¹⁷³ Enantioselectivity was improved by the addition of styrene in the conjugate addition reactions of

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¹¹⁶⁴ Yamamoto, Y.; Asao, N.; Ueyehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5427.

¹¹⁶⁵ Chapdelaine, M.J.; Hulce, M. *Org. React.* **1990**, *38*, 225; Taylor, R.J.K. *Synthesis* **1985**, 364; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1609–1612, 1826.

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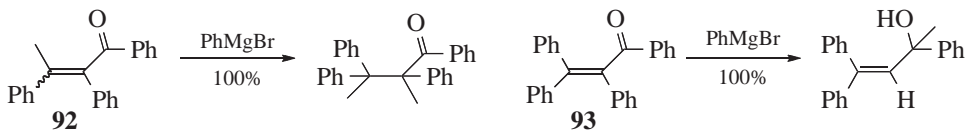
¹¹⁷⁰ Wu, J.; Mampreian, D.M.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2005**, *127*, 4584; Knöpfel, T.F.; Zarotti, P.; Ichikawa, T.; Carreira, E.M. *J. Am. Chem. Soc.* **2005**, *127*, 9682; Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774; De Roma, A.; Ruffo, F.; Woodward, S. *Chem. Commun.* **2008**, 5384.

¹¹⁷¹ Kanai, M.; Koga, K.; Tomioka, K. *Tetrahedron Lett.* **1992**, *33*, 7193.

¹¹⁷² Jensen, K.B.; Thorhauge, J.; Hazell, R.G.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* **2001**, *40*, 160.

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α -halo enones.¹¹⁷⁴ Enantioselectivity is effectively controlled by the choice of ligand and its interaction with the copper compound, where different ligands on the metal may lead to differences in selectivity.¹¹⁷⁵ Chiral templates have also been used with *Grignard reagents*, directly¹¹⁷⁶ and in the presence of AlMe_2Cl .¹¹⁷⁷



Other organometallic compounds add to conjugated systems. *Grignard reagents* add to conjugated substrates (e.g., α,β -unsaturated ketones, cyano-ketones,¹¹⁷⁸ esters, and nitriles),¹¹⁷⁹ but 1,2-addition may seriously compete.¹¹⁸⁰ The extent of 1,4-addition of *Grignard reagents* can be increased by the use of a Cu catalyst [e.g., CuCl and $\text{Cu}(\text{OAc})_2$],¹¹⁸¹ forming a magnesium cuprate *in situ*. Formation of the conjugate addition product is often controlled by steric factors. Thus **92** with phenylmagnesium bromide gives 100% 1,4-addition, while **93** gives 100% 1,2-addition. In general, substitution at the carbonyl group increases 1,4-addition, while substitution at the double bond increases 1,2-addition. In most cases, both products are obtained, but α,β -unsaturated *aldehydes* nearly always give exclusive 1,2-addition when treated with *Grignard reagents*. *Grignard reagents* mixed with CeCl_3 generates a reactive species that gives primarily 1,4-addition.¹¹⁸² It is likely that alkylcopper reagents, formed from RMgX and Cu^+ (cupric acetate is reduced to cuprous ion by excess RMgX), are the actual reactive species in these cases.¹¹³⁴ Alkylidene malonic ester derivatives [$\text{C}=\text{C}(\text{CO}_2\text{R})$] increase the facility of 1,4-addition with the two electron-withdrawing groups.¹¹⁸³

A dialkyl copper–magnesium iodide complex ($\text{R}_2\text{Cu} \cdot \text{MgI}$) has been used for conjugate addition to chiral α,β -unsaturated amides.¹¹⁸⁴ Catalytic enantioselective conjugate addition has been reported with *Grignard reagents*.¹¹⁸⁵

Organolithium reagents¹¹⁸⁶ generally react with conjugated aldehydes, ketones, and esters by 1,2-addition,¹¹⁸⁷ but 1,4-addition was achieved with esters of the form

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¹¹⁷⁵ See Okamoto, M.; Yamamoto, Y.; Sakaguchi, S. *Chem. Commun.* **2009**, 7363.

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¹¹⁸⁶ See Hunt, D.A. *Org. Prep. Proced. Int.* **1989**, 21, 705–749.

¹¹⁸⁷ Cohen, T.; Abraham, W.D.; Myers, M. *J. Am. Chem. Soc.* **1987**, 109, 7923.

$\text{C}=\text{C}-\text{CO}_2\text{Ar}$, where Ar was a bulky group (e.g., 2,6-di-*tert*-butyl-4-methoxyphenyl).¹¹⁸⁸ Alkylolithium reagents can be made to give 1,4-addition with α,β -unsaturated ketones¹¹⁸⁹ and aldehydes,¹¹⁹⁰ if the reactions are conducted in the presence of HMPA.¹¹⁹¹ Among organolithium reagents that have been found to add 1,4 in this manner are 2-lithio-1,3-dithianes (see Reaction 10-71),¹¹⁹² vinylolithium reagents,¹¹⁹³ and α -lithio allylic amides.¹¹⁹⁴ Lithium-halogen exchange (12-22) generates an organolithium species that adds intramolecularly to conjugated esters to give cyclic and bicyclic products.¹¹⁹⁵ A reagent based on $\text{RMgX}-3\text{ MeLi}$ gave conjugate addition with α,β -unsaturated amides and carboxylic acid derivatives.¹¹⁹⁶ 1,4-Addition of alkylolithium reagents to α,β -unsaturated aldehydes can also be achieved by converting the aldehyde to a benzo-thiazole derivative (masking the aldehyde function),¹¹⁹⁷ from which the aldehyde group can be regenerated. α,β -Unsaturated nitro compounds undergo conjugate addition with aryllithium reagents, and subsequent treatment with acetic acid gives the α -aryl ketone.¹¹⁹⁸

If the organolithium reagent is complexed, 1,4-addition is more successful. The reaction of an aryllithium reagent with B(OMe)_3 , for example, led to a Rh catalyzed conjugate addition with excellent enantioselectivity when a chiral ligand was employed.¹¹⁹⁹ Allylic Te reagents that are treated with lithium diisopropyl amide and then conjugated esters give the 1,4-addition product, which cyclizes to form the corresponding cyclopropane derivative.¹²⁰⁰

Organozinc compounds add to conjugated systems, especially dialkyl zinc compounds (R_2Zn). Many dialkylzinc compounds can be used, including vinylzinc compounds.¹²⁰¹ The use of chiral ligands is effective for conjugate addition of dialkylzinc compounds to α,β -unsaturated ketones, esters, and so on,¹²⁰² including conjugated lactones.¹²⁰³ The addition of a chiral complex to dialkylzinc compounds leads to enantioselective conjugate addition in conjunction with Cu(OTf)_2 ¹²⁰⁴ CuCN ,¹²⁰⁵ or

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other copper compounds.¹²⁰⁶ Chiral ionic liquids have also been employed.¹²⁰⁷ Diethylzinc adds to conjugated nitro compounds in the presence of a catalytic amount of Cu(OTf)₂ to give the conjugate addition product.¹²⁰⁸ 1,6-Addition of dialkylzinc compounds has been reported, in the presence of a Rh catalyst.¹²⁰⁹ Other transition metal compounds can be used in conjunction with dialkylzinc compounds¹²¹⁰ or with arylzinc halides (ArZnCl).¹²¹¹ Reaction of alkyl iodides with Zn/CuI and ultrasound generates an organometallic that adds to conjugated esters.¹²¹² Diarylzinc compounds (prepared with the aid of ultrasound) in the presence of nickel acetylacetonate, undergo 1,4-addition not only to α,β -unsaturated ketones, but also to α,β -unsaturated aldehydes.¹²¹³ Mixed-alkylzinc compounds also add to conjugated systems.¹²¹⁴ Functionalized allylic groups can be added to terminal alkynes with allylic halides, zinc, and ultrasound, to give 1,4-dienes.¹²¹⁵ Internal alkynes undergo 1,4-addition to conjugated esters using a combination of zinc metal and a Co complex as catalysts.¹²¹⁶

Trialkylalanes (R₃Al) add 1,4 to α,β -unsaturated carbonyl compounds in the presence of nickel acetylacetonate¹²¹⁷ or Cu(OTf)₂.¹²¹⁸ In the presence of aluminum chloride, benzene reacts with conjugated amides to add a phenyl group to C-4.¹²¹⁹ Alkyl halides react via conjugate addition using BEt₃ or AlEt₃.¹²²⁰ Other metals are known to catalyze conjugate addition of alkyl or aryl groups, including Co.¹²²¹ An In/Cu mediated conjugate addition reaction is known using unactivated alkyl iodides.¹²²²

Terminal alkynes add to conjugated systems when using a Ru,¹²²³ Pd,¹²²⁴ Ni,¹²²⁵ or a Rh catalyst.¹²²⁶ Intramolecular addition of terminal alkynes, in the presence of

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¹²¹⁴ Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T.A.; Reddy, C.K. *Angew. Chem. Int. Ed.* **1997**, *36*, 1496.

¹²¹⁵ Knochel, P.; Normant, J.F. *J. Organomet. Chem.* **1986**, *309*, 1.

¹²¹⁶ Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 9696.

¹²¹⁷ Bagnell, L.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 817; Ashby, E.C.; Heinssohn, G. *J. Org. Chem.* **1974**, *39*, 3297. See also, Kunz, H.; Pees, K.J. *J. Chem. Soc. Perkin Trans. 1*, **1989**, 1168.

¹²¹⁸ Su, L.; Li, X.; Chan, W.L.; Jia, X.; Chan, A.S.C. *Tetrahedron Asymmetry* **2003**, *24*, 1865.

¹²¹⁹ Koltunov, K.Yu.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* **2004**, *45*, 3547.

¹²²⁰ Liu, J.-Y.; Jang, Y.-J.; Lin, W.-W.; Liu, J.-T.; Yao, C.-F. *J. Org. Chem.* **2003**, *68*, 4030.

¹²²¹ In the presence of Mn, see Amatore, M.; Gosmini, C.; Périchon, J. *J. Org. Chem.* **2006**, *71*, 6130.

¹²²² Shen, Z.-L.; Cheong, H.-L.; Loh, T.-P. *Tetrahedron Lett.* **2009**, *50*, 1051.

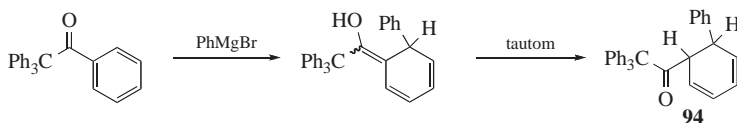
¹²²³ Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576.

¹²²⁴ Chen, L.; Li, C.-J. *Chem. Commun.* **2004**, 2362.

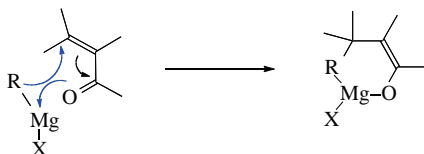
¹²²⁵ Herath, A.; Thompson, B.B.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 8712; Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 8132.

¹²²⁶ Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J.W. *J. Am. Chem. Soc.* **2002**, *124*, 12102; Lerum, R.V.; Chisholm, J.D. *Tetrahedron Lett.* **2004**, *45*, 6591.

phenylboronic acid and a Rh catalyst, leads to cyclic compounds.¹²²⁷ Lithium tetraalkylgallium reagents give 1,4-addition.¹²²⁸ Trimethyl(phenyl)tin and a Rh catalyst gives conjugate addition of a methyl group¹²²⁹ and tetraphenyltin and a Pd catalyst adds a phenyl group.¹²³⁰ Triphenylbismuth (Ph₃Bi) and a Rh catalyst give conjugate addition of the phenyl group upon exposure to air.¹²³¹ Similar reactivity is observed with a Pd catalyst in aqueous media.¹²³² Allyltin compounds add an allyl group in the presence of a Sc catalyst.¹²³³ Benzylic bromides add to conjugated nitriles using a 2:1 mixture of CrCl₃ and Mn metal.¹²³⁴ Aryl halides add in the presence of NiBr₂.¹²³⁵ Vinyl Zr complexes undergo conjugate addition when using a Rh catalyst.¹²³⁶



In certain cases, *Grignard reagents* add 1,4 to *aromatic* systems to give **94** after tautomerization (Sec. 2.N.i) of the initial formed enol.¹²³⁷ Such cyclohexadienes are easily oxidizable to benzenes (often by atmospheric oxygen), so this reaction becomes a method of alkylating and arylating suitably substituted (usually hindered) aryl ketones. A similar reaction has been reported for aromatic nitro compounds where 1,3,5-trinitrobenzene reacts with excess methylmagnesium halide to give 2,4,6-trinitro-1,3,5-trimethylcyclohexane.¹²³⁸



The mechanisms of most of these reactions are not well known. The 1,4-uncatalyzed *Grignard reaction* has been postulated to proceed by the cyclic mechanism shown, but there is evidence against it.¹²³⁹ The R₂CuLi¹²⁴⁰ and copper-catalyzed *Grignard additions* may

¹²²⁷ Chen, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, 128, 15598.

¹²²⁸ Han, Y.; Huang, Y.-Z.; Fang, L.; Tao, W.-T. *Synth. Commun.* **1999**, 29, 867.

¹²²⁹ Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, 58, 91.

¹²³⁰ Ohe, T.; Uemura, S. *Tetrahedron Lett.* **2002**, 43, 1269.

¹²³¹ Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* **2001**, 42, 781.

¹²³² Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **2004**, 1822.

¹²³³ Williams, D.R.; Mullins, R.J.; Miller, N.A. *Chem. Commun.* **2003**, 2220.

¹²³⁴ Augé, J.; Gil, R.; Kalsey, S. *Tetrahedron Lett.* **1999**, 40, 67.

¹²³⁵ Condon, S.; Dupré, D.; Falgayrac, G.; Nédélec, J.-Y. *Eur. J. Org. Chem.* **2002**, 105.

¹²³⁶ Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* **2004**, 60, 1293.

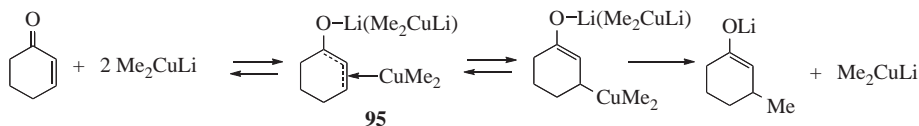
¹²³⁷ This example is from Schmidlin, J.; Wohl, J. *Ber.* **1910**, 43, 1145; Mosher, W.A.; Huber, M.B. *J. Am. Chem. Soc.* **1953**, 75, 4604. See Fuson, R.C. *Adv. Organomet. Chem.* **1964**, 1, 221.

¹²³⁸ See Bartoli, G. *Acc. Chem. Res.* **1984**, 17, 109; Bartoli, G.; Dalpozzo, R.; Grossi, L. *J. Chem. Soc. Perkin Trans. 2*, **1989**, 573. For a study of the mechanism, see Bartoli, G.; Bosco, M.; Cantagalli, G.; Dalpozzo, R.; Ciminale, F. *J. Chem. Soc. Perkin Trans. 2*, **1985**, 773.

¹²³⁹ House, H.O.; Thompson, H.W. *J. Org. Chem.* **1963**, 28, 360; Klein, J. *Tetrahedron* **1964**, 20, 465. See, however, Marets, J.; Rivière, H. *Bull. Soc. Chim. Fr.* **1970**, 4320.

¹²⁴⁰ Kingsbury, C.L.; Smith, R.A.J. *J. Org. Chem.* **1997**, 62, 4629. See, Bertz, S.H.; Miao, G.; Rossiter, B.E.; Snyder, J.P. *J. Am. Chem. Soc.* **1995**, 117, 11023; Snyder, J.P. *J. Am. Chem. Soc.* **1995**, 117, 11025.

involve a number of mechanisms, since the actual attacking species and substrates are so diverse.¹²⁴¹ A free radical mechanism of some type (perhaps SET) has been suggested¹²⁴² although the fact that retention of configuration at R has been demonstrated in several cases completely rules out a free R[•] radical.¹²⁴³ For simple α,β -unsaturated ketones (e.g., 2-cyclohexenone and Me₂CuLi), there is evidence¹²⁴⁴ for this mechanism:

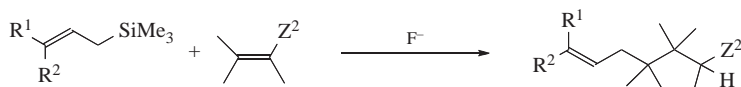


95 is a d, π^* complex, with bonding between copper, as a base supplying a pair of d electrons, and the enone as a Lewis acid using the π^* orbital of the allylic system.¹²⁴² The ¹³C NMR spectrum of an intermediate similar to **95** has been reported.¹²⁴⁵

For the addition of organocopper reagents to alkynes and conjugated dienes, see Reaction **15-22**.

OS IV, 93; V, 762; VI, 442, 666, 762, 786; VIII, 112, 257, 277, 479; IX, 328, 350, 640.

15-26 The Sakurai Reaction



Allylic silanes (R₂C=CHCH₂SiMe₃) can be added to conjugated systems rather than silyl enol ethers in what is known as the *Sakurai reaction*.¹²⁴⁶ For example, an allyl group can be added to α,β -unsaturated carboxylic esters, amides and nitriles, with CH₂=CHCH₂SiMe₃ and F[−] ion (see Reaction **15-47**).¹²⁴⁷ This reagent gave better results than lithium diallylcuprate (Reaction **15-25**). Catalytic *Sakurai reactions* are known.¹²⁴⁸ The Pd catalyzed reaction of conjugated ketones with PhSi(OEt)₃ and SbCl₃ and Bu₄NF in acetic acid gave the 1,4-addition product.¹²⁴⁹ A similar reaction was reported using PhSi(OMe)₃ with a Rh catalyst.¹²⁵⁰ Silver fluoride was used to catalyze the reaction with allyl (trimethoxy)silane.¹²⁵¹ In a related reaction, Ph₂SiCl₂, NaF, and a Rh catalyst gives conjugate addition of a phenyl group to α,β -unsaturated ketones.¹²⁵² An interesting Rh catalyzed, conjugate addition of a phenyl group was reported using a siloxane polymer

¹²⁴¹ See Yamamoto, Y.; Yamada, J.; Ueyhara, T. *J. Am. Chem. Soc.* **1987**, 109, 5820; Ullenius, C.; Christenson, B. *Pure Appl. Chem.* **1988**, 60, 57; Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, 45, 523; Krause, N. *Tetrahedron Lett.* **1989**, 30, 5219.

¹²⁴² See Wigal, C.T.; Grunwell, J.R.; Hershberger, J. *J. Org. Chem.* **1991**, 56, 3759.

¹²⁴³ Whitesides, G.M.; Kendall, P.E. *J. Org. Chem.* **1972**, 37, 3718.

¹²⁴⁴ Corey, E.J.; Hannon, F.J.; Boaz, N.W. *Tetrahedron* **1989**, 45, 545.

¹²⁴⁵ Bertz, S.H.; Smith, R.A.J. *J. Am. Chem. Soc.* **1989**, 111, 8276.

¹²⁴⁶ Sakurai, H.; Hosomi, A.; Hayashi, J. *Org. Synth.* **VII**, 443; Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* **1998**, 39, 3215; Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, 37, 57, see p. 127, 335–370; Schinzer, D. *Synthesis* **1988**, 263.

¹²⁴⁷ Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem.* **1986**, 51, 1745.

¹²⁴⁸ See Lee, P.H.; Lee, K.; Sung, S.-y.; Chang, S. *J. Org. Chem.* **2001**, 66, 8646.

¹²⁴⁹ Denmark, S.E.; Amishiro, N. *J. Org. Chem.* **2003**, 68, 6997.

¹²⁵⁰ Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, 5, 97.

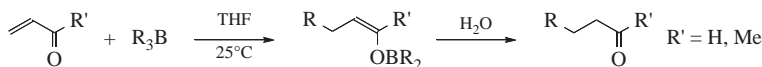
¹²⁵¹ Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, 127, 14556.

¹²⁵² Huang, T.-S.; Li, C.-J. *Chem. Commun.* **2001**, 2348.

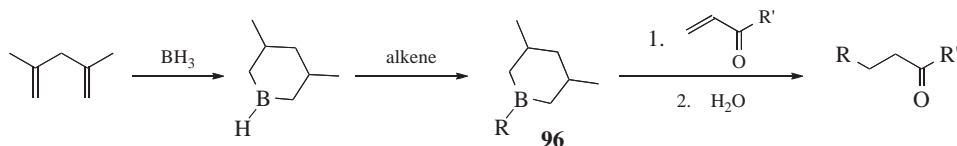
bearing Si—Ph units.¹²⁵³ The *Sakurai reaction* has been used in multi-component reactions.¹²⁵⁴

15-27 Conjugate Addition of Boranes to Activated Double Bonds

Hydro-alkyl-addition (overall transformation)



Just as trialkylboranes add to simple alkenes (Reaction 15-16), they rapidly add to the double bonds of acrolein, methyl vinyl ketone, and certain related derivatives in THF to give enol borinates (also see Reaction 10-68), which can be hydrolyzed to aldehydes or ketones.¹²⁵⁵ If water is present in the reaction medium from the beginning, the reaction can be run in one laboratory step. Since the boranes can be prepared from alkenes (Reaction 15-16), this reaction provides a means of lengthening a carbon chain by three or four carbons, respectively. Compounds containing a terminal alkyl group [e.g., such as crotonaldehyde ($\text{CH}_3\text{CH}=\text{CHCHO}$) and 3-penten-2-one], fail to react under these conditions, as does acrylonitrile, but these compounds can be induced to react by the slow and controlled addition of O_2 or by initiation with peroxides or UV light.¹²⁵⁶ A disadvantage is that only one of the



three R groups of R_3B adds to the substrate, so that the other two are wasted. This difficulty is overcome by the use of a β -alkyl borinate (e.g., **96**),¹²⁵⁷ which can be prepared as shown. Borinate (**96**, $\text{R} = \text{tert-butyl}$) can be made by treatment of **96** ($\text{R} = \text{OMe}$) with *t*-BuLi. The use of this reagent permits *tert*-butyl groups to be added. β -1-Alkenyl-9-BBN compounds $\beta\text{-RCH}=\text{CR}'\text{-9-BBN}$ (prepared by treatment of alkynes with 9-BBN or of $\text{RCH}=\text{CR}'\text{Li}$ with β -methoxy-9-BBN¹²⁵⁸) add to methyl vinyl ketones to give, after hydrolysis, γ,δ -unsaturated ketones,¹²⁵⁹ although $\beta\text{-R-9-BBN}$, where $\text{R} = \text{a saturated group}$, are not useful here, because the R group of these reagents does not preferentially add to the substrate.¹²⁵³ Transition metals catalyze the addition of trialkylboranes to conjugated systems (e.g., the addition of allylboranes in the presence of a Ni catalyst).¹²⁶⁰ The Ni catalyzed addition was enhanced by the addition of methanol.¹²⁶¹

¹²⁵³ Koike, T.; Du, X.; Mori, A.; Osakada, K. *Synlett* **2002**, 301.

¹²⁵⁴ Pospíšil, J.; Kumamoto, T.; Markó, I.E. *Angew. Chem. Int. Ed.* **2006**, 45, 3357.

¹²⁵⁵ Köster, R.; Zimmermann, H.; Fenzl, W. *Liebigs Ann. Chem.* **1976**, 1116. See Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*, Academic Press, NY, **1988**, pp. 301–305, 318–323; Brown, H.C. *Boranes in Organic Chemistry* Cornell University Press, Ithaca, NY, **1972**, pp. 413–433.

¹²⁵⁶ Brown, H.C.; Kabalka, G.W. *J. Am. Chem. Soc.* **1970**, 92, 712, 714. See also, Miyaura, N.; Kashiwagi, M.; Itoh, M.; Suzuki, A. *Chem. Lett.* **1974**, 395.

¹²⁵⁷ Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* **1971**, 93, 3777.

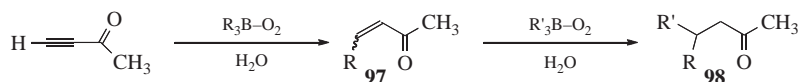
¹²⁵⁸ Brown, H.C.; Bhat, N.G.; Rajagopalan, S. *Organometallics* **1986**, 5, 816.

¹²⁵⁹ Satoh, Y.; Serizawa, H.; Hara, S.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, 107, 5225. See also, Hara, S.; Hyuga, S.; Aoyama, M.; Sato, M.; Suzuki, A. *Tetrahedron Lett.* **1990**, 31, 247.

¹²⁶⁰ Sieber, J.D.; Liu, S.; Morken, J.P. *J. Am. Chem. Soc.* **2007**, 129, 2214.

¹²⁶¹ Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, 9, 1541.

The corresponding β -1-alkynyl-9-BBN compounds also give the reaction.¹²⁶² Since the product **97** is an α,β -unsaturated ketone, it can be made to react with another BR_3 , the same or different, to produce a wide variety of ketones (**98**).



Vinyl boranes add to conjugated ketones in the presence of a Rh catalyst (with high asymmetric induction in the presence of BINAP).¹²⁶³ Alkynyl-boranes also add to conjugated ketones, in the presence of BF_3 .¹²⁶⁴

Other boron reagents add to conjugated carbonyl compounds.¹²⁶⁵ Tetraphenylborates add to conjugated alkynes in the presence of a Pd catalyst in a reaction known as hydrophenylation.¹²⁶⁶ Alkynyl boronate esters (Reaction **12-28**) give conjugate addition¹²⁶⁷ in the presence of boron trifluoride etherate,¹²⁶⁸ as do arylboronic acids (Reaction **12-28**) with a Rh,¹²⁶⁹ Pd,¹²⁷⁰ or a Bi catalyst.¹²⁷¹ Diethylzinc has also been used.¹²⁷² Aryl boronic acids add to the double bond of vinyl sulfones in the presence of a Rh catalyst.¹²⁷³ Vinylboronic acids add directly to conjugated ketones.¹²⁷⁴ An Ir catalyzed 1,6-addition of arylboronic acids is known.¹²⁷⁵ Conjugated alkynes undergo conjugate addition with arylboronic acids in the presence of a Cu catalyst.¹²⁷⁶ Organocatalysts have also been used for the conjugate addition of arylboronic acids to conjugated systems.¹²⁷⁷ Potassium vinyltrifluoroborates (see Reactions **10-59**, **13-10**, and **13-13**) give 1,4-addition with a Rh catalyst,¹²⁷⁸ as do

¹²⁶² Sinclair, J.A.; Molander, G.A.; Brown, H.C. *J. Am. Chem. Soc.* **1977**, *99*, 954. See also, Molander, G.A.; Brown, H.C. *J. Org. Chem.* **1977**, *42*, 3106.

¹²⁶³ Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479.

¹²⁶⁴ Fujishima, H.; Takada, E.; Hara, S.; Suzuki, A. *Chem. Lett.* **1992**, 695.

¹²⁶⁵ Kabalka, G.W.; Das, B.C.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2323.

¹²⁶⁶ Zeng, H.; Hua, R. *J. Org. Chem.* **2008**, *73*, 558.

¹²⁶⁷ Wu, T.R.; Chong, J.M. *J. Am. Chem. Soc.* **2005**, *127*, 3244; Pellegrinet, S.C.; Goodman, J.M. *J. Am. Chem. Soc.* **2006**, *128*, 3116.

¹²⁶⁸ Chong, J.M.; Shen, L.; Taylor, N.J. *J. Am. Chem. Soc.* **2000**, *122*, 1822.

¹²⁶⁹ Paquin, J.-F.; Defieber, C.; Stephenson, C.R.J.; Carreira, E.M. *J. Am. Chem. Soc.* **2005**, *127*, 10850; Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628; Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130; Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172; Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503; Stemmler, R.T.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 9925; Paquin, J.-F.; Stephenson, C.R.J.; Defieber, C.; Carreira, E.M. *Org. Lett.* **2005**, *7*, 3821; Martina, S.L.X.; Minnaard, A.J.; Hessen, B.; Feringa, B.L. *Tetrahedron Lett.* **2005**, *46*, 7159.

¹²⁷⁰ Lu, X.; Lin, S. *J. Org. Chem.* **2005**, *70*, 9651.

¹²⁷¹ Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944.

¹²⁷² Dong, L.; Xu, Y.-J.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Synthesis* **2004**, 1057.

¹²⁷³ With a chiral ligand, see Mauleón, P.; Carretero, J.C. *Org. Lett.* **2004**, *6*, 3195.

¹²⁷⁴ Wu, T.R.; Chong, J.M. *J. Am. Chem. Soc.* **2007**, *129*, 4908.

¹²⁷⁵ Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 5164.

¹²⁷⁶ Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008**, 2010.

¹²⁷⁷ Sugiura, M.; Tokudomi, M.; Nakajima, M. *Chem. Commun.* **2010**, 7799.

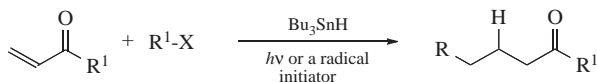
¹²⁷⁸ Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J.A.F.; de Vries, A.H.M.; de Vries, J.G.; Minnaard, A.J.; Feringa, B.L. *J. Org. Chem.* **2004**, *69*, 8045.

aryltrifluoroborates.¹²⁷⁹ The Rh catalyzed addition of vinyl tetrafluoroborates has been reported.¹²⁸⁰

In the presence of a Rh catalyst, LiBPh(OMe)₃ gave conjugate addition of the phenyl group to α,β -unsaturated esters.¹²⁸¹ The fact that these reactions are catalyzed by free radical initiators and inhibited by galvinoxyl¹²⁸² (a free radical inhibitor) indicates that free-radical mechanisms are involved.

15-28 Radical Addition to Activated Double Bonds

Hydro-alkyl-addition



In a reaction similar to **15-25**, alkyl groups can be added to alkenes activated by such groups as COR', CO₂R', CN, and even Ph.¹²⁸³ This is a radical addition reaction.¹²⁸⁴ In the method illustrated above, the R group comes from an alkyl halide (R = primary, secondary, or tertiary alkyl; X = Br or I) and the hydrogen from the tin hydride (H atom transfer agents). The reaction of tert-butyl bromide, Bu₃SnH and AIBN (Sec. 14.A.i), for example, adds a tert-butyl group to a conjugated ester via 1,4-addition.¹²⁸⁵ An alkene is converted to an alkylborane with catecholborane (Reaction **12-28**) and when treated with a conjugated ketone and O₂, radical conjugate addition leads to the β -substituted ketone.¹²⁸⁶ The Bu₃SnH can also be generated in situ, from R₃SnX and NaBH₄. Like Reaction **15-27**, these additions have free radical mechanisms. The reaction has been used for free radical cyclizations of the type discussed in Reaction **15-30**.¹²⁸⁷ Such cyclizations normally give predominant formation of five-membered rings, but large rings (11–20 members) have also been synthesized by this reaction.¹²⁸⁸

¹²⁷⁹ Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159; Navarre, L.; Pucheault, M.; Darses, S.; Genet, J.-P. *Tetrahedron Lett.* **2005**, *46*, 4247.

¹²⁸⁰ Lalic, G.; Corey, E.J. *Tetrahedron Lett.* **2008**, *49*, 4894; Gendrineau, T.; Genet, J.-P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486.

¹²⁸¹ Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron Asymmetry* **1999**, *10*, 4047.

¹²⁸² Kabalka, G.W.; Brown, H.C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *J. Am. Chem. Soc.* **1970**, *92*, 710. See also, Arase, A.; Masuda, Y.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2275.

¹²⁸³ Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, **1986**, pp. 36–68; Giese, B. *Angew. Chem. Int. Ed.* **1985**, *24*, 553; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, **1985**, pp. 263–273. See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1809–1813.

¹²⁸⁴ Srikanth, G.S.C.; Castle, S.L. *Tetrahedron* **2005**, *61*, 10377.

¹²⁸⁵ Hayen, A.; Koch, R.; Metzger, J.O. *Angew. Chem. Int. Ed.* **2000**, *39*, 2758.

¹²⁸⁶ Ollivier, C.; Renaud, P. *Chem. Eur. J.* **1999**, *5*, 1468.

¹²⁸⁷ See Jasperse, C.P.; Curran, D.P.; Fevig, T.L. *Chem. Rev.* **1991**, *91*, 1237; Curran, D.P. *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, *1*, 121; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, **1986**, pp. 151–169. See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 413–418.

¹²⁸⁸ See Porter, N.A.; Chang, V.H. *J. Am. Chem. Soc.* **1987**, *109*, 4976.

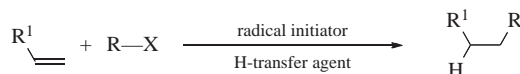
A BEt_3 (see Sec. 14.A.i) initiated reaction of conjugated amides with an alkyl iodide, in the presence of Bu_3SnH and O_2 , leads to conjugate addition of the alkyl group.¹²⁸⁹ Enantioselective radical addition has been reported.¹²⁹⁰

Conjugate addition is possible using photolysis. The photoinduced 1,4-addition of indoles to enones proceeds when irradiated at 350 nm.¹²⁹¹

OS VII, 105.

15-29 Radical Addition to Unactivated Double Bonds¹²⁹²

Alkyl-hydro-addition



Radical addition to alkenes is usually difficult, except when addition occurs to conjugated carbonyl compounds (Reaction 15-24). An important exception involves radicals bearing a heteroatom α to the carbon bearing the radical center. Such radicals are much more stable and can add to alkenes, usually with *anti-Markovnikov* orientation, as in the radical induced addition of HBr to alkenes (Reaction 15-2).¹²⁹³

Examples of this type of reaction include the use of alcohol-, ester-,¹²⁹⁴ amino-, and aldehyde-stabilized radicals.⁴⁸³ The alkyl group of alkyl iodides adds to alkenes with BEt_3/O_2 as the initiator and in the presence of a tetraalkylammonium hypophosphite.¹²⁹⁵ The radical generated from $(\text{EtO})_2\text{POCH}_2\text{Br}$ adds to alkenes to generate a new phosphonate ester.¹²⁹⁶ α -Bromo esters add to alkenes in the presence of BEt_3/air to give a γ -bromo ester.¹²⁹⁷ α -Bromo amides add the Br and the acyl carbon to an alkene using $\text{Yb}(\text{OTf})_3$ with BEt_3/O_2 as the radical initiator.¹²⁹⁸ α -Iodo amides add to alkenes using a water-soluble azobis initiator (see Sec. 14.A.i) to give the iodo ester, which cyclizes under the reaction conditions to give a lactone.¹²⁹⁹ β -Keto dithiocarbonates $[\text{RC}(=\text{O})-\text{C}-\text{SC}(=\text{S})\text{OEt}]$ generate the radical in the presence of a peroxide and add to alkenes.¹³⁰⁰ 2-Fluoropyridyl derivatives of allylic alcohols react with xanthates in the presence of lauroyl peroxide to give alkenes.¹³⁰¹ Malonate derivatives add to alkenes in the presence of a mixture of Mn/Co catalyst, in oxygenated acetic acid.¹³⁰²

¹²⁸⁹ Sibi, M.P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, *127*, 2390; Sibi, M.P.; Patil, K. *Org. Lett.* **2005**, *7*, 1453; He, L.; Srikanth, G.S.C.; Castle, S.L. *J. Org. Chem.* **2005**, *70*, 8140. Also see Sibi, M.P.; Zimmerman, J. *J. Am. Chem. Soc.* **2006**, *128*, 13346.

¹²⁹⁰ Lee, S.; Lim, C.J.; Kim, S.; Subramaniam, R.; Zimmerman, J.; Sibi, M.P. *Org. Lett.* **2006**, *8*, 4311.

¹²⁹¹ Moran, J.; Suen, T.; Beauchemin, A.M. *J. Org. Chem.* **2006**, *71*, 676.

¹²⁹² See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 1278–1282.

¹²⁹³ See Curran, D.P. *Synthesis* **1988**, 489 (see pp. 497–498).

¹²⁹⁴ Deng, L.X.; Kutateladze, A.G. *Tetrahedron Lett.* **1997**, *38*, 7829.

¹²⁹⁵ Jang, D.O.; Cho, D.H.; Chung, C.-M. *Synlett* **2001**, 1923.

¹²⁹⁶ Bałczewski, P.; Mikołajczyk, M. *Synthesis* **1995**, 392.

¹²⁹⁷ Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2001**, *66*, 7776.

¹²⁹⁸ Mero, C.L.; Porter, N.A. *J. Am. Chem. Soc.* **1999**, *121*, 5155.

¹²⁹⁹ Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1963.

¹³⁰⁰ Ouvry, G.; Zard, S.Z. *Chem. Commun.* **2003**, 778.

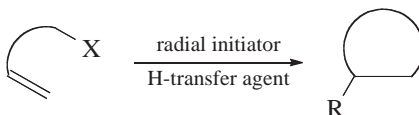
¹³⁰¹ Charrier, N.; Quiclet-Sire, B.; Zard, S.Z. *J. Am. Chem. Soc.* **2008**, *130*, 8898.

¹³⁰² Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 970.

Other radicals can add to alkenes, and the rate constant for the addition of methyl radicals to alkenes has been studied.¹³⁰³ The rate of radical additions to alkenes in general has also been studied.¹³⁰⁴ The kinetic and thermodynamic control of a radical addition regiochemistry has also been studied.¹³⁰⁵ Alkynes are generally less reactive than alkenes in radical coupling reactions.¹³⁰⁶ Nonradical nucleophiles usually react faster with alkynes than with alkenes, however.¹³⁰⁷

15-30 Radical Cyclization¹³⁰⁸

Alkyl-hydro-addition



ω -Haloalkenes generate radicals upon treatment with radical initiator reagents (e.g., AIBN) or under photolysis conditions,¹³⁰⁹ and the radical carbon adds to the alkene to form cyclic compounds.¹³¹⁰ This intramolecular addition of a radical to an alkene is called *radical cyclization*. In a typical example, haloalkene (**101**) reacts with the radical produced by AIBN to give radical **100**. The radical can add to the more substituted carbon to give **102** via a 5-exo-trig reaction (Sec. 6.E).¹³¹¹ If the radical adds to the less substituted carbon, **103** is formed via a 6-endo-trig reaction.¹³¹² In both cases, the product is another radical, which must be converted to an unreactive product. This is generally accomplished by adding a hydrogen-transfer agent¹³¹³ [e.g., tributyltin hydride (Bu_3SnH)], which reacts with **102** to form methylcyclopentane and $\text{Bu}_3\text{Sn}^\bullet$, or with **103** to give cyclohexane. The $\text{Bu}_3\text{Sn}^\bullet$ formed in both cases usually dimerizes to form $\text{Bu}_3\text{SnSnBu}_3$. Cyclization can compete with hydrogen transfer¹³¹⁴ from Bu_3SnH to **100** to give **99**, the reduction product. Atom-transfer cyclization is possible with other atoms (e.g., halogen), catalyzed by InCl_3 ¹³¹⁵ or CuBr .¹³¹⁶ Tin-free radical cyclizations are known using peroxyacids.¹³¹⁷

¹³⁰³ Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* **1996**, 118, 437.

¹³⁰⁴ Avila, D.V.; Ingold, K.U.; Luszyk, J.; Dolbier, Jr., W.R.; Pan, H.-Q. *J. Org. Chem.* **1996**, 61, 2027.

¹³⁰⁵ Leach, A.G.; Wang, R.; Wohlhieter, G.E.; Khan, S.I.; Jung, M.E.; Houk, K.N. *J. Am. Chem. Soc.* **2003**, 125, 4271.

¹³⁰⁶ Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* **1982**, 21, 768.

¹³⁰⁷ Dickstein, J.I.; Miller, G.I. in *The Chemistry of Carbon Carbon Triple Bonds*, Vol. 2, Patai, S. (Ed.), Wiley, NY **1978**.

¹³⁰⁸ See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 1283–1295; Rheault, T.R.; Sibi, M.P. *Synthesis* **2003**, 803.

¹³⁰⁹ See Pandey, G.; Reddy, G.D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 219.

¹³¹⁰ Chang, S.-Y.; Jiang, W.-T.; Chergn, C.-D.; Tang, K.-H.; Huang, C.-H.; Tsai, Y.-M. *J. Org. Chem.* **1997**, 62, 9089. See McCarroll, A.J.; Walton, J.C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215.

¹³¹¹ Chatgililoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, Z.T. *J. Am. Chem. Soc.* **2002**, 124, 10765. See Guan, X.; Phillips, D.L.; Yang, D. *J. Org. Chem.* **2006**, 71, 1984.

¹³¹² See Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695.

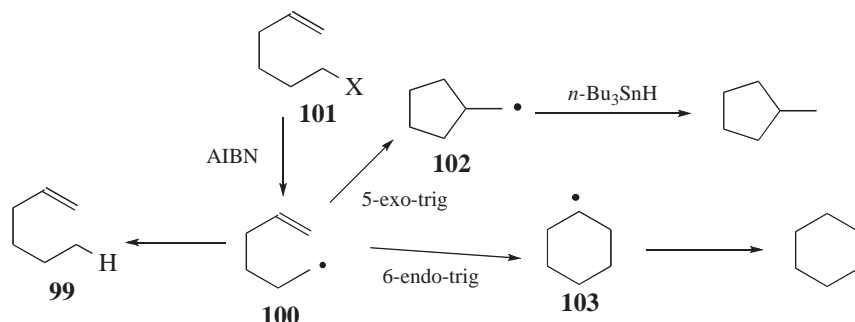
¹³¹³ See Ha, C.; Horner, J.H.; Newcomb, M.; Varick, T.R.; Arnold, B.R.; Luszyk, J. *J. Org. Chem.* **1993**, 58, 1194.

¹³¹⁴ See Furxhi, E.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* **1999**, 64, 4064; Tauh, P.; Fallis, A.G. *J. Org. Chem.* **1999**, 64, 6960.

¹³¹⁵ Cook, G.R.; Hayashi, R. *Org. Lett.* **2006**, 8, 1045.

¹³¹⁶ Clark, A.J.; Wilson, P. *Tetrahedron Lett.* **2008**, 49, 4848.

¹³¹⁷ Smith, D.M.; Pulling, M.E.; Norton, J.R. *J. Am. Chem. Soc.* **2007**, 129, 770.



In general, formation of the five-membered ring dominates the cyclization, but if addition to the C=C unit is relatively slow, the reduction product is formed preferentially. Radical rearrangements can also diminish the yield of the desired product.¹³¹⁸ Given a choice between a larger and a smaller ring, radical cyclization generally gives the smaller ring,¹³¹⁹ but not always.¹³²⁰ Formation of other size rings is possible of course. A 4-exo-trig radical cyclization has been studied,¹³²¹ selectivity in a 7-endo versus 6-exo cyclization,¹³²² and also an 8-endo-trig reaction.¹³²³ In radical cyclization to form large rings, 1,5- and 1,9-hydrogen atom abstractions can pose a problem.¹³²⁴ Ring expansion during radical cyclization is possible when the terminal intermediate is a cyclobutylcarbinyl radical.¹³²⁵

The mechanism of this reaction has been discussed.¹³²⁶ Cyclization via 5-endo-dig transition states require reorientation of the radical orbital needed to reach the in-plane acetylene π orbital in the bond-forming step, with accompanying loss of conjugative stabilization, and an increase in the activation energy. Therefore, many 5-endo cyclizations undergo H abstraction or equilibration with an isomeric radical.¹³²⁷

In cases where hydrogen atom transfer gives primarily reduced products, one solution to promote cyclization generates the radical by photochemical cleavage of Bu₃Sn—SnBu₃ and the resulting carbon radical can cyclize (see Reaction 15-46).¹³²⁸ A halogen atom transfer agent (e.g., iodoethane) is used rather than a hydrogen-transfer agent, so the final product is an alkyl iodide.

A mixture of a *Grignard reagent* and CoCl₂ has been used to initiate aryl radical cyclizations.¹³²⁹ Titanium(III)-mediated radical cyclizations are known,¹³³⁰ and SmI₂

¹³¹⁸ Mueller, A.M.; Chen, P. *J. Org. Chem.* **1998**, 63, 4581.

¹³¹⁹ Bogen, S.; Malacria, M. *J. Am. Chem. Soc.* **1996** 118, 3992.; Beckwith, A.L.J.; Ingold, K.U. in Vol. 1 of *Rearrangements in Ground States and Excited States*, de Mayo, P., Ed., Academic Press, NY **1980**, pp. 162–283. Gómez, A.M.; Company, M.D.; Uriel, C.; Valverde, S.; López, J.C. *Tetrahedron Lett.* **2002**, 43, 4997.

¹³²⁰ Mayon, P.; Chapleur, Y. *Tetrahedron Lett.* **1994**, 35, 3703; Marco-Contelles, J.; Sánchez, B. *J. Org. Chem.* **1993**, 58, 4293.

¹³²¹ Jung, M.E.; Marquez, R.; Houk, K.N. *Tetrahedron Lett.* **1999**, 40, 2661.

¹³²² Kamimura, A.; Taguchi, Y. *Tetrahedron Lett.* **2004**, 45, 2335.

¹³²³ Wang, Li.C. *J. Org. Chem.* **2002**, 67, 1271.

¹³²⁴ Kraus, G.A.; Wu, Y. *J. Am. Chem. Soc.* **1992** 114, 8705.

¹³²⁵ Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1995**, 36, 8539.

¹³²⁶ Bailey, W.F.; Carson, M.W. *Tetrahedron Lett.* **1999**, 40, 5433.

¹³²⁷ Alabugin, I.V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, 127, 9534

¹³²⁸ Afor a polymer-bound Sn catalyst see Hernán, A.G.; Kilburn, J.D. *Tetrahedron Lett.* **2004**, 45, 831.

¹³²⁹ Clark, A.J.; Davies, D.I.; Jones, K.; Millbanks, C. *J. Chem. Soc., Chem. Commun.* **1994**, 41.

¹³³⁰ Barrero, A.F.; Oltra, J.E.; Cuerva, J.M.; Rosales, A. *J. Org. Chem.* **2002**, 67, 2566.

mediated reactions are possible in the presence of a Ni catalyst.¹³³¹ Organoborane-mediated radical cyclizations are known (see Sec. 14.A.i).¹³³² The influence of the halogen atom on radical cyclization has been studied.¹³³³

Both phenylthio¹³³⁴ and phenylseleno groups¹³³⁵ can be used as “leaving groups” for radical cyclization, where S or Se atom transfer leads to formation of the radical. A seleno ester ($R_2N-CH_2C(-O)SeMe$) has also been used with $(Me_3Si)_3SiH$ (tristrimethylsilyl-lane, TTMSS) and AIBN to generate $R_2NCH_2\cdot$.¹³³⁶ *O*-Phosphonate esters have also served as the leaving group.¹³³⁷ *N*-(2-bromophenylbenzyl)methylamino have been used as leaving groups for formation of a radical.¹³³⁸

Radical cyclization reaction often proceeds with high diastereoselectivity¹³³⁹ and high asymmetric induction when chiral precursors are used. Internal alkynes are good substrates for radical cyclization,¹³⁴⁰ but terminal alkynes tend to give mixtures of *exo/endo-dig* products (Sec. 6.E).¹³⁴¹ Radical cyclization has been used to transfer asymmetry from transient atropisomers to form lactams.¹³⁴²

Radical cyclization is compatible with the presence of other functional groups, and heterocyclic rings may be formed via radical cyclization.¹³⁴³ Aryl radicals participate in radical cyclization reactions when the aromatic ring has an alkene or alkyne substituent. *o*-Iodo aryl allyl ethers cyclize to benzofuran derivatives, for example, when treated with AIBN, $aq\ H_3PO_2$ and $NaHCO_3$ in ethanol.¹³⁴⁴ Cyclization of vinyl radicals¹³⁴⁵ and allenyl radicals¹³⁴⁶ are also well known. Treatment of $XCH_2CON(R)-C(R^1)=CH_2$ derivatives ($X = Cl, Br, I$) with Ph_3SnH and AIBN led to formation of a lactam via radical cyclization.¹³⁴⁷ Cyclization of *N*-iodoethyl-5-vinyl-2-pyrrolidinone led to the corresponding bicyclic lactam,¹³⁴⁸ and there are other examples of radical cyclization with molecules containing a lactam unit¹³⁴⁹ or an amide unit.¹³⁵⁰ β -Lactams can be produced by radical

¹³³¹ Molander, G.A.; St. Jean, Jr., D.J. *J. Org. Chem.* **2002**, *67*, 3861.

¹³³² Becattini, B.; Ollivier, C.; Renaud, P. *Synlett* **2003**, 1485.

¹³³³ Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537.

¹³³⁴ See Ikeda, M.; Shikaura, J.; Maekawa, N.; Daibuzono, K.; Teranishi, H.; Teraoka, Y.; Oda, N.; Ishibashi, H. *Heterocycles* **1999**, *50*, 31.

¹³³⁵ See Ericsson, C.; Engman, L. *Org. Lett.* **2001**, *3*, 3459.

¹³³⁶ Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 2323.

¹³³⁷ Crich, D.; Ranganathan, K.; Huang, X. *Org. Lett.* **2001**, *3*, 1917.

¹³³⁸ Andrukiewicz, R.; Loska, R.; Prisyahnyuk, V.; Stalinski, K. *J. Org. Chem.* **2003**, *68*, 1552.

¹³³⁹ See Bouvier, J.-P.; Jung, G.; Liu, Z.; Guérin, B.; Guindon, Y. *Org. Lett.* **2001**, *3*, 1391; Bailey, W.F.; Longstaff, S.C. *Org. Lett.* **2001**, *3*, 2217; Stalinski, K.; Curran, D.P. *J. Org. Chem.* **2002**, *67*, 2982.

¹³⁴⁰ See Sha, C.-K.; Shen, C.-Y.; Jean, T.-S.; Chiu, R.-T.; Tseng, W.-H. *Tetrahedron Lett.* **1993**, *34*, 764; Miyabe, H.; Takemoto, Y. *Chemistry: European J.* **2007**, *13*, 7280.

¹³⁴¹ Kano, S.; Yuasa, Y.; Asami, K.; Shibuya, S. *Chem. Lett.* **1986**, 735; Robertson, J.; Lam, H.W.; Abazi, S.; Roseblade, S.; Lush, R.K. *Tetrahedron* **2000**, *56*, 8959.

¹³⁴² Petit, M.; Lapierre, A.J.B.; Curran, D.P. *J. Am. Chem. Soc.* **2005**, *127*, 14994.

¹³⁴³ Majumdar, K.C.; Basu, P.K.; Mukhopadhyay, P.P. *Tetrahedron* **2005**, *61*, 10603; *Tetrahedron* **2007**, *63*, 793.

¹³⁴⁴ Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104.

¹³⁴⁵ Sha, C.-K.; Zhan, Z.-P.; Wang, F.-S. *Org. Lett.* **2000**, *2*, 2011.

¹³⁴⁶ Wartenberg, F.-H.; Junga, H.; Blechert, S. *Tetrahedron Lett.* **1993**, *34*, 5251. See Shi, J.; Zhang, M.; Fu, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 12681.

¹³⁴⁷ Gilbert, B.C.; Kalz, W.; Lindsay, C.I.; McGrail, P.T.; Parsons, A.F.; Whittaker, D.T.E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1187. See El Bialy, S.A.A.; Ohtani, S.; Sato, T.; Ikeda, M. *Heterocycles* **2001**, *54*, 1021; Liu, L.; Wang, X.; Li, C. *Org. Lett.* **2003**, *5*, 361.

¹³⁴⁸ Keusenkothen, P.F.; Smith, M.B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2485.

¹³⁴⁹ Padwa, A.; Rashatasakhon, P.; Ozdemir, A.D.; Willis, J. *J. Org. Chem.* **2005**, *70*, 519.

¹³⁵⁰ Beckwith, A.L.J.; Joseph, S.P.; Mayadunne, R.T.A. *J. Org. Chem.* **1993**, *58*, 4198.

cyclization, using $\text{Mn}(\text{OAc})_3$.¹³⁵¹ Radical cyclization occurs with enamines as well.¹³⁵² Radical cyclization occurs with oximes to form the corresponding heterocyclic ring.¹³⁵³ Phenylseleno *N*-allylamines led to cyclic amines.¹³⁵⁴ ω -Iodo acrylate esters cyclize to form lactones,¹³⁵⁵ and allylic acetoxy compounds of the type $\text{C}=\text{C}-\text{C}-\text{O}_2\text{C}-\text{CH}_2\text{I}$ cyclize in a similar manner to give lactones.¹³⁵⁶ Iodolactonization (see Reaction **15-41**) occurs under standard radical cyclization conditions using allylic acetoxy compounds¹³⁵⁷ and $\text{HGaCl}_2/\text{BEt}_3$ has been used to initiate the radical process.¹³⁵⁸ α -Bromo mixed acetals give α -alkoxy THF derivatives¹³⁵⁹ and α -iodoacetals cyclize to give similar products.¹³⁶⁰ The reaction of an *o*-alkynyl aryl isonitrile with AIBN and 2.2 equiv of Bu_3SnH gave an indole via 5-exo-dig cyclization.¹³⁶¹ Indole derivatives have also been prepared from *o*-iodoaniline derivatives, using AIBN and TTMSS.¹³⁶² Samarium(II) has been used to initial 5-exo-trig ketyl-alkene coupling, and the mechanism of the reaction has been examined.¹³⁶³

Acyl radicals can be generated and they cyclize in the usual manner.¹³⁶⁴ Molecular orbital calculations have shown that acyl, as well as silyl radicals, simultaneously use SOMO–LUMO (SOMO = singly occupied molecular orbital and LUMO = lowest unoccupied molecular orbital) and LUMO–HOMO interactions in reactions with alkenes.¹³⁶⁵ A polyene-cyclization reaction generated four rings, initiating the sequence by treatment of a phenylseleno ester with $\text{Bu}_3\text{SnH}/\text{AIBN}$ to form the acyl radical, which added to the first alkene unit.¹³⁶⁶ The newly formed carbon radical added to the next alkene, and so on. Acyl radicals generated from Ts(R)NCOSePh derivatives cyclize to form lactams.¹³⁶⁷

Radical cyclization of iodo aldehydes or ketones, at the carbon of the carbonyl, is effectively an acyl addition reaction (**16-24** and **16-25**). This cyclization is often reversible, and there are many fewer examples of addition to an alkene or alkyne. In one example, a δ -iodo aldehyde was treated with BEt_3/O_2 to initiate formation of the radical, and in the presence of Bu_3SnH cyclization gave a cyclopentanol.¹³⁶⁸ The reaction of an

¹³⁵¹ D'Annibale, A.; Nanni, D.; Trogolo, C.; Umami, F. *Org. Lett.* **2000**, 2, 401. See Lee, E.; Kim, S.K.; Kim, J.Y.; Lim, J. *Tetrahedron Lett.* **2000**, 41, 5915. For a related reaction with tin hydride, see Curran, D.P.; Guthrie, D.B.; Geib, S.J. *J. Am. Chem. Soc.* **2008**, 130, 8437. For a discussion of mechanism, see Snider, B.B. *Tetrahedron* **2009**, 65, 10738.

¹³⁵² Glover, S.A.; Warkentin, J. J. *Org. Chem.* **1993**, 58, 2115.

¹³⁵³ Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2008**, 81, 539.

¹³⁵⁴ Gupta, V.; Besev, M.; Engman, L. *Tetrahedron Lett.* **1998**, 39, 2429.

¹³⁵⁵ Ryu, I.; Nagahara, K.; Yamazaki, H.; Tsunoi, S.; Sonoda, N. *Synlett* **1994**, 643.

¹³⁵⁶ Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, 122, 6496.

¹³⁵⁷ Ollivier, C.; Bark, T.; Renaud, P. *Synthesis* **2000**, 1598.

¹³⁵⁸ Mikami, S.; Fujita, K.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, 3, 1853.

¹³⁵⁹ Villar, F.; Equey, O.; Renaud, P. *Org. Lett.* **2000**, 2, 1061.

¹³⁶⁰ Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, 4, 2257.

¹³⁶¹ Rainer, J.D.; Kennedy, A.R.; Chase, E. *Tetrahedron Lett.* **1999**, 40, 6325.

¹³⁶² Kizil, M.; Patro, B.; Callaghan, O.; Murphy, J.A.; Hursthouse, M.B.; Hobbs, D. J. *Org. Chem.* **1999**, 64, 7856.

¹³⁶³ Sadasivam, D.V.; Antharjanam, P.K.S.; Prasad, E.; Flowers II, R.A. *J. Am. Chem. Soc.* **2008**, 130, 7228.

¹³⁶⁴ See Jiaang, W.-T.; Lin, H.-C.; Tang, K.-H.; Chang, L.-B.; Tsai, Y.-M. *J. Org. Chem.* **1999**, 64, 618.

¹³⁶⁵ Schiesser, C.H.; Matsubara, H.; Ritsner, I.; Wille, U. *Chem. Commun.* **2006**, 1067.

¹³⁶⁶ Pattenden, G.; Roberts, L.; Blake, A.J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 863. Also see, Pattenden, G.; Smithies, A.J.; Tapolczay, D.; Walter, D.S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 7.

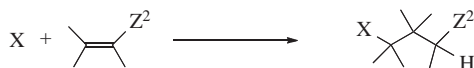
¹³⁶⁷ Rigby, J.H.; Danca, D.M.; Horner, J.H. *Tetrahedron Lett.* **1998**, 39, 8413.

¹³⁶⁸ Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* **1999**, 40, 5511.

aldehyde-alkene with AIBN, 0.5 PhSiH₃ and 0.1 Bu₃SnH generated a radical from the alkene, which cyclized at the aldehyde to give cyclopentanol derivatives.¹³⁶⁹ An aldehyde-*O*-methyloxime generated a radical adjacent to nitrogen under standard conditions, which cyclized at the carbonyl to give a cyclic α -hydroxy *N*-methoxyamine.¹³⁷⁰ Alternatively, an α -bromoacetal-*O*-methyl oxime cyclized at the C=NOMe unit under electrolytic conditions in the presence of cobaloxime.¹³⁷¹ Alkynyl-imines are cyclized to the imino carbon to form alkylidene lactams under radical conditions in the presence of CO.¹³⁷²

The attacking radical in radical cyclization reactions is not limited to a carbon, and a number of heterocycles can be prepared.¹³⁷³ Amidyl radicals are known and give cyclization reactions.¹³⁷⁴ Aminyl radical cyclizations have been reported.¹³⁷⁵ *N*-Chloroamine-alkenes give an aminyl radical when treated with TiCl₃·BF₃, and cyclization gave a pyrrolidine derivative with a pendant chloromethyl group.¹³⁷⁶ *N*-(*S*-substituted) amines give similar results using AIBN/Bu₃SnH.¹³⁷⁷ Oxime-alkenes cyclize to imines when treated with PhSSPh and TEMPO (Sec. 5.C.i).¹³⁷⁸ An oxygen radical can be generated under photochemical conditions, and they add to alkenes in a normal manner.¹³⁷⁹ Note that radical substitution occurs, and reaction of Ph₃SnH/AIBN and an *O*-amidyl compound having a phosphonate ester elsewhere in the molecule gave cyclization to a THF derivative.¹³⁸⁰

15-31 Conjugate Addition with Heteroatom Nucleophiles



Heteroatom nucleophiles add to conjugated systems to give *Michael-type* products. Conjugated carbonyl compounds react via conjugate addition with amines to give β -amino derivatives (See Reaction 15-31)¹³⁸¹ Conjugate addition of nitrogen-containing compounds is often called the *aza-Michael reaction*.¹³⁸² Amines add to conjugated systems in the presence of In,¹³⁸³ Pd,¹³⁸⁴ Sm,¹³⁸⁵ Bi,¹³⁸⁶ Cu,¹³⁸⁷

¹³⁶⁹ Hays, D.S.; Fu, G.C. *Tetrahedron*. **1999**, 55, 8815.

¹³⁷⁰ Naito, T.; Nakagawa, K.; Nakamura, T.; Kasei, A.; Ninomiya, I.; Kiguchi, T. *J. Org. Chem.* **1999**, 64, 2003.

¹³⁷¹ Inokuchi, T.; I.; Kawafuchi, H. *Synlett* **2001**, 421.

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Ce,¹³⁸⁸ La,¹³⁸⁹ or Yb compounds¹³⁹⁰ to give β -amino derivatives. This reaction can be initiated photochemically¹³⁹¹ or with microwave irradiation.¹³⁹² Aniline derivatives add to conjugated aldehydes in the presence of a catalytic amount of DBU,¹³⁹³ and indeed, DBU promotes the *aza-Michael reaction*.¹³⁹⁴ Lithium amides add to conjugated esters to give the β -amino ester.¹³⁹⁵ Amidocuprates add to conjugated systems to give β -nitrogen compounds, and a β -silyl group has an activating effect of the amidocuprate.¹³⁹⁶ A solvent-free conjugate addition of amines occurs on alumina in the presence of a Ce catalyst.¹³⁹⁷ Boric acid has been used as a catalyst of *aza-Michael reactions* in water.¹³⁹⁸ An intramolecular addition of an amine unit to a conjugated ketone in the presence of a Pd catalyst, or photochemically, led to cyclic amines.¹³⁹⁹ Amines add to conjugated thiolactams.¹⁴⁰⁰

There are asymmetric versions of the *aza-Michael reaction*,¹⁴⁰¹ and high enantioselectivity is possible using an organocatalyst.¹⁴⁰² Chiral catalysts lead to enantioselective reactions.¹⁴⁰³ Chiral additives (e.g., chiral Cinchona alkaloids¹⁴⁰⁴ or chiral naphthol derivatives)¹⁴⁰⁵ have also been used. Chiral imines add in a highly stereoselective manner.¹⁴⁰⁶ Chiral catalysts have been used for the conjugated addition of carbamates.¹⁴⁰⁷ Indoles add to nitro alkenes in the presence of an organocatalyst.¹⁴⁰⁸ Other N-heterocycles add with good enantioselectivity in the presence of an organocatalyst.¹⁴⁰⁹

Lactams have been shown to add to conjugated esters in the presence of Si(OEt)₄ and CsF.¹⁴¹⁰ Phthalimide adds to alkylidene malononitriles via 1,4-addition with a Pd catalyst, and the resulting anion can be alkylated with an added allylic halide.¹⁴¹¹ Alkylidene

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amido-amides, $C=C(NHAc)CONHR$, react with secondary amines in water to give the β -amino amido amide.¹⁴¹² Amines also add in a conjugate manner to alkynyl phosphonate esters, $C\equiv C-PO(OEt)_2$, using a CuI catalyst.¹⁴¹³ Hydroxylamines add to conjugated nitro compounds to give 2-nitro hydroxylamines.¹⁴¹⁴ *N,O*-Trimethylsilyl hydroxylamines add to conjugated esters, via nitrogen, using a Cu catalyst.¹⁴¹⁵ Trimethylsilyl azide with acetic acid reacts with conjugated ketones to give the β -azido ketone.¹⁴¹⁶ Sodium azide adds to conjugated ketones in aq acetic acid and 20% PBu_3 .¹⁴¹⁷ An interesting variation involves a double *Michael addition* of amido amines, amido alcohols or amido thiols to conjugated alkynes, forming pyrrolidine, oxazolidine, or thiazolidine derivatives.¹⁴¹⁸

The nitrogen of carbamates adds to conjugated ketones with a Pt,¹⁴¹⁹ Pd,¹⁴²⁰ Cu,¹⁴²¹ or with a bis(triflamide) organocatalyst.¹⁴²² The amine moiety of a carbamate adds to conjugated ketones with a polymer-supported acid catalyst,¹⁴²³ or with $BF_3 \cdot OEt_2$.¹⁴²⁴ The reaction of ammonium formate with 1,4-diphenylbut-2-en-1,4-dione, in PEG-200 and a Pd catalyst under microwave irradiation, gave 2,5-diphenylpyrrole.¹⁴²⁵

Phosphines react similarly to amines under certain conditions. Conjugate addition of R_2PH and a Ni catalyst give conjugate addition to α,β -unsaturated nitriles.¹⁴²⁶ A Pd catalyzed addition of diarylphosphines proceeds with good enantioselectivity to give chiral phosphines.¹⁴²⁷ Phosphites add to nitroalkenes in the presence of a chiral organocatalyst to give the corresponding nitro phosphite compound.¹⁴²⁸

Alcohols add to conjugated ketones with a PMe_3 catalyst to give the β -alkoxy ketone.¹⁴²⁹ This reaction is called an *oxy-Michael reaction*.¹⁴³⁰ Alcohol addition is catalyzed by *N*-heterocyclic carbenes¹⁴³¹ and other organocatalysts,¹⁴³² often with enantioselectivity.¹⁴³³ The conjugate addition of peroxide anions (HOO^- and ROO^-) to α,β -unsaturated carbonyl compounds is discussed in Reaction 15-48. An intramolecular variation is known that produces dihydropyrones.¹⁴³⁴

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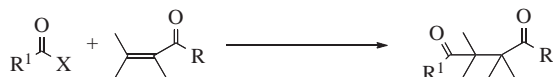
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Thiophenol and butyllithium (lithium phenylthiolate) adds to conjugated esters.¹⁴³⁵ Similar addition is observed with selenium compounds (RSeLi).¹⁴³⁶ Thiols react with conjugated amides via 1,4-addition with the addition of 10% Hf(OTf)₄ or other lanthanide triflates¹⁴³⁷ or to conjugated ketones in ionic solvents.¹⁴³⁸ Alkyl thiols add to conjugated carbonyl compounds with high enantioselectivity using an organocatalyst.¹⁴³⁹ Iron(III)-catalyzed addition of thiols occurs under solvent-free conditions.¹⁴⁴⁰ Thiols add without a catalyst in water¹⁴⁴¹ in PEG,¹⁴⁴² or in ionic liquids.¹⁴⁴³ Thiol addition is also catalyzed by iodine under solvent-free conditions.¹⁴⁴⁴ Ceric ammonium nitrate promotes the conjugate addition of thiols.¹⁴⁴⁵ Thioaryl moieties can be added in the presence of Yb¹⁴⁴⁶ or a catalytic amount of (DHQD)₂PYR (a dihydroquinidine, see Reaction **15-48**).¹⁴⁴⁷ Thioalkyl units (e.g., BuS—) add to conjugated ketones using BuS—SnBu and In—I.¹⁴⁴⁸ Addition of conjugated lactones is possible to produce β-arylthiolated lactones.¹⁴⁴⁹ Dithiocarbamates are prepared by the reaction of an amine, CS₂, and a conjugated carbonyl compound.¹⁴⁵⁰ α,β-Unsaturated sulfones undergo conjugate addition of a cyano group using Et₂AlCN.¹⁴⁵¹

15-32 Acylation of Activated Double Bonds and of Triple Bonds

Hydro-acyl-addition



Under some conditions, acid derivatives add directly to activated double bonds. Acetic anhydride, Mg metal, and Me₃SiCl react with conjugated esters to give a γ-keto ester.¹⁴⁵² Similar reaction with vinyl phosphonate esters leads to a γ-keto phosphonate ester.¹⁴⁵³ Thioesters undergo conjugate addition to α,β-unsaturated ketones in the presence of SmI₂.¹⁴⁵⁴ Using DBU and a thioimidazolium salt, acyl silanes, Ar(C=O)SiMe₃, add in a

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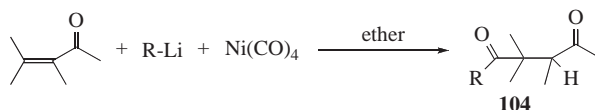
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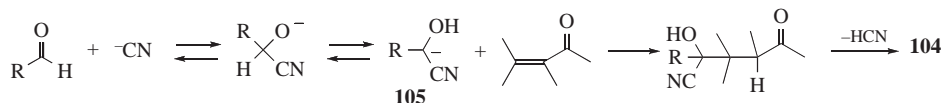
¹⁴⁵³ Kyoda, M.; Yokoyama, T.; Maekawa, H.; Ohno, T.; Nishiguchi, I. *Synlett* **2001**, 1535.

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similar manner.¹⁴⁵⁵ Under microwave irradiation, aldehydes add to conjugated ketones using DBU/ Al_2O_3 and a thiazolium salt.¹⁴⁵⁶ The conjugate addition of acyl zirconium complexes in the presence of $\text{BF}_3\cdot\text{OEt}_2$ is catalyzed by palladium acetate.¹⁴⁵⁷



An acyl group can be introduced into the 4 position of an α,β -unsaturated ketone by treatment with an organolithium compound and nickel carbonyl¹⁴⁵⁸ to give a 1,4-diketone (**104**). The R group may be aryl or primary alkyl. The reaction can also be applied to alkynes, which need not be activated, in which case 2 molar equivalents add and the product is also a 1,4-diketone (e.g., $\text{R}'\text{C}\equiv\text{CH} \rightarrow \text{RCOCHR}'\text{CH}_2\text{COR}$).¹⁴⁵⁹ In a different procedure, α,β -unsaturated ketones and aldehydes are acylated by treatment at -110°C with $\text{R}_2(\text{CN})\text{CuLi}_2$ and CO. This method is successful for R = primary, secondary, and tertiary alkyl.¹⁴⁶⁰ For secondary and tertiary groups, $\text{R}(\text{CN})\text{CuLi}$, which does not waste an R group, can be used instead.¹⁴⁶¹



The reaction of an aldehyde and cyanide ion (See Reaction **16-52**) in a polar aprotic solvent (e.g., DMF or DMSO) leads to a cyanohydrin, which generates a diketone via loss of HCN.¹⁴⁶² This method has been applied to α,β -unsaturated ketones, esters, and nitriles to give the corresponding 1,4-diketones, γ -keto esters, and γ -keto nitriles, respectively (see also, Reaction **16-55**). The initial product of this reaction is ion **105**, which is a synthon for the unavailable $\text{R}^-\text{C}=\text{O}$ anion (see Reaction **10-68**). It is a masked $\text{R}^-\text{C}=\text{O}$ anion that upon reaction with the conjugated carbonyl gives **104** after loss of HCN from the cyanohydrin addition product. Other masked carbanions that have been used in this reaction are the $\text{RC}^-(\text{CN})\text{NR}$ ion,¹⁴⁶³ the EtSCRSOEt ion,¹⁴⁶⁴ the $\text{CH}_2=\text{C}^-\text{OEt}$ ion,¹⁴⁶⁵ $\text{CH}_2=\text{C}(\text{OEt})\text{CuLi}$,¹⁴⁶⁶ $\text{CH}_2=\text{CMe}(\text{SiMe}_3)$,¹⁴⁶⁶ and the $\text{RC}^-(\text{OCHMeOEt})\text{CN}$ ion.¹⁴⁶⁷ In the last case, best results are obtained when R is a vinylic group. Anions of 1,3-dithianes

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(Reaction **10-71**) do not give 1,4-addition to these substrates (except in the presence of HMPA, see Reaction **15-25**), but add 1,2 to the C=O group instead (Reaction **16-38**).

Interestingly, acylation occurs at the α -position of an enone when an α,β -unsaturated ketone is treated with an acid chloride and Et_2Zn in the presence of a Rh catalyst.¹⁴⁶⁸

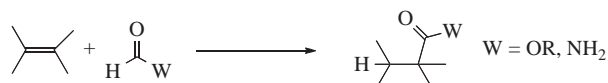
In another procedure, acyl radicals derived from phenyl selenoesters (ArCOSePh) (by treatment with Bu_3SnH) add to α,β -unsaturated esters and nitriles to give γ -keto esters and γ -keto nitriles, respectively.¹⁴⁶⁹

OS VI, 866; VIII, 620.

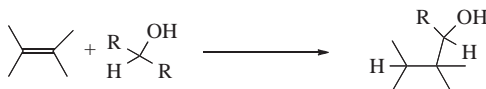
15-33 Addition of Alcohols, Amines, Carboxylic Esters, Aldehydes, and so on

Hydro-acyl-addition, and so on

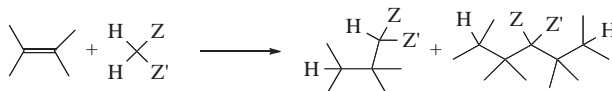
Formates, primary and secondary alcohols, amines, ethers, alkyl halides, compounds of the type $\text{Z}-\text{CH}_2-\text{Z}'$, and a few other compounds add to double bonds in the presence of free radical initiators.¹⁴⁷⁰ This is formally the addition of RH to a double bond, but the “R” is not just any carbon, but one connected to an oxygen or a nitrogen, a halogen, or to two Z groups (defined as in Sec. 15.A.ii). Formates and formamides¹⁴⁷¹ add similarly:



Alcohols, ethers, amines, and alkyl halides add as follows (shown for alcohols):



The $\text{ZCH}_2\text{Z}'$ compounds react at the carbon bearing the active hydrogen¹⁴⁷²:



Similar additions have been successfully carried out with carboxylic acids, anhydrides,¹⁴⁷³ acyl halides, carboxylic esters, nitriles, and other types of compounds.¹⁴⁷⁴

Similar reactions have been carried out on acetylene.¹⁴⁷⁵ In an interesting variation, thiocarbonates add to alkynes in the presence of a Pd catalyst to give a β -phenylthio α,β -unsaturated ester.¹⁴⁷⁶ Aldehydes add to alkynes in the presence of a Rh catalyst to give

¹⁴⁶⁸ Sato, K.; Yamazoe, S.; Yamamoto, R.; Ohata, S.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Org. Lett.* **2008**, *10*, 2405.

¹⁴⁶⁹ Boger, D.L.; Mathvink, R.J. *J. Org. Chem.* **1989**, *54*, 1777.

¹⁴⁷⁰ See Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, **1986**, pp. 69–77; Vogel, H. *Synthesis* **1970**, 99; Dang, H.-S.; Roberts, B.P. *Chem. Commun.* **1996**, 2201.

¹⁴⁷¹ Elad, D. *Fortschr. Chem. Forsch.* **1967**, *7*, 528, see pp. 530–543.

¹⁴⁷² See Hájek, M.; Málek, J. *Coll. Czech. Chem. Commun.* **1979**, *44*, 3695.

¹⁴⁷³ de Klein, W.J. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 48.

¹⁴⁷⁴ Cadogan, J.I.G. *Pure Appl. Chem.* **1967**, *15*, 153, pp. 153–158. See also, Giese, B.; Zwick, W. *Chem. Ber.* **1982**, *115*, 2526; Giese, B.; Erfort, U. *Chem. Ber.* **1983**, *116*, 1240.

¹⁴⁷⁵ See DiPietro, J.; Roberts, W.J. *Angew. Chem. Int. Ed.* **1966**, *5*, 415.

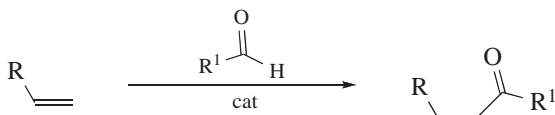
¹⁴⁷⁶ Hua, R.; Takeda, H.; Onozawa, S.-y.; Abe, Y.; Tanaka, M. *J. Am. Chem. Soc.* **2001**, *123*, 2899.

conjugated ketones.¹⁴⁷⁷ In a cyclic version of the addition of aldehydes, 4-pentenal was converted to cyclopentanone with a Rh complex catalyst.¹⁴⁷⁸ An intramolecular acyl addition to an alkyne was reported using silyl ketones, acetic acid, and a Rh catalyst.¹⁴⁷⁹ Formamides add to alkynes in the presence of a Pd catalyst to form conjugated amides.¹⁴⁸⁰

OS IV, 430; V, 93; VI, 587, 615.

15-34 Addition of Aldehydes

Alkyl-carbonyl-addition



In the presence of metal catalysts (e.g., Rh¹⁴⁸¹ or Yb¹⁴⁸²), aldehydes can add directly to alkenes to form ketones. Additives play an important role in such reactions.¹⁴⁸³ The reaction of ω -alkenyl aldehydes with a Rh catalyst leads to cyclic ketones,¹⁴⁸⁴ with high enantioselectivity if chiral ligands are employed. A carbene organocatalyst was used for an enantioselective intramolecular reaction.¹⁴⁸⁵ β,γ -Unsaturated ketones are prepared by the Rh catalyzed addition of aldehydes to dienes.¹⁴⁸⁶ The addition of aldehydes to activated double bonds, mediated by a catalytic amount of thiazolium salt in the presence of a weak base, is called the *Stetter reaction*,¹⁴⁸⁷ An internal addition of an alkynyl aldehyde, catalyzed by a Rh complex, led to a cyclopentenone derivative.¹⁴⁸⁸ These reactions are not successful when the alkene contains electron-withdrawing groups (e.g., halo or carbonyl groups). A free radical initiator is required,¹⁴⁸⁹ usually peroxides or UV light. The mechanism is illustrated for aldehydes, but is similar for the other compounds:

¹⁴⁷⁷ Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, 62, 4564.

¹⁴⁷⁸ Fairlie, D.P.; Bosnich, B. *Organometallics* **1988**, 7, 936, 946. Also see, Barnhart, R.W.; Wang, X.; Noheda, P.; Bergens, S.H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, 116, 1821.

¹⁴⁷⁹ Yamane, M.; Amemiya, T.; Narasaka, K. *Chem. Lett.* **2001**, 1210.

¹⁴⁸⁰ Fujihara, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, 132, 2094.

¹⁴⁸¹ Willis, M.C.; Randell-Sly, H.E.; Woodward, R.L.; McNally, S.J.; Currie, G.S. *J. Org. Chem.* **2006**, 71, 5291; Imai, M.; Tanaka, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2007**, 72, 2543. For a discussion of the mechanism, see Roy, A.H.; Lenges, C.P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, 129, 2082.

¹⁴⁸² Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* **2003**, 552.

¹⁴⁸³ See Jo, E.-A.; Jun, C.-H. *Tetrahedron Lett.* **2009**, 50, 3338.

¹⁴⁸⁴ Barnhart, R.W.; McMorran, D.A.; Bosnich, B. *Chem. Commun.* **1997**, 589.

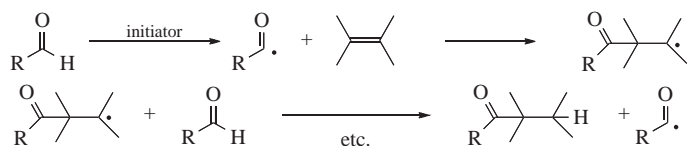
¹⁴⁸⁵ de Alaniz, J.R.; Rovis, T. *J. Am. Chem. Soc.* **2005**, 127, 6284; Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, 128, 2552; Kundu, K.; McCullagh, J.V.; Morehead, Jr., A.T. *J. Am. Chem. Soc.* **2005**, 127, 16042; Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989.

¹⁴⁸⁶ Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, 130, 14094. For a related reaction, see Shibahara, F.; Bower, J.F.; Krische, M.J. *J. Am. Chem. Soc.* **2008**, 130, 14120.

¹⁴⁸⁷ Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, 40, 407; Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, 126, 8876; Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025; Mennen, S.; Blank, J.; Tran-Dube, M.B.; Imbriglio, J.E.; Miller, S.J. *Chem. Commun.* **2005**, 195. See also, Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* **2004**, 126, 2314.

¹⁴⁸⁸ Tanaka, K.; Fu, G.C. *J. Am. Chem. Soc.* **2002**, 124, 10296.

¹⁴⁸⁹ See Lee, E.; Tae, J.S.; Chong, Y.H.; Park, Y.C.; Yun, M.; Kim, S. *Tetrahedron Lett.* **1994**, 35, 129 for an example.

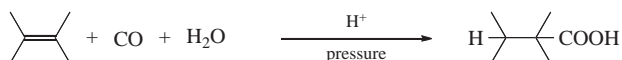


In the presence of BF_3 and a Ag salt, aldehydes add to alkynes to give the corresponding conjugated ketone.¹⁴⁹⁰ Polymers are often side products. Photochemical addition of aldehyde to conjugated $\text{C}=\text{C}$ units can be efficient when a triplet sensitizer (Sec. 7.A.vi, category 5, e.g., benzophenone) is used.¹⁴⁹¹

A variation that is more of an acyl addition (Reaction **16-25**) involves the reaction of an allylic alcohol with benzaldehyde. With a Ru catalyst and in an ionic liquid, the $\text{C}=\text{C}$ unit reacts with the aldehyde, with concomitant oxidation of the allylic alcohol unit, to give a β -hydroxy ketone, $\text{PhCHO} + \text{C}=\text{C}-\text{CH}(\text{OH})\text{R} \rightarrow \text{PhCH}(\text{OH})-\text{CH}(\text{Me})\text{COR}$.¹⁴⁹² In another variation, formate esters add to alkenes using a Ru catalyst to give an alkyl ester via a formylation process.¹⁴⁹³

15-35 Hydrocarboxylation

Hydro-carboxy-addition



The acid-catalyzed hydrocarboxylation of alkenes (the *Koch reaction*) can be performed in a number of ways.¹⁴⁹⁴ In one method, the alkene is treated with CO and water at 100–350°C and 500–1000-atm pressure with a mineral acid catalyst. However, the reaction can also be performed under milder conditions. If the alkene is first treated with CO and catalyst and then water added, the reaction can be accomplished at 0–50°C and 1–100 atm. If formic acid is used as the source of both the CO and the water, the reaction can be carried out at room temperature and atmospheric pressure.¹⁴⁹⁵ The formic acid procedure is called the *Koch–Haaf reaction* (the Koch–Haaf reaction can also be applied to alcohols, see Reaction **10-77**). Nearly all alkenes can be hydrocarboxylated by one of these procedures. However, conjugated dienes are polymerized under these conditions. Hydrocarboxylation can also be accomplished under mild conditions (160°C and 50 atm) by the use of nickel carbonyl as catalyst. Acid catalysts are used along with the nickel carbonyl, but basic catalysts can also be employed.¹⁴⁹⁶ The $\text{Ni}(\text{CO})_4$ catalyzed oxidative carbonylation with

¹⁴⁹⁰ Rhee, J.U.; Krische, M.J. *Org. Lett.* **2005**, 7, 2493.

¹⁴⁹¹ Kraus, G.A.; Liu, P. *Tetrahedron Lett.* **1994**, 35, 7723.

¹⁴⁹² Yang, X.-F.; Wang, M.; Varma, R.S.; Li, C.-J. *Org. Lett.* **2003**, 5, 657.

¹⁴⁹³ Na, Y.; Ko, S.; Hwang, L.K.; Chang, S. *Tetrahedron Lett.* **2003**, 44, 4475.

¹⁴⁹⁴ See Lapidus, A.L.; Pirozhkov, S.D. *Russ. Chem. Rev.* **1989**, 58, 117; Anderson, G.K.; Davies, J.A. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, **1985**, pp. 335–359, 335–348; in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, **1980**, the articles by Mullen, A. pp. 243–308; and Bahrmann, H. pp. 372–413; Falbe, J. *Carbon Monoxide in Organic Synthesis*, Springer: Berlin, **1970**, pp. 78–174.

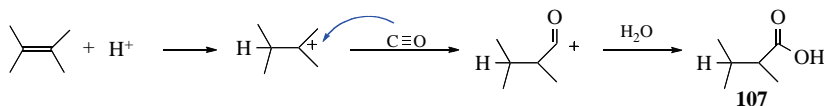
¹⁴⁹⁵ Haaf, W. *Chem. Ber.* **1966**, 99, 1149; Christol, H.; Solladié, G. *Bull. Soc. Chim. Fr.* **1966**, 1307.

¹⁴⁹⁶ Sternberg, H.W.; Markby, R.; Wender, P. *J. Am. Chem. Soc.* **1960**, 82, 3638.

CO and H₂O as a nucleophile is often called *Reppe carbonylation*.¹⁴⁹⁷ The toxic nature of nickel tetracarbonyl has led to development of other catalysts.¹⁴⁹⁸ Indeed, variations in the reaction procedure include the use of Pd,¹⁴⁹⁹ Pt,¹⁵⁰⁰ and Rh¹⁵⁰¹ catalysts. This reaction converts alkenes, alkynes, and dienes and is tolerant of a wide variety of functional groups. When the additive is alcohol or acid, saturated or unsaturated acids, esters, or anhydrides are produced (see Reaction 15-36). The transition metal catalyzed carbonylation has been done enantioselectively, with moderate-to-high optical yields, by the use of an optically active palladium-complex catalyst.¹⁵⁰² Alkenes also react with Fe(CO)₅ and CO to give carboxylic acids.¹⁵⁰³ Electrochemical carboxylation procedures have been developed, including the conversion of alkenes to 1,4-butanedicarboxylic acids.¹⁵⁰⁴ A reductive carboxylation of alkenes with CO and cesium carbonate has been reported.¹⁵⁰⁵

When applied to triple bonds, hydrocarboxylation gives α,β -unsaturated acids under very mild conditions. Triple bonds give unsaturated acids and saturated dicarboxylic acids when treated with CO₂ and an electrically reduced Ni complex catalyst.¹⁵⁰⁶ Alkynes also react with NaHFe(CO)₄, followed by CuCl₂ • 2 H₂O, to give alkenyl acid derivatives.¹⁵⁰⁷ A related reaction with CO and Pd catalysts in the presence of SnCl₂ leads to conjugated acid derivatives.¹⁵⁰⁸ Terminal alkynes react with CO₂ and Ni(cod)₂ (cod = 1,5-cyclooctadiene), and subsequent treatment with DBU gives the α,β -unsaturated carboxylic acid.¹⁵⁰⁹

When acid catalysts are employed, in the absence of nickel carbonyl, the mechanism¹⁵¹⁰ involves initial attack on a proton, followed by attack by CO on the resulting carbocation to give an acyl cation, and subsequent reaction with water gives the product **107**. *Markovnikov's rule* is followed, and carbon skeleton rearrangements and double-bond isomerizations (prior to attack by CO) are frequent.



¹⁴⁹⁷ Tsuji, J. *Palladium Reagents and Catalysts* Wiley, NY, **1999**; Hohn, A. in *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 1* VCH, NY, **1996**, p. 137; Beller, M.; Tafesh, A.M. in *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 1* VCH, NY, **1996**, p. 187; Drent, E.; Jager, W.W.; Keijsper, J.J.; Niele, F.G.M. in *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 1* VCH, NY, **1996**, p. 1119.; Bertoux, F.; Monflier, E.; Castanet, Y.; Mortreux, A. *J. Mol. Catal. A: Chem.* **1999**, *143*, 11; Beller, M.; Cornils, B.; Frohning, C.D.; Kohlpaintner, C.W. *J. Mol. Catal. A: Chem.* **1995**, *104*, 17; Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428; Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144; Bird, C.W. *Chem. Rev.* **1962**, *62*, 283.

¹⁴⁹⁸ For a review, see Kiss, G. *Chem. Rev.* **2001**, *101*, 3435.

¹⁴⁹⁹ See Heck, R.F. *Palladium Reagents in Organic Synthesis* Academic Press, NY, **1985**, pp. 381–395; Mukhopadhyay, K.; Sarkar, B.R.; Chaudhari, R.V. *J. Am. Chem. Soc.* **2002**, *124*, 9692; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254.

¹⁵⁰⁰ Xu, Q.; Fujiwara, M.; Tanaka, M.; Souma, Y. *J. Org. Chem.* **2000**, *65*, 8105.

¹⁵⁰¹ Xu, Q.; Nakatani, H.; Souma, Y. *J. Org. Chem.* **2000**, *65*, 1540.

¹⁵⁰² Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803.

¹⁵⁰³ Brunet, J.-J.; Neibecker, D.; Srivastava, R.S. *Tetrahedron Lett.* **1993**, *34*, 2759.

¹⁵⁰⁴ Senboku, H.; Komatsu, H.; Fujimura, Y.; Tokuda, M. *Synlett* **2001**, 418.

¹⁵⁰⁵ Williams, C.M.; Johnson, J.B.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14936.

¹⁵⁰⁶ Duñach, E.; Dérien, S.; Périchon, J. *J. Organomet. Chem.* **1989**, *364*, C33.

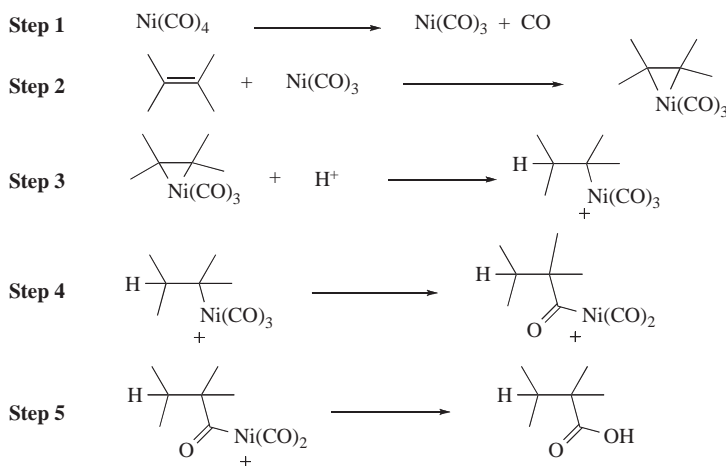
¹⁵⁰⁷ Periasamy, M.; Radhakrishnan, U.; Rameshkumar, C.; Brunet, J.-J. *Tetrahedron Lett.* **1997**, *38*, 1623.

¹⁵⁰⁸ Takeuchi, R.; Sugiura, M. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1031.

¹⁵⁰⁹ Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 3975. See also, Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* **2001**, *3*, 3345.

¹⁵¹⁰ See Hogeveen, H. *Adv. Phys. Org. Chem.* **1973**, *10*, 29.

For the transition metal catalyzed reactions, the nickel carbonyl reaction has been well studied and the addition is syn for both alkenes and alkynes.¹⁵¹¹ The following is the accepted mechanism:¹⁵¹¹

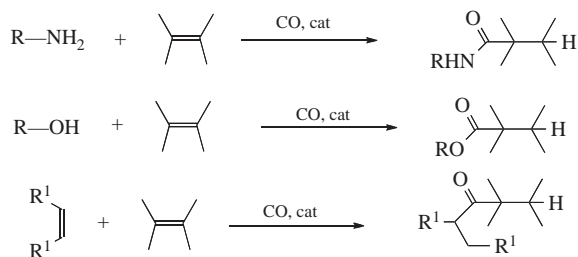


Step 3 is an electrophilic substitution. The principal step of the mechanism, step 4, is a rearrangement.

An indirect method for hydrocarboxylation involves the reaction of an alkene with a borate $[(\text{RO})_2\text{BH}]$ and a Rh catalyst. Subsequent reaction with LiCHCl_2 , and then NaClO_2 , gives the *Markovnikov* carboxylic acid $(\text{RC}=\text{C} \rightarrow \text{RC}(\text{CO}_2\text{H})\text{CH}_3)$.¹⁵¹² When a chiral ligand is used, the reaction proceeds with good enantioselectivity.

15-36 Carbonylation, Alkoxy carbonylation, and Aminocarbonylation of Double and Triple Bonds

Alkyl, Alkoxy, or Amino-carbonyl-addition



In the presence of certain metal catalysts, alkenes and alkynes can be carbonylated or converted to give an amide or an ester.¹⁵¹³ There are several variations. The reaction of an alkyl iodide and a conjugated ester with CO, $(\text{Me}_3\text{Si})_3\text{SiH}$, and AIBN in supercritical CO_2 (Sec. 9.D.ii) gave a γ -keto ester.¹⁵¹⁴ Terminal alkynes react with

¹⁵¹¹ Bird, C.W.; Cookson, R.C.; Hudec, J.; Williams, R.O. *J. Chem. Soc.* **1963**, 410.

¹⁵¹² Chen, A.; Ren, L.; Crudden, C.M.; *J. Org. Chem.* **1999**, *64*, 9704.

¹⁵¹³ See Fallis, A.G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899.

¹⁵¹⁴ Kishimoto, Y.; Ikariya, T. *J. Org. Chem.* **2000**, *65*, 7656.

CO and methanol in the presence of CuCl_2 and PdCl_2 to give a β -chloro- α,β -unsaturated methyl ester.¹⁵¹⁵ Conjugated dienes react with thiophenol, CO and $\text{Pd}(\text{OAc})_2$ to give the β,γ -unsaturated thioester.¹⁵¹⁶ Allene reacts with CO, CH_3OH , and a Ru catalyst to give methacrylic acid.¹⁵¹⁷ Alkynes react with thiophenol and CO with a Pd¹⁵¹⁸ or Pt¹⁵¹⁹ catalyst to give a conjugated thioester. Terminal alkynes react with CO and CH_3OH , using a combination of a palladium(II) halide and a copper(II) halide, to give a conjugated diester, $\text{MeO}_2\text{C}-\text{C}=\text{C}-\text{CO}_2\text{Me}$.¹⁵²⁰ A similar reaction with alkenes using a combination of a Pd and a Mo catalyst led to a saturated diester ($\text{MeO}_2\text{C}-\text{C}-\text{C}-\text{CO}_2\text{Me}$).¹⁵²¹ Alkenes were converted to the dimethyl ester of 1,4-butanedioic acid derivatives with CO/O_2 and a combination of PdCl_2 and CuCl catalysts.¹⁵²² Note that alkenes primarily are converted to the *anti-Markovnikov* ester upon treatment with arylmethyl formate esters (ArCH_2OCHO) and a Ru catalyst.¹⁵²³ Terminal alkynes react with tosyl azide, water, and a catalytic amount of CuI to give an *N*-tosyl amide.¹⁵²⁴

A bicyclic ketone was generated when 1,2-diphenylethyne was heated with carbon monoxide, methanol and a dirhodium catalyst.¹⁵²⁵ 2-Iodostyrene reacted at 100°C with CO and a Pd catalyst to give the bicyclic ketone 1-indanone.¹⁵²⁶ Another variation reacted a conjugated allene-alkene with 5 atm of CO and a Rh catalyst to give a bicyclic ketone.¹⁵²⁷ An intermolecular version of this reaction is known using a Co catalyst, giving a cyclopentenone¹⁵²⁸ in a reaction related to the *Pauson-Khand reaction* (see below). The reaction of a conjugated diene having a distal alkene unit and CO with a Rh catalyst led to a bicyclic conjugated ketone.¹⁵²⁹ When a *Stille coupling* (Reaction 12-15) is done in a CO atmosphere, conjugated ketones of the type $\text{C}=\text{C}-\text{CO}-\text{C}=\text{C}$ are formed,¹⁵³⁰ suitable for a *Nazarov cyclization* (Reaction 15-20). Alkynes were converted to cyclobutenones using $\text{Fe}_3(\text{CO})_{12}$ to form an initial complex, followed by reaction with copper(II) chloride.¹⁵³¹ An interesting variation treated cyclohexene with 5 molar equivalents of Oxone and a RuCl_3 catalyst to give 2-hydroxycyclohexanone.¹⁵³²

¹⁵¹⁵ Li, J.; Jiang, H.; Feng, A.; Jia, L. *J. Org. Chem.* **1999**, *64*, 5984. See also, Clarke, M.L. *Tetrahedron Lett.* **2004**, *45*, 4043.

¹⁵¹⁶ Xiao, W.-J.; Alper, H. *J. Org. Chem.* **2001**, *66*, 6229.

¹⁵¹⁷ Zhou, D.-Y.; Yoneda, E.; Onitsuka, K.; Takahashi, S. *Chem. Commun.* **2002**, 2868.

¹⁵¹⁸ Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1999**, *64*, 2080.

¹⁵¹⁹ Kawakami, J.-i.; Mihara, M.; Kamiya, I.; Takeba, M.; Ogawa, A.; Sonoda, N. *Tetrahedron* **2003**, *59*, 3521.

¹⁵²⁰ Li, J.; Jiang, H.; Chen, M. *Synth. Commun.* **2001**, *31*, 3131; El Ali, B.; Tijani, J.; El-Ghanam, A.; Fettohi, M. *Tetrahedron Lett.* **2001**, *42*, 1567.

¹⁵²¹ Yokota, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 5005.

¹⁵²² Dai, M.; Wang, C.; Dong, G.; Xiang, J.; Luo, J.; Liang, B.; Chen, J.; Yang, Z. *Eur. J. Org. Chem.* **2003**, 4346.

¹⁵²³ Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750.

¹⁵²⁴ Cho, S.H.; Yoo, E.J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046.

¹⁵²⁵ Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* **1999**, *40*, 7811.

¹⁵²⁶ Gagnier, S.V.; Larock, R.C. *J. Am. Chem. Soc.* **2003**, *125*, 4804.

¹⁵²⁷ Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4130.

¹⁵²⁸ Jeong, N.; Hwang, S.H. *Angew. Chem. Int. Ed.* **2000**, *39*, 636.

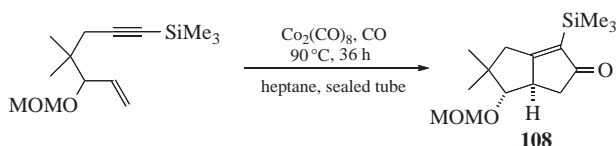
¹⁵²⁹ Lee, S.I.; Park, J.H.; Chung, Y.K.; Lee, S.-G. *J. Am. Chem. Soc.* **2004**, *126*, 2714.

¹⁵³⁰ Mazzola, Jr., R.D.; Giese, S.; Benson, C.L.; West, F.G. *J. Org. Chem.* **2004**, *69*, 220.

¹⁵³¹ Rameshkumar, C.; Periasamy, M. *Tetrahedron Lett.* **2000**, *41*, 2719.

¹⁵³² Plietker, B. *J. Org. Chem.* **2004**, *69*, 8287.

The reaction of dienes, diynes, or enynes with transition metals¹⁵³³ (usually Co)¹⁵³⁴ forms organometallic coordination complexes. Rhodium,¹⁵³⁵ Ti,¹⁵³⁶ Mo,¹⁵³⁷ and W¹⁵³⁸ complexes have been used for this reaction. In the presence of CO, the metal complexes derived primarily from enynes (alkene–alkynes) generate cyclopentenone derivatives in what is known as the *Pauson–Khand reaction*.¹⁵³⁹ This reaction involves (1) formation of a hexacarbonyldicobalt–alkyne complex and (2) decomposition of the complex in the presence of an alkene.¹⁵⁴⁰ A typical example is the preparation of **108**.¹⁵⁴¹ Cyclopentenones can be prepared by an intermolecular reaction of a vinyl silane and an alkyne using CO and a Ru catalyst.¹⁵⁴² Carbonylation of an alkene–diene using a Rh catalyst leads to cyclization to an α -vinyl cyclopentanone.¹⁵⁴³ An yne–diene can also be used for the *Pauson–Khand reaction*.¹⁵⁴⁴



The reaction can be promoted photochemically¹⁵⁴⁵ and the rate is enhanced by the presence of primary amines.¹⁵⁴⁶ Coordinating ligands also accelerate the reaction,¹⁵⁴⁷ polymer-supported promoters have been developed¹⁵⁴⁸ and there are many possible variations in reaction conditions.¹⁵⁴⁹ The *Pauson–Khand reaction* has been done under heterogeneous reaction conditions,¹⁵⁵⁰ with Co nanoparticles,¹⁵⁵¹ and in water.¹⁵⁵² A

¹⁵³³ See Krafft, M.E.; Hirosawa, C.; Bonaga, L.V.R. *Tetrahedron Lett.* **1999**, 40, 9177.

¹⁵³⁴ See Krafft, M.E.; Boñaga, L.V.R.; Hirosawa, C. *J. Org. Chem.* **2001**, 66, 3004.

¹⁵³⁵ Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* **1998**, 249. An entrapped-Rh catalyst has been used: Park, K.H.; Son, S.U.; Chung, Y.K. *Tetrahedron Lett.* **2003**, 44, 2827.

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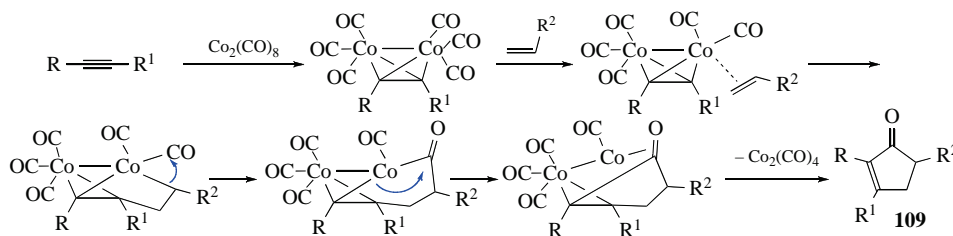
¹⁵⁵⁰ Kim, S.-W.; Son, S.U.; Lee, S.I.; Hyeon, T.; Chung, Y.K. *J. Am. Chem. Soc.* **2000**, 122, 1550.

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dendritic Co catalyst has been used.¹⁵⁵³ Ultrasound promoted¹⁵⁵⁴ and microwave promoted¹⁵⁵⁵ reactions have been developed. Polycyclic compounds (tricyclic and higher) are prepared in a relatively straightforward manner using this reaction.¹⁵⁵⁶ Asymmetric *Pauson–Khand* reactions are known.¹⁵⁵⁷

The *Pauson–Khand reaction* is compatible with other groups or heteroatoms elsewhere in the molecule. These include ethers and aryl halides,¹⁵⁵⁸ esters,¹⁵⁵⁹ amides,¹⁵⁶⁰ alcohols,¹⁵⁶¹ diols,¹⁵⁶² and an indole unit.¹⁵⁶³ A silicon-tethered *Pauson–Khand reaction* is known.¹⁵⁶⁴ Allenes are reaction partners in the *Pauson–Khand reaction*.¹⁵⁶⁵ This type of reaction can be extended to form six-membered rings using a Ru catalyst.¹⁵⁶⁶ A double-*Pauson–Khand process* was reported.¹⁵⁶⁷ In some cases, an aldehyde can serve as the source of the carbonyl for carbonylation.¹⁵⁶⁸



The accepted mechanism was proposed by Magnus and Principe,¹⁵⁶⁹ shown for the formation of **109**,¹⁵⁷⁰ and supported by Krafft's work.¹⁵⁷¹ It has been shown that CO is lost from the *Pauson–Khand* complex prior to alkene coordination and insertion.¹⁵⁷² Calculations

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¹⁵⁷⁰ For a review, see Brummond, K.M.; Kent, J.L. *Tetrahedron* **2000**, 56, 3263.

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concluded that the LUMO of the coordinated alkene plays a crucial role in alkene reactivity by determining the degree of back-donation in the complex.¹⁵⁷³

Other carbonylation methods are available. Carbonylation occurs with conjugated ketones to give 1,4-diketones, using phenylboronic acid (see Reaction **13-12**), CO and a Rh catalyst.¹⁵⁷⁴ A noncarbonylation route treated a conjugated diene with an excess of *tert*-butyllithium, and quenching with CO₂ led to a cyclopentadienone.¹⁵⁷⁵ When quenched with CO rather than CO₂, a nonconjugated cyclopentenone was formed.¹⁵⁷⁶ Note that a carbonylation reaction with CO, a diyne, and an Ir¹⁵⁷⁷ or a Co catalyst¹⁵⁷⁸ provided similar molecules.

With any method, if the alkene contains a functional group (e.g., OH, NH₂, or CONH₂), the corresponding lactone (Reaction **16-63**),¹⁵⁷⁹ lactam (Reaction **16-74**), or cyclic imide may be the product.¹⁵⁸⁰ Titanium,¹⁵⁸¹ Pd,¹⁵⁸² Ru,¹⁵⁸³ and Rh¹⁵⁸⁴ catalysts have been used to generate lactones. Allenic alcohols are converted to butenolides with 10 atm of CO and a Ru catalyst.¹⁵⁸⁵ Larger ring conjugated lactones can also be formed by this route using the appropriate allenic alcohol.¹⁵⁸⁶ Propargylic alcohols lead to β -lactones¹⁵⁸⁷ or to butenolides with CO/H₂O and a Rh catalyst.¹⁵⁸⁸ Allenic tosyl-amides are converted to *N*-tosyl α,β -unsaturated pyrrolidinones using 20 atm of CO and a Ru catalyst.¹⁵⁸⁹ Conjugated imines are converted to similar products with CO, ethylene, and a Ru catalyst.¹⁵⁹⁰ Propargyl alcohols generate lactones when treated with a chromium pentacarbonyl carbene complex.¹⁵⁹¹ Amines add to allenes, in the presence of CO and a Pd catalyst, to form conjugated amides.¹⁵⁹²

The reaction of a secondary amine, CO, a terminal alkyne, and *t*-BuMe₂SiH with a Rh catalyst led to a conjugated amide bearing the silyl group of the C=C unit.¹⁵⁹³ Reaction of a molecule containing an amine and an alkene unit was carboxylated with CO in the presence of a Pd catalyst to give a lactam.¹⁵⁹⁴ A similar reaction with a molecule containing an amine and an alkyne also generated a lactam, in the presence of CO and

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¹⁵⁷⁹ Dong, C.; Alper, H. *J. Org. Chem.* **2004**, 69, 5011.

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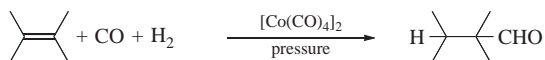
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a Rh catalyst.¹⁵⁹⁵ An intramolecular carbonylation reaction of a conjugated imine, with CO, ethylene and a Ru catalyst, led to a highly substituted β,γ -unsaturated lactam.¹⁵⁹⁶

15-37 Hydroformylation

Hydro-formyl-addition



Alkenes can be hydroformylated¹⁵⁹⁷ by treatment with CO and hydrogen over a catalyst, usually a Co carbonyl (see below for a description of the mechanism) or a Rh complex,¹⁵⁹⁸ but other transition metal compounds have also been used. Cobalt catalysts are less active than the Rh type, and catalysts of other metals are generally less active.¹⁵⁹⁹ Commercially, this is called the *oxo process*, but it can be carried out in the laboratory in an ordinary hydrogenation apparatus. The order of reactivity is straight-chain terminal alkenes > straight-chain internal alkenes > branched-chain alkenes. With terminal alkenes, for example, the aldehyde unit is formed on both the primary and secondary carbon, but proper choice of catalyst and additive leads to selectivity for the secondary¹⁶⁰⁰ or primary product.¹⁶⁰¹ Alkylidenecyclopropane derivatives undergo hydroformylation to give aldehydes with a quaternary center.¹⁶⁰²

Good yields for hydroformylation have been reported using Rh catalysts in the presence of certain other additives.¹⁶⁰³ Among the side reactions are the *aldol Reaction* (**16-34**), acetal formation, the *Tischenko Reaction* (**19-82**), and polymerization. In one case using a Rh catalyst, 2-octene gave nonanal, presumably via a η^3 -allyl complex (Sec. 3.C).¹⁶⁰⁴ Conjugated dienes give dialdehydes when Rh catalysts are used¹⁶⁰⁵ but saturated monoaldehydes (the second double bond is reduced) with cobalt carbonyls. Both 1,4- and 1,5-dienes may give cyclic ketones.¹⁶⁰⁶

Hydroformylation of triple bonds proceeds very slowly, and few examples have been reported.¹⁶⁰⁷ However, in the presence of a Rh catalyst, the triple bond of a conjugated

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¹⁶⁰⁷ See Botteghi, C.; Salomon, C. *Tetrahedron Lett.* **1974**, 4285. For an indirect method, see Campi, E.; Fitzmaurice, N.J.; Jackson, W.R.; Perlmutter, P.; Smallridge, A.J. *Synthesis* **1987**, 1032.

enyne is formylated.¹⁶⁰⁸ The Rh catalyzed reaction can be regioselective.¹⁶⁰⁹ Many functional groups (e.g., OH, CHO, CO₂R,¹⁶¹⁰ CN), can be present in the molecule, although halogens usually interfere. Stereoselective syn addition has been reported,¹⁶¹¹ and also stereoselective anti addition.¹⁶¹²

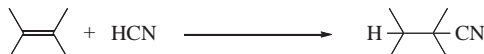
Asymmetric hydroformylation of alkenes has been accomplished with a chiral catalyst,¹⁶¹³ and in the presence of chiral additives.¹⁶¹⁴ The choice of ligand is important in such reactions.¹⁶¹⁵ Cyclization to prolinal derivatives has been reported with allylic amines.¹⁶¹⁶

When dicobalt octacarbonyl [Co(CO)₄]₂ is the catalyst, the species that actually adds to the double bond is tricarbonylhydrocobalt [HCo(CO)₃].¹⁶¹⁷ Carbonylation [RCo(CO)₃ + CO → RCo(CO)₄] takes place followed by a rearrangement and a reduction of the C–Co bond, similar to steps 4 and 5 of the nickel carbonyl mechanism shown in Reaction 15-35. The reducing agent in the reduction step is tetracarbonylhydrocobalt [HCo(CO)₄],¹⁶¹⁸ or, under some conditions, H₂.¹⁶¹⁹ When HCo(CO)₄ was the agent used to hydroformylate styrene, the observation of CIDNP (Sec. 5.C.i) indicated that the mechanism is different, and involves free radicals.¹⁶²⁰ Key intermediates have been detected in the Co catalyzed hydroformylation reaction.¹⁶²¹ Alcohols can be obtained by allowing the reduction to continue after all the CO is used up. It has been shown¹⁶²² that the formation of alcohols is a second step, occurring after the formation of aldehydes, and that HCo(CO)₃ is the reducing agent.

OS VI, 338.

15-38 Addition of HCN

Hydro-cyano-addition



Ordinary alkenes do not react with HCN, but polyhalo alkenes and alkenes of the form C=C–Z add HCN to give nitriles.¹⁶²³ The reaction is therefore a nucleophilic addition

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¹⁶²² Aldridge, C.L.; Jonassen, H.B. *J. Am. Chem. Soc.* **1963**, *85*, 886.

¹⁶²³ See Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 2, Wiley, NY, **1983**, pp. 1345–1390; Nagata, W.; Yoshioka, M. *Org. React.* **1977**, *25*, 255; Brown, E.S. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, **1977**, pp. 655–672.

and is base catalyzed. Hydrogen cyanide can be added to ordinary alkenes in the presence of dicobalt octacarbonyl¹⁶²⁴ or certain other transition metal compounds.¹⁶²⁵ When Z is COR or, more especially, CHO, 1,2-addition (Reaction **16-53**) is an important competing reaction and may be the only reaction. An acid-catalyzed hydrocyanation is also known.¹⁶²⁶ Triple bonds react very well when catalyzed by an aqueous solution of CuCl, NH₄Cl, and HCl or by Ni or Pd compounds.¹⁶²⁷ The HCN can be generated *in situ* from acetone cyanohydrin (see Reaction **16-52**), avoiding the use of the poisonous HCN.¹⁶²⁸ Alkenes react with HCN via this procedure to give a nitrile in the presence of a Ni complex.¹⁶²⁹

One or 2 molar equivalents of HCN can be added to a triple bond, since the initial product is a *Michael-type* substrate. Acrylonitrile is commercially prepared this way, by the addition of HCN to acetylene. Alkylaluminum cyanides (e.g., Et₂AlCN), or mixtures of HCN and trialkylalanes (R₃Al) are especially good reagents for conjugate addition of HCN¹⁶³⁰ to α,β -unsaturated ketones and α,β -unsaturated acyl halides. An indirect method for the addition of HCN to ordinary alkenes uses an isocyanide (RNC) and *Schwartz's reagent* (see Reaction **15-17**); this method gives anti-Markovnikov addition.¹⁶³¹ *tert*-Butyl isocyanide and TiCl₄ have been used to add HCN to C=C—Z alkenes.¹⁶³² Pretreatment with NaI/Me₃SiCl followed by CuCN converts alkynes to vinyl nitriles.¹⁶³³

When an alkene is treated with Me₃SiCN and AgClO₄, followed by aq NaHCO₃, the product is the isonitrile (RNC) formed with *Markovnikov* selectivity.¹⁶³⁴ Enantioselective cyanation using TMSCN and HCN, and a Gd catalyst, leads to β -cyano amides.¹⁶³⁵

OS **I**, 451; **II**, 498; **III**, 615; **IV**, 392, 393, 804; **V**, 239, 572; **VI**, 14.

For addition of ArH, see Reaction **11-12** (Friedel–Crafts alkylation).

15.C.iii. Reactions in Which Hydrogen Adds to Neither Side

Some of these reactions are *cycloadditions* (Reactions **15-50**, **15-62**, **15-54**, and **15-57–15-66**). In such cases, addition to the multiple bond closes a ring:



¹⁶²⁴ Arthur, Jr., P.; England, D.C.; Pratt, B.C.; Whitman, G.M. *J. Am. Chem. Soc.* **1954**, 76, 5364.

¹⁶²⁵ See Brown, E.S. in Wender, P.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, **1977**, pp. 658–667; Tolman, C.A.; McKinney, R.J.; Seidel, W.C.; Druliner, J.D.; Stevens, W.R. *Adv. Catal.* **1985**, 33, 1. For studies of the mechanism see McKinney, R.J.; Roe, D.C. *J. Am. Chem. Soc.* **1986**, 108, 5167; Funabiki, T.; Tatsami, K.; Yoshida, S. *J. Organomet. Chem.* **1990**, 384, 199. See also, Bini, L.; Müller, C.; Vogt, D. *Chem. Commun.* **2010**, 8325.

¹⁶²⁶ Yanagisawa, A.; Nezu, T.; Mohri, S.-i. *Org. Lett.* **2009**, 11, 5286.

¹⁶²⁷ Jackson, W.R.; Lovel, C.G. *Aust. J. Chem.* **1983**, 36, 1975.

¹⁶²⁸ Jackson, W.R.; Perlmutter, P. *Chem. Br.* **1986**, 338.

¹⁶²⁹ Yan, M.; Xu, Q.-Y.; Chan, A.S.C. *Tetrahedron Asymmetry* **2000**, 11, 845.

¹⁶³⁰ See Nagata, W.; Yoshioka, M. *Org. React.* **1977**, 25, 255.

¹⁶³¹ Buchwald, S.L.; LeMaire, S.J. *Tetrahedron Lett.* **1987**, 28, 295.

¹⁶³² Ito, Y.; Kato, H.; Imai, H.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, 104, 6449.

¹⁶³³ Luo, F.-T.; Ko, S.-L.; Chao, D.-Y. *Tetrahedron Lett.* **1997**, 38, 8061.

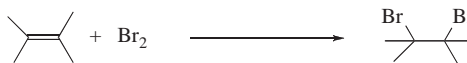
¹⁶³⁴ Kitano, Y.; Chiba, K.; Tada, M. *Synlett* **1999**, 288.

¹⁶³⁵ Mita, T.; Kazuki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, 127, 514.

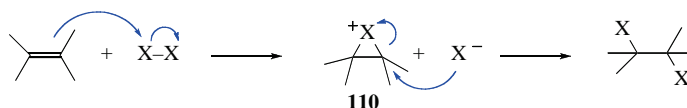
A. Halogen on One or Both Sides

15-39 Halogenation of Double and Triple Bonds (Addition of Halogen, Halogen)

Dihalo-addition



Most double bonds are easily halogenated¹⁶³⁶ with bromine, chlorine, or inter-halogen compounds.¹⁶³⁷ Substitution can compete with addition in some cases.¹⁶³⁸ Iodination has also been accomplished, but the reaction is slower.¹⁶³⁹ Under free radical conditions, iodination proceeds more easily.¹⁶⁴⁰ However, *vic*-diiodides are generally unstable and tend to revert to iodine and the alkene.



The mechanism is usually electrophilic (see Sec. 15.A.i), involving formation of an halonium ion (Reaction **110**),¹⁶⁴¹ followed by nucleophilic ring opening to give the *vic*-dihaloalkane. Nucleophilic attack occurs with selectivity for the less substituted carbon. When free radical initiators (or UV light) are present, addition can occur by a free radical mechanism.¹⁶⁴² Once Br^\bullet or Cl^\bullet radicals are formed, however, substitution may compete (Reactions **14-1** and **14-3**). This is especially important when the alkene has allylic or benzylic hydrogen atoms. Under free radical conditions (UV light) bromine or chlorine adds to a benzene substituent to give, respectively, hexabromo- and hexachlorocyclohexane. These are mixtures of stereoisomers (see Sec. 4.K.ii).¹⁶⁴³

Under ordinary conditions fluorine itself is too reactive to give simple addition, and mixtures are obtained.¹⁶⁴⁴ However, F_2 has been successfully added to certain double bonds in an inert solvent at low temperatures (-78°C), usually by diluting the F_2 gas with Ar or N_2 .¹⁶⁴⁵ Addition of fluorine has also been accomplished with other reagents (e.g., *p*-Tol- $\text{IF}_2/\text{Et}_3\text{N}\cdot 5\text{ HF}$),¹⁶⁴⁶ and a mixture of PbO_2 and SF_4 .¹⁶⁴⁷ The Au catalyzed reaction of $\text{Et}_3\text{N}\text{--HF}$ with alkynes gives vinyl fluorides.¹⁶⁴⁸

¹⁶³⁶ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 629–632.

¹⁶³⁷ de la Mare, P.B.D. *Electrophilic Halogenation* Cambridge University Press, Cambridge, **1976**; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 422–431.

¹⁶³⁸ McMillen, D.W.; Grutzner, J.B. *J. Org. Chem.* **1994**, *59*, 4516.

¹⁶³⁹ Zanger, M.; Rabinowitz, J.L. *J. Org. Chem.* **1975**, *40*, 248.

¹⁶⁴⁰ Ayres, R.L.; Michejda, C.J.; Rack, E.P. *J. Am. Chem. Soc.* **1971**, *93*, 1389.

¹⁶⁴¹ See Lenoir, D.; Chiappe, C. *Chem. Eur. J.* **2003**, *9*, 1037. For a theoretical study of these intermediates, see Okazaki, T.; Laali, K.K. *J. Org. Chem.* **2005**, *70*, 9139. Also see Zabalov, M.V.; Karlov, S.S.; Lemenovskii, D.A.; Zaitseva, G.S. *J. Org. Chem.* **2005**, *70*, 9175.

¹⁶⁴² See Dessau, R.M. *J. Am. Chem. Soc.* **1979**, *101*, 1344.

¹⁶⁴³ See Cais, M. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, **1964**, pp. 993.

¹⁶⁴⁴ See Fuller, G.; Stacey, F.W.; Tatlow, J.C.; Thomas, C.R. *Tetrahedron* **1962**, *18*, 123.

¹⁶⁴⁵ Rozen, S.; Brand, M. *J. Org. Chem.* **1986**, *51*, 3607.

¹⁶⁴⁶ Hara, S.; Nakahigashi, J.; Ishi-i, K.; Sawaguchi, M.; Sakai, H.; Fukuhara, T.; Yoneda, N. *Synlett* **1998**, 495.

¹⁶⁴⁷ Bissell, E.R.; Fields, D.B. *J. Org. Chem.* **1964**, *29*, 1591.

¹⁶⁴⁸ Akana, J.A.; Bhattacharyya, K.X.; Müller, P.; Sadighi, J.P. *J. Am. Chem. Soc.* **2007**, *129*, 7736.

The reaction with bromine is very rapid and is easily carried out at room temperature,¹⁶⁴⁹ although the reaction is reversible under some conditions.¹⁶⁵⁰ In the case of bromine, an alkene $\cdot\text{Br}_2$ complex has been detected in at least one case.¹⁶⁵¹ Bromine is often used as a qualitative or quantitative test for unsaturation¹⁶⁵² because the vast majority of double bonds can be successfully brominated. Even when functions (aldehyde, ketone, amine, etc.) are present in the molecule, they do not interfere, since the reaction with double bonds is faster. Bromination has been carried out in an ionic liquid.¹⁶⁵³

Several reagents other than chlorine gas add Cl_2 to double bonds, among them $\text{Me}_3\text{SiCl}^-\text{MnO}_2$,¹⁶⁵⁴ $\text{BnNEt}_3\text{MnO}_4/\text{Me}_3\text{SiCl}$,¹⁶⁵⁵ and KMnO_4 -oxalyl chloride.¹⁶⁵⁶ A convenient reagent for the addition of Br_2 to a double bond on a small scale is the commercially available pyridinium bromide perbromide ($\text{C}_5\text{H}_5\text{NH}^+\text{Br}_3^-$).¹⁶⁵⁷ Potassium bromide with ceric ammonium nitrate, in water/dichloromethane, gives the dibromide.¹⁶⁵⁸ A combination of KBr and Selectfluor also give the dibromide.¹⁶⁵⁹ A combination of CuBr_2 in aq THF and a chiral ligand led to the dibromide with good enantioselectivity.¹⁶⁶⁰ Either Br_2 or Cl_2 can also be added using CuBr_2 or CuCl_2 in the presence of acetonitrile, methanol, or triphenylphosphine.¹⁶⁶¹ Alkenes are brominated using KBr and diacetoxiodobenzene.¹⁶⁶² Note that theoretical and experimental studies have shown that in nonpolar solvents the bromination of acetylene via a covalent tribromide adduct is strongly favored over the textbook mechanism via a bridged bromonium ion.

Mixed halogenations have also been achieved, and the order of activity for some of the reagents is $\text{BrCl} > \text{ICl}^{1663} > \text{Br}_2 > \text{IBr} > \text{I}_2$.¹⁶⁶⁴ Mixtures of Br_2 and Cl_2 have been used to give bromochlorination,¹⁶⁶⁵ as has tetrabutylammonium dichlorobromate ($\text{Bu}_4\text{NBrCl}_2$).¹⁶⁶⁶ Iodochlorination has been achieved with KICl_2 ,¹⁶⁶⁷ CuCl_2 , and either I_2 , HI , or CdI_2 ; iodofluorination¹⁶⁶⁸ with mixtures of AgF and I_2 ,¹⁶⁶⁹ and mixtures of N -bromo amides in anhydrous HF give bromofluorination.¹⁶⁷⁰ Bromo-, iodo-, and

¹⁶⁴⁹ See Bellucci, G.; Chiappe, C. *J. Org. Chem.* **1993**, 58, 7120.

¹⁶⁵⁰ Zheng, C.Y.; Slebocka-Tilk, H.; Nagorski, R.W.; Alvarado, L.; Brown, R.S. *J. Org. Chem.* **1993**, 58, 2122.

¹⁶⁵¹ Bellucci, G.; Chiappe, C.; Bianchini, R.; Lenoir, D.; Herges, R. *J. Am. Chem. Soc.* **1995**, 117, 12001.

¹⁶⁵² See Kuchar, E.J. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, **1964**, pp. 273–280.

¹⁶⁵³ Chiappe, C.; Capraro, D.; Conte, V.; Piccaccini, D. *Org. Lett.* **2001**, 3, 1061.

¹⁶⁵⁴ Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* **1989**, 108, 360.

¹⁶⁵⁵ Markó, I.E.; Richardson, P.R.; Bailey, M.; Maguire, A.R.; Coughlan, N. *Tetrahedron Lett.* **1997**, 38, 2339.

¹⁶⁵⁶ Markó, I.E.; Richardson, P.F. *Tetrahedron Lett.* **1991**, 32, 1831.

¹⁶⁵⁷ Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1, Wiley, NY, **1967**, pp. 967–970. For a discussion of the mechanism, see Bellucci, G.; Bianchini, R.; Vecchiani, S. *J. Org. Chem.* **1986**, 51, 4224.

¹⁶⁵⁸ Nair, V.; Panicker, S.B.; Augustine, A.; George, T.G.; Thomas, S.; Vairamani, M. *Tetrahedron* **2001**, 57, 7417.

¹⁶⁵⁹ Ye, C.; Shreeve, J.M. *J. Org. Chem.* **2004**, 69, 8561.

¹⁶⁶⁰ El-Quaisiri, A.K.; Qaseer, H.A.; Katsigras, G.; Lorenzi, P.; Tribedi, U.; Tracz, S.; Hartman, A.; Miller, J.A.; Henry, P.M. *Org. Lett.* **2003**, 5, 439.

¹⁶⁶¹ Uemura, S.; Okazaki, H.; Onoe, A.; Okano, M. *J. Chem. Soc. Perkin Trans. 1*, **1977**, 676.

¹⁶⁶² Das, B.; Srinivas, Y.; Sudhakar, C.; Damodar, K.; Narender, R. *Synth. Commun.* **2009**, 39, 220.

¹⁶⁶³ See McClelland, C.W. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, **1983**, pp. 85–164.

¹⁶⁶⁴ White, E.P.; Robertson, P.W. *J. Chem. Soc.* **1939**, 1509.

¹⁶⁶⁵ Buckles, R.E.; Forrester, J.L.; Burham, R.L.; McGee, T.W. *J. Org. Chem.* **1960**, 25, 24.

¹⁶⁶⁶ Negoro, T.; Ikeda, Y. *Bull. Chem. Soc. Jpn.* **1986**, 59, 3519.

¹⁶⁶⁷ Zefirov, N.S.; Sereda, G.A.; Sosounek, S.E.; Zyk, N.V.; Likhomanova, T.I. *Synthesis* **1995**, 1359.

¹⁶⁶⁸ See Sharts, C.M.; Sheppard, W.A. *Org. React.* **1974**, 21, 125, see pp. 137–157; Boguslavskaya, L.S. *Russ. Chem. Rev.* **1984**, 53, 1178.

¹⁶⁶⁹ Evans, R.D.; Schauble, J.H. *Synthesis* **1987**, 551; Kuroboshi, M.; Hiyama, T. *Synlett* **1991**, 185.

¹⁶⁷⁰ Pattison, F.L.M.; Peters, D.A.V.; Dean, F.H. *Can. J. Chem.* **1965**, 43, 1689. For other methods, see Shimizu, M.; Nakahara, Y.; Yoshioka, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1881.

chlorofluorination have also been achieved by treatment of the substrate with a solution of Br_2 , I_2 , or an *N*-halo amide in polyhydrogen fluoride–pyridine;¹⁶⁷¹ while addition of I along with Br, Cl, or F has been accomplished with the reagent bis(pyridine)iody(I) tetrafluoroborate $[\text{I}(\text{Py})_2\text{BF}_4]$ and Br^- , Cl^- , or F^- , respectively.¹⁶⁷² This reaction, which is also successful for triple bonds,¹⁶⁷³ can be extended to addition of I and other nucleophiles (e.g., NCO , OH , OAc , and NO_2).¹⁶⁷³

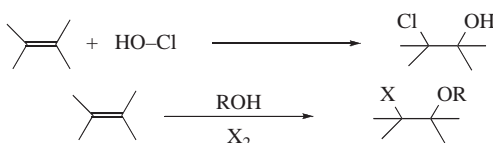
Conjugated systems give both 1,2- and 1,4-addition.¹⁶⁴⁴ Triple bonds add bromine, although generally more slowly than double bonds (see Sec. 15.B.i). Molecules that contain both double and triple bonds are preferentially attacked at the double bond. Addition of 2 molar equivalents of bromine to triple bonds gives tetrabromo products. There is evidence that the addition of the first molar equivalent of bromine to a triple bond may take place by a nucleophilic mechanism.¹⁶⁷⁴ Molecular diiodine on Al_2O_3 adds to triple bonds to give good yields of 1,2-diiodoalkenes.¹⁶⁷⁵ Interestingly, 1,1-diiodo alkenes are prepared from an alkynyltin compound, via initial treatment with $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$, and then 2.15 equiv of iodine.¹⁶⁷⁶ A mixture of NaBO_3 and NaBr adds two bromine atoms across a triple bond.¹⁶⁷⁷ With allenes it is easy to stop the reaction after only 1 equiv has added, to give $\text{X}-\text{C}=\text{C}-\text{CX}=\text{C}$.¹⁶⁷⁸ Addition of halogen to ketenes gives α -halo acyl halides, but the yields are not good.

OS **I**, 205, 521; **II**, 171, 177, 270, 408; **III**, 105, 123, 127, 209, 350, 526, 531, 731, 785; **IV**, 130, 195, 748, 851, 969; **V**, 136, 370, 403, 467; **VI**, 210, 422, 675, 862, 954; **IX**, 117; **76**, 159.

15-40 Addition of Hypohalous Acids and Hypohalites (Addition of Halogen, Oxygen)

Hydroxy-chloro-addition, and so on.¹⁶⁷⁹

Alkoxy-chloro-addition, and so on



Hypohalous acids (HOCl , HOBr , and HOI) react with alkenes¹⁶⁸⁰ to produce halohydrins.¹⁶⁸¹ Both HOBr and HOCl can be generated *in situ* by the reaction between water and Br_2 or Cl_2 , respectively. The compound HOI , generated from I_2 and H_2O , also adds to

¹⁶⁷¹ Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* **1979**, *44*, 3872. See Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *J. Org. Chem.* **1989**, *54*, 4294; Ichihara, J.; Funabiki, K.; Hanafusa, T. *Tetrahedron Lett.* **1990**, *31*, 3167.

¹⁶⁷² Barluenga, J.; González, J.M.; Campos, P.J.; Asensio, G. *Angew. Chem. Int. Ed.* **1985**, *24*, 319.

¹⁶⁷³ Barluenga, J.; Rodríguez, M.A.; González, J.M.; Campos, P.J.; Asensio, G. *Tetrahedron Lett.* **1986**, *27*, 3303.

¹⁶⁷⁴ Sinn, H.; Hopperditzel, S.; Sauermann, D. *Monatsh. Chem.* **1965**, *96*, 1036.

¹⁶⁷⁵ Hondrogianis, G.; Lee, L.C.; Kabalka, G.W.; Pagni, R.M. *Tetrahedron Lett.* **1989**, *30*, 2069.

¹⁶⁷⁶ Dabdoub, M.J.; Dabdoub, V.B.; Baroni, A.C.M. *J. Am. Chem. Soc.* **2001**, *123*, 9694.

¹⁶⁷⁷ Kabalka, G.W.; Yang, K. *Synth. Commun.* **1998**, *28*, 3807; Kabalka, G.W.; Yang, K.; Reddy, N.K.; Narayana, A. *Synth. Commun.* **1998**, *28*, 925.

¹⁶⁷⁸ See Jacobs, T.L. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, **1982**, pp. 466–483.

¹⁶⁷⁹ Addends are listed in order of priority in the Cahn–Ingold–Prelog system (Sec. 4.E.i).

¹⁶⁸⁰ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 638–642.

¹⁶⁸¹ See Boguslavskaya, L.S. *Russ. Chem. Rev.* **1972**, *41*, 740.

double bonds, if the reaction is carried out in tetramethylene sulfone–CHCl₃¹⁶⁸² or if an oxidizing agent (e.g., HIO₃) is present.¹⁶⁸³ Iodine and cerium sulfate in aq acetonitrile generates iodohydrins,¹⁶⁸⁴ as do iodine and ammonium acetate in acetic acid,¹⁶⁸⁵ or NaIO₄ with sodium bisulfite.¹⁶⁸⁶

The HOBr can also be conveniently added by the use of a reagent consisting of an *N*-bromo amide (e.g., NBS or *N*-bromoacetamide) and a small amount of water in a solvent (e.g., DMSO or dioxane).¹⁶⁸⁷ *N*-Iodosuccinimide in aq dimethoxyethane leads to the iodohydrin.¹⁶⁸⁸ An especially powerful reagent for HOCl addition is *tert*-butyl hydroperoxide (or di-*tert*-butyl peroxide) along with TiCl₄.¹⁶⁸⁹ Chlorohydrins can be conveniently prepared by treatment of the alkene with Chloramine T (TsNCl[−] Na⁺)¹⁶⁹⁰ in acetone–water.¹⁶⁹¹ The compound HOI can be added by treatment of alkenes with periodic acid and NaHSO₃.¹⁶⁹² There are Se catalyzed iodohydrin forming reactions.¹⁶⁹³ The reaction of an alkene with polymeric (SnO)_m and then HCl with Me₃SiOOSiMe₃, leads to the chlorohydrin.¹⁶⁹⁴ Hypervalent iodine compounds react with an alkene and iodine in aqueous media to give the iodohydrin.¹⁶⁹⁵ Halohydrins are produced in ionic liquids.¹⁶⁹⁶ *N*-Bromo and *N*-iodosaccharin have been used to prepare the corresponding halohydrins.¹⁶⁹⁷

The compound HOF has also been added, but this reagent is difficult to prepare in a pure state and *explosions have occurred*.¹⁶⁹⁸

The mechanism of HOX addition is electrophilic, with initial attack by the alkene on the positive halogen end of the HOX dipole. Following *Markovnikov's rule*, the positive halogen goes to the side of the double bond that has more hydrogen atoms (forming a more stable carbocation). This carbocation (or bromonium or iodonium ion in the absence of an aqueous solvent) reacts with [−]OH or H₂O to give the product. If the substrate is treated with Br₂ or Cl₂ (or another source of positive halogen, e.g., NBS) in an alcohol or a carboxylic acid solvent, it is possible to obtain, directly C—C—C—OR or X—C—C—OCOR, respectively (see also, Reaction 15-48).¹⁶⁹⁹ Even the weak nucleophile CF₃SO₂O[−] can participate in the second step. The addition of Cl₂ or Br₂ to alkenes in the presence of this ion resulted in the formation of some β-haloalkyl triflates.¹⁷⁰⁰ There is evidence that the mechanism with Cl₂ and H₂O is

¹⁶⁸² Cambie, R.C.; Noall, W.I.; Potter, G.J.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1*, **1977**, 266.

¹⁶⁸³ See Antonioletti, R.; D'Auria, M.; De Mico, A.; Piancatelli, G.; Scettri, A. *Tetrahedron* **1983**, 39, 1765.

¹⁶⁸⁴ Horiuchi, C.A.; Ikeda, A.; Kanamori, M.; Hosokawa, H.; Sugiyama, T.; Takahashi, T.T. *J. Chem. Res. (S)* **1997**, 60.

¹⁶⁸⁵ Myint, Y.Y.; Pasha, M.A. *Synth. Commun.* **2004**, 34, 4477.

¹⁶⁸⁶ Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, 59, 5550.

¹⁶⁸⁷ See Dalton, D.R.; Dutta, V.P. *J. Chem. Soc. B* **1971**, 85; Sisti, A.J. *J. Org. Chem.* **1970**, 35, 2670.

¹⁶⁸⁸ Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **2000**, 41, 193.

¹⁶⁸⁹ Klunder, J.M.; Caron, M.; Uchiyama, M.; Sharpless, K.B. *J. Org. Chem.* **1985**, 50, 912.

¹⁶⁹⁰ See Bremner, D.H. in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, **1985**, pp. 9–59; Campbell, M.M.; Johnson, G. *Chem. Rev.* **1978**, 78, 65.

¹⁶⁹¹ Damin, B.; Garapon, J.; Sillion, B. *Synthesis* **1981**, 362.

¹⁶⁹² Ohta, M.; Sakata, Y.; Takeuchi, T.; Ishii, Y. *Chem. Lett.* **1990**, 733.

¹⁶⁹³ Carrera, I.; Brovotto, M.C.; Seoane, G.A. *Tetrahedron Lett.* **2006**, 47, 7849.

¹⁶⁹⁴ Sakurada, I.; Yamasaki, S.; Göttlich, R.; Iida, T.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, 122, 1245.

¹⁶⁹⁵ DeCorso, A.R.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* **2001**, 42, 7245.

¹⁶⁹⁶ Yadav, J.S.; Reddy, B.V.S.; Baishya, G.; Harshavardhan, S.J.; Chary, Ch.J.; Gupta, M.K. *Tetrahedron Lett.* **2005**, 46, 3569.

¹⁶⁹⁷ Urankar, D.; Rutar, I.; Modéc, B.; Dolenc, D. *Eur. J. Org. Chem.* **2005**, 2349.

¹⁶⁹⁸ Migliorese, K.G.; Appelman, E.H.; Tsangaris, M.N. *J. Org. Chem.* **1979**, 44, 1711.

¹⁶⁹⁹ Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 642–643.

¹⁷⁰⁰ Zefirov, N.S.; Koz'min, A.S. *Acc. Chem. Res.* **1985**, 18, 154; *Sov. Sci. Rev. Sect. B* **1985**, 7, 297.

different from that with HOCl.¹⁷⁰¹ Both HOCl and HOBr can be added to triple bonds to give dihalo carbonyl compounds ($-\text{CX}_2-\text{CO}-$).

Alcohols and halogens react with alkenes to form halo ethers. When a homoallylic alcohol is treated with bromine, cyclization occurs to give a 3-bromotetrahydrofuran derivative.¹⁷⁰² *tert*-Butyl hypochlorite (Me_3COCl), hypobromite, and hypoiodite¹⁷⁰³ add to double bonds to give halogenated *tert*-butyl ethers ($\text{X}-\text{C}-\text{C}-\text{OCMe}_3$). This is a convenient method for the preparation of tertiary ethers. Iodine and ethanol convert some alkenes to iodo-ethers.¹⁷⁰⁴ Iodine, alcohol, and a $\text{Ce}(\text{OTf})_2$ catalyst also generates the iodo-ether.¹⁷⁰⁵ When Me_3COCl or Me_3COBr is added to alkenes in the presence of excess ROH, the ether $\text{X}-\text{C}-\text{C}-\text{OR}$ is produced.¹⁷⁰⁶ Vinylic ethers give β -halo acetals.¹⁷⁰⁷ Chlorine acetate [solutions of which are prepared by treating Cl_2 with $\text{Hg}(\text{OAc})_2$ in an appropriate solvent] adds to alkenes to give acetoxy chlorides.¹⁷⁰⁸ Acetoxy fluorides have been obtained by treatment of alkenes with CH_3COOF .¹⁷⁰⁹

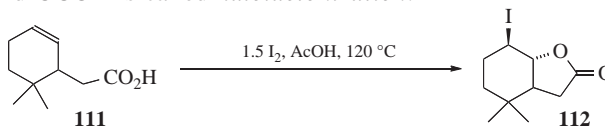
For a method of iodoacetyl addition, see Reaction 15-48.

OS I, 158; IV, 130, 157; VI, 184, 361, 560; VII, 164; VIII, 5, 9.

15-41 Halolactonization and Halolactamization

Halo-alkoxylation

Halo esters can be formed by addition of halogen atoms and ester groups to an alkene. Alkene carboxylic acids give a tandem reaction of formation of a halonium ion followed by intramolecular displacement of the carboxylic group to give a halo lactone. This tandem addition of X and OCOR is called *halolactonization*.¹⁷¹⁰



The most common version of this reaction is known as *iodolactonization*,¹⁷¹¹ and a typical example is the conversion of **111** to **112**.¹⁷¹² Bromo lactones and, to a lesser extent, chloro lactones have also been prepared. In general, addition of the halogen to an alkenyl acid, as shown, leads to the halo-lactone. Other reagents include $\text{I}^+(\text{collidine})_2\text{PF}_6^-$,¹⁷¹³ KI/sodium

¹⁷⁰¹ Buss, E.; Rockstuhl, A.; Schnurpfeil, D. *J. Prakt. Chem.* **1982**, 324, 197.

¹⁷⁰² Chirskaya, M.V.; Vasil'ev, A.A.; Sergovskaya, N.L.; Shovshinev, S.V.; Sviridov, S.I. *Tetrahedron Lett.* **2004**, 45, 8811.

¹⁷⁰³ Glover, S.A.; Goosen, A. *Tetrahedron Lett.* **1980**, 21, 2005.

¹⁷⁰⁴ Sanseverino, A.M.; de Mattos, M.C.S. *Synthesis* **1998**, 1584. See Horiuchi, C.A.; Hosokawa, H.; Kanamori, M.; Muramatsu, Y.; Ochiai, K.; Takahashi, E. *Chem. Lett.* **1995**, 13.

¹⁷⁰⁵ Iranpoor, N.; Shekarriz, M. *Tetrahedron* **2000**, 56, 5209.

¹⁷⁰⁶ Bresson, A.; Dauphin, G.; Geneste, J.; Kergomard, A.; Lacourt, A. *Bull. Soc. Chim. Fr.* **1970**, 2432; **1971**, 1080.

¹⁷⁰⁷ Weissmehl, K.; Lederer, M. *Chem. Ber.* **1963**, 96, 77.

¹⁷⁰⁸ Wilson, M.A.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 2*, **1976**, 141. See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 643–644.

¹⁷⁰⁹ Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* **1985**, 50, 4753.

¹⁷¹⁰ See Cardillo, G.; Orena, M. *Tetrahedron* **1990**, 46, 3321; Dowle, M.D.; Davies, D.I. *Chem. Soc. Rev.* **1979**, 8, 171. For a list of reagents that accomplish this, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1870–1876. Also see Bartlett, P.A. in Morrison, J.D. *Organic Synthesis* Vol. 3, Wiley, NY, **1984**, pp. 411–454, 416–425.

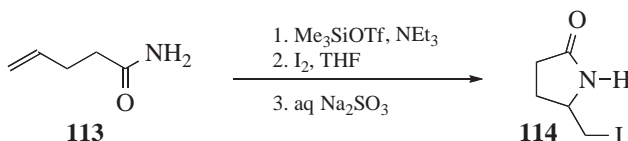
¹⁷¹¹ Corey, E.J.; Albonico, S.M.; Koelliker, V.; Schaaf, T.K.; Varma, R.K. *J. Am. Chem. Soc.* **1971**, 93, 1491.

¹⁷¹² Yaguchi, Y.; Akiba, M.; Harada, M.; Kato, T. *Heterocycles* **1996**, 43, 601.

¹⁷¹³ Homsí, F.; Rousseau, G. *J. Org. Chem.* **1998**, 63, 5255.

persulfate.¹⁷¹⁴ The Ti^{1715} and Y^{1716} reagents, along with the halogen, have also been used. An enantioselective 5-endo-halolactonization procedure has been reported using systems, such as iodobis(collidine) hexafluorophosphate or AgSbF_6 , followed by iodine.¹⁷¹⁷ When done in the presence of a chiral Ti reagent, I_2 , and CuO , lactones are formed with good enantioselectivity.¹⁷¹⁸ Iodine monochloride (ICl) has been used, with formation of a quaternary center at the oxygen-bearing carbon of the lactone.¹⁷¹⁹ Organocatalysts have also been used to mediate asymmetric halolactonization reactions.¹⁷²⁰ Enantioselective iodolactonization occurs with pentenoic acid derivatives in the presence of a chiral $\text{Co}(\text{salen})$ complex.¹⁷²¹

In the case of γ,δ -unsaturated acids, five-membered rings (γ -lactones) are predominantly formed (as shown above; note that *Markovnikov's rule* is followed), but six-membered and even four-membered lactones have also been made by this procedure. There is a *gem-dimethyl effect* that favors formation of 7–11 membered ring lactones by this procedure.¹⁷²²

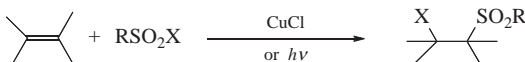


Formation of halo-lactams (Reaction **15-43**) by a procedure similar to halolactonization is difficult, but the problems have been overcome. Formation of a triflate from **113** followed by treatment with iodine leads to the iodolactam (**114**).¹⁷²³ A related cyclization of *N*-sulfonyl-amino alkenes and NBS gave the bromo-lactam,¹⁷²⁴ and a dichloro-*N,N*-bis(allylamide) was converted to a dichloro-lactam with FeCl_2 .¹⁷²⁵ Note that lactone formation is possible from unsaturated amides

OS IX, 516

15-42 Addition of Sulfur Compounds (Addition of Halogen, Sulfur)

Alkylsulfonyl-chloro-addition, and so on¹⁷²⁶



¹⁷¹⁴ Royer, A.C.; Mebane, R.C.; Swafford, A.M. *Synlett* **1993**, 899.

¹⁷¹⁵ See Cambie, R.C.; Rutledge, P.S.; Somerville, R.F.; Woodgate, P.D. *Synthesis* **1988**, 1009, and references cited therein.

¹⁷¹⁶ Genovese, S.; Epifano, F.; Pelucchini, C.; Procopio, A.; Curini, M. *Tetrahedron Lett.* **2010**, 51, 5992.

¹⁷¹⁷ Garnier, J.M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281.

¹⁷¹⁸ Inoue, T.; Kitagawa, O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett.* **1995**, 36, 1479.

¹⁷¹⁹ Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, 4, 297.

¹⁷²⁰ Whitehead, D.C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, 132, 3298; Zhou, L.; Tan, C.K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, 132, 15474; Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem. Int. Ed.* **2010**, 49, 9174.

¹⁷²¹ Ning, Z.; Jin, R.; Ding, J.; Gao, L. *Synlett* **2009**, 2291.

¹⁷²² Simonot, B.; Rousseau, G. *Tetrahedron Lett.* **1993**, 34, 4527.

¹⁷²³ Knapp, S.; Rodriques, K.E. *Tetrahedron Lett.* **1985**, 26, 1803.

¹⁷²⁴ Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, 25, 1063.

¹⁷²⁵ Tseng, C.K.; Teach, E.G.; Simons, R.W. *Synth. Commun.* **1984**, 14, 1027.

¹⁷²⁶ When a general group (e.g., halo) is used, its priority is that of the lowest member of its group (see Ref. 1680). Thus the general name for this transformation is halo-alkylsulfonyl addition because “halo” has the same priority as “fluoro”, its lowest member.

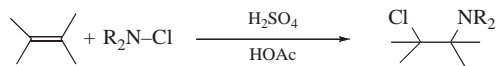
Sulfonyl halides add to double bonds to give β -halo sulfones, in the presence of free radical initiators or UV light. A particularly good catalyst is cuprous chloride.¹⁷²⁷ In the presence of TsCl, AIBN and a Ru catalyst, β -chloro sulfones are generated from alkenes.¹⁷²⁸ A combination of the anion ArSO_2Na , NaI, and ceric ammonium nitrate converts alkenes to vinyl sulfones.¹⁷²⁹ Triple bonds behave similarly, to give β -halo- α,β -unsaturated sulfones.¹⁷³⁰ In a similar reaction, sulfonyl chlorides, (RSCl) give β -halo thioethers.¹⁷³¹ The latter may be free radical or electrophilic additions, depending on conditions. The addition of MeS and Cl has also been accomplished by treating the alkene with Me_3SiCl and Me_2SO .¹⁷³² The use of Me_3SiBr and Me_2SO does not give this result; dibromides (Reaction 15-39) are formed instead.

β -Iodothiocyanates can be prepared from alkenes by treatment with I_2 and isothiocyanatotributylstannane (Bu_3SnNCS).¹⁷³³ Bromothiocyation can be accomplished with Br_2 and thallium(I) thiocyanate.¹⁷³⁴ Lead(II) thiocyanate reacts with terminal alkynes in the presence of PhICl_2 to give the bis(thiocyanato) alkene $[\text{ArC}(\text{SCN})-\text{CHSCN}]$.¹⁷³⁵ Such compounds were also prepared from alkenes using KSCN and FeCl_3 ¹⁷³⁶ or iodine thiocyanate.¹⁷³⁷ β -Halo disulfides, formed by addition of arenethiosulfonyl chlorides to double-bond compounds, are easily converted to thiiranes by treatment with sodium amide or sodium sulfide.¹⁷³⁸

OS VIII, 212. See also, OS VII, 251.

15-43 Addition of Halogen and a Nitrogen Group (Addition of Halogen, Nitrogen)

Dialkylamino-chloro-addition



The groups R_2N and Cl can be added directly to alkenes, allenes, conjugated dienes, and alkynes, by treatment with dialkyl-*N*-chloroamines and acids.¹⁷³⁹ *N*-Halo amides (RCONHX) add RCONH and X to double bonds under the influence of UV light or chromous chloride.¹⁷⁴⁰ *N*-Bromoamides add to alkenes in the presence of a transition metal

¹⁷²⁷ Sinnreich, J.; Asscher, M. *J. Chem. Soc. Perkin Trans. 1*, **1972**, 1543.

¹⁷²⁸ Quebatte, L.; Thommes, K.; Severin, K. *J. Am. Chem. Soc.* **2006**, 128, 7440.

¹⁷²⁹ Nair, V.; Augustine, A.; George, T.G.; Nair, L.G. *Tetrahedron Lett.* **2001**, 42, 6763.

¹⁷³⁰ Amiel, Y. *J. Org. Chem.* **1974**, 39, 3867; Okuyama, T.; Izawa, K.; Fueno, T. *J. Org. Chem.* **1974**, 39, 351.

¹⁷³¹ See Rasteikiene, L.; Greiciute, D.; Lin'kova, M.G.; Knunyants, I.L. *Russ. Chem. Rev.* **1977**, 46, 548; Kühle, E. *Synthesis* **1971**, 563.

¹⁷³² Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* **1987**, 238. See also, Liu, H.; Nyangulu, J.M. *Tetrahedron Lett.* **1988**, 29, 5467.

¹⁷³³ Woodgate, P.D.; Janssen, S.J.; Rutledge, P.S.; Woodgate, S.D.; Cambie, R.C. *Synthesis* **1984**, 1017, and references cited therein. See also, Watanabe, N.; Uemura, S.; Okano, M. *Bull. Chem. Soc. Jpn.* **1983**, 56, 2458.

¹⁷³⁴ Cambie, R.C.; Larsen, D.S.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1*, **1981**, 58.

¹⁷³⁵ Prakash, O.; Sharma, V.; Batra, H.; Moriarty, R.M. *Tetrahedron Lett.* **2001**, 42, 553.

¹⁷³⁶ Yadav, J.S.; Reddy, B.V.S.; Gupta, M.K. *Synthesis* **2004**, 1983.

¹⁷³⁷ For a discussion of substituent effects, see Brammer, C.N.; Nelson, D.J.; Li, R. *Tetrahedron Lett.* **2007**, 48, 3237.

¹⁷³⁸ Fujisawa, T.; Kobori, T. *Chem. Lett.* **1972**, 935; Capozzi, F.; Capozzi, G.; Menichetti, S. *Tetrahedron Lett.* **1988**, 29, 4177.

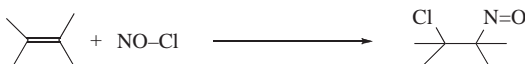
¹⁷³⁹ See Mirskova, A.N.; Drozdova, T.I.; Levkovskaya, G.G.; Voronkov, M.G. *Russ. Chem. Rev.* **1989**, 58, 250; Neale, R.S. *Synthesis* **1971**, 1.

¹⁷⁴⁰ Tuailon, J.; Couture, Y.; Lessard, J. *Can. J. Chem.* **1987**, 65, 2194, and other papers in this series. For a review, see Labeish, N.N.; Petrov, A.A. *Russ. Chem. Rev.* **1989**, 58, 1048.

catalyst (e.g., SnCl_4) to give the corresponding β -bromo amide.¹⁷⁴¹ The reaction of TsNCl_2 and a ZnCl_2 catalyst gave the chloro tosylamine.¹⁷⁴² Aminochlorination of alkenes occurs in a CO_2 promoted reaction with Chloramine-T ($\text{ToISO}_2\text{N}^-\text{—Cl}$).¹⁷⁴³ These are free radical additions, with initial attack by the $\text{R}_2\text{NH}^{\bullet+}$ radical ion.¹⁷⁴⁴ Amines add to allenes in the presence of a Pd catalyst.¹⁷⁴⁵ A mixture of N -(2-nosyl) NCl_2 and sodium N -(2-nosyl) NH^- with a CuOTf catalyst reacted with conjugated esters to give the *vicinal* (*E*)-3-chloro-2-amino ester.¹⁷⁴⁶ A variation of this latter reaction was done in an ionic liquid.¹⁷⁴⁷

15-44 Addition of NOX and NO_2X (Addition of Halogen, Nitrogen)

Nitroso-chloro-addition



There are three possible products when NOCl is added to alkenes, a β -halo nitroso compound, an oxime, or a β -halo nitro compound.¹⁷⁴⁸ The initial product is always the β -halo nitroso compound,¹⁷⁴⁹ but these are stable only if the carbon bearing the nitrogen has no hydrogen. If it has, the nitroso compound tautomerizes to the oxime, $\text{H—C—N=O} \rightarrow \text{C=N—OH}$. With some alkenes, the initial β -halo nitroso compound is oxidized by the NOCl to a β -halo nitro compound.¹⁷⁵⁰ Many functional groups may be present without interference (e.g., CO_2H , CO_2R , CN , OR). The mechanism in most cases is probably simple electrophilic addition, and the addition is usually anti, although syn addition has been reported in some cases.¹⁷⁵¹ *Markovnikov's rule* is followed, the positive NO going to the carbon that has more hydrogen atoms.

Nitryl chloride (NO_2Cl) also adds to alkenes, to give β -halo nitro compounds, but this is a free radical process. The NO_2 goes to the less-substituted carbon.¹⁷⁵² Nitryl chloride also adds to triple bonds to give the expected 1-nitro-2-chloro alkenes.¹⁷⁵³ The compound FNO_2 can be added to alkenes¹⁷⁵⁴ by treatment with HF in HNO_3 ¹⁷⁵⁵ or by addition of the alkene to a solution of nitronium tetrafluoroborate ($\text{NO}_2^+ \text{BF}_4^-$; see Reaction 11-2) in 70% polyhydrogen fluoride–pyridine solution¹⁷⁵⁶ (see also, Reaction 15-37).

OS IV, 711; V, 266, 863.

¹⁷⁴¹ Yeung, Y.-Y.; Gao, X.; Corey, E.J. *J. Am. Chem. Soc.* **2006**, 128, 9644.

¹⁷⁴² Wei, H.-X.; Ki, S.H.; Li, G. *Tetrahedron* **2001**, 57, 3869.

¹⁷⁴³ Minakata, S.; Yoneda, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2006**, 8, 967.

¹⁷⁴⁴ See Chow, Y.L.; Danen, W.C.; Nelson, S.F.; Rosenblatt, D.H. *Chem. Rev.* **1978**, 78, 243.

¹⁷⁴⁵ Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, 36, 3857.

¹⁷⁴⁶ Li, G.; Wei, H.-X.; Kim, S.H. *Tetrahedron* **2001**, 57, 8407.

¹⁷⁴⁷ Xu, X.; Kotti, S.R.S.S.; Liu, J.; Cannon, J.F.; Headley, A.D.; Li, G. *Org. Lett.* **2004**, 6, 4881.

¹⁷⁴⁸ See Kadzyauskas, P.P.; Zefirov, N.S. *Russ. Chem. Rev.* **1968**, 37, 543.

¹⁷⁴⁹ See Gowenlock, B.G.; Richter-Addo, G.B. *Chem. Rev.* **2004**, 104, 3315.

¹⁷⁵⁰ Shvekhgeimer, G.A.; Smirnyagin, V.A.; Sadykov, R.A.; Novikov, S.S. *Russ. Chem. Rev.* **1968**, 37, 351.

¹⁷⁵¹ See Meinwald, J.; Meinwald, Y.C.; Baker, III, T.N. *J. Am. Chem. Soc.* **1964**, 86, 4074.

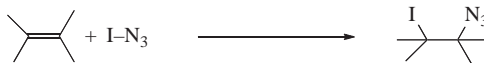
¹⁷⁵² Shechter, H. *Rec. Chem. Prog.*, **1964**, 25, 55–76.

¹⁷⁵³ Schlubach, H.H.; Braun, A. *Liebigs Ann. Chem.* **1959**, 627, 28.

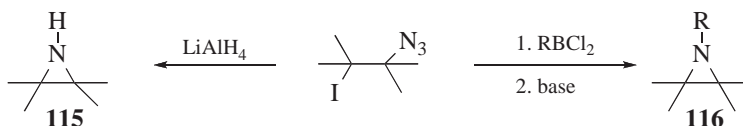
¹⁷⁵⁴ Sharts, C.M.; Sheppard, W.A. *Org. React.* **1974**, 21, 125–406, see pp. 236–243.

¹⁷⁵⁵ Knunyants, I.L.; German, L.S.; Rozhkov, I.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1963**, 1794.

¹⁷⁵⁶ Olah, G.A.; Nojima, M. *Synthesis* **1973**, 785.

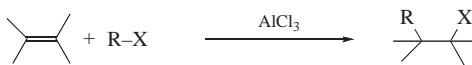
15-45 Addition of XN_3 (Addition of Halogen, Nitrogen)**Azido-iodo-addition**

The addition of iodine azide to double bonds gives β -iodo azides.¹⁷⁵⁷ The reagent can be prepared *in situ* from $\text{KI}—\text{NaN}_3$ in the presence of Oxone–wet alumina.¹⁷⁵⁸ The addition is stereospecific and anti, suggesting that the mechanism involves a cyclic iodonium ion intermediate.¹⁷⁵⁹ The reaction has been performed on many double-bond compounds, including allenes¹⁷⁶⁰ and α,β -unsaturated ketones. Similar reactions can be performed with BrN_3 ¹⁷⁶¹ and ClN_3 . 1,4-Addition has been found with acyclic conjugated dienes.¹⁷⁶² In the case of BrN_3 , both electrophilic and free radical mechanisms are important,¹⁷⁶³ while with ClN_3 the additions are chiefly free radical.¹⁷⁶⁴ Iodine monoazide (IN_3) also adds to triple bonds to give β -iodo- α,β -unsaturated azides.¹⁷⁶⁵



β -Iodo azides can be reduced to aziridines (**115**) with LiAlH_4 ¹⁷⁶⁶ or converted to *N*-alkyl- or *N*-arylaziridines (**116**) by treatment with an alkyl- or aryl-dichloroborane followed by a base.¹⁷⁶⁷ In both cases the azide is first reduced to the corresponding amine (primary or secondary, respectively) and ring closure (Reaction **10-31**) follows. With Chloramine T ($\text{TsNCl}^- \text{Na}^+$) and 10% of pyridinium bromide perbromide, however, the reaction with alkenes give an *N*-tosyl aziridine directly.¹⁷⁶⁸

OS VI, 893.

15-46 Addition of Alkyl Halides (Addition of Halogen, Carbon)**Alkyl-halo-addition**¹¹³⁵

¹⁷⁵⁷ Dehnicke, K. *Angew. Chem. Int. Ed.* **1979**, 18, 507; Hassner, A. *Acc. Chem. Res.* **1971**, 4, 9; Biffin, M.E.C.; Miller, J.; Paul, D.B. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, **1971**, pp. 136–147. See Nair, V.; George, T.G.; Sheeba, V.; Augustine, A.; Balagopal, L.; Nair, L.G. *Synlett* **2000**, 1597.

¹⁷⁵⁸ Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Tetrahedron Lett.* **2002**, 43, 1201.

¹⁷⁵⁹ See, however, Cambie, R.C.; Hayward, R.C.; Rutledge, P.S.; Smith-Palmer, T.; Swedlund, B.E.; Woodgate, P. D. *J. Chem. Soc. Perkin Trans. 1*, **1979**, 180.

¹⁷⁶⁰ Hassner, A.; Keogh, J. *J. Org. Chem.* **1986**, 51, 2767.

¹⁷⁶¹ Olah, G.A.; Wang, Q.; Li, X.; Prakash, G.K.S. *Synlett* **1990**, 487.

¹⁷⁶² Hassner, A.; Keogh, J. *Tetrahedron Lett.* **1975**, 1575.

¹⁷⁶³ Hassner, A.; Teeter, J.S. *J. Org. Chem.* **1971**, 36, 2176.

¹⁷⁶⁴ See Cambie, R.C.; Jurlina, J.L.; Rutledge, P.S.; Swedlund, B.E.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1*, **1982**, 327. Also see Hassner, A. *Intra-Sci. Chem. Rep.*, **1970**, 4, 109.

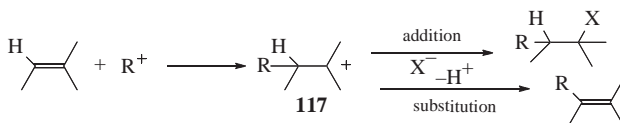
¹⁷⁶⁵ Hassner, A.; Isbister, R.J.; Friederang, A. *Tetrahedron Lett.* **1969**, 2939.

¹⁷⁶⁶ Hassner, A.; Matthews, G.J.; Fowler, F.W. *J. Am. Chem. Soc.* **1969**, 91, 5046.

¹⁷⁶⁷ Levy, A.B.; Brown, H.C. *J. Am. Chem. Soc.* **1973**, 95, 4067.

¹⁷⁶⁸ Ali, S.I.; Nikalje, M.D.; Sudalai, A. *Org. Lett.* **1999**, 1, 705.

Alkyl halides can be added to alkenes in the presence of a *Friedel–Crafts catalyst*, most often AlCl_3 .¹⁷⁶⁹ The yields are best for tertiary R. Secondary R can also be used, but primary R give rearrangement products (as with Reaction 11-11). The reactive species is the carbocation formed from the alkyl halide and the catalyst (see Reaction 11-11).¹⁷⁷⁰ The reaction with an alkene follows *Markovnikov's rule*, and generates the more stable carbocation from the alkene after reaction with the carbocation. Methyl and ethyl halides, which cannot rearrange to a more stable secondary or tertiary carbocation, give no reaction at all. Substitution is a side reaction, arising from loss of hydrogen from the carbocation (117). Conjugated dienes give 1,4-addition.¹⁷⁷¹ Triple bonds also undergo the reaction, to give vinylic halides.¹⁷⁷²



Simple polyhalo alkanes (e.g., CCl_4 , BrCCl_3 , ICF_3 and related molecules) add to alkenes in good yield.¹⁷⁷³ These are free radical additions and require initiation, for example,¹⁷⁷⁴ by peroxides, metal halides (e.g., FeCl_2 , CuCl),¹⁷⁷⁵ Ru catalysts,¹⁷⁷⁶ or UV light. The initial reaction generates the more stable radical intermediate, as in most free radical reactions with alkenes:



Polyhalo alkanes add to halogenated alkenes in the presence of AlCl_3 by an electrophilic mechanism. This has been called the *Prins reaction* (not to be confused with the other *Prins Reaction*, 16-54).¹⁷⁷⁷

α -Iodolactones add to alkenes in the presence of BEt_3/O_2 to give the addition product.¹⁷⁷⁸ Other α -iodoesters add under similar conditions to give the lactone.¹⁷⁷⁹ Iodoesters also add to alkenes in the presence of BEt_3 to give iodo-esters that have not cyclized.¹⁷⁸⁰

A variant of the free radical addition method has been used for ring closure (see Reaction 15-30).

For another method of adding R and I to a triple bond, see Reaction 15-23.

OS II, 312; IV, 727; V, 1076; VI, 21; VII, 290.

¹⁷⁶⁹ Schmerling, L. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, **1964**, pp. 1133–1174; Mayr, H.; Schade, C.; Rubow, M.; Schneider, R. *Angew. Chem. Int. Ed.* **1987**, 26, 1029.

¹⁷⁷⁰ See Pock, R.; Mayr, H.; Rubow, M.; Wilhelm, E. *J. Am. Chem. Soc.* **1986**, 108, 7767.

¹⁷⁷¹ Kolyaskina, Z.N.; Petrov, A.A. *J. Gen. Chem. USSR* **1962**, 32, 1067.

¹⁷⁷² See Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc. Perkin Trans. 1*, **1973**, 2491; **1974**, 353.

¹⁷⁷³ See Freidlina, R.Kh.; Velichko, F.K. *Synthesis* **1977**, 145; Freidlina, R.Kh.; Chukovskaya, E.C. *Synthesis* **1974**, 477.

¹⁷⁷⁴ For other initiators, see Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron* **1985**, 41, 393; Phelps, J.C.; Bergbreiter, D.E.; Lee, G.M.; Villani, R.; Weinreb, S.M. *Tetrahedron Lett.* **1989**, 30, 3915.

¹⁷⁷⁵ See Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Bellus, D. *Tetrahedron* **1985**, 41, 4057. Also see Mitani, M.; Nakayama, M.; Koyama, K. *Tetrahedron Lett.* **1980**, 21, 4457.

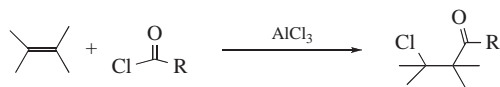
¹⁷⁷⁶ Simal, F.; Wlodarczak, L.; Demonceau, A.; Noels, A.F. *Eur. J. Org. Chem.* **2001**, 2689.

¹⁷⁷⁷ For a review with respect to fluoroalkenes, see Paleta, O. *Fluorine Chem. Rev.* **1977**, 8, 39.

¹⁷⁷⁸ Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1998**, 1351.

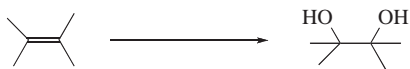
¹⁷⁷⁹ Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, 63, 8604.

¹⁷⁸⁰ Baciocchi, E.; Muraglia, E. *Tetrahedron Lett.* **1994**, 35, 2763.

15-47 Addition of Acyl Halides (Addition of Halogen, Carbon)**Acyl-halo-addition**

Acyl halides add to many alkenes using *Friedel–Crafts* catalysts, although polymerization is a problem. The reaction has been applied to straight-chain, branched, and cyclic alkenes, but to very few containing functional groups, other than halogen.¹⁷⁸¹ The mechanism is similar to that of Reaction 15-46, and, as in that case, substitution competes (Reaction 12-16). Increasing temperature favors substitution,¹⁷⁸² but good yields of addition products can be achieved if the temperature is kept under 0°C. The reaction usually fails with conjugated dienes, since polymerization predominates.¹⁷⁸³ Iodo acetates have been formed from alkenes using iodine and Pb(OAc)₂ in acetic acid.¹⁷⁸⁴ Rhodium-catalyzed variations are known.¹⁷⁸⁵ The reaction can be performed on triple-bond compounds, producing compounds of the form RCO–C≡C–Cl.¹⁷⁸⁶ A *formyl* group and a halogen can be added to triple bonds by treatment with *N,N*-disubstituted formamides and POCl₃ (*Vilsmeier conditions*, Reaction 11-18).¹⁷⁸⁷ Chloroformates add to allenes in the presence of a Rh catalyst to give a β-chloro, β,γ-unsaturated ester.¹⁷⁸⁸

OS IV, 186; VI, 883; VIII, 254.

B. Oxygen, Nitrogen, or Sulfur on One or Both Sides**15-48 Dihydroxylation and Dialkoxylation (Addition of Oxygen, Oxygen)****Dihydroxy-addition, Dialkoxy-addition**

There are many reagents that add two OH groups to a double bond (dihydroxylation).¹⁷⁸⁹ The most common are OsO₄,¹⁷⁹⁰ first used by Criegee in 1936,¹⁷⁹¹ and alkaline KMnO₄.¹⁷⁹² Both give syn addition from the less-hindered side of the double bond. Less

¹⁷⁸¹ See Groves, J.K. *Chem. Soc. Rev.* **1972**, 1, 73; Nenitzescu, C.D.; Balaban, A.T. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, **1964**, pp. 1033–1152.

¹⁷⁸² Jones, N.; Taylor, H.T.; Rudd, E. *J. Chem. Soc.* **1961**, 1342.

¹⁷⁸³ See Melikyan, G.G.; Babayan, E.V.; Atanesyan, K.A.; Badanyan, Sh.O. *J. Org. Chem. USSR* **1984**, 20, 1884.

¹⁷⁸⁴ Bedekar, A.V.; Nair, K.B.; Soman, R. *Synth. Commun.* **1994**, 24, 2299.

¹⁷⁸⁵ Hua, R.; Onozawa, S.-y.; Tanaka, M. *Chemistry: European J.* **2005**, 11, 3621.

¹⁷⁸⁶ See Brownstein, S.; Morrison, A.; Tan, L.K. *J. Org. Chem.* **1985**, 50, 2796.

¹⁷⁸⁷ Yen, V.Q. *Ann. Chim. (Paris)* **1962**, [13] 7, 785.

¹⁷⁸⁸ Hua, R.; Tanaka, M. *Tetrahedron Lett.* **2004**, 45, 2367.

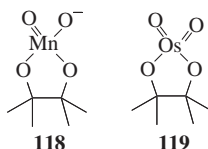
¹⁷⁸⁹ See Hudlicky, M. *Oxidations in Organic Chemistry* American Chemical Society, Washington, **1990**, pp. 67–73; Haines, A.H. *Methods for the Oxidation of Organic Compounds* Academic Press, NY, **1985**, pp. 73–98, 278–294; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds* Academic Press, NY, **1981**, pp. 162–171, 294–296. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 996–1003.

¹⁷⁹⁰ See Schröder, M. *Chem. Rev.* **1980**, 80, 187. Also see, Norrby, P.-O.; Gable, K.P. *J. Chem. Soc. Perkin Trans. 2*, **1996**, 171; Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* **1992**, 33, 5113.

¹⁷⁹¹ Criegee, R. *Liebigs Ann. Chem.* **1936**, 522, 75.

¹⁷⁹² See Fatiadi, A.J. *Synthesis* **1987**, 85; Nelson, D.J.; Henley, R.L. *Tetrahedron Lett.* **1995**, 36, 6375.

substituted double bonds are oxidized more rapidly than more substituted alkenes.¹⁷⁹³ Permanganate adds to alkenes to form an intermediate manganate ester (Reaction **118**), which is decomposed under alkaline conditions. Transition state structures and the energetics of the permanganate oxidation of alkenes has been studied using molecular mechanics.¹⁷⁹⁴ Bases catalyze the decomposition of **118** by coordinating with the ester. Note that there are alternative Mn complexes that may be used for *cis*-dihydroxylation of alkenes.¹⁷⁹⁵ Osmium tetroxide adds rather slowly but almost quantitatively to form a cyclic osmate ester (e.g., **119**) as an intermediate,¹⁷⁹⁶ which may be isolated in some cases, but is usually decomposed in solution with sodium sulfite (Na₂SO₃) in ethanol or other reagents.¹⁷⁹⁷



The chief drawbacks to the use of OsO₄ are the facts that it is expensive and toxic, but the reaction is made catalytic in OsO₄ by using *N*-methylmorpholine-*N*-oxide (NMO),¹⁷⁹⁸ *tert*-butyl hydroperoxide in alkaline solution,¹⁷⁹⁹ H₂O₂,¹⁸⁰⁰ peroxyacid,¹⁸⁰¹ K₃Fe(CN)₆,¹⁸⁰² and non-heme iron catalysts.¹⁸⁰³ Polymer-bound OsO₄,¹⁸⁰⁴ and encapsulated OsO₄ have been shown to give the diol in the presence of NMO,¹⁸⁰⁵ as well as OsO₄²⁻ on an ion exchange resin.¹⁸⁰⁶ Dihydroxylation has also been reported in ionic liquids.¹⁸⁰⁷ Other metals have been used to catalyze dihydroxylation, including Fe¹⁸⁰⁸ or Ru catalyzed¹⁸⁰⁹ reactions with H₂O₂. A catalytic amount of K₂OsO₄ with a Cinchona alkaloid on an ordered inorganic support, in the presence of K₃Fe(CN)₆, gives the *cis*-diol.¹⁸¹⁰

¹⁷⁹³ Crispino, G.A.; Jeong, K.-S.; Kolb, H.C.; Wang, Z.-M.; Xu, D.; Sharpless, K.B. *J. Org. Chem.* **1993**, 58, 3785.

¹⁷⁹⁴ Wiberg, K.B.; Wang, Y.-g.; Sklenak, S.; Deutsch, C.; Trucks, G. *J. Am. Chem. Soc.* **2006**, 128, 11537.

¹⁷⁹⁵ de Boer, J.W.; Brinksma, J.; Browne, W.R.; Meetsma, A.; Alsters, P.L.; Hage, R.; Feringa, B.L. *J. Am. Chem. Soc.* **2005**, 127, 7990.

¹⁷⁹⁶ See Jørgensen, K.A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986**, 108, 1867.

¹⁷⁹⁷ See Ogino, T.; Hasegawa, K.; Hoshino, E. *J. Org. Chem.* **1990**, 55, 2653. See, however, Freeman, F.; Kappos, J.C. *J. Org. Chem.* **1989**, 54, 2730, and other papers in this series.

¹⁷⁹⁸ Iwasawa, N.; Kato, T.; Narasaka, K. *Chem. Lett.* **1988**, 1721. See also, Ray, R.; Matteson, D.S. *Tetrahedron Lett.* **1980**, 449.

¹⁷⁹⁹ Akashi, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* **1978**, 43, 2063.

¹⁸⁰⁰ See Usui, Y.; Sato, K.; Tanaka, M. *Angew. Chem. Int. Ed.* **2003**, 42, 5623.

¹⁸⁰¹ Bergstad, K.; Piet, J.J.N.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, 64, 2545.

¹⁸⁰² Torii, S.; Liu, P.; Tanaka, H. *Chem. Lett.* **1995**, 319; Soderquist, J.A.; Rane, A.M.; López, C.J. *Tetrahedron Lett.* **1993**, 34, 1893. See Corey, E.J.; Noe, M.C.; Grogan, M.J. *Tetrahedron Lett.* **1994**, 35, 6427; Imada, Y.; Saito, T.; Kawakami, T.; Murahashi, S.-I. *Tetrahedron Lett.* **1992**, 33, 5081 for oxidation using an asymmetric ligand.

¹⁸⁰³ Chen, K.; Costas, M.; Kim, J.; Tipton, A.K.; Que, Jr., L. *J. Am. Chem. Soc.* **2002**, 124, 3026.

¹⁸⁰⁴ Ley, S.V.; Ramarao, C.; Lee, A.-L.; Ostergaard, N.; Smith, S.C.; Shirley, I.M. *Org. Lett.* **2003**, 5, 185.

¹⁸⁰⁵ Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, 63, 6094.

¹⁸⁰⁶ Choudary, B.M.; Chowdari, N.S.; Jyothi, K.; Kantam, M.L. *J. Am. Chem. Soc.* **2002**, 124, 5341.

¹⁸⁰⁷ Closson, A.; Johansson, M.; Bäckvall, J.-E. *Chem. Commun.* **2004**, 1494; Branco, L.C.; Serbanovic, A.; da Ponte, M.N.; Afonso, C.A.M. *Chem. Commun.* **2005**, 107.

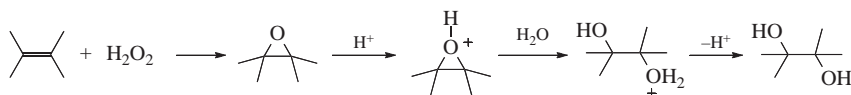
¹⁸⁰⁸ Oldenburg, P.D.; Shteinman, A.A.; Que, Jr., L. *J. Am. Chem. Soc.* **2005**, 127, 15672.

¹⁸⁰⁹ Yip, W.-P.; Ho, C.-M.; Zhu, N.; Lau, T.-C.; Che, C.-M. *Chemistry: Asian J.* **2008**, 3, 70.

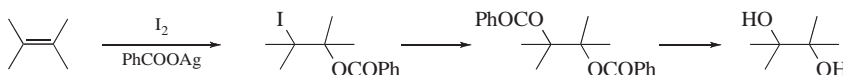
¹⁸¹⁰ Motorina, I.; Crudden, C.M. *Org. Lett.* **2001**, 3, 2325.

The end product of the reaction is a 1,2-diol. Potassium permanganate is a strong oxidizing agent and can oxidize the glycol product¹⁸¹¹ (see Reaction **19-7** and **19-10**). In acidic and neutral solution, it always does so; hence glycols must be prepared with alkaline¹⁸¹² permanganate, but the conditions must be mild. Even so, yields are seldom >50%, although they can be improved with phase-transfer catalysis¹⁸¹³ or increased stirring.¹⁸¹⁴ The use of ultrasound with permanganate has resulted in good yields of the diol.¹⁸¹⁵ This reaction is the basis of the *Baeyer test* for the presence of double bonds. The oxidation is compatible with a number of functional groups, including trichloroacetamides.¹⁸¹⁶

Anti-hydroxylation can be achieved by treatment with H₂O₂ and formic acid. In this case, epoxidation (Reaction **15-50**) occurs first, followed by an S_N2 reaction, which results in overall anti addition:



The same result can be achieved in one step with *m*-chloroperoxybenzoic acid and water.¹⁸¹⁷ Overall anti addition can also be achieved by the method of Prévost (the *Prévost reaction*). In this method, the alkene is treated with iodine and silver benzoate in a 1:2 molar ratio. The initial addition is anti and results in a β-halo benzoate, as shown. These can be isolated, and this represents a method of addition of IOCOPh. However, under normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction via the neighboring-group mechanism (Sec. 10.C), so the groups are still anti:



Hydrolysis of the ester does not change the configuration. The *Woodward modification* of the Prévost reaction is similar, but results in overall syn hydroxylation.¹⁸¹⁸ In this procedure, the alkene is treated with iodine and silver acetate in a 1:1 molar ratio in acetic acid containing water. Here again, the initial product is a β-halo ester; the addition is anti and a nucleophilic replacement of the iodine occurs. However, in the presence of water, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal S_N2 process,¹⁸¹⁹ so the monoacetate is syn and

¹⁸¹¹ See Wolfe, S.; Ingold, C.F.; Lemieux, R.U. *J. Am. Chem. Soc.* **1981**, *103*, 938; Wolfe, S.; Ingold, C.F. *J. Am. Chem. Soc.* **1981**, *103*, 940. Also see, Lohray, B.B.; Bhushan, V.; Kumar, R.K. *J. Org. Chem.* **1994**, *59*, 1375.

¹⁸¹² See Taylor, J.E.; Green, R. *Can. J. Chem.* **1985**, *63*, 2777.

¹⁸¹³ See Ogino, T.; Mochizuki, K. *Chem. Lett.* **1979**, 443.

¹⁸¹⁴ Taylor, J.E.; Williams, D.; Edwards, K.; Otonnaa, D.; Samanich, D. *Can. J. Chem.* **1984**, *62*, 11; Taylor, J.E. *Can. J. Chem.* **1984**, *62*, 2641.

¹⁸¹⁵ Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* **1998**, *39*, 7463.

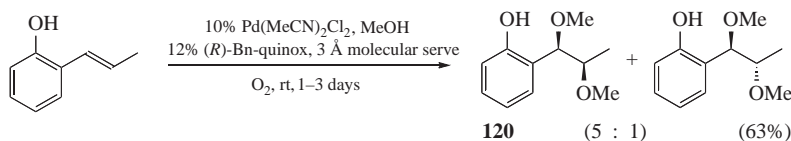
¹⁸¹⁶ Donohoe, T.J.; Blades, K.; Moore, P.R.; Waring, M.J.; Winter, J.J.G.; Helliwell, M.; Newcombe, N.J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946.

¹⁸¹⁷ Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. *Synth. Commun.* **1989**, *19*, 1939.

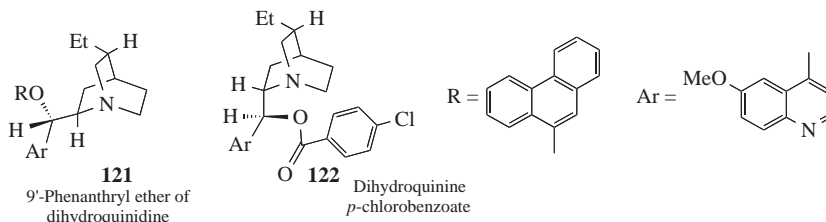
¹⁸¹⁸ See Brimble, M.A.; Nairn, M.R. *J. Org. Chem.* **1996**, *61*, 4801.

¹⁸¹⁹ For another possible mechanism: Woodward, R.B.; Brutcher, Jr., F.V. *J. Am. Chem. Soc.* **1958**, *80*, 209.

hydrolysis gives the diol as the product, with overall syn addition. Although the *Woodward* method results in overall syn addition, the product may be different from that with OsO_4 or KMnO_4 , since the overall syn process is from the *more hindered side* of the alkene.¹⁸²⁰ Both the *Prévost* and the *Woodward* methods¹⁸²¹ have been carried out in high yields with thallium(I) acetate and thallium(I) benzoate instead of the silver carboxylates.¹⁸²² Note that cyclic sulfates can be prepared from alkenes by reaction with PhIO and $\text{SO}_3 \cdot \text{DMF}$.¹⁸²³ Diacetates have been prepared from alkenes using a Cu catalyzed reaction with $\text{PhI}(\text{OAc})_2$ as the oxidizing agent.¹⁸²⁴ A similar Pd/Cu catalyzed reaction is known using O_2 as the oxidant.¹⁸²⁵



Dialkoxylation reactions are possible. The reaction of an aryl alkene with CH_3OH , O_2 , and a Pd catalyst leads to the dimethoxy compound (see Reaction **120**), with moderate enantioselectivity if a chiral ligand is used.¹⁸²⁶ Dihydroxylation to alkenes of the form $\text{RCH}=\text{CH}_2$ has been made enantioselective, and addition to $\text{RCH}=\text{CHR}'$ both diastereoselective¹⁸²⁷ and enantioselective,¹⁸²⁸ using chiral additives or chiral catalysts¹⁸²⁹ (e.g., **121** or **122**, derivatives of the naturally occurring quinine and quinuclidine),¹⁸³⁰ along with OsO_4 , in what is called



¹⁸²⁰ Also see Corey, E.J.; Das, J. *Tetrahedron Lett.* **1982**, 23, 4217.

¹⁸²¹ See Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* **1988**, 1209; Campi, E.M.; Deacon, G.B.; Edwards, G.L.; Fitzroy, M.D.; Giunta, N.; Jackson, W.R.; Trainor, R. *J. Chem. Soc., Chem. Commun.* **1989**, 407.

¹⁸²² Cambie, R.C.; Hayward, R.C.; Roberts, J.L.; Rutledge, P.S. *J. Chem. Soc. Perkin Trans. 1*, **1974**, 1858, 1864; Cambie, R.C.; Rutledge, P.S. *Org. Synth.* **VI**, 348.

¹⁸²³ Robinson, R.I.; Woodward, S. *Tetrahedron Lett.* **2003**, 44, 1655.

¹⁸²⁴ Seayad, J.; Seayad, A.M.; Chai, C.L.L. *Org. Lett.* **2010**, 12, 1412.

¹⁸²⁵ Schultz, M.J.; Sigman, M.S. *J. Am. Chem. Soc.* **2006**, 128, 1460.

¹⁸²⁶ Zhang, Y.; Sigman, M.S. *J. Am. Chem. Soc.* **2007**, 129, 3076.

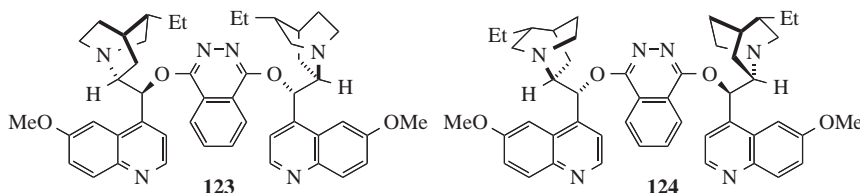
¹⁸²⁷ For diastereoselective, but not enantioselective, addition of OsO_4 , see Vedejs, E.; McClure, C.K. *J. Am. Chem. Soc.* **1986**, 108, 1094; Evans, D.A.; Kaldor, S.W. *J. Org. Chem.* **1990**, 55, 1698.

¹⁸²⁸ Lohray, B.B. *Tetrahedron Asymmetry* **1992**, 3, 1317; Zaitsev, A.B.; Adolfsson, H. *Synthesis* **2006**, 1725.

¹⁸²⁹ McNamara, C.A.; King, F.; Bradley, M. *Tetrahedron Lett.* **2004**, 45, 8527; Jiang, R.; Kuang, Y.; Sun, X.; Zhang, S. *Tetrahedron Asymmetry* **2004**, 15, 743.

¹⁸³⁰ Wai, J.S.M.; Marko, I.; Svendsen, J.S.; Finn, M.G.; Jacobsen, E.N.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989**, 111, 1123; Sharpless, K.B.; Amberg, W.; Beller, M.; Chens, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, 56, 4585.

*Sharpless asymmetric dihydroxylation.*¹⁸³¹ Other chiral ligands¹⁸³² have also been used, as well as polymer¹⁸³³ and silica-bound¹⁸³⁴ *Cinchona* alkaloids. These amines bind to the OsO_4 *in situ* as chiral ligands, causing it to add asymmetrically.¹⁸³⁵ This has been done both with the stoichiometric and with the catalytic method.¹⁸³⁶ The catalytic method has been extended to conjugated ketones¹⁸³⁷ and to conjugated dienes, which give tetrahydroxy products diastereoselectively.¹⁸³⁸ Asymmetric dihydroxylation has also been reported with chiral alkenes.¹⁸³⁹ Ligands **121** and **122** not only cause enantioselective addition, but also accelerate the reaction, so that they may be useful even where enantioselective addition is not required.¹⁸⁴⁰ Although **121** and **122** are not enantiomers, they give enantioselective addition to a given alkene in the opposite sense; for example, styrene predominantly gave the (*R*) diol with **121**, and the (*S*) diol with **122**.¹⁸⁴¹ Note that ionic liquids have been used in asymmetric dihydroxylation.¹⁸⁴²



Two phthalazine derivatives,¹⁸⁴³ (DHQD)₂PHAL (**123**) and (DHQ)₂PHAL (**124**) are used in conjunction with an Os reagent to improve the efficiency and ease of use, and are commercially available as AD-mix- β (using **123**) and AD-mix- α (using **124**). Catalyst **123** is prepared from dihydroquinidine (DHQD) and 1,4-dichlorophthalazine (PHAL), and **124** is prepared from dihydroquinine (DHQ) and PHAL. The actual oxidation using AD-mix α or β uses **124** or **123**, respectively, mixed with potassium osmate [$\text{K}_2\text{OsO}_2(\text{OH})_6$], powdered $\text{K}_3\text{Fe}(\text{CN})_6$, and powdered K_2CO_3 in an aqueous solvent mixture.¹⁸⁴³ One study

¹⁸³¹ Kolb, H.C.; Van Nieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, 94, 2483. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 294–301.

¹⁸³² Wang, L.; Sharpless, K.B. *J. Am. Chem. Soc.* **1992**, 114, 7568; Xu, D.; Crispino, G.A.; Sharpless, K.B. *J. Am. Chem. Soc.* **1992**, 114, 7570; Rosini, C.; Tanturli, R.; Pertici, P.; Salvadori, P. *Tetrahedron Asymmetry* **1996**, 7, 2971; Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, 57, 2768.

¹⁸³³ Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21. For a review, see Karjalainen, J.K.; Hormi, O.E.O.; Sherrington, D.C. *Tetrahedron Asymmetry* **1998**, 9, 1563.

¹⁸³⁴ Song, C.E.; Yang, J.W.; Ha, H.-J. *Tetrahedron Asymmetry* **1997**, 8, 841.

¹⁸³⁵ See Corey, E.J.; Noe, M.C. *J. Am. Chem. Soc.* **1996**, 118, 319; Norrby, P.-O.; Kolb, H.C.; Sharpless, K.B. *J. Am. Chem. Soc.* **1994**, 116, 8470; Wu, Y.-D.; Wang, Y.; Houk, K.N. *J. Org. Chem.* **1992**, 57, 1362. Also see Nelson, D.W.; Gypser, A.; Ho, P.T.; Kolb, H.C.; Kondo, T.; Kwong, H.-L.; McGrath, D.V.; Rubin, A.E.; Norrby, P.-O.; Gable, K.P.; Sharpless, K.B. *J. Am. Chem. Soc.* **1997**, 119, 1840.

¹⁸³⁶ See Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Stefanelli, S. *Tetrahedron Lett.* **1987**, 28, 3139; Hirama, M.; Oishi, T.; Itô, S. *J. Chem. Soc., Chem. Commun.* **1989**, 665.

¹⁸³⁷ Walsh, P.J.; Sharpless, K.B. *Synlett* **1993**, 605.

¹⁸³⁸ Park, C.Y.; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* **1991**, 32, 1003.

¹⁸³⁹ Oishi, T.; Iida, K.; Hirama, M. *Tetrahedron Lett.* **1993**, 34, 3573.

¹⁸⁴⁰ See Jacobsen, E.N.; Marko, I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989**, 111, 737.

¹⁸⁴¹ Jacobsen, E.N.; Marko, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, 110, 1968.

¹⁸⁴² See Branco, L.C.; Afonso, C.A.M. *J. Org. Chem.* **2004**, 69, 4381.

¹⁸⁴³ Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, 57, 2768.

showed that osmylation does not always occur preferentially on the most electron-rich double bond. There are examples of the less-rich double bond reacting preferentially, and such preferences may be amplified using AD type reagents, which adds significant steric hindrance to the overall system.¹⁸⁴⁴

These additives have been used in conjunction with microencapsulated OsO₄,¹⁸⁴⁵ and polymer bound **123** has been used.¹⁸⁴⁶ An asymmetric dihydroxylation was reported catalyzed by ionic polymer-supported OsO₄.¹⁸⁴⁷ A catalytic amount of flavin has been used.¹⁸⁴⁸ Both **123**¹⁸⁴⁹ and **124**¹⁸⁵⁰ have been used to generate diols with high enantioselectivity. Oxidation of a terminal alkene with AD-mix and then oxidation with TEMPO/NaOCl/NaOCl₂ leads to α -hydroxyl carboxylic acids with high enantioselectivity.¹⁸⁵¹

Enantioselective and diastereoselective addition have also been achieved by using preformed derivatives of OsO₄, already containing chiral ligands,¹⁸⁵² and by the use of OsO₄ on alkenes that have a chiral group elsewhere in the molecule.¹⁸⁵³ A Rh catalyzed diboration of alkenes in the presence of a chiral ligand, leads to the corresponding diol with good enantioselectivity after oxidation.¹⁸⁵⁴

Alkenes can also be oxidized with metallic acetates [e.g., lead tetraacetate¹⁸⁵⁵ or thallium(III) acetate]¹⁸⁵⁶ to give bis(acetates) of glycols.¹⁸⁵⁷ Oxidizing agents (e.g., benzoquinone, MnO₂, or O₂), along with palladium acetate, have been used to convert conjugated dienes to 1,4-diacetoxy-2-alkenes (1,4-addition).¹⁸⁵⁸

1,2-Diols are also generated from terminal alkynes by two sequential reactions with a Pt catalyst and then a Pd catalyst, both with HSiCl₃, and a final oxidation with H₂O₂—KF.¹⁸⁵⁹ The dihydroxylation of a vinyl ether, derived from an alkyne, leads to α -hydroxy aldehydes.¹⁸⁶⁰ Dihydroxylation of alkenes has been reported using a lipase and hydrogen peroxide, under microwave irradiation.¹⁸⁶¹ A Pd catalyzed diacetoxylation is also known.¹⁸⁶²

¹⁸⁴⁴ For a review, see Français, A.; Bedel, O.; Haudrechy, A. *Tetrahedron* **2008**, *64*, 2495.

¹⁸⁴⁵ Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* **2001**, *3*, 2649.

¹⁸⁴⁶ Kuang, Y.-Q.; Zhang, S.-Y.; Wei, L.-L. *Tetrahedron Lett.* **2001**, *42*, 5925.

¹⁸⁴⁷ Lee, B.S.; Mahajan, S.; Janda, K.D. *Tetrahedron Lett.* **2005**, *46*, 4491.

¹⁸⁴⁸ Jonsson, S.Y.; Adolfsson, H.; Bäckvall, J.-E. *Org. Lett.* **2001**, *3*, 3463.

¹⁸⁴⁹ Krief, A.; Colaux-Castillo, C. *Tetrahedron Lett.* **1999**, *40*, 4189.

¹⁸⁵⁰ Junttila, M.H.; Hormi, O.E.O. *J. Org. Chem.* **2004**, *69*, 4816.

¹⁸⁵¹ Aladro, F.J.; Guerra, I.M.; Moreno-Dorado, F.J.; Bustamante, J.M.; Jorge, Z.D.; Massanet, G.M. *Tetrahedron Lett.* **2000**, *41*, 3209.

¹⁸⁵² Kokubo, T.; Sugimoto, T.; Uchida, T.; Tanimoto, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1983**, 769.

¹⁸⁵³ Hauser, F.M.; Ellenberger, S.R.; Clardy, J.C.; Bass, L.S. *J. Am. Chem. Soc.* **1984**, *106*, 2458; Johnson, C.R.; Barbachyn, M.R. *J. Am. Chem. Soc.* **1984**, *106*, 2459.

¹⁸⁵⁴ Trudeau, S.; Morgan, J.B.; Shrestha, M.; Morken, J.P. *J. Org. Chem.* **2005**, *70*, 9538.

¹⁸⁵⁵ For a review, see Moriarty, R.M. *Sel. Org. Transform.* **1972**, *2*, 183–237.

¹⁸⁵⁶ See Uemura, S.; Miyoshi, H.; Tabata, A.; Okano, M. *Tetrahedron* **1981**, *37*, 291; Uemura, S. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 473–538, 497–513; Uemura, S. in Pizey, J. S. *Synthetic Reagents*, Vol. 5, Wiley, NY, **1983**, pp. 165–187.

¹⁸⁵⁷ For another method see Fristad, W.E.; Peterson, J.R. *Tetrahedron* **1984**, *40*, 1469.

¹⁸⁵⁸ See Bäckvall, J.E.; Awasthi, A.K.; Renko, Z.D. *J. Am. Chem. Soc.* **1987**, *109*, 4750 and references cited therein; Bäckvall, J.E. *Bull. Soc. Chim. Fr.* **1987**, 665; *New J. Chem.* **1990**, *14*, 447. For another method, see Uemura, S.; Fukuzawa, S.; Patil, S.R.; Okano, M. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 499.

¹⁸⁵⁹ Shimada, T.; Mukaide, K.; Shinohara, A.; Han, J.W.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *124*, 1584.

¹⁸⁶⁰ DeBergh, J.R.; Spivey, K.M.; Ready, J.M. *J. Am. Chem. Soc.* **2008**, *130*, 7828.

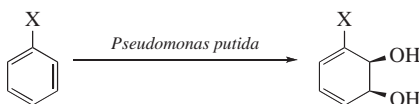
¹⁸⁶¹ Sarma, K.; Borthakur, N.; Goswami, A. *Tetrahedron Lett.* **2007**, *48*, 6776.

¹⁸⁶² Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846.

1,2-Dithiols can be prepared from alkenes by largely indirect methods.¹⁸⁶³
OS II, 307; III, 217; IV, 317; V, 647; VI, 196, 342, 348; IX, 251, 383.

15-49 Dihydroxylation of Aromatic Rings

Dihydroxy-addition

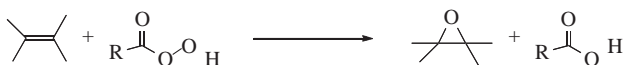


One π bond of an aromatic ring can be converted to a cyclohexadiene 1,2-diol by reaction with enzymes associated with *P. putida*.¹⁸⁶⁴ A variety of substituted aromatic compounds can be oxidized, including bromobenzene, chlorobenzene,¹⁸⁶⁵ and toluene.¹⁸⁶⁶ In these latter cases, introduction of the hydroxyl groups generates a chiral molecule that can be used as a template for asymmetric syntheses.¹⁸⁶⁷

OS X, 217.

15-50 Epoxidation (Addition of Oxygen, Oxygen)

epi-Oxy-addition



Alkenes are converted to epoxides (oxiranes) by reaction with many peroxyacids.¹⁸⁶⁸ The reaction, called the *Prilezhaev reaction*, has wide utility.¹⁸⁶⁹ The most common is probably *m*-chloroperoxybenzoic acid, but peroxyacetic and peroxybenzoic are available, and trifluoroperoxyacetic acid¹⁸⁷⁰ and 3,5-dinitroperoxybenzoic acid¹⁸⁷¹ are particularly reactive. The limiting factor concerning choice of the peroxyacid is usually whether or not it is commercially available because an in-lab preparation is potentially rather dangerous. Magnesium monoperoxyphthalate (MMPP)¹⁸⁷² is commercially available, and has been shown to be a good substitute for *m*-chloroperoxybenzoic acid in a number of reactions.

¹⁸⁶³ Elgemeie, G.H.; Sayed, S.H. *Synthesis* **2001**, 1747.

¹⁸⁶⁴ Gibson, D.T.; Koch, J.R.; Kallio, R.E. *Biochemistry* **1968**, 7, 2653; Brown, S.M. in Hudlicky, T. *Organic Synthesis: Theory and Practice* JAI Press, Greenwich, CT., **1993**, Vol. 2, p. 113; Carless, H.A.J. *Tetrahedron Asymmetry* **1992**, 3, 795.

¹⁸⁶⁵ Gibson, D.T.; Koch, J.R.; Schuld, C.L.; Kallio, R.E. *Biochemistry* **1968**, 7, 3795; Hudlicky, T.; Price, J.D. *Synlett*, **1990**, 159.

¹⁸⁶⁶ Gibson, D.T.; Hensley, M.; Yoshioka, H.; Mabry, T.J. *Biochemistry*, **1970**, 9, 1626.

¹⁸⁶⁷ Hudlicky, T.; Gonzalez, D.; Gibson, D.T. *Aldrichimica Acta* **1999**, 32, 35; Ley, S.V.; Redgrave, A.J. *Synlett* **1990**, 393. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 303–306.

¹⁸⁶⁸ For a list of reagents, including peroxyacids and others, used for epoxidation, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 915–927.

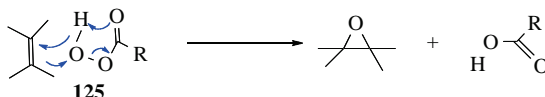
¹⁸⁶⁹ See Hudlicky, M. *Oxidations in Organic Chemistry* American Chemical Society, Washington, **1990**, pp. 60–64; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1985**, pp. 98–117, 295–303; Dryuk, V.G. *Russ. Chem. Rev.* **1985**, 54, 986; Plesnicar, B. in Trahanovsky, W.S. *Oxidation in Organic Chemistry* pt. C, Academic Press, NY, **1978**, pp. 211–252; Hiatt, R. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2; Marcel Dekker, NY, **1971**, pp. 113–140.

¹⁸⁷⁰ Emmons, W.D.; Pagano, A.S. *J. Am. Chem. Soc.* **1955**, 77, 89.

¹⁸⁷¹ Rastetter, W.H.; Richard, T.J.; Lewis, M.D. *J. Org. Chem.* **1978**, 43, 3163.

¹⁸⁷² Foti, C.J.; Fields, J.D.; Kropp, P.J. *Org. Lett.* **1999**, 1, 903.

Alkyl, aryl, hydroxyl, ester, and other groups may be present, but not amino groups since they are oxidized by the reagent. The presence of electron-donating groups increases the rate, and the reaction is particularly rapid with tetraalkyl alkenes. Conditions are mild and yields are high. Transition metal catalysts can facilitate epoxidation of alkenes at low temperatures or with alkenes that may otherwise react sluggishly.¹⁸⁷³



The one-step mechanism involving a transition state (e.g., **125**)¹⁸⁷⁴ was proposed by Bartlett.¹⁸⁷⁵ Evidence for this concerted mechanism is as follows¹⁸⁷⁶: (1) The reaction is second order. If ionization were the rate-determining step, it would be first order in peroxyacid. (2) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited.¹⁸⁷⁷ (3) Measurements of the effect on the reaction rate of changes in the substrate structure show that there is no carbocation character in the transition state.¹⁸⁷⁸ (4) The addition is stereospecific (i.e., a *trans*-alkene gives a *trans*-epoxide and a *cis*-alkene gives a *cis*-epoxide) even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate.¹⁸⁷⁹ However, where there is an OH group in the allylic or homoallylic position, the stereospecificity diminishes or disappears, with both *cis* and *trans* isomers giving predominantly and exclusively the product where the incoming oxygen is syn to the OH group. This probably indicates a transition state in which there is hydrogen bonding between the OH group and the peroxyacid.¹⁸⁸⁰

In general, peroxides (HOOH¹⁸⁸¹ and ROOH) are poor reagents for epoxidation of simple alkenes since OH and OR are poor leaving groups in the concerted mechanism shown above.¹⁸⁸² Transition metal catalysts¹⁸⁸³ have been used with alkyl hydroperoxides,¹⁸⁸⁴

¹⁸⁷³ Stack, T.D.P. *Org. Lett.* **2003**, 5, 2469; Murphy, A.; Pace, A.; Stack, T.D.P. *Org. Lett.* **2004**, 6, 3119.

¹⁸⁷⁴ See Finn, M.G.; Sharpless, K.B. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Wiley, NY, **1985**, pp. 247–308; Bach, R.D.; Canepa, C.; Winter, J.E.; Blanchette, P.E. *J. Org. Chem.* **1997**, 62, 5191; Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* **2002**, 67, 8519.

¹⁸⁷⁵ Bartlett, P.D. *Rec. Chem. Prog.*, **1957**, 18, 111. For other proposed mechanisms see Kwart, H.; Hoffman, D.M. *J. Org. Chem.* **1966**, 31, 419; Hanzlik, R.P.; Shearer, G.O. *J. Am. Chem. Soc.* **1975**, 97, 5231.

¹⁸⁷⁶ Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* **2004**, 69, 7479. See also, Vedejs, E.; Dent III, W.H.; Kendall, J.T.; Oliver, P.A. *J. Am. Chem. Soc.* **1996**, 118, 3556.

¹⁸⁷⁷ See Gisdakis, P.; Rösch, N. *Eur. J. Org. Chem.* **2001**, 719.

¹⁸⁷⁸ Schneider, H.; Becker, N.; Philippi, K. *Chem. Ber.* **1981**, 114, 1562; Batog, A.E.; Savenko, T.V.; Batrak, T.A.; Kucher, R.V. *J. Org. Chem. USSR* **1981**, 17, 1860.

¹⁸⁷⁹ See Freccero, M.; Gandolfi, R.; Sarzi-Amade, M.; Rastelli, A. *J. Org. Chem.* **2000**, 65, 8948.

¹⁸⁸⁰ See Houk, K.N.; Liu, J.; DeMello, N.C.; Condroski, K.R. *J. Am. Chem. Soc.* **1997**, 119, 10147.

¹⁸⁸¹ Arends, I.W.C.E. *Angew. Chem. Int. Ed.* **2006**, 45, 6250.

¹⁸⁸² See Deubel, D.V.; Frenking, G.; Gisdakis, P.; Herrmann, W.A.; Rösch, N.; Sundermeyer, J. *Acc. Chem. Res.* **2004**, 37, 645.

¹⁸⁸³ **La**: Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, 124, 14544. **Mn**: Lane, B.S.; Vogt, M.; De Rose, V.T.; Burgess, K. *J. Am. Chem. Soc.* **2002**, 124, 11946. **Ti**: Lattanzi, A.; Iannece, P.; Scretti, A. *Tetrahedron Lett.* **2002**, 43, 5629. **Pd**: Yu, J.-Q.; Corey, E.J. *Org. Lett.* **2002**, 4, 2727. **Ru**: Adam, W.; Alsters, P.L.; Neumann, R.; Saha-Möller, C.; Sloboda-Rozner, D.; Zhang, R. *Synlett* **2002**, 2011. **V**: Sharpless, K.B.; Verhoeven, T.R. *Aldrichimica Acta* **1979**, 12, 63; Torres, G.; Torres, W.; Prieto, J.A. *Tetrahedron* **2004**, 60, 10245.

¹⁸⁸⁴ See Hiatt, R. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, **1971**, p 124.

however. Epoxidation occurs with Fe,¹⁸⁸⁵ and with Ti¹⁸⁸⁶ or V catalysts.¹⁸⁸⁷ In the presence of some other reagents,¹⁸⁸⁸ peroxides give good yields of the epoxide. These coreagents include DCC,¹⁸⁸⁹ magnesium aluminates,¹⁸⁹⁰ metalloporphyrins,¹⁸⁹¹ hydrotalcite¹⁸⁹² with microwave irradiation,¹⁸⁹³ and arsines in fluorous solvents.¹⁸⁹⁴ The catalyst MeReO₃¹⁸⁹⁵ has been used for epoxidation using sodium percarbonate and pyrazole,¹⁸⁹⁶ or hydrogen peroxide,¹⁸⁹⁷ or urea–H₂O₂.¹⁸⁹⁸

Epoxidation has been done in ionic liquids using 10% H₂O₂ with MnSO₄¹⁸⁹⁹ or an Fe catalyst.¹⁹⁰⁰ Hypervalent iodine compounds [e.g., PhI(OAc)₂], in conjunction with a Ru catalyst in aqueous media, converts alkenes to epoxides.¹⁹⁰¹ This reagent has been used in an ionic liquid with a Mn catalyst.¹⁹⁰² Sodium chlorite (NaClO₂) in water gives epoxidation from alkenes.¹⁹⁰³ Microwave assisted epoxidations are known using H₂O₂.¹⁹⁰⁴ Epoxidation of vinyl ethers has been studied.¹⁹⁰⁵

Several homogeneous and heterogeneous asymmetric epoxidation protocols have been developed.¹⁹⁰⁶ Enzymatic epoxidation¹⁹⁰⁷ and epoxidation with catalytic antibodies¹⁹⁰⁸ have been reported. Organocatalysts (e.g., chiral iminium salts) have been used.¹⁹⁰⁹ Asymmetric *Weitz–Scheffer epoxidation*¹⁹¹⁰ (epoxidation of electron-deficient alkenes

¹⁸⁸⁵ Anilkumar, G.; Bitterlich, B.; Gelalcha, F.G.; Tse, M.K.; Beller, M. *Chem. Commun.* **2007**, 289; Bitterlich, B.; Schröder, K.; Tse, M.K.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4867.

¹⁸⁸⁶ Sawada, Y.; Matsumoto, K.; Katsuki, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4559; Malkov, A.V.; Bourhani, Z.; Kočovský, P. *Org. Biomol. Chem.* **2005**, *3*, 3194; Matsumoto, K.; Sawada, Y.; Katsuki, T. *Pure Appl. Chem.* **2008**, *80*, 1071.

¹⁸⁸⁷ Zeng, W.; Ballard, T.E.; Melander, C. *Tetrahedron Lett.* **2006**, *47*, 5923. See Malkov, A.V.; Czemerys, L.; Malyshev, D.A. *J. Org. Chem.* **2009**, *74*, 3350.

¹⁸⁸⁸ See Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* **1989**, *22*, 205.

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¹⁸⁹⁰ Yamaguchi, K.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* **1999**, *64*, 2966.

¹⁸⁹¹ Chan, W.-K.; Liu, P.; Yu, W.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2004**, *6*, 1597.

¹⁸⁹² For an example without microwave irradiation, see Pillai, U.R.; Sahle-Demessie, E.; Varma, R.S. *Synth. Commun.* **2003**, *33*, 2017.

¹⁸⁹³ Pillai, U.R.; Sahle-Demessie, E.; Varma, R.S. *Tetrahedron Lett.* **2002**, *43*, 2909.

¹⁸⁹⁴ Van Vliet, M.C.A.; Arends, I.W.C.E.; Sheldon, R.A. *Tetrahedron Lett.* **1999**, *40*, 5239.

¹⁸⁹⁵ Yamazaki, S. *Tetrahedron* **2008**, *64*, 9253; Yamazaki, S. *Org. Biomol. Chem.* **2007**, *5*, 2109–2113; Saladino, R.; Neri, V.; Pelliccia, A.R.; Caminiti, R.; Sadun, C. *J. Org. Chem.* **2002**, *67*, 1323.

¹⁸⁹⁶ Vaino, A.R. *J. Org. Chem.* **2000**, *65*, 4210.

¹⁸⁹⁷ See Iskra, J.; Bonnet-Delpon, D.; Bégue, J.-P. *Tetrahedron Lett.* **2002**, *43*, 1001.

¹⁸⁹⁸ Owens, G.S.; Abu-Omar, M.M. *Chem. Commun.* **2000**, 1165.

¹⁸⁹⁹ Tong, K.-H.; Wong, K.-Y.; Chan, T.H. *Org. Lett.* **2003**, *5*, 3423.

¹⁹⁰⁰ Srinivas, K.A.; Kumar, A.; Chauhan, S.M.S. *Chem. Commun.* **2002**, 2456.

¹⁹⁰¹ Tse, M.K.; Bhor, S.; Klawonn, M.; Döbler, C.; Beller, M. *Tetrahedron Lett.* **2003**, *44*, 7479.

¹⁹⁰² Li, Z.; Xia, C.-G. *Tetrahedron Lett.* **2003**, *44*, 2069.

¹⁹⁰³ Geng, X.-L.; Wang, Z.; Li, X.-Q.; Zhang, C. *J. Org. Chem.* **2005**, *70*, 9610.

¹⁹⁰⁴ Bogdal, D.; Lukasiewicz, M.; Pielichowski, J.; Bednars, S. *Synth. Commun.* **2005**, *35*, 2973.

¹⁹⁰⁵ Orendt, A.M.; Roberts, S.W.; Rainier, J.D. *J. Org. Chem.* **2006**, *71*, 5565.

¹⁹⁰⁶ Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603.

¹⁹⁰⁷ Kubo, T.; Peters, M.W.; Meinhold, P.; Arnold, F.H. *Chemistry: European J.* **2006**, *12*, 1216. For a method of electrochemical regeneration of monooxygenase, see Hollmann, F.; Hofstetter, K.; Habicher, T.; Hauer, B.; Schmid, A. *J. Am. Chem. Soc.* **2005**, *127*, 6540.

¹⁹⁰⁸ Chen, Y.; Reymond, J.-L. *Synthesis* **2001**, 934.

¹⁹⁰⁹ Bulman Page, P.C.; Buckley, B.R.; Rassias, G.A.; Blacker, A.J. *Eur. J. Org. Chem.* **2006**, 803.

¹⁹¹⁰ Weitz, E.; Scheffer, A. *Chem. Ber.* **1921**, *54*, 2327. See Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem. Int. Ed.* **1996**, *35*, 1725.

using H_2O_2 in a strong alkaline solution) is common. Cinchona-derived phase-transfer catalysts, initially used by Wynberg, are now common.¹⁹¹¹ Enantioselectivities can be significantly improved by changes of the catalyst structure, as well as the type of oxidant.¹⁹¹² A Yb—BINOL complex, with *t*-BuOOH led to epoxidation of conjugated ketones with high asymmetric induction,¹⁹¹³ as did a mixture of NaOCl and a *Cinchona* alkaloid.¹⁹¹⁴ Treatment with aq NaOCl¹⁹¹⁵ or with an alkyl hydroperoxide¹⁹¹⁶ and a chiral phase-transfer agent leads to chiral nonracemic epoxy-ketones. Epoxides can also be prepared by treating alkenes with oxygen or with an alkyl peroxide¹⁹¹⁷ catalyzed by a complex of a transition metal (e.g., V, Mo, Ti, La,¹⁹¹⁸ Y,¹⁹¹⁹ or Co).¹⁹²⁰ The use of chiral additive leads to enantioselective epoxidation,¹⁹²¹ and organocatalysts have been used as well.¹⁹²² Chiral hydroperoxides have been used for enantioselective epoxidation.¹⁹²³

Other epoxidation methods are available. Dioxiranes,¹⁹²⁴ (e.g., dimethyl dioxirane, **126**),¹⁹²⁵ either isolated or generated *in situ*,¹⁹²⁶ are important epoxidation reagents. With dimethyloxirane, C—H insertion reactions can occur preferentially.¹⁹²⁷ The reaction with alkenes is rapid, mild, safe, and a variety of methods have been developed using an oxidant as a coreagent. Substituent effects in such reactions have been studied¹⁹²⁸ and also substrate variations.¹⁹²⁹ The most commonly used coreagent is probably potassium peroxomonosulfate (KHSO_5). Oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) is a common source of KHSO_5 . Oxone reacts with ketones¹⁹³⁰ and sodium bicarbonate to convert an alkene to

¹⁹¹¹ Helder, R.; Hummelen, J.C.; Laane, R.W.P.M.; Wiering, J.S.; Wynberg, H. *Tetrahedron Lett.* **1976**, 17, 1831; Wynberg, H.; Marsman, B. *J. Org. Chem.* **1980**, 45, 158; Pluim, H.; Wynberg, H. *J. Org. Chem.* **1980**, 45, 2498.

¹⁹¹² Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, 55, 6375; Corey, E.J.; Zhang, F.-Y. *Org. Lett.* **1999**, 1, 1287; Lygo, B.; Wainwright, P.G. *Tetrahedron* **1999**, 55, 6289. See Adam, W.; Rao, P.B.; Degen, H.-G.; Levai, A.; Patonay, T.; Saha-Möller, C.R. *J. Org. Chem.* **2002**, 67, 259.

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¹⁹²⁰ See Jørgensen, K.A. *Chem. Rev.* **1989**, 89, 431.

¹⁹²¹ Wang, X.; Reisinger, C.M.; List, B. *J. Am. Chem. Soc.* **2008**, 130, 6070; Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, 130, 8134.

¹⁹²² Lu, J.; Xu, Y.-H.; Liu, F.; Loh, T.-P. *Tetrahedron Lett.* **2008**, 49, 6007.

¹⁹²³ Košnik, W.; Bocian, W.; Kozerski, L.; Tvaroška, I.; Chmielewski, M. *Chemistry: European J.* **2008**, 14, 6087.

¹⁹²⁴ Murray, R.W. *Chem. Rev.* **1989**, 89, 1187; Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* **1989**, 22, 205; Curci, R.; Dinoi, A.; Rubino, M.E. *Pure Appl. Chem.* **1995**, 67, 811; Clennan, E.L. *Trends in Organic Chemistry* **1995**, 5, 231; Denmark, S.E.; Wu, Z. *Synlett* **1999**, 847; Annese, C.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gandolfi, R.; Curci, R. *J. Am. Chem. Soc.* **2008**, 130, 1197.

¹⁹²⁵ Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, 63, 6425. See Angelis, Y.; Zhang, X.; Organopoulos, M. *Tetrahedron Lett.* **1996**, 37, 5991 for a discussion of the mechanism of this oxidation.

¹⁹²⁶ See Denmark, S.E.; Wu, Z. *J. Org. Chem.* **1998**, 63, 2810 and references cited therein; Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Cheung, K.-K. *J. Org. Chem.* **1998**, 63, 9888 and references cited therein; Masuyama, A.; Yamaguchi, T.; Abe, M.; Nojima, M. *Tetrahedron Lett.* **2005**, 46, 213.

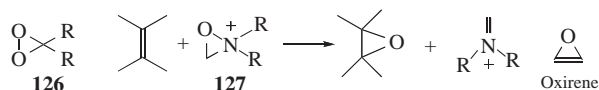
¹⁹²⁷ Adam, W.; Prechtel, F.; Richter, M.J.; Smerz, A.K. *Tetrahedron Lett.* **1993**, 34, 8427.

¹⁹²⁸ Düfert, A.; Werz, D.B. *J. Org. Chem.* **2008**, 73, 5514.

¹⁹²⁹ Nieto, N.; Munslow, I.J.; Fernández-Pérez, H.; Vidal-Ferran, A. *Synlett* **2008**, 2856.

¹⁹³⁰ Sartori, G.; Armstrong, A.; Maggi, R.; Mazzacani, A.; Sartorio, R.; Bigi, F.; Dominguez-Fernandez, B. *J. Org. Chem.* **2003**, 68, 3232.

an epoxide. Oxone converts alkenes to epoxides in the presence of certain additives (e.g., *N,N*-dialkylalloxans).¹⁹³¹ Oxone, with hydrogen peroxide or a similar oxidant, can be used with chiral ketones¹⁹³² or aldehydes to convert alkenes to chiral, nonracemic epoxides.¹⁹³³ This reaction probably converts alkenes to epoxides with good enantioselectivity by *in situ* generation of dioxirane.¹⁹³⁴ Chiral dioxiranes have reportedly given nonracemic epoxides.¹⁹³⁵ This transformation with chiral carbohydrates is sometimes called *Shi epoxidation*.¹⁹³⁶ Epoxidation does not occur in good yields with these reagents in most other solvents, and it is suggested that the active agent that generates dioxirane is peroxyimide acid [MeC(=NH)OOH].¹⁹³⁷ Note that benzaldehyde with Chloramine-M¹⁹³⁸ will convert alkenes to epoxides.¹⁹³⁹



Oxone oxidizes iminium salts to an oxaziridinium intermediate (**127**), which can transfer oxygen to an alkene to form an epoxide and regenerate the iminium salt.¹⁹⁴⁰ This variation has been applied to asymmetric¹⁹⁴¹ epoxidations using chiral iminium salt precursors.¹⁹⁴² Other asymmetric epoxidation reactions of alkenes use chiral ketones and iminium salts with an organocatalyst.¹⁹⁴³ Direct epoxidation of alkenes has been done using oxaziridinium salts.¹⁹⁴⁴

¹⁹³¹ Carnell, A.J.; Johnstone, R.A.W.; Parsy, C.C.; Sanderson, W.R. *Tetrahedron Lett.* **1999**, 40, 8029.

¹⁹³² Shi, Y. *Acc. Chem. Res.* **2004**, 37, 488; Yang, D. *Acc. Chem. Res.* **2004**, 37, 497; Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O.A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, 71, 1715; Crane, Z.; Goeddel, D.; Gan, Y.; Shi, Y. *Tetrahedron* **2005**, 61, 6409; Armstrong, A.; Tsuchiya, T. *Tetrahedron* **2006**, 62, 257; Boutureira, O.; McGouran, J.F.; Stafford, R.L.; Emmerson, D.P.G.; Davis, B. *Org. Biomol. Chem.* **2009**, 7, 4285; Armstrong, A.; Bettati, M.; White, A.J.P. *Tetrahedron* **2010**, 66, 6309.

¹⁹³³ See Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, 67, 2435; Denmark, S.E.; Matsushashi, H. *J. Org. Chem.* **2002**, 67, 3479; Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B.R.; Wailes, J.S. *J. Org. Chem.* **2002**, 67, 8610; Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, 124, 8792; Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* **2003**, 44, 7403; Chan, W.-K.; Yu, W.-y.; Che, C.-M.; Wong, M.-K. *J. Org. Chem.* **2003**, 68, 6576.

¹⁹³⁴ Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, 40, 8721. DFT modeling of the ee is discussed in Schneebeli, S.T.; Hall, M.L.; Breslow, R.; Friesner, R. *J. Am. Chem. Soc.* **2009**, 131, 3965.

¹⁹³⁵ Burke, C.P.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, 45, 4475.

¹⁹³⁶ Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, 119, 11224; Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979; Shi, Y. *Acc. Chem. Res.* **2004**, 37, 488; Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. USA* **2004**, 101, 5794.

¹⁹³⁷ Arias, L.A.; Adkins, S.; Nagel, C.J.; Bach, R.D. *J. Org. Chem.* **1983**, 48, 888.

¹⁹³⁸ See Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. *Angew. Chem. Int. Ed.* **1996**, 35, 2810.

¹⁹³⁹ Yang, D.; Zhang, C.; Wang, X.-C. *J. Am. Chem. Soc.* **2000**, 122, 4039.

¹⁹⁴⁰ See Bohé, L.; Kammoun, M. *Tetrahedron Lett.* **2002**, 43, 803; Bohé, L.; Kammoun, M. *Tetrahedron Lett.* **2004**, 45, 747.

¹⁹⁴¹ See Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, 122, 2948.

¹⁹⁴² See Jacobson, E. N. in Ojima, I. *Catalytic Asymmetric Synthesis* VCH, NY, **1993**, pp. 159–203; Page, P.C.B.; Barros, D.; Buckley, B.R.; Ardakani, A.; Marples, B.A. *J. Org. Chem.* **2004**, 69, 3595; Page, P.C.B.; Buckley, B.R.; Blacker, A.J. *Org. Lett.* **2004**, 6, 1543.

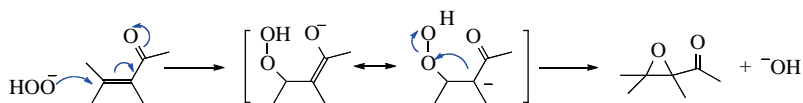
¹⁹⁴³ Wong, O.A.; Shi, Y. *Chem. Rev.* **2008**, 108, 3958; Page, P.C.B.; Buckley, B.R.; Farah, M.M.; Blacker, A.J. *Eur. J. Org. Chem.* **2009**, 3413.

¹⁹⁴⁴ Biscoe, M.R.; Breslow, R. *J. Am. Chem. Soc.* **2005**, 127, 10812.

Although cis–trans isomerization of epoxides is not formally associated with this section, it is a potential issue in the conversion of an alkene to an epoxide. There are several catalysts for this process.¹⁹⁴⁵

It would be useful if triple bonds could be similarly epoxidized to give oxirenes (see oxirene, above), but they are not stable compounds.¹⁹⁴⁶ Two oxirenes have been trapped in solid argon matrices at very low temperatures, but they decayed upon warming to 35 K.¹⁹⁴⁷ Oxirenes probably form in the reaction,¹⁹⁴⁸ but react further before they can be isolated. Note that oxirenes bear the same relationship to cyclobutadiene that furan does to benzene and may therefore be expected to be antiaromatic (Sec. 2.B and 2.K.ii).

Conjugated dienes can be epoxidized (1,2-addition), although the reaction is slower than for corresponding alkenes, but α,β -unsaturated ketones do not generally give epoxides when treated with peroxyacids.¹⁹⁴⁹ The epoxidation of α,β -unsaturated ketones with H_2O_2 under basic conditions is known as the *Waits–Scheffer epoxidation*, discovered in 1921.¹⁹⁵⁰ This fundamental reaction has been extended to α,β -unsaturated ketones (including quinones), aldehydes, and sulfones.¹⁹⁵¹ This is a nucleophilic addition by a *Michael-type* mechanism, involving attack by HO_2^- ¹⁹⁵²: This reaction is another example of 1,4-addition of a heteroatom-containing species, as discussed in Reaction 15-31.



α,β -Unsaturated compounds can be epoxidized alkyl hydroperoxides and a base,¹⁹⁵³ or with H_2O_2 and a base¹⁹⁵⁴ or heteropoly acids.¹⁹⁵⁵ The reaction has been done with LiOH and polymer-bound quaternary ammonium salts.¹⁹⁵⁶

Another important asymmetric epoxidation of a conjugated system is the reaction of alkenes with polyleucine,¹⁹⁵⁷ DBU, and urea– H_2O_2 , giving an epoxy–carbonyl compound with good enantioselectivity.¹⁹⁵⁸ The hydroperoxide anion epoxidation of conjugated

¹⁹⁴⁵ Lo, C.-Y.; Pal, S.; Odedra, A.; Liu, R.-S. *Tetrahedron Lett.* **2003**, 44, 3143.

¹⁹⁴⁶ See Lewars, E.G. *Chem. Rev.* **1983**, 83, 519.

¹⁹⁴⁷ Torres, M.; Bourdelande, J.L.; Clement, A.; Strausz, O.P. *J. Am. Chem. Soc.* **1983**, 105, 1698. See also, Laganis, E.D.; Janik, D.S.; Curphey, T.J.; Lemal, D.M. *J. Am. Chem. Soc.* **1983**, 105, 7457.

¹⁹⁴⁸ Ibne-Rasa, K.M.; Pater, R.H.; Ciabattoni, J.; Edwards, J.O. *J. Am. Chem. Soc.* **1973**, 95, 7894; Ogata, Y.; Sawaki, Y.; Inoue, H. *J. Org. Chem.* **1973**, 38, 1044.

¹⁹⁴⁹ Exceptions are known. See Hart, H.; Verma, M.; Wang, I. *J. Org. Chem.* **1973**, 38, 3418. For diiron-catalysis, see Marchi-Delapierre, C.; Jorge-Robin, A.; Thibon, A.; Ménage, S. *Chem. Commun.* **2007**, 1166.

¹⁹⁵⁰ Weitz, E.; Scheffer, A. *Ber. Dtsch. Chem. Ges.* **1921**, 54, 2327.

¹⁹⁵¹ See Zwanenburg, B.; ter Wiel, J. *Tetrahedron Lett.* **1970**, 935.

¹⁹⁵² Apeloig, Y.; Karni, M.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, 105, 2784. See Patai, S.; Rappoport, Z. in Patai, S. *The Chemistry of Alkenes*, pt. 1, Wiley, NY, **1964**, pp. 512–517.

¹⁹⁵³ Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* **2002**, 58, 1623; Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron Asymmetry* **2001**, 12, 1113; Honma, T.; Nakajo, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2002**, 43, 6229.

¹⁹⁵⁴ See Marigo, M.; Franzén, J.; Poulsen, T.B.; Zhuang, W.; Jørgensen, K.A. *J. Am. Chem. Soc.* **2005**, 127, 6964.

¹⁹⁵⁵ Oguchi, T.; Sakata, Y.; Takeuchi, N.; Kaneda, K.; Ishii, Y.; Ogawa, M. *Chem. Lett.* **1989**, 2053.

¹⁹⁵⁶ Anand, R.V.; Singh, V.K. *Synlett* **2000**, 807.

¹⁹⁵⁷ For a mechanistic discussion of polypeptide catalyzed epoxidation, see Mathew, S.P.; Gunathilagan, S.; Roberts, S.M.; Blackmond, D.G. *Org. Lett.* **2005**, 7, 4847.

¹⁹⁵⁸ Allen, J.V.; Drauz, K.-H.; Flood, R.W.; Roberts, S.M.; Skidmore, J. *Tetrahedron Lett.* **1999**, 40, 5417; Geller, T.; Roberts, S.M. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1397; Bentley, P.A.; Bickley, J.F.; Roberts, S.M.; Steiner, A. *Tetrahedron Lett.* **2001**, 42, 3741.

carbonyl compounds with a polyamino acid (e.g., poly-L-alanine or poly-L-leucine is known as the *Juliá–Colonna epoxidation*.¹⁹⁵⁹ Epoxidation of conjugated ketones to give nonracemic epoxy-ketones was done with aq NaOCl and a Cinchona alkaloid derivative as catalyst.¹⁹⁶⁰ A triphasic phase-transfer catalysis protocol has also been developed.¹⁹⁶¹ β -Peptides have been used as catalysts in this reaction.¹⁹⁶²

When a carbonyl group is elsewhere in the molecule, but not conjugated with the double bond, the *Baeyer–Villiger Reaction* (**18-19**) may compete. Allenes¹⁹⁶³ are converted by peroxyacids to allene oxides¹⁹⁶⁴ or spiro dioxides, both of which species can in certain cases be isolated,¹⁹⁶⁵ but more often are unstable under the reaction conditions and react further to give other products.¹⁹⁶⁶

Allylic alcohols can be converted to epoxy-alcohols with *tert*-butylhydroperoxide on molecular sieves,¹⁹⁶⁷ or with peroxyacids.¹⁹⁶⁸ The addition of an appropriate chiral ligand to the metal-catalyzed hydroperoxide epoxidation of allylic alcohols leads to high enantioselectivity. This important modification is known as the *Sharpless asymmetric epoxidation*,¹⁹⁶⁹ where allylic alcohols are converted to optically active epoxides with excellent enantioselectivity by treatment with *t*-BuOOH, titanium tetrakisopropoxide, and optically active diethyl tartrate.¹⁹⁷⁰ The $\text{Ti}(\text{OCHMe}_2)_4$ and diethyl tartrate can be present in catalytic amounts (15–10 mol%) if molecular sieves are present.¹⁹⁷¹ Polymer-supported catalysts have also been reported.¹⁹⁷² The use of a tartrate–PEG reagent (PEG₃₅₀ or PEG₇₅₀) allows generation of both enantiomers.¹⁹⁷³ Both (+) and (–) diethyl tartrate are readily available, so either enantiomer of the product can be prepared. The method has been successful for a wide range of primary allylic alcohols, including substrates where the double bond is mono-, di-, tri-, and tetrasubstituted,¹⁹⁷⁴ and is highly useful in natural product synthesis. The mechanism of the Sharpless epoxidation is believed to involve attack on the substrate by a compound¹⁹⁷⁵ formed from the titanium

¹⁹⁵⁹ Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S.; Guixer, J. *Tetrahedron*, **1984**, 40, 5207. For reviews, see Lin, P. *Tetrahedron: Asymmetry* **1998**, 9, 1457; Ebrahim, S.; Wills, M. *Tetrahedron: Asymmetry* **1997**, 8, 3163.

¹⁹⁶⁰ Lygo, B.; Wainwright, P.G. *Tetrahedron* **1999**, 55, 6289.

¹⁹⁶¹ Geller, T.; Krüger, C.M.; Militzer, H.-C. *Tetrahedron Lett.* **2004**, 45, 5069.

¹⁹⁶² Coffey, P.E.; Drauz, K.-H.; Roberts, S.M.; Skidmore, J.; Smith, J.A. *Chem. Commun.* **2001**, 2330.

¹⁹⁶³ See Jacobs, T.L. in Landor, S.R. *The Chemistry of Allenes* Vol. 2, Academic Press, NY, **1982**, pp. 417–510, 483–491.

¹⁹⁶⁴ For a review of allene oxides, see Chan, T.H.; Ong, B.S. *Tetrahedron* **1980**, 36, 2269.

¹⁹⁶⁵ Crandall, J.K.; Batal, D.J. *J. Org. Chem.* **1988**, 53, 1338.

¹⁹⁶⁶ See Crandall, J.K.; Rambo, E. *J. Org. Chem.* **1990**, 55, 5929.

¹⁹⁶⁷ Antonioletti, R.; Bonadies, F.; Locati, L.; Scettri, A. *Tetrahedron Lett.* **1992**, 33, 3205.

¹⁹⁶⁸ Fringuelli, F.; Germani, R.; Pizzo, F.; Santinelli, F.; Savelli, G. *J. Org. Chem.* **1992**, 57, 1198.

¹⁹⁶⁹ See Pfenninger, A. *Synthesis* **1986**, 89; Rossiter, B.E. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, **1985**, pp. 193–246. For histories of its discovery, see Sharpless, K.B. *Chem. Br.* **1986**, 38. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 284–290.

¹⁹⁷⁰ Sharpless, K.B.; Woodard, S.S.; Finn, M.G. *Pure Appl. Chem.* **1983**, 55, 1823 and references cited therein.

¹⁹⁷¹ Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, 109, 5765. See Massa, A.; D'Ambrosi, A.; Proto, A.; Scettri, A. *Tetrahedron Lett.* **2001**, 42, 1995. For another improvement, see Wang, Z.; Zhou, W. *Tetrahedron* **1987**, 43, 2935.

¹⁹⁷² Canali, L.; Karjalainen, J.K.; Sherrington, D.C.; Hormi, O. *Chem. Commun.* **1997**, 123.

¹⁹⁷³ Reed, N.N.; Dickerson, T.J.; Boldt, G.E.; Janda, K.D. *J. Org. Chem.* **2005**, 70, 1728.

¹⁹⁷⁴ See the table in Finn, M.G.; Sharpless, K.B. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, **1985**, pp. 249–250. See also, Schweiter, M.J.; Sharpless, K.B. *Tetrahedron Lett.* **1985**, 26, 2543.

¹⁹⁷⁵ See Williams, I.D.; Pedersen, S.F.; Sharpless, K.B.; Lippard, S.J. *J. Am. Chem. Soc.* **1984**, 106, 6430.

alkoxide and the diethyl tartrate to produce a complex that also contains the substrate and the *t*-BuOOH.¹⁹⁷⁶

Ordinary alkenes (without an allylic OH group) do not give optically active alcohols by the Sharpless protocol because binding to the catalyst is necessary for enantioselectivity. Homoallylic alcohols have been converted to the epoxide, however, using a V catalyst in the presence of a chiral bis(hydroxyamide).¹⁹⁷⁷ Simple alkenes can be epoxidized enantioselectively with sodium hypochlorite (NaOCl, commercial bleach) and an optically active manganese complex catalyst.¹⁹⁷⁸ Apart from the commonly used NaOCl, urea-H₂O₂ has been used.¹⁹⁷⁹

The use of a manganese-salen complex¹⁹⁸⁰ with various oxidizing agents, in what is called the *Jacobsen-Katsuki reaction*.¹⁹⁸¹ Simple alkenes can be epoxidized with high enantioselectivity.¹⁹⁸² In addition to Mn, Cr-salen,¹⁹⁸³ Ti-salen,¹⁹⁸⁴ and Ru-salen complexes¹⁹⁸⁵ have been used for epoxidation.¹⁹⁸⁶ Note that salen ligands are based on salen. The mechanism of this reaction has been examined.¹⁹⁸⁷ Radical intermediates have been suggested for this reaction.¹⁹⁸⁸ A polymer-bound Mn(III)-salen complex, in conjunction with NaOCl, has been used for asymmetric epoxidation,¹⁹⁸⁹ and manganese porphyrin complexes have also been used.¹⁹⁹⁰ Cobalt complexes give similar results.¹⁹⁹¹ A related epoxidation reaction used an iron complex with molecular oxygen and isopropanol.¹⁹⁹² Nonracemic epoxides can be prepared from racemic epoxides with (salen) cobalt(II) catalysts following a modified procedure for kinetic resolution.¹⁹⁹³

¹⁹⁷⁶ See Finn, M.G.; Sharpless, K.B. in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, **1985**, p. 247. Also see Corey, E.J. *J. Org. Chem.* **1990**, *55*, 1693; Woodard, S.S.; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991**, *113*, 106; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991**, *113*, 113; Takano, S.; Iwebuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1991**, *113*, 2786; Cui, M.; Adam, W.; Shen, J.H.; Luo, X.M.; Tan, X.J.; Chen, K.X.; Ji, R.Y.; Jiang, H.L. *J. Org. Chem.* **2002**, *67*, 1427.

¹⁹⁷⁷ Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286.

¹⁹⁷⁸ Jacobsen, E.N.; Zhang, W.; Muci, A.R.; Ecker, J.R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. See also, Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1991**, *32*, 1055; Halterman, R.L.; Jan, S. *J. Org. Chem.* **1991**, *56*, 5253.

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¹⁹⁸⁰ Wu, M.; Wang, B.; Wang, S.; Xia, C.; Sun, W. *Org. Lett.* **2009**, *11*, 3622. See Adam, W.; Mock-Knoblauch, C.; Saha-Moller, C.R.; Herderich, M. *J. Am. Chem. Soc.* **2000**, *122*, 9685.

¹⁹⁸¹ Brandes, B.D.; Jacobsen, E.N. *Tetrahedron Lett.* **1995**, *36*, 5123; Nishikori, H.; Ohta, C.; Katsuki, T. *Synlett* **2000**, 1557; Tangestaninejad, S.; Habibi, M.H.; Mirkhani, V.; Moghadam, M. *Synth. Commun.* **2002**, *32*, 3331. See Fristrup, P.; Dideriksen, B.B.; Tanner, D.; Norrby, P.-O. *J. Am. Chem. Soc.* **2005**, *127*, 13672. For a discussion on the origin of enantioselectivity, see Kürti, L.; Blewett, M.M.; Corey, E.J. *Org. Lett.* **2009**, *11*, 4592.

¹⁹⁸² See Nishida, T.; Miyafuji, A.; Ito, Y.N.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 7053.

¹⁹⁸³ Daly, A.M.; Renahan, M.F.; Gilheany, D.G. *Org. Lett.* **2001**, *3*, 663; O'Mahony, C.P.; McGarrigle, E.M.; Renahan, M.F.; Ryan, K.M.; Kerrigan, N.J.; Bousquet, C.; Gilheany, D.G. *Org. Lett.* **2001**, *3*, 3435. See the references cited therein.

¹⁹⁸⁴ Matsumoto, K.; Oguma, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 7432.

¹⁹⁸⁵ Nakata, K.; Takeda, T.; Mihara, J.; Hamada, T.; Irie, R.; Katsuki, T. *Chem. Eur. J.* **2001**, *7*, 3776.

¹⁹⁸⁶ McGarrigle, E.M.; Gilheany, D.G. *Chem. Rev.* **2005**, *105*, 1563.

¹⁹⁸⁷ See Linker, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2060; Adam, W.; Roschmann, K.J.; Saha-Möller, C.R. *Eur. J. Org. Chem.* **2000**, 3519. Also see Cavallo, L.; Jacobsen, H. *J. Org. Chem.* **2003**, *68*, 6202.

¹⁹⁸⁸ Cavallo, L.; Jacobsen, H. *Angew. Chem. Int. Ed.* **2000**, *39*, 589.

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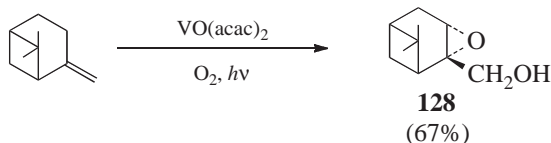
¹⁹⁹⁰ Konishi, K.; Oda, K.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 1313.

¹⁹⁹¹ Takai, T.; Hata, E.; Yorozu, K.; Mukaiyama, T. *Chem. Lett.* **1992**, 2077.

¹⁹⁹² Saalfrank, R.W.; Reihs, S.; Hug, M. *Tetrahedron Lett.* **1993**, *34*, 6033.

¹⁹⁹³ Savle, P.S.; Lamoreaux, M.J.; Berry, J.F.; Gandour, R.D. *Tetrahedron Asymmetry* **1998**, *9*, 1843.

In a different type of reaction, alkenes are photooxygenated (with singlet O_2 , see Reaction 14-7) in the presence of a Ti, V, or Mo complex to give epoxy alcohols (e.g., **128**), formally derived from allylic hydroxylation followed by epoxidation.¹⁹⁹⁴ In other cases, modification of the procedure gives simple epoxidation.¹⁹⁹⁵ Alkenes react with aldehydes and oxygen, with Pd-on-silica¹⁹⁹⁶ or a Ru catalyst,¹⁹⁹⁷ to give the epoxide.

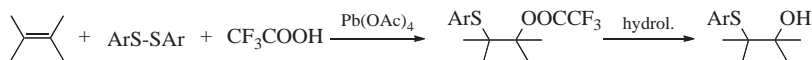


Thiiranes can be prepared directly from alkenes using specialized reagents.¹⁹⁹⁸ Thiourea with a tin catalyst gives the thiirane, for example.¹⁹⁹⁹ Interestingly, internal alkynes were converted to 1,2-dichorothiiranes by reaction with S_2Cl_2 (sulfur monochloride).²⁰⁰⁰ Note that epoxides are converted to thiiranes with ammonium thiocyanate and a cerium complex.²⁰⁰¹ A trans-thiiration reaction occurs with a Mo catalyst, in which an alkene reacts with styrene thiirane to give the new thiirane.²⁰⁰²

OS I, 494; IV, 552, 860; V, 191, 414, 467, 1007; VI, 39, 320, 679, 862; VII, 121, 126, 461; VIII, 546; IX, 288; X, 29; **80**, 9.

15-51 Hydroxysulfenylation (Addition of Oxygen, Sulfur)

Hydroxy-arylthio-addition (overall transformation)



Both hydroxy and an arylthio group are added to a double bond by treatment with an aryl disulfide and lead tetraacetate in the presence of trifluoroacetic acid.²⁰⁰³ Manganese and copper acetates have been used instead of $\text{Pb}(\text{OAc})_4$.²⁰⁰⁴ Addition of the groups OH and RSO has been achieved by treatment of alkenes with O_2 and a thiol (RSH).²⁰⁰⁵ Addition to RS groups to give *vic*-dithiols was observed by treatment of the alkene

¹⁹⁹⁴ Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* **1989**, *111*, 203.

¹⁹⁹⁵ See Iwahama, T.; Hatta, G.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 163.

¹⁹⁹⁶ Ragagnin, G.; Knochel, P. *Synlett* **2004**, 951.

¹⁹⁹⁷ Srikanth, A.; Nagendrappa, G.; Chandrasekaran, S. *Tetrahedron* **2003**, *59*, 7761; Qi, J.Y.; Qiu, L.Q.; Lam, K.H.; Yip, C.W.; Zhou, Z.Y.; Chan, A.S.C. *Chem. Commun.* **2003**, 1058.

¹⁹⁹⁸ Adam, W.; Bargon, R.M. *Eur. J. Org. Chem.* **2001**, 1959; See Sugihara, Y.; Onda, K.; Sato, M.; Suzu, T. *Tetrahedron Lett.* **2010**, *51*, 4110.

¹⁹⁹⁹ Tangestaninejad, S.; Mirkhani, V. *Synth. Commun.* **1999**, *29*, 2079.

²⁰⁰⁰ Nakayama, J.; Takahashi, K.; Watanabe, T.; Sugihara, Y.; Ishii, A. *Tetrahedron Lett.* **2000**, *41*, 8349.

²⁰⁰¹ Iranpoor, N.; Tamami, B.; Shekarraz, M. *Synth. Commun.* **1999**, *29*, 3313.

²⁰⁰² Adam, W.; Bargon, R.M.; Schenk, W.A. *J. Am. Chem. Soc.* **2003**, *125*, 3871.

²⁰⁰³ Trost, B.M.; Ochiai, M.; McDougal, P.G. *J. Am. Chem. Soc.* **1978**, *100*, 7103; See Zefirov, N.S.; Zyk, N.V.; Kutateladze, A.G.; Kolbasenko, S.I.; Lapin, Yu.A. *J. Org. Chem. USSR* **1986**, *22*, 190.

²⁰⁰⁴ Bewick, A.; Mellor, J.M.; Owton, W.M. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 1039; Bewick, A.; Mellor, J.M.; Milano, D.; Owton, W.M. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 1045; Samii, Z.K.M.A.E.; Ashmawy, M.I.A.; Mellor, J.M. *Tetrahedron Lett.* **1986**, *27*, 5289.

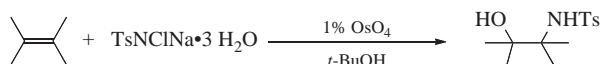
²⁰⁰⁵ Chung, M.; D'Souza, V.T.; Szmant, H.H. *J. Org. Chem.* **1987**, *52*, 1741, and other papers in this series.

with a disulfide (RSSR) and BF_3 -etherate.²⁰⁰⁶ This reaction has been carried out intramolecularly.²⁰⁰⁷ In a similar manner, the reaction of alkenes with ceric ammonium nitrate and diphenyl diselenide in methanol leads to vicinally substituted phenylselenenyl methyl ethers.²⁰⁰⁸ Dimethyl diselenide adds to alkenes to form vicinal bis(methylselenenyl) compounds, in the presence of tin tetrachloride.²⁰⁰⁹

Halo-ethers can be formed by the reaction of alkenyl alcohols with various reagents. Hept-6-en-1-ol reacts with $(\text{collidine})_2\text{I}^+\text{PF}_6^-$, for example, to form 2-iodomethyl-1-oxacycloheptane.²⁰¹⁰

15-52 Oxyamination (Addition of Oxygen, Nitrogen)

Tosylamino-hydroxy-addition



N-Tosylated β -hydroxy alkylamines, which can be easily hydrolyzed to β -hydroxy-amines²⁰¹¹, can be prepared²⁰¹² by treatment of alkenes with the trihydrate of Chloramine-T (*N*-chloro-*p*-toluenesulfonamide sodium salt)¹⁶⁹⁰ and a catalytic amount of OsO_4 .²⁰¹³ In some cases, yields can be improved by the use of phase-transfer catalysis.²⁰¹⁴ The reaction has been carried out enantioselectively.²⁰¹⁵ Alkenes can be converted to amido alcohols enantioselectivity by modification of this basic scheme. The *Sharpless asymmetric aminohydroxylation* employs a catalyst consisting of *Cinchona* alkaloid derived ligands and an osmium species in combination with a stoichiometric nitrogen source that also functions as the oxidant.²⁰¹⁶ The Cu catalyzed reaction of an alkene with a *N*-sulfone oxaziridine leads to an oxazolidine.²⁰¹⁷ *N*-Chlorosulfonyl isocyanate has been used to prepare 1,2-amino alcohols.²⁰¹⁸ The Cu catalyzed hydroxyamination of alkenes was reported using Boc-hydroxylamine.²⁰¹⁹

The reaction of a carbamate with $(\text{DHQ})_2\text{PHAL}$ (**124**) and the osmium compound, with NaOH and *tert*-butyl hypochlorite, leads to a diastereomeric mixture of amido alcohols **129** and **130**, each formed with high enantioselectivity.²⁰²⁰ An enantioselective amino-hydroxylation of acrylamides has been reported.²⁰²¹

²⁰⁰⁶ Inoue, H.; Murata, S. *Heterocycles* **1997**, *45*, 847.

²⁰⁰⁷ Tuladhar, S.M.; Fallis, A.G. *Tetrahedron Lett.* **1987**, *28*, 523. See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 905–908.

²⁰⁰⁸ Bosman, C.; D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.* **1994**, *35*, 6525. See Ogawa, A.; Tanaka, H.; Yokoyama, H.; Obayashi, R.; Yokoyama, K.; Sonoda, N. *J. Org. Chem.* **1992**, *57*, 111.

²⁰⁰⁹ Hermans, B.; Colard, N.; Hevesi, L. *Tetrahedron Lett.* **1992**, *33*, 4629.

²⁰¹⁰ Brunel, Y.; Rousseau, G. *Synlett* **1995**, 323.

²⁰¹¹ See Bäckvall, J.E.; Oshima, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* **1979**, *44*, 1953.

²⁰¹² Sharpless, K.B.; Chong, A.O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177. See Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. *Angew. Chem. Int. Ed.* **1996**, *35*, 2810.

²⁰¹³ See Fokin, V.V.; Sharpless, K.B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3455.

²⁰¹⁴ Herranz, E.; Sharpless, K.B. *J. Org. Chem.* **1978**, *43*, 2544.

²⁰¹⁵ Hassine, B.B.; Gorsane, M.; Pecher, J.; Martin, R.H. *Bull. Soc. Chim. Belg.* **1985**, *94*, 759.

²⁰¹⁶ For a review, see Bodkin, J.A.; McLeod, M.D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733.

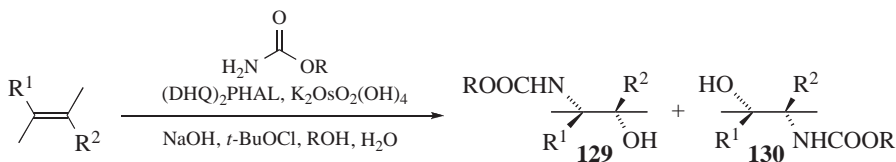
²⁰¹⁷ Michaelis, D.J.; Shaffer, C.J.; Yoon, T.P. *J. Am. Chem. Soc.* **2007**, *129*, 1866.

²⁰¹⁸ Kim, J.D.; Kim, I.S.; Hua, J.C.; Zee, O.P.; Jung, Y.H. *Tetrahedron Lett.* **2005**, *46*, 1079.

²⁰¹⁹ Kalita, B.; Nicholas, K.M. *Tetrahedron Lett.* **2005**, *46*, 1451.

²⁰²⁰ Li, G.; Chang, H.-T.; Sharpless, K.B. *Angew. Chem., Int. Ed.* **1996**, *35*, 451.

²⁰²¹ Streuff, J.; Osterath, B.; Nieger, M.; Muñoz, K. *Tetrahedron Asymmetry* **2005**, *16*, 3492.



In general, the nitrogen adds to the less sterically hindered carbon of the alkene to give the major product. *N*-Bromoamides, in the presence of a catalytic amount of (DHQ)₂PHAL and LiOH converts conjugated esters to β-amido-α-hydroxy esters with good enantioselectivity.²⁰²² Another oxyamination reaction involves treatment of a Pd complex of the alkene with a secondary or primary amine, followed by lead tetraacetate or another oxidant.²⁰²³

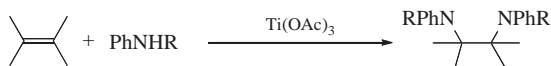
The organolanthanide-catalyzed alkene hydroamination has been reported.²⁰²⁴ With this approach, amino alkenes (not enamines) can be cyclized to form cyclic amines,²⁰²⁵ and amino alkynes lead to cyclic imine.²⁰²⁶ The use of synthesized C-1²⁰²⁷ and C-2 symmetric²⁰²⁸ chiral organolanthanide complexes give the amino alcohol with good enantioselectivity.

β-Amino alcohols can be prepared by treatment of an alkene with a reagent prepared from HgO and HBF₄ along with aniline to give an aminomercurial compound (PhHN—C—C—HgBF₄, aminomercuriation; see Reaction 15-7), which is hydrolyzed to PhHN—C—C—OH.²⁰²⁹ The use of an alcohol instead of water gives the corresponding amino ether. β-Azido alcohols are prepared by the reaction of an alkene with Me₃SiOOSiMe₃, Me₃SiN₃, and 20% (Cl₂SnO)_n, followed by treatment with aqueous acetic acid.²⁰³⁰

OS VII, 223, 375.

15-53 Diamination (Addition of Nitrogen, Nitrogen)

Di(alkylaryl)amino)-addition



Primary (R = H) and secondary aromatic amines react with alkenes in the presence of thallium(III) acetate to give *vic*-diamines in good yields.²⁰³¹ The reaction is not successful for primary aliphatic amines. In another procedure, alkenes can be diaminated by treatment

²⁰²² Demko, Z.P.; Bartsch, M.; Sharpless, K.B. *Org. Lett.* **2000**, 2, 2221.

²⁰²³ Bäckvall, J.E.; Björkman, E.E. *Acta Chem. Scand. Ser. B* **1984**, 38, 91; Bäckvall, J.E.; Bystrom, S.E. *J. Org. Chem.* **1982**, 47, 1126.

²⁰²⁴ Ryu, J.-S.; Li, G.Y.; Marks, T.J. *J. Am. Chem. Soc.* **2003**, 125, 12584. For a review, see Hong, S.; Marks, T.J. *Acc. Chem. Res.* **2004**, 37, 673.

²⁰²⁵ Gagné, M.R.; Stern, C.L.; Marks, T.J. *J. Am. Chem. Soc.* **1992**, 114, 275.

²⁰²⁶ Li, Y.; Marks, T.J. *J. Am. Chem. Soc.* **1998**, 120, 1757.

²⁰²⁷ Douglass, M.R.; Ogasawara, M.; Hong, S.; Metz, M.V.; Marks, T.J. *Organometallics* **2002**, 21, 283; Giardello, M.A.; Conticello, V.P.; Brard, L.; Gagné, M.R.; Marks, T.J. *J. Am. Chem. Soc.* **1994**, 116, 10241; Giardello, M.A.; Conticello, V.P.; Brard, L.; Sabat, M.; Rheingold, A.L.; Stern, C.L.; Marks, T.J. *J. Am. Chem. Soc.* **1994**, 116, 10212.

²⁰²⁸ Hong, S.; Tian, S.; Metz, M.V.; Marks, T.J. *J. Am. Chem. Soc.* **2003**, 125, 14768.

²⁰²⁹ Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* **1981**, 376.

²⁰³⁰ Sakurada, I.; Yamasaki, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2000**, 41, 2415.

²⁰³¹ Gómez Aranda, V.; Barluenga, J.; Aznar, F. *Synthesis* **1974**, 504.

with the Os compounds R_3NOsO ($R = t\text{-Bu}$) and R_2NOsO_2 ,²⁰³² analogous to the Os compound mentioned at Reaction 15-52.²⁰³³ The Pd promoted method of Reaction 15-52 has also been extended to diamination.²⁰³⁴ Alkenes can also be diaminated²⁰³⁵ indirectly by treatment of the aminomercurial compound mentioned in Reaction 15-52 with a primary or secondary aromatic amine.²⁰³⁶ The reaction of an alkene with *N*-arylsulfonyl dichloroamines ($ArSO_2NCl_2$) followed by reaction with aq Na_2SO_3 , gives the *anti*-vic-diacetamide.²⁰³⁷ The Pd catalyzed addition of saccharin and $H(NTs)_2$ with an alkene, in the presence of a hypervalent iodine oxidant leads to a precursor that can be converted to a 1,2-diamine.²⁰³⁸

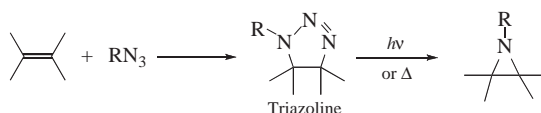
Two azido groups can be added to double bonds by treatment with sodium azide and iodosobenzene in acetic acid, $C=C + NaN_3 + PhIO \rightarrow N_3-C-C-N_3$.²⁰³⁹

Dienes react with ureas in the presence of a Pd catalyst, to give an oxazolidinone.²⁰⁴⁰ A Pd catalyzed reaction of dienes with di-*tert*-butyldiaziridinone also leads to an oxazolidinone.²⁰⁴¹

Alkynes react with the bis(tosylate) of ethylenediamine, in the presence of a CuI catalyst, to give a dihydropiperazine.²⁰⁴²

15-54 Formation of Aziridines (Addition of Nitrogen, Nitrogen)

epi-Arylimino-addition, and so on



Aziridines can be prepared directly from double-bond compounds by photolysis or thermolysis of a mixture of the substrate and an azide.²⁰⁴³ The reaction has been carried out with $R = \text{aryl, cyano, EtOOC, and RSO}_2$, as well as other groups. The reaction can take place by at least two pathways.

In one pathway, a 1,3-dipolar addition (Reaction 15-58) takes place to give a triazoline, which can be isolated, followed thermal by extrusion of nitrogen (Reaction 17-34). Evidence for the nitrene pathway is most compelling for $R = \text{acyl groups}$. In the other, the azide is converted to a nitrene, which adds to the double bond in a manner analogous to

²⁰³² Chong, A.O.; Oshima, K.; Sharpless, K.B. *J. Am. Chem. Soc.* **1977**, *99*, 3420. See also, Sharpless, K.B.; Singer, S.P. *J. Org. Chem.* **1976**, *41*, 2504.

²⁰³³ For a X-ray structure of the osmium intermediate, see Muñiz, K.; Iesato, A.; Nieger, M. *Chem. Eur.J.* **2003**, *9*, 5581.

²⁰³⁴ Bäckvall, J. *Tetrahedron Lett.* **1978**, 163.

²⁰³⁵ See Osowska-Pacewicz, K.; Zwierzak, A. *Synthesis* **1990**, 505.

²⁰³⁶ Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* **1979**, 962.

²⁰³⁷ Li, G.; Kim, S.H.; Wei, H.-X. *Tetrahedron Lett.* **2000**, *41*, 8699.

²⁰³⁸ Iglesias, Á.; Pérez, E.G.; Muñiz, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 8109.

²⁰³⁹ Moriarty, R.M.; Khosrowshahi, J.S. *Tetrahedron Lett.* **1986**, *27*, 2809. See Fristad, W.E.; Brandvold, T.A.; Peterson, J.R.; Thompson, S.R. *J. Org. Chem.* **1985**, *50*, 3647.

²⁰⁴⁰ Bar, G.L.J.; Lloyd-Jones, G.C.; Booker-Milburn, K.I. *J. Am. Chem. Soc.* **2005**, *127*, 7308.

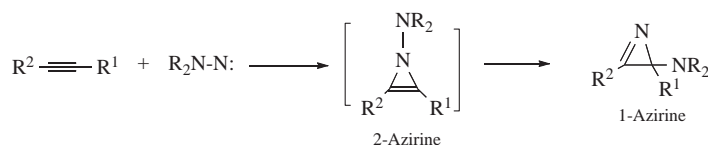
²⁰⁴¹ Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762; Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496; Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688.

²⁰⁴² Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820.

²⁰⁴³ See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines* Academic Press, NY, **1969**, pp. 68–79; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, **1967**. See Singh, G.S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080.

that of carbene addition (Reaction **15-64**). Sulfonyloxy amines (e.g., $\text{ArSO}_2\text{ONHCO}_2\text{Et}$) form an aziridine when treated with CaO in the presence of a conjugated carbonyl compound.²⁰⁴⁴ In the presence of Cu ,²⁰⁴⁵ Co ,²⁰⁴⁶ or Rh complexes,²⁰⁴⁷ ethyl diazoacetate adds to imines to give aziridines. Diazirenes (Sec. 5.D.ii) with *n*-butyllithium converted conjugated amides to the α,β -aziridino amide.²⁰⁴⁸ Calcium oxide has also been used to generate the nitrene,²⁰⁴⁹ including nitrene precursors that have an attached chiral ester.²⁰⁵⁰ Other specialized reagents have also been used.²⁰⁵¹ As discussed in Section 5.E, singlet nitrenes add stereospecifically while triplet nitrenes do not. Aminonitrenes ($\text{R}_2\text{NN:}$) have been shown to add to alkenes²⁰⁵² to give *N*-substituted aziridines and to triple bonds to give 1-azirines, which arise from rearrangement of the initially formed 2-azirines.²⁰⁵³ *N*-Aminophthalimide generates a nitrene in the presence of a Pd catalyst, giving an *N*-phthalimido aziridine upon reaction with electron-deficient alkenes.²⁰⁵⁴ Alkyl azides add to conjugated alkenes in the presence of an acid.²⁰⁵⁵ Intramolecular aziridination reactions are known (e.g., the Pd catalyzed addition of *N*-tosyloxycarbamates to alkenes to form the bicyclic oxaziridinone).²⁰⁵⁶ Tosylamines react with alkenes in the presence of a Rh catalyst²⁰⁵⁷ or with iodine/ $\text{PhI}(\text{OAc})_2$.²⁰⁵⁸ Trichloroethylsulfamate esters react with $\text{PhI}(\text{OAc})_2$ and a Rh catalyst to give the corresponding *N*-sulfonyl aziridine.²⁰⁵⁹

Like oxirenes (see Reaction **15-50**), 2-azirines are unstable. 1-Azirines can be reduced to give chiral aziridines.²⁰⁶⁰



²⁰⁴⁴ Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Synthesis* **2001**, 1975. For an enantioselective version, see Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *J. Org. Chem.* **2002**, 67, 4972.

²⁰⁴⁵ Sanders, C.J.; Gillespie, K.M.; Scott, P. *Tetrahedron Asymmetry* **2001**, 12, 1055; Ma, J.-A.; Wang, L.-X.; Zhang, W.; Zhou, W.; Zhou, Q.-L. *Tetrahedron Asymmetry* **2001**, 12, 2801.

²⁰⁴⁶ Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* **2001**, 406.

²⁰⁴⁷ Mohan, J.M.; Uphade, T.S.S.; Choudhary, V.R.; Ravindranathan, T.; Sudalai, A. *Chem. Commun.* **1997**, 1429; Moran, M.; Bernardinelli, G.; Müller, P. *Helv. Chim. Acta* **1995**, 78, 2048.

²⁰⁴⁸ Ishihara, H.; Ito, Y.N.; Katsuki, T. *Chem. Lett.* **2001**, 984.

²⁰⁴⁹ Carducci, M.; Fioravanti, S.; Loreta, M.A.; Pellacani, L.; Tardella, P.A. *Tetrahedron Lett.* **1996**, 37, 3777.

²⁰⁵⁰ Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Tetrahedron Lett.* **2003**, 44, 3031.

²⁰⁵¹ Aires-de-Sousa, J.; Labo, A.M.; Prabhakar, S. *Tetrahedron Lett.* **1996**, 37, 3183.

²⁰⁵² Siu, T.; Yudin, A.K. *J. Am. Chem. Soc.* **2002**, 124, 530.

²⁰⁵³ Anderson, D.J.; Gilchrist, T.L.; Rees, C.W. *Chem. Commun.* **1969**, 147.

²⁰⁵⁴ Siu, T.; Picard, C.J.; Yudin, A.K. *J. Org. Chem.* **2005**, 70, 932.

²⁰⁵⁵ Mahoney, J.M.; Smith, C.R.; Johnston, J.N. *J. Am. Chem. Soc.* **2005**, 127, 1354.

²⁰⁵⁶ Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, 127, 14198.

²⁰⁵⁷ Catino, A.J.; Nichols, J.M.; Forslund, R.E.; Doyle, M.P. *Org. Lett.* **2005**, 7, 2787.

²⁰⁵⁸ Fan, R.; Pu, D.; Gan, J.; Wang, B. *Tetrahedron Lett.* **2008**, 49, 4925.

²⁰⁵⁹ Espino, C.G.; Wehn, P.M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, 123, 6935; Wehn, P.M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, 5, 4823; Espino, C.G.; Fiori, K.W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, 126, 15378; Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, 124, 13672; Keaney, G.F.; Wood, J.L. *Tetrahedron Lett.* **2005**, 46, 4031; Guthikonda, K.; Wehn, P.M.; Caliendo, B.J.; Du Bois, J. *Tetrahedron* **2006**, 62, 11331.

²⁰⁶⁰ Roth, P.; Andersson, P.G.; Somfai, P. *Chem. Commun.* **2002**, 1752.

An alternative preparation of aziridines reacts an alkene with iodine and Chloramine-T, generating the corresponding *N*-tosyl aziridine.²⁰⁶¹ Chloramine T and NBS also give the *N*-tosyl aziridine,²⁰⁶² and Bromamine-T (TsNBr⁻Na⁺) or TsNIK and have also been used in a similar manner.^{2063,2064} Diazoalkanes react with imines to give aziridines.²⁰⁶⁵ Another useful reagent is NsN=IPh, which reacts with alkenes in the presence of Rh compounds²⁰⁶⁶ or Cu complexes²⁰⁶⁷ to give *N*-Ns aziridines. Other sulfonamide reagents can be used,²⁰⁶⁸ including PhI=NTs.²⁰⁶⁹ Enantioselective aziridination is possible using this reaction with chiral ligands.²⁰⁷⁰ This reagent has been used in ionic liquids with a Cu catalyst.²⁰⁷¹ Palladium catalyzes such reactions²⁰⁷² and we can also use methyl trioxorhenium (MeReO₃).²⁰⁷³ Manganese(salen) catalysts have also been used with this reagent.²⁰⁷⁴ A nitrido Mn(salen) complex was used with ditosyl anhydride, converting a conjugated diene to an allylic *N*-tosylaziridine.²⁰⁷⁵ Arylsulfonamides react with alkenes via the nitrene using an Au²⁰⁷⁶ or a Cu catalyst.²⁰⁷⁷

Organocatalysts have been used for the enantioselective aziridination of the C=C unit in conjugated aldehydes.²⁰⁷⁸

Nitrenes can add to aromatic rings to give ring-expansion products analogous to those mentioned in Reaction 15-62.²⁰⁷⁹

OS VI, 56.

²⁰⁶¹ Wu, H.; Xu, L.-W.; Xia, C.-G.; Ge, J.; Yang, L. *Synth. Commun.* **2005**, *35*, 1413; Karabal, P.U.; Chouthaiwale, P.V.; Shaikh, T.M.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett.* **2010**, *51*, 6460. Also see Chen, D.; Timmons, C.; Guo, L.; Xu, X.; Li, G. *Synthesis* **2004**, 2479.

²⁰⁶² Thakur, V.V.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 989.

²⁰⁶³ Vyas, R.; Chanda, B.M.; Bedekar, A.V. *Tetrahedron Lett.* **1998**, *39*, 4715; Hayer, M.F.; Hossain, M.M. *J. Org. Chem.* **1998**, *63*, 6839. See Antunes, A.M.M.; Bonifácio, V.D.B.; Nascimento, S.C.C.; Lobo, A.M.; Branco, P.S.; Prabhakar, S. *Tetrahedron* **2007**, *63*, 7009.

²⁰⁶⁴ Jain, S.L.; Sain, B. *Tetrahedron Lett.* **2003**, *44*, 575.

²⁰⁶⁵ Casarrubios, L.; Pérez, J.A.; Brookhart, M.; Templeton, J.L. *J. Org. Chem.* **1996**, *61*, 8358.

²⁰⁶⁶ Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* **1996**, *52*, 1543. Also see, Södergren, M.J.; Alonso, D.A.; Bedekar, A.V.; Andersson, P.G. *Tetrahedron Lett.* **1997**, *38*, 6897.

²⁰⁶⁷ Knight, J.G.; Muldowney, M.P. *Synlett* **1995**, 949. See also, Mohr, F.; Binfield, S.A.; Fettingner, J.C.; Vedernikov, A.N. *J. Org. Chem.* **2005**, *70*, 4833.

²⁰⁶⁸ See GuthiKonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672. See also, Dichenna, P.H.; Robert-Peillard, F.; Dauban, P.; Dodd, R.H. *Org. Lett.* **2004**, *6*, 4503; Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 3965.

²⁰⁶⁹ Vedernikov, A.N.; Caulton, K.G. *Org. Lett.* **2003**, *5*, 2591; Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202. See Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2002**, *67*, 2101.

²⁰⁷⁰ See Gillespie, K.M.; Sanders, C.J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C.P.; Cott, P. *J. Org. Chem.* **2002**, *67*, 3450.

²⁰⁷¹ Kantam, M.L.; Neeraja, V.; Kavita, B.; Haritha, Y. *Synlett* **2004**, 525.

²⁰⁷² Antunes, A.M.M.; Marto, S.J.L.; Branco, P.S.; Prabhakar, S.; Lobo, A.M. *Chem. Commun.* **2001**, 405.

²⁰⁷³ Jean, H.-J.; Nguyen, S.B.T. *Chem. Commun.* **2001**, 235.

²⁰⁷⁴ Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245.

²⁰⁷⁵ Nishimura, M.; Minakata, S.; Thonchant, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **2000**, *41*, 7089.

²⁰⁷⁶ Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876.

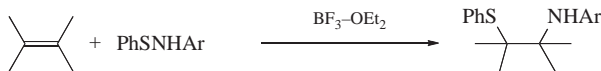
²⁰⁷⁷ Jain, S.L.; Sharma, V.B.; Sain, B. *Synth. Commun.* **2005**, *35*, 9.

²⁰⁷⁸ Vesely, J.; Ibrahim, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 778.

²⁰⁷⁹ See Lwowski, W.; Johnson, R.L. *Tetrahedron Lett.* **1967**, 891.

15-55 Aminosulfenylation (Addition of Nitrogen, Sulfur)

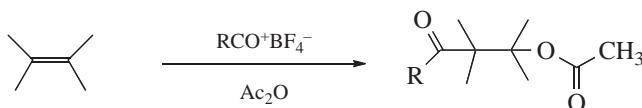
Arylamino-arylthio-addition



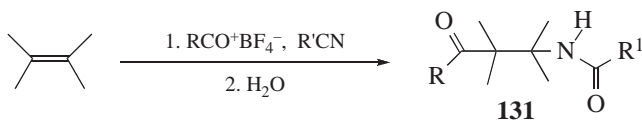
An amino and an arylthio group can be added to a double bond by treatment with a sulfenanilide (PhSNHAr) in the presence of BF_3 -etherate.²⁰⁸⁰ The addition is anti, and the mechanism probably involves a thiiranium ion.²⁰⁸¹ In another aminosulfenylation procedure, the substrate is treated with dimethyl(methylthio)sulfonium fluoroborate ($\text{MeSSMe}_2 \text{BF}_4^-$) and ammonia or an amine,²⁰⁸² the latter acting as a nucleophile. This reaction was extended to other nucleophiles:²⁰⁸³ N_3^- ,²⁰⁸⁴ NO_2^- , CN^- , OH^- , and OAc^- to give $\text{MeS}-\text{C}-\text{C}-\text{A}$, where $\text{A} = \text{N}_3$, NO_2 , CN , OH , and OAc , respectively. An RS ($\text{R} = \text{alkyl or aryl}$) and an NHCome group have been added in an electrochemical procedure.²⁰⁸⁵

15-56 Acylacyloxylation and Acylamidation (Addition of Oxygen, Carbon, or Nitrogen, Carbon)

Acyl-acyloxy-addition



An acyl and an acyloxy group can be added to a double bond by treatment with an acyl fluoroborate and acetic anhydride.²⁰⁸⁶ As expected, the addition follows Markovnikov's rule, with the electrophile Ac^+ going to the carbon with more hydrogen atoms. In an analogous reaction, an acyl and an amido group can be added to give **131**, if a nitrile is used in place of the anhydride. Similarly, halo-acetoxylation is known.²⁰⁸⁷ This reaction has also been carried out on triple bonds, to give the unsaturated analogues of **131** (syn addition).²⁰⁸⁸



²⁰⁸⁰ Benati, L.; Montavecchi, P.C.; Spagnolo, P. *Tetrahedron Lett.* **1984**, 25, 2039. See also, Brownbridge, P. *Tetrahedron Lett.* **1984**, 25, 3759.

²⁰⁸¹ See Ref. 21.

²⁰⁸² Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.* **1982**, 104, 3225; Caserio, M.C.; Kim, J.K. *J. Am. Chem. Soc.* **1982**, 104, 3231.

²⁰⁸³ Trost, B.M.; Shibata, T.; Martin, S.J. *J. Am. Chem. Soc.* **1982**, 104, 3228; Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.* **1982**, 104, 3225. For an extension that allows A to be $\text{C}\equiv\text{CR}$, see Trost, B.M.; Martin, S.J. *J. Am. Chem. Soc.* **1984**, 106, 4263.

²⁰⁸⁴ Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Chem. Commun.* **1997**, 1133.

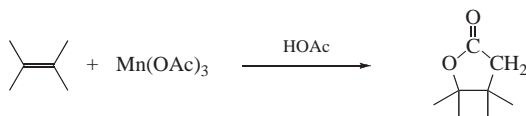
²⁰⁸⁵ Bewick, A.; Coe, D.E.; Mellor, J.M.; Owton, M.W. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 1033.

²⁰⁸⁶ Shastin, A.V.; Balenkova, E.S. *J. Org. Chem. USSR* **1984**, 20, 870.

²⁰⁸⁷ Hashem, Md.A.; Jung, A.; Ries, M.; Kirschning, A. *Synlett* **1998**, 195.

²⁰⁸⁸ Gridnev, I.D.; Balenkova, E.S. *J. Org. Chem. USSR* **1988**, 24, 1447.

15-57 The Conversion of Alkenes or Alkynes to Lactones (Addition of Oxygen, Carbon)



This reaction is clearly related to forming esters and lactones by reaction of carboxylic acids with alkenes (Reaction 15-6), but the Mn reagent leads to differences. Alkenes react with manganese(III) acetate to give γ -lactones.²⁰⁸⁹ The mechanism is probably free radical, involving addition of $\bullet\text{CH}_2\text{COOH}$ to the double bond. Ultrasound improves the efficiency of the reaction.²⁰⁹⁰ In a related reaction, cyclohexene reacted with $\text{MeO}_2\text{CCH}_2\text{CO}_2\text{K}$ and $\text{Mn}(\text{OAc})_3$ to give an α -carbomethoxy bicyclic lactone.²⁰⁹¹ The use of dimethyl malonate and ultrasound in this reaction gave the same type of product.²⁰⁹² Lactone formation has also been accomplished by treatment of alkenes with α -bromo carboxylic acids in the presence of benzoyl peroxide as catalyst,²⁰⁹³ and with alkylidene $\text{Cr}(\text{CO})_5$ complexes.²⁰⁹⁴ Alkenes can also be converted to γ -lactones by indirect routes.²⁰⁹⁵ Chromium carbene complexes add to alkenes to give β -lactones using ultrasound.²⁰⁹⁶

Cyclic dienes react with β -keto esters, in the presence of a Ga²⁰⁹⁷ catalyst and water, to give an α -acyl bicyclic lactone.

Alkenyl acids cyclize to the corresponding lactone upon treatment with sodium hypochlorite and a Lewis acid.²⁰⁹⁸ Alkynyl acids cyclize upon treatment with PIFA [phenyliodine(III)-bis(trifluoroacetate)] to give ω -acyl lactones.²⁰⁹⁹ A variation of this reaction also employs a diselenide.²¹⁰⁰ Treatment of alkynyl acids with a Au catalyst²¹⁰¹ leads to an alkylidene lactone.

An intramolecular variation of this reaction is known, involving amides, which generate a lactam.²¹⁰²

OS VII, 400.

Note that the related halolactonization reaction, including iodolactonization, is discussed in Reaction 15-41.

For addition of aldehydes and ketones, see the *Prins reaction* (16-54), and Reactions 16-95 and 16-96.

²⁰⁸⁹ Shundo, R.; Nishiguchi, I.; Matsubara, Y.; Hirashima, T. *Tetrahedron* **1991**, 47, 831. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* **1985**, 26, 4291.

²⁰⁹⁰ D'Annibale, A.; Trogolo, C. *Tetrahedron Lett.* **1994**, 35, 2083.

²⁰⁹¹ Lamarque, L.; Méou, A.; Brun, P. *Tetrahedron* **1998**, 54, 6497.

²⁰⁹² Allegretti, M.; D'Annibale, A.; Trogolo, C. *Tetrahedron* **1993**, 49, 10705.

²⁰⁹³ Nakano, T.; Kayama, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* **1987**, 60, 1049. See also, Kraus, G.A.; Landgrebe, K. *Tetrahedron Lett.* **1984**, 25, 3939.

²⁰⁹⁴ Wang, S.L.B.; Su, J.; Wulff, W.D. *J. Am. Chem. Soc.* **1992**, 114, 10665.

²⁰⁹⁵ See Bäuml, E.; Tscheschlok, K.; Pock, R.; Mayr, H. *Tetrahedron Lett.* **1988**, 29, 6925.

²⁰⁹⁶ Caldwell, J.J.; Harrity, J.P.A.; Heron, N.M.; Kerr, W.J.; McKendry, S.; Middlemiss, D. *Tetrahedron Lett.* **1999**, 40, 3481; Caldwell, J.J.; Kerr, W.J.; McKendry, S. *Tetrahedron Lett.* **1999**, 40, 3485.

²⁰⁹⁷ Nguyen, R.V.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, 127, 17184.

²⁰⁹⁸ López-López, J.A.; Guerra, F.M.; Moreno-Dorado, F.J.; Jorge, Z.D.; Massanet, G.M. *Tetrahedron Lett.* **2007**, 48, 1749.

²⁰⁹⁹ Tellitu, I.; Serna, S.; Herrero, M.T.; Moreno, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2007**, 72, 1526;

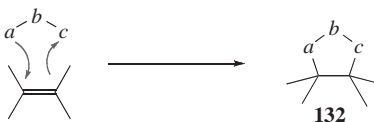
²¹⁰⁰ Browne, D.M.; Niyomura, O.; Wirth, T. *Org. Lett.* **2007**, 9, 3169.

²¹⁰¹ Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2006**, 47, 6273.

²¹⁰² Davies, D.T.; Kapur, N.; Parsons, A.F. *Tetrahedron Lett.* **1998**, 39, 4397.

15.C.iv. Cycloaddition Reactions

15-58 1,3-Dipolar Addition (Addition of Oxygen, Nitrogen, Carbon)



There are a large group of reactions ([3 + 2]-cycloadditions) in which five-membered heterocyclic compounds are prepared by addition of 1,3-dipolar compounds to double bonds. This reaction is quite useful in the synthesis of alkaloids,²¹⁰³ including asymmetric syntheses.²¹⁰⁴ These dipolar compounds have a sequence of three atoms $a-b-c$, of which a has a sextet of electrons in the outer shell and c has an octet with at least one unshared pair (see Table 15.3).²¹⁰⁵ The reaction can then be formulated as shown to generate **132**. Note that the initial reaction of potassium permanganate (Reaction **15-48**) occurs by [3 + 2]-cycloaddition to give a manganate ester (**119**).²¹⁰⁶ [3 + 2]-Cycloaddition occurs with other metal oxides.²¹⁰⁷ Hydrazones have also been reported to give [3 + 2]-cycloadditions.²¹⁰⁸

1,3-Dipoles of the type shown in Table 15.3 have an atom with six electrons in the outer shell, which is usually unstable. Such compounds will delocalize the charge to alleviate this electronic arrangement (they are resonance stabilized). 1,3-Dipolar compounds can be divided into two main types:

1. Those in which the dipolar canonical form has a double bond on the sextet atom and the other canonical form has a triple bond on that atom:



²¹⁰³ See Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905.

²¹⁰⁴ Karlsson, S.; Högberg, H.-E. *Org. Prep. Proceed. Int.* **2001**, 33, 103.

²¹⁰⁵ See Carruthers, W. *Cycloaddition Reactions in Organic Synthesis* Pergamon, Elmsford, NY, **1990**; Huisgen, R. *Helv. Chim. Acta* **1967**, 50, 2421; *Angew. Chem. Int. Ed.* **1963**, 2, 565, 633; Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis* VCH, NY, **1988**; Scriven, E.F.V. *Azides and Nitrenes* Academic Press, NY, **1984**; Stanovnik, B. *Tetrahedron* **1991**, 47, 2925 (diazoalkanes); Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, 30, 719 (nitrile oxides); Paton, R.M. *Chem. Soc. Rev.* **1989**, 18, 33 (nitrile sulfides); Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1988**, 27, 981; Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, 105, 2765 (azomethine ylids); Vedejs, E. *Adv. Cycloaddit.* **1988**, 1, 33 (azomethine ylids); DeShong, P.; Lander, Jr., S.W.; Leginus, J.M.; Dicken, C.M. *Adv. Cycloaddit.* **1988**, 1, 87 (nitrones); Balasubramanian, N. *Org. Prep. Proceed. Int.* **1985**, 17, 23 (nitrones); Confalone, P.N.; Huie, E.M. *Org. React.* **1988**, 36, 1 (nitrones); Padwa, A. in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, **1984**, pp. 313–374 (nitrile ylids); Bianchi, G.; Gandolfi, R.; Grünanger, P. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, **1983**, pp. 752–784 (nitrile oxides); Stuckwisch, C.G. *Synthesis* **1973**, 469 (azomethine ylids, azomethine imines). For reviews of intramolecular 1,3-dipolar additions see Padwa, A. in Padwa, A. treatise cited above, Vol. 2, pp. 277–406; Padwa, A.; Schoffstall, A.M. *Adv. Cycloaddit.* **1990**, 2, 1; Tsuge, O.; Hatta, T.; Hisano, T. in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, **1989**, pp. 345–475; Padwa, A. *Angew. Chem. Int. Ed.* **1976**, 15, 123. For a review of azomethine ylids, see Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, 45, 231. For reviews of 1,3-dipolar cycloreversions, see Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem. Int. Ed.* **1979**, 18, 721. For the use of this reaction to synthesize natural products, see papers in *Tetrahedron* **1985**, 41, 3447.

²¹⁰⁶ Houk, K.N.; Strassner, T. *J. Org. Chem.* **1999**, 64, 800.

²¹⁰⁷ See Gisdakis, P.; Rösch, N. *J. Am. Chem. Soc.* **2001**, 123, 697.

²¹⁰⁸ Kobayashi, S.; Hirabayashi, R.; Shimizu, H.; Ishitani, H.; Yamashita, Y. *Tetrahedron Lett.* **2003**, 44, 3351.

TABLE 15.3 Some Common 1,3-Dipolar Compounds

Compound	Reaction
Type 1	
Azide	$\text{R}-\text{N}^--\text{N}=\text{N}^+ \longleftrightarrow \text{R}-\text{N}^--\text{N}^+\equiv\text{N}$
Diazoalkane ^a	$\text{R}_2\text{C}^--\text{N}=\text{N}^+ \longleftrightarrow \text{R}_2\text{C}^--\text{N}^+\equiv\text{N}$
Nitrous oxide	$\text{O}^--\text{N}=\text{N}^+ \longleftrightarrow \text{O}^--\text{N}^+\equiv\text{N}$
Nitile imine ^b	$\text{R}-\text{N}^--\text{N}=\text{CR}'^+ \longleftrightarrow \text{R}-\text{N}^--\text{N}^+\equiv\text{CR}'$
Nitrile ylid ^c	$\text{R}_2\text{C}^--\text{N}=\text{CR}'^+ \longleftrightarrow \text{R}_2\text{C}^--\text{N}^+\equiv\text{CR}'$
Nitrile oxide ^d	$^-\text{O}-\text{N}=\text{CR}^+ \longleftrightarrow ^-\text{O}-\text{N}^+\equiv\text{CR}$
Type 2	
Azomethine imine ^e	$\text{R}_2\text{C}^--\text{N}(\text{R}^2)-\text{N}^+\text{R}' \longleftrightarrow \text{R}_2\text{C}^--\text{N}^+(\text{R}^2)=\text{NR}'$
Azoxy compound	$^-\text{O}-\text{N}(\text{R})-\text{N}^+\text{R}' \longleftrightarrow ^-\text{O}-\text{N}^+(\text{R})=\text{NR}'$
Azomethine ylid ^f	$\text{R}_2\text{C}^--\text{N}(\text{R}^2)-\text{CR}'_2^+ \longleftrightarrow \text{R}_2\text{C}^--\text{N}^+(\text{R}^2)=\text{CR}'_2$
Nitrone	$^-\text{O}-\text{N}(\text{R}')-\text{CR}_2^+ \longleftrightarrow ^-\text{O}-\text{N}^+(\text{R}')=\text{CR}_2$
Carbonyl oxide ^g	$^-\text{O}-\text{O}-\text{CR}_2^+ \longleftrightarrow ^-\text{O}-\text{O}^+=\text{CHR}_2$
Ozone	$^-\text{O}-\text{O}-\text{O}^+ \longleftrightarrow ^-\text{O}-\text{O}^+=\text{O}$
Carbonyl ylid ^h	$\text{H}_2\text{C}^--\text{O}^+=\text{CR}_2 \longleftrightarrow \text{H}_2\text{C}=\text{O}^+-\text{CR}_2$

^aSee Ref. 2109.^bSee Ref. 2110.^cSee Ref. 2111.^dSee Ref. 2112.^eSee Ref. 2113.^fSee Ref. 2114.^gSee Ref. 2115.^hSee Ref. 2116.²¹⁰⁹ See Baskaran, S.; Vasu, J.; Prasad, R.; Kodukulla, K.; Trivedi, G.K. *Tetrahedron* **1996**, 52, 4515.²¹¹⁰ Sibi, M.P.; Stanley, L.M.; Jasperse, C.P. *J. Am. Chem. Soc.* **2005**, 127, 8276.²¹¹¹ Raposo, C.; Wilcox, C.S. *Tetrahedron Lett.* **1999**, 40, 1285.²¹¹² See Nishiwaki, N.; Uehara, T.; Asaka, N.; Tohda, Y.; Ariga, M.; Kanemasa, S. *Tetrahedron Lett.* **1998**, 39, 4851; Jung, M.E.; Vu, B.T. *Tetrahedron Lett.* **1996**, 37, 451. See Muri, D.; Bode, J.W.; Carreira, E.M. *Org. Lett.* **2000**, 2, 539; Gissot, A.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2000**, 41, 1191. For a discussion of transition structures, see Luft, J.A.R.; Meleson, K.; Houk, K.N. *Org. Lett.* **2007**, 9, 555.²¹¹³ For a reaction using a chiral Si Lewis acid, see Shirakawa, S.; Lombardi, P.J.; Leighton, J.L. *J. Am. Chem. Soc.* **2005**, 127, 9974.²¹¹⁴ See Cabrera, S.; Arrayás, R.G.; Carretero, J.C. *J. Am. Chem. Soc.* **2005**, 127, 16394; Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, 130, 17250; Nájera, C.; Sansano, J.M. *Angew. Chem. Int. Ed.* **2005**, 44, 6272.²¹¹⁵ See Iesce, M.R.; Cermola, F.; Giordano, F.; Scarpati, R.; Graziano, M.L. *J. Chem. Soc. Perkin Trans. 1*, **1994**, 3295; MuCullough, K.J.; Sugimoto, T.; Tanaka, S.; Kusabayashi, S.; Nojima, M. *J. Chem. Soc. Perkin Trans. 1*, **1994**, 643.²¹¹⁶ Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, 127, 2709; Diev, V.V.; Kostikov, R.R.; Gleiter, R.; Molchanov, A.P. *J. Org. Chem.* **2006**, 71, 4066.

If the discussion is limited to the first row of the periodic table, b can only be nitrogen, c can be carbon or nitrogen, and a can be carbon, oxygen, or nitrogen; hence there are six types. Among these are azides ($a = b = c = \text{N}$) and diazoalkanes.

2. Those in which the dipolar canonical form has a single bond on the sextet atom and the other form has a double bond:



Here b can be nitrogen or oxygen, and a and c can be nitrogen, oxygen, or carbon, but there are only 12 types, since, for example, $\text{N} - \text{N} - \text{C}$ is only another form of $\text{C} - \text{N} - \text{N}$. Examples are shown in Table 15.3.

Of the 18 systems, some of which are unstable and must be generated *in situ*,²¹¹⁷ the reaction has been accomplished for at least 15, but not in all cases with a carbon–carbon double bond (the reaction also can be carried out with other double bonds²¹¹⁸). Not all alkenes undergo 1,3-dipolar addition equally well. The reaction is most successful for those that are good dienophiles in the *Diels–Alder Reaction* (15-60).

The addition is stereospecific and syn, and the mechanism is probably a one-step concerted process,²¹¹⁹ as illustrated above,²¹²⁰ largely controlled by Frontier Molecular Orbital considerations.²¹²¹ Reactivity has been shown to correlate with the energy required to distort 1,3-dipole and dipolarophiles to the transition state.²¹²² In-plane aromaticity has been invoked for these dipolar cycloadditions.²¹²³ As expected for this type of mechanism, the rates do not vary much with changes in solvent,²¹²⁴ although rate acceleration has been observed in ionic liquids.²¹²⁵ Nitrile oxide cycloadditions have also been done in supercritical carbon dioxide.²¹²⁶ There are no simple rules covering orientation in 1,3-dipolar additions. The regioselectivity has been explained by MO treatments,²¹²⁷ where overlap of the largest orbital coefficients of the atoms forming the new bonds leads to the major regioisomer. When the 1,3-dipolar compound is a thiocarbonyl ylid ($\text{R}_2\text{C}=\text{S}^{+}-\text{CH}_2^{-}$) the addition has been shown to be nonstereospecific with certain

²¹¹⁷ For a review of some aspects of this, see Grigg, R. *Chem. Soc. Rev.* **1987**, 16, 89.

²¹¹⁸ See Bianchi, G.; De Micheli, C.; Gandolfi, R. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, pt. 1, Wiley, NY, **1977**, pp. 369–532. Also see Dunn, A.D.; Rudorf, W. *Carbon Disulfide in Organic Chemistry*, Wiley, NY, **1989**, pp. 97–119.

²¹¹⁹ Di Valentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* **2000**, 65, 6112. For a theoretical study of transition states, see Lu, X.; Xu, X.; Wang, N.; Zhang, Q. *J. Org. Chem.* **2002**, 67, 515; DiValentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* **2000**, 65, 6112. For a discussion of loss of concertedness in reactions of azomethine ylids, see Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F.P. *J. Am. Chem. Soc.* **2000**, 122, 6078. See Ess, D.H.; Houk, K.N. *J. Am. Chem. Soc.* **2007**, 129, 10646.

²¹²⁰ For Huisgen, R. *Adv. Cycloaddit.* **1988**, 1, 1; Al-Sader, B.H.; Kadri, M. *Tetrahedron Lett.* **1985**, 26, 4661; Houk, K.N.; Firestone, R.A.; Munchausen, L.L.; Mueller, P.H.; Arison, B.H.; Garcia, L.A. *J. Am. Chem. Soc.* **1985**, 107, 7227; Majchrzak, M.W.; Warkentin, J. *J. Phys. Org. Chem.* **1990**, 3, 339.

²¹²¹ Caramella, P.; Gandour, R.W.; Hall, J.A.; Deville, C.G.; Houk, K.N. *J. Am. Chem. Soc.* **1977**, 99, 385 and references cited therein.

²¹²² Engels, B.; Christl, M. *Angew. Chem. Int. Ed.* **2009**, 48, 7968.

²¹²³ Cossío, F.P.; Marao, I.; Jiao, H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1999**, 121, 6737.

²¹²⁴ For a review of the role of solvents in this reaction, see Kadaba, P.K. *Synthesis* **1973**, 71.

²¹²⁵ Dubreuil, J.F.; Bazureau, J.P. *Tetrahedron Lett.* **2000**, 41, 7351.

²¹²⁶ Lee, C.K.Y.; Holmes, A.B.; Al-Duri, B.; Leeke, G.A.; Santos, R.C.D.; Seville, J.P.K. *Chem. Commun.* **2004**, 2622.

²¹²⁷ See Houk, K.N.; Yamaguchi, K. in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry* Vol. 2, Wiley, NY, **1984**, pp. 407–450. See also, Burdisso, M.; Gandolfi, R.; Quartieri, S.; Rastelli, A. *Tetrahedron* **1987**, 43, 159.

substrates, but stereospecific with others, indicating a nonsynchronous mechanism in these cases, and in fact, a diionic intermediate (see mechanism *c* in Reaction **15-63**, category 4) has been trapped in one such case.²¹²⁸ In a theoretical study of the 1,3-dipolar cycloadditions (diazomethane and ethene; fulminic acid $[H-C\equiv N-O]$ and ethyne),²¹²⁹ calculations based on valence bond descriptions suggest that many concerted 1,3-dipolar cycloaddition reactions follow an electronic heterolytic mechanism where the movement of well-identifiable orbital pairs is retained along the entire reaction path from reactants to product.²¹³⁰

An antibody-catalyzed $[3+2]$ -cycloaddition has been reported.²¹³¹ Metal-assisted dipolar additions are also known.²¹³² In a different metal-mediated reaction, alkenyl *Fischer carbene complexes* react with alkynes, in the presence of a Ni catalyst, to give cyclopentenones.²¹³³ Fischer carbene complexes take the form $R_2C=M(CO)_x$,²¹³⁴ and the metals include those of low oxidation state, and Fe, Mo, Cr, or W. Ligands include π -electron acceptors and π -donor substituents on methylene groups (e.g., alkoxy and amino groups).

Many of the cycloadducts formed from the dipoles in Table 15.3 are unstable, which lead to other products. The reaction of alkyl azides with alkenes generates triazolines (Reaction **15-54**), which extrude nitrogen ($N\equiv N$) upon heating or photolysis to give an aziridine.²¹³⁵ With a transition metal catalyst, alkyl azides add to alkynes to give triazoles.²¹³⁶ Retro $[3+2]$ -cycloaddition reactions are also known.²¹³⁷ Cycloaddition of azides to allenes leads to pyrrolidines.²¹³⁸

$[3+2]$ -Cycloaddition reactions occur intramolecularly to generate bicyclic and polycyclic compounds.²¹³⁹ The intramolecular cycloaddition of azomethine imines give bicyclic pyrazolidines, for example.²¹⁴⁰ When diazoalkanes (including diazo acetates, e.g., ethyl diazoacetate, N_2CHCO_2Et) react with an alkene and a Cr catalyst the initially formed product is a five-membered ring, a pyrazoline.²¹⁴¹ Pyrazolines are generally unstable and extrusion of nitrogen leads to a cyclopropane.²¹⁴² Rhodium-catalyzed cycloaddition using chiral ligands leads to formation of cyclopropanes with good enantioselectivity.²¹⁴³

²¹²⁸ Mloston, G.; Langhals, E.; Huisgen, R. *Tetrahedron Lett.* **1989**, 30, 5373; Huisgen, R.; Mloston, G. *Tetrahedron Lett.* **1989**, 30, 7041.

²¹²⁹ Karadakov, P.B.; Cooper, D.L.; Gerratt, J. *Theor. Chem. Acc.* **1998**, 100, 222.

²¹³⁰ Blavins, J.J.; Karadakov, P.B.; Cooper, D.L. *J. Org. Chem.* **2001**, 66, 4285.

²¹³¹ Toker, J.D.; Wentworth, Jr., P.; Hu, Y.; Houk, K.N.; Janda, K.D. *J. Am. Chem. Soc.* **2000**, 122, 3244.

²¹³² Kanemasa, S. *Synlett* **2002**, 1371.

²¹³³ Barluenga, J.; Barrio, P.; Riesgo, L.; López, L.A.; Tomás, M. *J. Am. Chem. Soc.* **2007**, 129, 14422.

²¹³⁴ See Fischer, H. *Chem. Ber.* **1980**, 113, 193.

²¹³⁵ For a discussion of reactivity and regioselectivity with strained alkenes and alkynes, see Schoenebeck, F.; Ess, D.H.; Jones, G.O.; Houk, K.N. *J. Am. Chem. Soc.* **2009**, 131, 8121.

²¹³⁶ Zhang, L.; Chen, X.; Xue, P.; Sun, H.H.Y.; Williams, I.D.; Sharpless, K.B.; Fokin, V.V.; Jia, G. *J. Am. Chem. Soc.* **2005**, 127, 15998; Kamata, K.; Nakagawa, Y.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2008**, 130, 15304.

²¹³⁷ da Silva, G.; Bozzelli, J.W. *J. Org. Chem.* **2008**, 73, 1343.

²¹³⁸ Feldman, K.S.; Iyer, M.R. *J. Am. Chem. Soc.* **2005**, 127, 4590.

²¹³⁹ See Padwa, A. *Angew. Chem. Int. Ed.* **1976**, 15, 123; Oppolzer, W. *Angew. Chem. Int. Ed.* **1977**, 16, 10 (see pp. 18–22).

²¹⁴⁰ Dolle, R.E.; Barden, M.C.; Brennan, P.E.; Ahmed, G.; Tran, V.; Ho, D.M. *Tetrahedron Lett.* **1999**, 40, 2907.

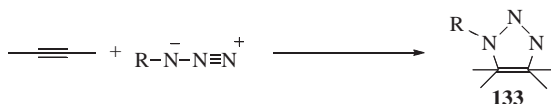
²¹⁴¹ For an enantioselective reaction, see Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, 128, 2174.

²¹⁴² Jan, D.; Simal, F.; Demonceau, A.; Noels, A.F.; Rufanov, K.A.; Ustynyuk, N.A.; Gourevitch, D.N. *Tetrahedron Lett.* **1999**, 40, 5695.

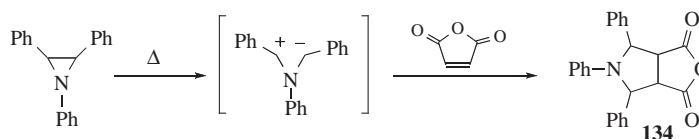
²¹⁴³ For a discussion of the mechanism and origin of enantioselectivity, see Nowlan, III, D.T.; Singleton, D.A. *J. Am. Chem. Soc.* **2005**, 127, 6190. Also see Jiao, L.; Ye, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, 130, 7178.

There are many cases where the [3 + 2]-cycloaddition leads to cycloadducts with high enantioselectivity.²¹⁴⁴ Cycloaddition of diazo esters with a Co catalyst having a chiral ligand leads to cyclopropane derivatives with good enantioselectivity.²¹⁴⁵ Cycloaddition of nitrones and pyrazolinones with a Cu catalyst and a chiral ligand leads to pyrrolidine derivatives with good enantioselectivity.²¹⁴⁶ In the presence of a Ni catalyst and a chiral ligand, nitrones react with activated cyclopropanes to give a tetrahydro-1,2-oxazine, with high enantioselectivity.²¹⁴⁷ Nitrones react with conjugated carbonyl compounds, with a transition metal catalyst (e.g., a Ti complex) to give an 1,2-oxazoline.²¹⁴⁸

Conjugated dienes generally give exclusive 1,2-addition, although 1,4-addition (a 3 + 4 cycloaddition) has been reported.²¹⁴⁹ Carbon–carbon triple bonds can also undergo 1,3-dipolar addition.²¹⁵⁰ For example, azides react to give triazoles, (**133**).



The 1,3-dipolar reagent can in some cases be generated by the *in situ* opening of a suitable three-membered ring system. For example, aziridines open to give a zwitterion (e.g., **134**), which can add to activated double bonds to give pyrrolidines.²¹⁵¹



Aziridines also add to $\text{C}\equiv\text{C}$ triple bonds, as well as to other unsaturated linkages, including $\text{C}=\text{O}$, $\text{C}=\text{N}$, and $\text{C}\equiv\text{N}$.²¹⁵² In some of these reactions, it is a C—N bond of the aziridine that opens rather than the C—C bond.

For other [3 + 2]-cycloadditions, see Reaction **15-59**.

OS **V**, 957, 1124; **VI**, 592, 670; **VIII**, 231. Also see, OS **IV**, 380.

²¹⁴⁴ Stanley, L.M.; Sibi, M.P. *Chem. Rev.* **2008**, *108*, 2887. See Bădoiu, A.; Brinkmann, Y.; Viton, F.; Kündig, E.P. *Pure Appl. Chem.* **2008**, *80*, 1013.

²¹⁴⁵ Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3647.

²¹⁴⁶ Sibi, M.P.; Ma, Z.; Jasperse, C.P. *J. Am. Chem. Soc.* **2004**, *126*, 718.

²¹⁴⁷ Sibi, M.P.; Ma, Z.; Jasperse, C.P. *J. Am. Chem. Soc.* **2005**, *127*, 5764.

²¹⁴⁸ Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926.

²¹⁴⁹ Baran, J.; Mayr, H. *J. Am. Chem. Soc.* **1987**, *109*, 6519.

²¹⁵⁰ See Bastide, J.; Hamelin, J.; Texier, F.; Quang, Y.V. *Bull. Soc. Chim. Fr.* **1973**, 2555; 2871; Fuks, R.; Viehe, H. G. in Viehe, H.G. *Acetylenes* Marcel Dekker, NY, **1969**, p. 460–477.

²¹⁵¹ Lown, J.W. in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, vol 1. Wiley, NY, **1984**, pp. 683–732.

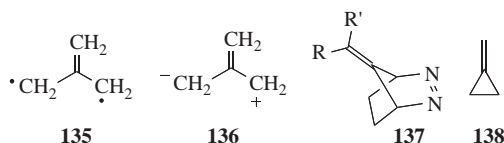
²¹⁵² See Lown, J.W. *Rec. Chem. Prog.* **1971**, *32*, 51; Gladysheva, F.N.; Sineokov, A.P.; Etlis, V.S. *Russ. Chem. Rev.* **1970**, *39*, 118.

C. Carbon on Both Sides

Reactions 15-58–15-64 are cycloaddition reactions.²¹⁵³

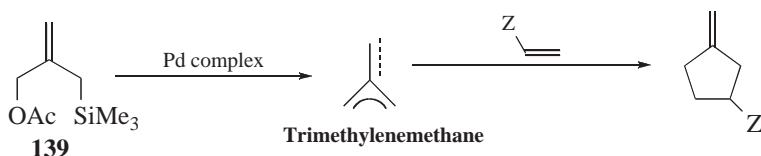
15-59 All-Carbon [3 + 2]-Cycloadditions²¹⁵⁴

Several methods have been reported for the formation of cyclopentanes by [3 + 2]-cycloadditions.²¹⁵⁵ Heating conjugated ketones with trialkylphosphines generates an intermediate that adds to conjugated alkynes.²¹⁵⁶ One type involves reagents that produce intermediates **135** or **136**.²¹⁵⁷ A synthetically useful example²¹⁵⁸ uses 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**139**), which is commercially available, and a Pd or other transition metal catalyst to generate **135** or **136**, which adds to double bonds to give cyclopentanes



with an exocyclic double bond. The reaction occurs with **139** to generate trimethylenemethane *in situ*, which reacts with alkenes to give methylenecyclopentane derivatives.²¹⁵⁹ A similar reaction occurs with imines to give methylene pyrrolidines.²¹⁶⁰ The Pd catalyzed reaction with CO₂ leads to butenolides.²¹⁶¹

Note that **136** also reacts with *N*-tosyl aziridines, with 20% *n*-butyllithium and 10% of Pd(OAc)₂, to give a vinylidene piperidine derivative.²¹⁶² Similar or identical intermediates generated from bicyclic azo compounds **137** (see Reaction 17-34) or methylenecyclopropane (**138**)²¹⁶³ also add to activated double bonds. With suitable substrates the addition can be enantioselective.²¹⁶⁴



²¹⁵³ For a system of classification of cycloaddition reactions, see Huisgen, R. *Angew. Chem. Int. Ed.* **1968**, 7, 321. See Posner, G.H. *Chem. Rev.* **1986**, 86, 831. See also, the series *Advances in Cycloaddition*.

²¹⁵⁴ See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 1101–1116.

²¹⁵⁵ See Trost, B.M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* **1989**, 111, 7487.

²¹⁵⁶ Wang, J.-C.; Ng, S.-S.; Krische, M.J. *J. Am. Chem. Soc.* **2003**, 125, 3682.

²¹⁵⁷ See Trost, B.M. *Pure Appl. Chem.* **1988**, 60, 1615; *Angew. Chem. Int. Ed.* **1986**, 25, 1.

²¹⁵⁸ See Trost, B.M.; Lynch, J.; Renaut, P.; Steinman, D.H. *J. Am. Chem. Soc.* **1986**, 108, 284.

²¹⁵⁹ Trost, B.M.; MacPherson, D.T. *J. Am. Chem. Soc.* **1987**, 109, 3483; Trost, B.M. *Angew. Chem. Int. Ed.* **1986**, 25, 1; Trost, B.M.; Stambuli, J.P.; Silverman, S.M.; Schwörer, U. *J. Am. Chem. Soc.* **2006**, 128, 13328; Trost, B.M.; Cramer, N.; Silverman, S.M. *J. Am. Chem. Soc.* **2007**, 129, 12396.

²¹⁶⁰ Trost, B.M.; Silverman, S.M.; Stambuli, J.P. *J. Am. Chem. Soc.* **2007**, 129, 12398.

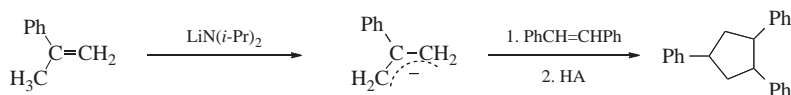
²¹⁶¹ Greco, G.E.; Gleason, B.L.; Lowery, T.A.; Kier, M.J.; Hollander, L.B.; Gibbs, S.A.; Worthy, A.D. *Org. Lett.* **2007**, 9, 3817.

²¹⁶² Hedley, S. J.; Moran, W. J.; Price, D.A.; Harrity, J.P.A. *J. Org. Chem.* **2003**, 68, 4286.

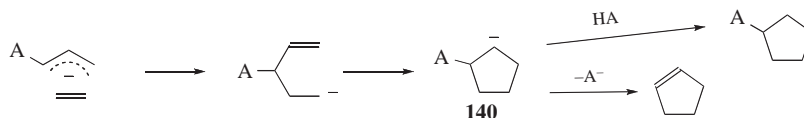
²¹⁶³ See Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1989**, 111, 7285.

²¹⁶⁴ See Chaigne, F.; Gotteland, J.; Malacria, M. *Tetrahedron Lett.* **1989**, 30, 1803.

In a different type of procedure, [3 + 2]-cycloadditions are performed with allylic anions. Such reactions are called 1,3-anionic cycloadditions.²¹⁶⁵ For example, α -methylstyrene adds to stilbene on treatment with the strong base LDA.²¹⁶⁶



The mechanism can be outlined as:

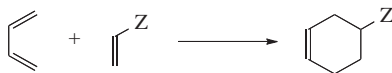


In the case above, **140** is protonated in the last step by the acid HA, but if the acid is omitted and a suitable nucleofuge is present, it may leave, resulting in a cyclopentene.²¹⁶⁷ In these cases, the reagent is an allylic anion, but similar [3 + 2]-cycloadditions involving allylic cations have also been reported.²¹⁶⁸

OS VIII,173, 347.

15-60 The Diels–Alder Reaction

(4 + 2) cyclo- Ethylene-1/4/addition or **(4 + 2) cyclo-**[Bu *t*-2-ene-1,4-diyl]-1/2/addition, and so on



In the prototype *Diels–Alder reaction*, the double bond of an alkene adds 1,4- to a conjugated diene (a [4 + 2]-cycloaddition),²¹⁶⁹ so the product is always a cyclohexene. The cycloaddition is not limited to alkenes or to dienes (see Reaction **15-61**), but the substrate that reacts with the diene is called a *dienophile*. The reaction is of very broad scope²¹⁷⁰ and reactivity of dienes and dienophiles can be predicted based on analysis of the HOMOs²¹⁷¹ and LUMOs of these species (FMO theory).²¹⁷² Ethylene and simple alkenes make poor dienophiles, unless high temperatures and/or pressures are used. Most dienophiles are of the form —C=C—Z or Z—C=C—Z' , where Z and Z' are

²¹⁶⁵ Kauffmann, T. *Top. Curr. Chem.* **1980**, 92, 109, pp. 111–116; *Angew. Chem. Int. Ed.* **1974**, 13, 627.

²¹⁶⁶ Eidenschink, R.; Kauffmann, T. *Angew. Chem. Int. Ed.* **1972**, 11, 292.

²¹⁶⁷ See Beak, P.; Burg, D.A. *J. Org. Chem.* **1989**, 54, 1647.

²¹⁶⁸ See Noyori, R.; Hayakawa, Y. *Tetrahedron* **1985**, 41, 5879.

²¹⁶⁹ Wasserman, A. *Diels–Alder Reactions* Elsevier, NY, **1965**; Roush, W.R. *Adv. Cycloaddit.* **1990**, 2, 91; Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, **1990**; Brieger, G.; Bennett, J.N. *Chem. Rev.* **1980**, 80, 63; Oppolzer, W. *Angew. Chem. Int. Ed.* **1977**, 16, 10; Sauer, J. *Angew. Chem. Int. Ed.* **1966**, 5, 211; **1967**, 6, 16; Taber, D.F. *Intramolecular Diels–Alder and Alder Ene Reactions*, Springer, NY, **1984**; Deslongchamps, P. *Aldrichimica Acta* **1991**, 24, 43; Craig, D. *Chem. Soc. Rev.* **1987**, 16, 187. For a long list of references to various aspects of the Diels–Alder reaction, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 523–544.

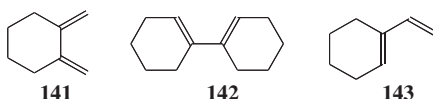
²¹⁷⁰ See Konovalov, A.I. *Russ. Chem. Rev.* **1983**, 52, 1064.

²¹⁷¹ See Nelson, D.J.; Li, R.; Brammer, C. *J. Org. Chem.* **2001**, 66, 2422.

²¹⁷² Spino, C.; Rezaei, H.; Dory, Y.L. *J. Org. Chem.* **2004**, 69, 757. For tables of HOMOs and LUMOs for dienes and dienophiles, see Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 999–1032, especially pp. 1003–1004 and 1008–1009.

electron-withdrawing groups²¹⁷³ (e.g., CHO, COR,²¹⁷⁴ CO₂H, CO₂R, COCl, COAr, CN,²¹⁷⁵ NO₂,²¹⁷⁶ Ar, CH₂OH, CH₂Cl, CH₂NH₂, CH₂CN, CH₂CO₂H, halogen, PO (OEt)₂,²¹⁷⁷ or C=C). In the last case, the dienophile is itself a diene.²¹⁷⁸

The low reactivity of simple alkenes can be overcome by incorporating an electron-withdrawing group to facilitate the cycloaddition, as indicated above. Electron-withdrawing groups may be incorporated to facilitate the *Diels–Alder reaction* and then removed after cycloaddition. An example is phenyl vinyl sulfone (PhSO₂CH=CH₂),²¹⁷⁹ and the PhSO₂ group can be easily removed with Na–Hg after the ring-closure reaction. Similarly, phenyl vinyl sulfoxide (PhSOCH=CH₂) can be used as a synthon for acetylene.²¹⁸⁰ In this case, PhSOH is lost from the sulfoxide product (Reaction 17-12).



Electron-donating substituents in the diene accelerate the reaction; electron-withdrawing groups retard it.²¹⁸¹ For the dienophile, it is just the reverse: donating groups decrease the rate, and withdrawing groups increase it. The s-cis (cisoid) conformation is required for the cycloaddition,²¹⁸² and acyclic dienes are conformationally mobile so the s-cis conformation will be available.²¹⁸³ Cyclic dienes, in which the s-cis conformation is built in, usually react faster than the corresponding open-chain compounds, which have to achieve the s-cis conformation by rotation.²¹⁸⁴ Dienes can be open-chain, inner-ring (e.g., **141**), outer-ring²¹⁸⁵ (e.g., **142**), across rings (e.g., **143**), or inner–outer (e.g., **145**), except that they may not be frozen into a s-trans (transoid) conformation (see category 3). They need no special activating groups, and nearly all conjugated dienes undergo the reaction with suitable dienophiles.²¹⁸⁶

²¹⁷³ See Domingo, L.R. *Eur. J. Org. Chem.* **2004**, 4788.

²¹⁷⁴ Fringuelli, F.; Taticchi, A.; Wenkert, E. *Org. Prep. Proced. Int.* **1990**, 22, 131.

²¹⁷⁵ See Butskus, P.F. *Russ. Chem. Rev.* **1962**, 31, 283; Also see Ciganek, E.; Linn, W.J.; Webster, O.W. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 449–453.

²¹⁷⁶ See Novikov, S.S.; Shuekhgeimer, G.A.; Dudinskaya, A.A. *Russ. Chem. Rev.* **1960**, 29, 79.

²¹⁷⁷ McClure, C.K.; Herzog, K.J.; Bruch, M.D. *Tetrahedron Lett.* **1996**, 37, 2153.

²¹⁷⁸ Johnstone, R.A.W.; Quan, P.M. *J. Chem. Soc.* **1963**, 935.

²¹⁷⁹ Carr, R.V.C.; Williams, R.V.; Paquette, L.A. *J. Org. Chem.* **1983**, 48, 4976; Kinney, W.A.; Crouse, G.D.; Paquette, L.A. *J. Org. Chem.* **1983**, 48, 4986.

²¹⁸⁰ De Lucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. *J. Org. Chem.* **1984**, 49, 596; Hermeling, D.; Schäfer, H.J. *Angew. Chem. Int. Ed.* **1984**, 23, 233; De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, 44, 6755.

²¹⁸¹ See Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *Tetrahedron* **2002**, 58, 4417.

²¹⁸² For ground state conformations, see Bur, S.K.; Lynch, S.M.; Padwa, A. *Org. Lett.* **2002**, 4, 473.

²¹⁸³ For a discussion of conformational thermodynamic and kinetic parameters of methyl 1,3-butadienes, see Squillacote, M.E.; Liang, F. *J. Org. Chem.* **2005**, 70, 6564.

²¹⁸⁴ Sauer, J.; Lang, D.; Mielert, A. *Angew. Chem. Int. Ed.* **1962**, 1, 268; Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* **1962**, 1, 269. See, however, Scharf, H.; Plum, H.; Fleischhauer, J.; Schleker, W. *Chem. Ber.* **1979**, 112, 862.

²¹⁸⁵ See Charlton, J.L.; Alauddin, M.M. *Tetrahedron* **1987**, 43, 2873; Oppolzer, W. *Synthesis* **1978**, 793.

²¹⁸⁶ For a monograph on dienes, with tables showing > 800 types, see Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*, Wiley, NY, **1990**. See Danishefsky, S. *Chemtracts: Org. Chem.* **1989**, 2, 273; Petrzilka, M.; Grayson, J.I. *Synthesis* **1981**, 753; Smith, M.B. *Org. Prep. Proced. Int.* **1990**, 22, 315; Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. *J. Org. Chem.* **2003**, 68, 9809; Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, 122, 5950.

While *Diels–Alder reactions* generally require no catalyst, Lewis acids are effective catalysts,²¹⁸⁷ particularly those in which Z in the dienophile is a C=O or C=N group.²¹⁸⁸ Chemoselectivity is related to the choice of Lewis acid or Brønsted–Lowry acid catalyst.²¹⁸⁹ A Lewis acid catalyst usually increases both the regioselectivity of the reaction (in the sense given above) and the extent of endo addition,²¹⁹⁰ and, in the case of enantioselective reactions, the extent of enantioselectivity. Copper catalysts have been used.²¹⁹¹ Brønsted acids have also been used to accelerate the rate of the *Diels–Alder reaction*.²¹⁹² *Diels–Alder reactions* have been done in ionic liquids (see Sec. 9.D.iii).²¹⁹³ Lanthanum triflate [La(OTf)₃] has been reported as a reusable catalyst²¹⁹⁴ and Me₃SiNTf₂ has been used as a green Lewis acid catalyst.²¹⁹⁵ Cationic *Diels–Alder* catalysts have been developed (e.g., oxazaborolidine catalysts).²¹⁹⁶ Some *Diels–Alder reactions* can also be catalyzed by the addition of a stable cation radical,²¹⁹⁷ for example, tris(4-bromophenyl)aminium hexachloroantimonate (Ar₃N^{•+} SbCl₆[−]).²¹⁹⁸ Zirconocene-catalyzed cationic *Diels–Alder reactions* are known.²¹⁹⁹ Certain antibodies have been developed that catalyze *Diels–Alder reactions*.²²⁰⁰ Photochemically induced *Diels–Alder reactions* are also known.²²⁰¹

A number of other methods have been reported for the acceleration of *Diels–Alder reactions*,²²⁰² including the use of microwave irradiation,²²⁰³ ultrasound,²²⁰⁴ absorption of the reactants on chromatographic absorbents,²²⁰⁵ via encapsulation techniques,²²⁰⁶ and the

²¹⁸⁷ Avalos, M.; Babiano, R.; Bravo, J.L.; Cintas, P.; Jiménez, J.L.; Palacios, J.C.; Silva, M.A. *J. Org. Chem.* **2000**, *65*, 6613; Kiselev, V.D.; Kononov, A.I. *Russ. Chem. Rev.* **1989**, *58*, 230; Zheng, M.; Zhang, M.-H.; Shao, J.-G.; Zhong, Q. *Org. Prep. Proceed. Int.* **1996**, *28*, 117; Yamabe, S.; Minato, T. *J. Org. Chem.* **2000**, *65*, 1830; Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 9561.

²¹⁸⁸ For a discussion of the effect of Lewis acids, see Celebi-Olcum, N.; Ess, D.H.; Aviyente, V.; Houk, K.N. *J. Org. Chem.* **2008**, *73*, 7472.

²¹⁸⁹ Nakashima, D.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1251; Shen, J.; Tan, C.-H. *Org. Biomol. Chem.* **2008**, *6*, 3229.

²¹⁹⁰ See Alston, P.V.; Ottenbrite, R.M. *J. Org. Chem.* **1975**, *40*, 1111.

²¹⁹¹ Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359.

²¹⁹² Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049.

²¹⁹³ For a study of the influence of Lewis acids in ionic liquids, see Silvero, G.; Arévalo, M.J.; Bravo, J.L.; Ávalos, M.; Jiménez, J.L.; López, I. *Tetrahedron* **2005**, *61*, 7105. See López, I.; Silvero, G.; Arévalo, M.J.; Babiano, R.; Palacios, J.C.; Bravo, J.L. *Tetrahedron* **2007**, *63*, 2901.

²¹⁹⁴ Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815.

²¹⁹⁵ Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219.

²¹⁹⁶ See Sprott, K.T.; Corey, E.J. *Org. Lett.* **2003**, *5*, 2465; Corey, E.J.; Shibata, T.; Lee, T.W. *J. Am. Chem. Soc.* **2002**, *124*, 3808; Ryu, D.H.; Lee, T.W.; Corey, E.J. *J. Am. Chem. Soc.* **2002**, *124*, 9992.

²¹⁹⁷ Gao, D.; Bauld, N.L. *J. Org. Chem.* **2000**, *65*, 6276. See Saettel, N.J.; Oxgaard, J.; Wiest, O. *Eur. J. Org. Chem.* **2001**, 1429.

²¹⁹⁸ For a review, see Bauld, N.L. *Tetrahedron* **1989**, *45*, 5307.

²¹⁹⁹ Wipf, P.; Xu, W. *Tetrahedron* **1995**, *51*, 4551.

²²⁰⁰ Zhang, X.; Deng, Q.; Yoo, S.H.; Houk, K.N. *J. Org. Chem.* **2002**, *67*, 9043.

²²⁰¹ Pandey, B.; Dalvi, P.V. *Angew. Chem. Int. Ed.* **1993**, *32*, 1612.

²²⁰² See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 1037–1049.

²²⁰³ Jankowski, C.K.; LeClair, G.; Bélanger, J.M.R.; Paré, J.R.J.; Van Calsteren, M.-R. *Can. J. Chem.* **2001**, *79*, 1906. For a review, see de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659; Kaval, N.; Dehaen, W.; Kappe, C.O.; van der Eycken, E. *Org. Biomol. Chem.* **2004**, *2*, 154.

²²⁰⁴ Raj, C.P.; Dhas, N.A.; Cherkinski, M.; Gedanken, A.; Braverman, S. *Tetrahedron Lett.* **1998**, *39*, 5413.

²²⁰⁵ Veselovsky, V.V.; Gybin, A.S.; Lozanova, A.V.; Moiseenkov, A.M.; Smit, W.A.; Caple, R. *Tetrahedron Lett.* **1988**, *29*, 175.

²²⁰⁶ Kang, J.; Hilmersson, G.; Sartamaría, J.; Rebek Jr., J. *J. Am. Chem. Soc.* **1998**, *120*, 3650; Diego-Castro, M.J.; Hailes, H.C. *Tetrahedron Lett.* **1998**, *39*, 2211.

use of an ultracentrifuge²²⁰⁷ (one of several ways to achieve reaction at high pressures).²²⁰⁸ Solid-state *Diels–Alder reactions* are known.²²⁰⁹ One of the most common methods is to use water as a solvent or a cosolvent (a hydrophobic effect).²²¹⁰ Catalysts have been developed for aq *Diels–Alder reactions*²²¹¹ that are suitable for ionic *Diels–Alder reactions*.²²¹² There are cases of hydrogen-bonding acceleration.²²¹³ The influence of the hydrophobicity of reactants on the reaction has been examined,²²¹⁴ as has micellar effects.²²¹⁵ Another alternative reaction medium is the use of 5M LiClO₄ in Et₂O as solvent.²²¹⁶ An alternative to lithium perchlorate in ether is lithium triflate in acetonitrile.²²¹⁷ The addition of HPO₄[−] to an aq ethanol solution has also been shown to give a small rate enhancement.²²¹⁸ This appears to be the only case where an anion is responsible for a rate enhancement. The *retro-Diels–Alder reaction* has also been done in water.²²¹⁹

Note that *Diels–Alder reactions* have been done with supercritical carbon monoxide²²²⁰ and with supercritical water²²²¹ as solvents. *Diels–Alder reactions* on solid supports also have been reported,²²²² and zeolites have been used in conjunction with catalytic agents.²²²³ Alumina has been used to promote *Diels–Alder reactions*.²²²⁴ *Diels–Alder reactions* can be done in ionic liquids,²²²⁵ including asymmetric *Diels–Alder reactions*.²²²⁶ Note that the rate of *Diels–Alder reactions* is faster in water than in ionic liquids.²²²⁷

When an unsymmetrical diene adds to an unsymmetrical dienophile, regioisomeric products (not counting stereoisomers) are possible. Rearrangements have been encountered in some cases.²²²⁸ In simple cases, 1-substituted dienes give cyclohexenes with a 1,2-

²²⁰⁷ Dolata, D.P.; Bergman, R. *Tetrahedron Lett.* **1987**, 28, 707.

²²⁰⁸ For reviews, see Isaacs, N.S.; George, A.V. *Chem. Br.* **1987**, 47–54; Asano, T.; le Noble, W.J. *Chem. Rev.* **1978**, 78, 407. See also, Firestone, R.A.; Smith, G.M. *Chem. Ber.* **1989**, 122, 1089.

²²⁰⁹ Kim, J.H.; Hubig, S.M.; Lindeman, S.V.; Kochi, J.K. *J. Am. Chem. Soc.* **2001**, 123, 87.

²²¹⁰ Breslow, R. *Acc. Chem. Res.* **1991**, 24, 159; Breslow, R.; Rizzo, C.J. *J. Am. Chem. Soc.* **1991**, 113, 4340; Engberts, J.B.F.N. *Pure Appl. Chem.* **1995**, 67, 823; Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, 93, 741; Otto, S.; Blokzijl, W.; Otto, S.; Egberts, J.B.F.N. *Pure. Appl. Chem.* **2000**, 72, 1365; Deshpande, S.S.; Kumar, A. *Tetrahedron* **2005**, 61, 8025; Hayashi, Y.; Takeda, M.; Shoji, M.; Morita, M. *Chem. Lett.* **2007**, 36, 68.

²²¹¹ See Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439; Otto, S.; Engberts, J.B.F. *N. Tetrahedron Lett.* **1995**, 36, 2645

²²¹² Chavan, S.P.; Sharma, P.; Krishna, G.R.; Thakkar, M. *Tetrahedron Lett.* **2003**, 44, 3001.

²²¹³ Pearson, R.J.; Kassianidis, E.; Philip, D. *Tetrahedron Lett.* **2004**, 45, 4777.

²²¹⁴ Meijer, A.; Otto, S.; Engberts, J.B.F.N. *J. Org. Chem.* **1998**, 63, 8989.

²²¹⁵ Jaeger, D.A.; Wang, J. *Tetrahedron Lett.* **1992**, 33, 6415.

²²¹⁶ Grieco, P.A.; Handy, S.T.; Beck, J.P. *Tetrahedron Lett.* **1994**, 35, 2663. See Handy, S.T.; Grieco, P.A.; Mineur, C.; Ghosez, L. *Synlett* **1995**, 565.

²²¹⁷ Augé, J.; Gil, R.; Kalsey, S.; Lubin-Germain, N. *Synlett* **2000**, 877.

²²¹⁸ Pai, C.K.; Smith, M.B. *J. Org. Chem.* **1995**, 60, 3731.

²²¹⁹ Wijnen, J.W.; Engberts, J.B.F.N. *J. Org. Chem.* **1997**, 62, 2039.

²²²⁰ Oakes, R.S.; Heppenstall, T.J.; Shezad, N.; Clifford, A.A.; Rayner, C.M. *Chem. Commun.* **1999**, 1459. For an asymmetric cycloaddition, see Fukuzawa, S.-i.; Metoki, K.; Esumi, S.-i. *Tetrahedron* **2003**, 59, 10445.

²²²¹ Harano, Y.; Sato, H.; Hirata, F. *J. Am. Chem. Soc.* **2000**, 122, 2289.

²²²² Yli-Kauhala, J. *Tetrahedron* **2001**, 57, 7053.

²²²³ Eklund, L.; Axelsson, A.-K.; Nordahl, Å.; Carlson, R. *Acta Chem. Scand.* **1993**, 47, 581.

²²²⁴ Pagni, R.M.; Kabalka, G.W.; Hondrogiannis, G.; Bains, S.; Anosike, P.; Kurt, R. *Tetrahedron* **1993**, 49, 6743.

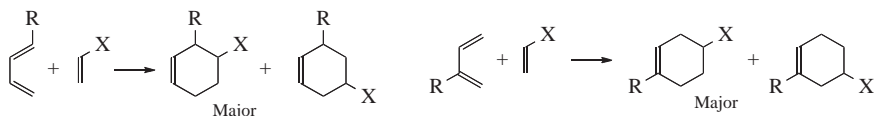
²²²⁵ Bini, R.; Chiappe, C.; Mestre, V.L.; Pomelli, C.S.; Welton, T. *Org. Biomol. Chem.* **2008**, 6, 2522. For reactions in low-melting sugar–urea–salt mixtures, see Imperato, G.; Eibler, E.; Niedermaier, J.; König, B. *Chem. Commun.* **2005**, 1170.

²²²⁶ Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, 44, 6465.

²²²⁷ Tiwari, S.; Kumar, A. *Angew. Chem. Int. Ed.* **2006**, 45, 4824.

²²²⁸ Murali, R.; Scheeren, H.W. *Tetrahedron Lett.* **1999**, 40, 3029.

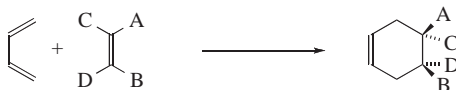
and a 1,3- substitution pattern. 2-Substituted dienes lead to 1,4- and 1,3-disubstituted products.



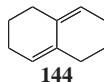
Although mixtures are often obtained, one usually predominates (the one shown lower major above), but selectivity depends on the nature of the substituents on both diene and alkene. This regioselectivity, in which the “ortho” or “para” product is favored over the “meta”, has been explained by molecular orbital considerations.²²²⁹ When X = NO₂, regioselectivity to give the “ortho” or “para” product was very high at room temperature. This method, combined with subsequent removal of the NO₂ (see Reaction **19-67**), has been used to perform regioselective *Diels–Alder reactions*.²²³⁰ Competing reactions are polymerization of the diene or dienophile, or both, and [1,2]-cycloaddition (**15-63**).

The stereochemistry of the *Diels–Alder reaction* can be considered from several aspects:²²³¹

1. With respect to the dienophile, the addition is stereospecifically syn, with very few exceptions.²²³² This means that groups that are *cis* in the alkene will be *cis* in the cyclohexene ring (A—B and C—D) and groups that are *trans* in the alkene will be *trans* in the cyclohexene ring (A—D and C—B).



2. With respect to 1,4-disubstituted dienes, fewer cases have been investigated, but here too the reaction is stereospecific and syn. Thus, *trans,trans*-1,4-diphenylbutadiene gives *cis*-1,4-diphenylcyclohexene derivatives. This selectivity is predicted by disrotatory motion of the substituent in the transition state²²³³ of the reaction (see **18-27**).
3. The diene must be in the *s-cis* conformation. If it is frozen into the *s-trans* conformation, as in **144**, the reaction does not take place. The diene either must be frozen into the *s-cis* conformation or must be able to achieve it during the reaction.



²²²⁹ Alston, P.V.; Gordon, M.D.; Ottenbrite, R.M.; Cohen, T. *J. Org. Chem.* **1983**, *48*, 5051; Kahn, S.D.; Pau, C.F.; Overman, L.E.; Hehre, W.J. *J. Am. Chem. Soc.* **1986**, *108*, 7381.

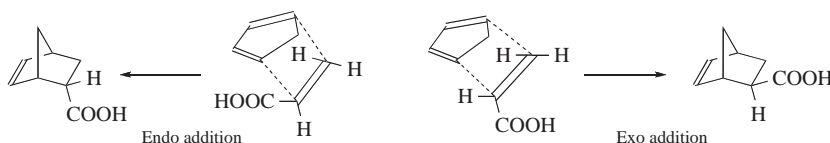
²²³⁰ Ono, N.; Miyake, H.; Kamimura, A.; Kaji, A. *J. Chem. Soc. Perkin Trans. 1*, **1987**, 1929. For another method of controlling regioselectivity, see Kraus, G.A.; Liras, S. *Tetrahedron Lett.* **1989**, *30*, 1907.

²²³¹ See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 1023–1032, 1066–1075; Bakalova, S.M.; Santos, A.G. *J. Org. Chem.* **2004**, *69*, 8475.

²²³² For an exception, see Meier, H.; Eckes, H.; Niedermann, H.; Kolshorn, H. *Angew. Chem. Int. Ed.* **1987**, *26*, 1046.

²²³³ Robiette, R.; Marchand-Brynaert, J.; Peeters, D. *J. Org. Chem.* **2002**, *67*, 6823.

4. There are two possible ways in which addition can occur to a cyclic diene, if the dienophile is not symmetrical: say a monosubstituted alkene. The substituent on the dienophile (usually an electron-withdrawing substituent) may approach under the ring (*endo addition*), or away from the ring (*exo addition*):



Most of the time, the addition is predominantly *endo*; that is, the more bulky side of the alkene is under the ring, and this is probably true for open-chain dienes also.²²³⁴ However, exceptions are known, and in many cases mixtures of *exo* and *endo* addition products are found.²²³⁵ An imidazolidone catalyst was used to give a 1:1.3 mixture favoring the *exo* isomer in a reaction of conjugated aldehydes and cyclopentadiene.²²³⁶ Secondary orbital interactions,²²³⁷ have been invoked, but this approach has been called into question.²²³⁸ There has been a direct evaluation of such interactions, however.²²³⁹ It has been argued that facial selectivity is not due to torsional angle decompression.²²⁴⁰ The *endo/exo* ratio can be influenced by the nature of the solvent.²²⁴¹

5. As seen previously, the *Diels–Alder reaction* can be both stereoselective and regioselective.²²⁴² In some cases, the *Diels–Alder reaction* can be made enantioselective,²²⁴³ as described above. Solvent effects are important in such reactions.²²⁴⁴ The role of reactant polarity on the course of the reaction has been examined.²²⁴⁵ Most enantioselective *Diels–Alder reactions* have used a chiral dienophile (e.g., **145**) and an achiral diene,²²⁴⁶ along with a Lewis acid catalyst (see below). In such cases, addition of the diene to the two

²²³⁴ See Baldwin, J.E.; Reddy, V.P. *J. Org. Chem.* **1989**, *54*, 5264. For a theoretical study for *endo* selectivity, see Imade, M.; Hirao, H.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1999**, *64*, 6697.

²²³⁵ See Mülle, P.; Bernardinelli, G.; Rodriguez, D.; Pfyffer, J.; Schaller, J. *Chimia* **1987**, *41*, 244.

²²³⁶ Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

²²³⁷ Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* **1965**, *87*, 4388, 4389.

²²³⁸ García, J.I.; Mayoral, J.A.; Salvatella, L. *Acc. Chem. Res.* **2000**, *33*, 658; García, J.-I.; Mayoral, J.A.; Salvatella, L. *Eur. J. Org. Chem.* **2005**, 85.

²²³⁹ Arrieta, A.; Cossío, F.P.; Lecea, B. *J. Org. Chem.* **2001**, *66*, 6178.

²²⁴⁰ Hickey, E.R.; Paquette, L.A. *Tetrahedron Lett.* **1994**, *35*, 2309, 2313.

²²⁴¹ Cainelli, G.; Galletti, P.; Giacomini, D.; Quintavalla, A. *Tetrahedron Lett.* **2003**, *44*, 93.

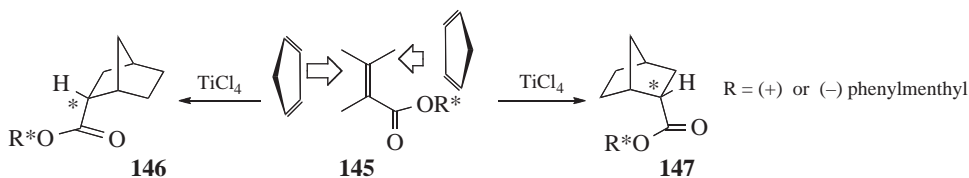
²²⁴² Domingo, L.R.; Picher, M.T.; Andrés, J.; Safont, V.S. *J. Org. Chem.* **1997**, *62*, 1775. Also see, Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 1023–1032, 1066–1075; Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* **2008**, *130*, 8952.

²²⁴³ See Corey, E.J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089; Taschner, M.J. *Org. Synth: Theory Appl.* **1989**, *1*, 1; Helmchen, G.; Karge, R.; Weetman, J. *Mod. Synth. Methods* **1986**, *4*, 261; Oppolzer, W. *Angew. Chem. Int. Ed.* **1984**, *23*, 876. See also Macaulay, J.B.; Fallis, A.G. *J. Am. Chem. Soc.* **1990**, *112*, 1136.

²²⁴⁴ Ruiz-López, M.F.; Assfeld, X.; García, J.I.; Mayoral, J.A.; Salvatella, L. *J. Am. Chem. Soc.* **1993**, *115*, 8780.

²²⁴⁵ Sustmann, R.; Sicking, W. *J. Am. Chem. Soc.* **1996**, *118*, 12562.

²²⁴⁶ For the use of chiral dienes, see Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* **1990**, *112*, 6743; **1991**, *113*, 7630; Rieger, R.; Breitmaier, E. *Synthesis* **1990**, 697.



faces²²⁴⁷ of **145** takes place at different rates, and **146** and **147** are formed in different amounts.²²⁴⁸ An achiral compound can be converted to a chiral compound by a chemical reaction with a compound that is enantiopure. After the reaction, the resulting diastereomers can be separated, providing enantiopure compounds, each with a bond between the molecule of interest and chiral compound (a chiral auxiliary). Common chiral auxiliaries include chiral carboxylic acids, alcohols, or sultams. In the case illustrated, hydrolysis of the product removes the chiral R group, making it a chiral auxiliary in this reaction. Asymmetric *Diels–Alder reactions* have also been carried out with achiral dienes and dienophiles, but with an optically active catalyst.²²⁴⁹ Many chiral catalysts have been developed.²²⁵⁰ In many cases, asymmetric Lewis acids form a chiral complex with the dienophile.²²⁵¹ Chiral organocatalysts are increasingly important.²²⁵²

Triple bond compounds ($-C\equiv C-Z$ or $Z-C\equiv C-Z'$) may be dienophiles,²²⁵³ generating nonconjugated cyclohexadienes (**148**). This reaction can be catalyzed by transition metal compounds.²²⁵⁴ Aromatic rings can be generated by cycloaddition of aryl alkynes.²²⁵⁵ Allenes react as dienophiles, but without activating groups are

²²⁴⁷ See Xidos, J.D.; Poirier, R.A.; Pye, C.C.; Burnell, D.J. *J. Org. Chem.* **1998**, *63*, 105.

²²⁴⁸ Tomioka, K.; Hamada, N.; Suenaga, T.; Koga, K. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 426; Cativiela, C.; López, P.; Mayoral, J.A. *Tetrahedron: Asymmetry* **1990**, *1*, 61.

²²⁴⁹ Narasaka, K. *Synthesis* **1991**, 1; Corey, E.J.; Imai, N.; Zhang, H. *J. Am. Chem. Soc.* **1991**, *113*, 728; Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387; Hawkins, J.M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794; Evans, D.A.; Barnes, D.M.; Johnson, J.S.; Lectka, T.; von Matt, P.; Miller, S.J.; Murry, J.A.; Norcross, R.D.; Shaughnessy, E.A.; Campos, K.R. *J. Am. Chem. Soc.* **1999**, *121*, 7582.

²²⁵⁰ See Corey, E.J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1651; Doyle, M.P.; Phillips, I.M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366; Owens, T.D.; Hollander, F.J.; Oliver A.G.; Ellman, J.A. *J. Am. Chem. Soc.* **2001**, *123*, 1539; Faller, J.W.; Grimmond, B.J.; D'Alliessi, D.G. *J. Am. Chem. Soc.* **2001**, *123*, 2525; Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830; Fukuzawa, S.; Komuro, Y.; Nakano, N.; Obara, S. *Tetrahedron Lett.* **2003**, *44*, 3671.

²²⁵¹ Hawkins, J.M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657. See Sibi, M.P.; Venkatraman, L.; Liu, M.; Jaspersé, C.P. *J. Am. Chem. Soc.* **2001**, *123*, 8444.

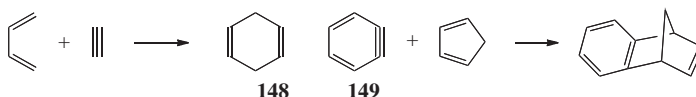
²²⁵² Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504; Liu, D.; Canales, E.; Corey, E.J. *J. Am. Chem. Soc.* **2007**, *129*, 1498; Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B.M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364; Payette, J.N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9536; Singh, R.P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422; Futatsugi, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 1484; Paddon-Row, M.N.; Kwan, L.C.H.; Willis, A.C.; Sherburn, M.S. *Angew. Chem. Int. Ed.* **2008**, *47*, 7013.

²²⁵³ See Bastide, J.; Henri-Rousseau, O. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, **1978**, pp. 447–522; Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 477–508.

²²⁵⁴ See Paik, S.-J.; Son, S.U.; Chung, Y.K. *Org. Lett.* **1999**, *1*, 2045.

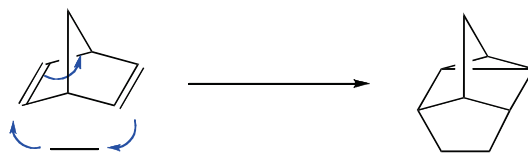
²²⁵⁵ This type of Diels–Alder reaction has been called the Dehydro-Diels–Alder. See Wessig, P.; Gunnar Müller, G. *Chem. Rev.* **2008**, *108*, 2051; Dunetz, J.R.; Danheiser, R.L. *J. Am. Chem. Soc.* **2005**, *127*, 5776; Dai, M.; Sarlah, D.; Yu, M.; Danishefsky, S.J.; Jones, G.O.; Houk, K.N. *J. Am. Chem. Soc.* **2007**, *129*, 645.

very poor dienophiles.²²⁵⁶ Ketenes, however, do not undergo *Diels–Alder reactions*.²²⁵⁷



Many interesting compounds can be prepared by the *Diels–Alder reaction*,²²⁵⁸ some of which would be hard to make in any other way. Some aromatic compounds can behave as dienes,²²⁵⁹ but benzene is very unreactive toward dienophiles,²²⁶⁰ and very few dienophiles (one of them is benzyne) have been reported to give *Diels–Alder* adducts with it.²²⁶¹ Benzyne (e.g., **149**), although not isolable, act as dienophiles and can be trapped with dienes.²²⁶² The interesting compound triptycene can be prepared by a *Diels–Alder reaction* between benzyne and anthracene.²²⁶³ Naphthalene and phenanthrene are poor reaction partners, although naphthalene has given *Diels–Alder addition* at high pressures.²²⁶⁴ Anthracene and other compounds with at least three linear benzene rings give *Diels–Alder reactions* readily.

For both all-carbon and hetero systems, the “diene” can be a conjugated enyne. If the geometry of the molecule is suitable, the diene can even be nonconjugated, for example,²²⁶⁵



This last reaction is known as the *homo-Diels–Alder reaction*. A similar reaction has been reported with alkynes, using a mixture of a Co complex, ZnI_2 , and tetrabutylammonium borohydride.²²⁶⁶

²²⁵⁶ See Hopf, H. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, **1982**, pp. 563–577. See Nendel, M.; Tolbert, L.M.; Herring, L.E.; Islam, Md.N.; Houk, K.N. *J. Org. Chem.* **1999**, *64*, 976.

²²⁵⁷ Ketenes react with conjugated dienes to give 1,2-addition (see Reaction **15-49**).

²²⁵⁸ See Nicolaou, K.C.; Snyder, S.A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1669.

²²⁵⁹ For a review, see Wagner-Jauregg, T. *Synthesis* **1980**, 165, 769. See also, Balaban, A.T.; Biermann, D.; Schmidt, W. *Nouv. J. Chim.* **1985**, *9*, 443.

²²⁶⁰ However, see Chordia, M.D.; Smith, P.L.; Meiere, S.H.; Sabat, M.; Harman, W.D. *J. Am. Chem. Soc.* **2001**, *123*, 10756.

²²⁶¹ Friedman, L. *J. Am. Chem. Soc.* **1967**, *89*, 3071; Liu, R.S.H.; Krespan, C.G. *J. Org. Chem.* **1969**, *34*, 1271.

²²⁶² See Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*; Academic Press, NY, **1967**, pp. 200–239; Bryce, M. R.; Vernon, J.M. *Adv. Heterocycl. Chem.* **1981**, *28*, 183–229. Also see Liu, W.; You, F.; Mocella, C.J.; Harman, W. D. *J. Am. Chem. Soc.* **2006**, *128*, 1426.

²²⁶³ Wittig, G.; Niethammer, K. *Chem. Ber.* **1960**, *93*, 944; Wittig, G.; Härle, H.; Knauss, E.; Niethammer, K. *Chem. Ber.* **1960**, *93*, 951.

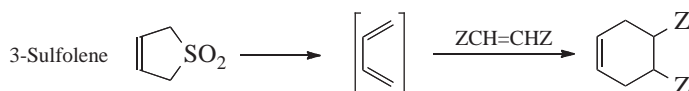
²²⁶⁴ Plieninger, H.; Wild, D.; Westphal, J. *Tetrahedron* **1969**, *25*, 5561.

²²⁶⁵ See Paquette, L.A.; Kesselmayer, M.A.; Künzer, H. *J. Org. Chem.* **1988**, *53*, 5183.

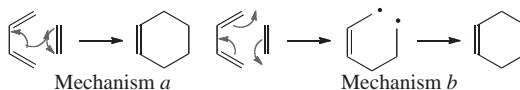
²²⁶⁶ Hilt, G.; du Mesnil, F.-X. *Tetrahedron Lett.* **2000**, *41*, 6757.

Intramolecular versions of the *Diels–Alder reaction* are well known,²²⁶⁷ and this is a powerful method for the synthesis of mono- and polycyclic compounds.²²⁶⁸ There are many examples and variations, including Lewis acid catalysis.²²⁶⁹ The origin of cis/trans stereoselectivity has been examined using density functional theory.²²⁷⁰

Internal *Diels–Alder reactions* can be viewed as linking the diene and alkene by a tether, usually of carbon atoms. Dienophile twisting and substituent effects influence the rate of cycloaddition.²²⁷¹ If the tether is replaced by functional groups that allow the selectivity inherent to the intramolecular cycloaddition, but can be cleaved afterward, a powerful modification is available. Indeed, such tethered cycloaddition reactions are increasingly common. After cycloaddition, the tether can be cleaved to give a functionalized cyclohexene derivative. Such tethered reactions allow enhancement of stereoselectivity²²⁷² and sometimes reactivity, relative to an untethered reaction, giving an indirect method for enhancing those parameters. Tethers or linkages include C—O—SiR₂—C²²⁷³ or a C—O—SiR₂—O—C,²²⁷⁴ or hydroxamides.²²⁷⁵ The nature of the tether plays a role in cis/trans selectivity for the intramolecular reaction.²²⁷⁶ Transient tethers can be used, as in the reaction of a diene having an allylic alcohol unit in a reaction with allyl alcohol, with AlMe₃ to give the cycloadduct with good selectivity.²²⁷⁷



The *Diels–Alder reaction* is usually reversible, although the retro reaction typically occurs at significantly higher temperatures than the forward reaction. However, the reaction is reversible²²⁷⁸ and this fact has been used. A convenient substitute for butadiene in the *Diels–Alder reaction* is the compound 3-sulfolene, since the latter is a solid, which is easy to handle while the former is a gas.²²⁷⁹ Butadiene is generated *in situ* by a reverse *Diels–Alder reaction* (see 17-20).



²²⁶⁷ For a review of natural product syntheses using Diels–Alder reactions, see Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, 105, 4779.

²²⁶⁸ Oppolzer, W. *Angew. Chem. Int. Ed.* **1977**, 16, 1; Brieger, G.; Bennett, J.N. *Chem. Rev.* **1980**, 80, 63 (see p. 67); Fallis, A.G. *Can. J. Chem.* **1984**, 62, 183; Smith, M.B. *Org. Prep. Proceed. Int.* **1990**, 22, 315.

²²⁶⁹ Au catalyst: Nieto-Oberhuber, C.; López, S.; Echavarren, A.M. *J. Am. Chem. Soc.* **2005**, 127, 6178.

²²⁷⁰ Paddon-Row, M.N.; Moran, D.; Jones, G.A.; Sherburn, M.S. *J. Org. Chem.* **2005**, 70, 10841.

²²⁷¹ Khuong, K.S.; Beaudry, C.M.; Trauner, D.; Houk, K.N. *J. Am. Chem. Soc.* **2005**, 127, 3688.

²²⁷² See Tantillo, D.J.; Houk, K.N.; Jung, M.E. *J. Org. Chem.* **2001**, 66, 1938.

²²⁷³ Stork, G.; Chan, T.Y.; Breault, G.A. *J. Am. Chem. Soc.* **1992**, 114, 7578.

²²⁷⁴ Craig, D.; Reader, J.C. *Tetrahedron Lett.* **1992**, 33, 6165.

²²⁷⁵ Ishikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S.; Kobayashi, H. *J. Am. Chem. Soc.* **2001**, 123, 4607.

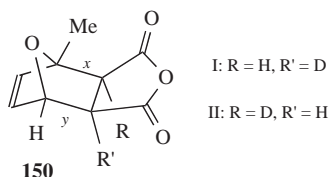
²²⁷⁶ Paddon-Row, M.N.; Longshaw, A.I.; Willis, A.C.; Sherburn, M.S. *Chemistry: Asian J.* **2009**, 4, 126.

²²⁷⁷ Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* **2000**, 2, 1283.

²²⁷⁸ See Ichihara, A. *Synthesis* **1987**, 207; Lasne, M.; Ripoll, J.L. *Synthesis* **1985**, 121; Kwart, H.; King, K. *Chem. Rev.* **1968**, 68, 415.

²²⁷⁹ Sample, Jr., T.E.; Hatch, L.F. *Org. Synth.* **VI**, 454. For a review, see Chou, T.; Tso, H. *Org. Prep. Proceed. Int.* **1989**, 21, 257.

There are, broadly speaking, three possible mechanisms that have been considered for the uncatalyzed *Diels–Alder reaction*.²²⁸⁰ In mechanism *a*, there is a cyclic six-centered transition state and no intermediate. The reaction is concerted and occurs in one step. In mechanism *b*, one end of the diene fastens to one end of the dienophile first to give a diradical, and then, in a second step, the other ends become fastened.²²⁸¹ A diradical formed in this manner must be a singlet; that is, the two unpaired electrons must have opposite spins, by an argument similar to that outlined in Section 5.C.i. The third mechanism (*c*, not shown) is similar to mechanism *b*, but the initial bond and the subsequent bond are formed by movements of electron pairs and the intermediate is a diion. Electrophilicity–nucleophilicity indices have been analyzed to understand the mechanism of polar *Diels–Alder reactions*.²²⁸² There have been many mechanistic investigations of the *Diels–Alder reaction*. The bulk of the evidence suggests that most *Diels–Alder reactions* take place by the one-step cyclic mechanism *a*,²²⁸³ although it is possible that a diradical²²⁸⁴ or even a diion²²⁸⁵ mechanism may be taking place in some cases. Radical cation *Diels–Alder reactions* have been considered.²²⁸⁶ The main evidence in support of mechanism *a* is as follows: (1) the reaction is stereospecific in both the diene and dienophile. A completely free diradical or diion probably would not be able to retain its configuration. (2) In general, the rates of *Diels–Alder reactions* depend very little on the nature of the solvent. This would rule out a diion intermediate because polar solvents increase the rates of reactions that develop charges in the transition state. (3) It was shown that, in the decomposition of **150**, the isotope effect k_I/k_{II} was equal to 1.00 within experimental error.²²⁸⁷ If bond *x* were



to break before bond *y*, there should surely be a secondary isotope effect. This result strongly indicates that the bond breaking of *x* and *y* is simultaneous. This is the reverse of a *Diels–Alder reaction*, and by the principle of microscopic reversibility, the mechanism of the forward reaction should involve simultaneous formation of bonds *x* and *y*.

²²⁸⁰ See Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed.* **1980**, 19, 779; Houk, K.N. *Top. Curr. Chem.* **1979**, 79, 1; Babichev, S.S.; Kovtunenkov, V.A.; Voitenko, Z.V.; Tyltin, A.K. *Russ. Chem. Rev.* **1988**, 57, 397. For a discussion of synchronous versus nonsynchronous mechanisms see Beno, B.R.; Houk, K.N.; Singleton, D.A. *J. Am. Chem. Soc.* **1996**, 118, 9984; Singleton, D.A.; Schulmeier, B.E.; Hang, C.; Thomas, A.A.; Leung, S.-W.; Merrigan, S.R. *Tetrahedron* **2001**, 57, 5149. Also see, Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* **1993**, 115, 7478.

²²⁸¹ See Orlova, G.; Goddard, J.D. *J. Org. Chem.* **2001**, 66, 4026.

²²⁸² Domingo, L.R.; Sáez, J.A. *Org. Biomol. Chem.* **2009**, 7, 3576. See also, Soto-Delgado, J.; Domingo, L.R.; Contreras, R. *Org. Biomol. Chem.* **2010**, 8, 3678.

²²⁸³ For a contrary view, see Dewar, M.J.S.; Olivella, S.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1986**, 108, 5771. For arguments against this view, see Houk, K.N.; Lin, Y.; Brown, F.K. *J. Am. Chem. Soc.* **1986**, 108, 554; Gajewski, J. J.; Peterson, K.B.; Kagel, J.R.; Huang, Y.C.J. *J. Am. Chem. Soc.* **1989**, 111, 9078.

²²⁸⁴ See Van Mele, B.; Huybrechts, G. *Int. J. Chem. Kinet.* **1987**, 19, 363; **1989**, 21, 967.

²²⁸⁵ See Gassman, P.G.; Gorman, D.B. *J. Am. Chem. Soc.* **1990**, 112, 8624.

²²⁸⁶ Haberl, U.; Wiest, O.; Steckhan, E. *J. Am. Chem. Soc.* **1999**, 121, 6730.

²²⁸⁷ Seltzer, S. *J. Am. Chem. Soc.* **1965**, 87, 1534; Gajewski, J.J. *Isot. Org. Chem.* **1987**, 7, 115–176.

Subsequently, a similar experiment was carried out on the forward reaction²²⁸⁸ and the result was the same. There is other evidence for mechanism *a*.²²⁸⁹ However, the fact that the mechanism is concerted does not necessarily mean that it is synchronous.²²⁹⁰ In the transition state of a synchronous reaction both new σ bonds would be formed to the same extent, but a *Diels–Alder reaction* with nonsymmetrical components might very well be nonsynchronous;²²⁹¹ that is, it could have a transition state in which one bond has been formed to a greater degree than the other.^{2291,2292} A biradical mechanism has been proposed for some *Diels–Alder reactions*.²²⁹³

In another aspect of the mechanism, the effects of electron-donating and electron-withdrawing substituents (see above) indicate that the diene behaves as a nucleophile and the dienophile as an electrophile. However, this can be reversed. Perchlorocyclopentadiene reacts better with cyclopentene than with maleic anhydride and not at all with tetracyanoethylene, although the latter is normally the most reactive dienophile known. This diene is said to be the electrophile in its *Diels–Alder reactions*.²²⁹⁴ Reactions of this type are said to proceed with *inverse electron demand*.²²⁹⁵ It is known that alkynylboronates participate in inverse electron demand cyclization.²²⁹⁶

The *Diels–Alder reaction* generally takes place rapidly and conveniently. In sharp contrast, the apparently similar dimerization of alkenes to cyclobutanes (Reaction 15-63) gives very poor results in most cases, except when photochemically induced. Woodward and Hoffmann²²⁹⁷ showed that these contrasting results can be explained by the *principle of conservation of orbital symmetry*, which predicts that certain reactions are allowed and others are forbidden. The orbital-symmetry rules (also called the *Woodward–Hoffmann rules*)²²⁹⁸ apply only to concerted reactions (e.g., mechanism *a*) and are based on the principle that reactions take place in such a way as to maintain maximum bonding throughout the course of the reaction. In a separate work, Fukui used MO arguments to

²²⁸⁸ Van Sickle, D.E.; Rodin, J.O. *J. Am. Chem. Soc.* **1964**, *86*, 3091.

²²⁸⁹ See Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. *Chem. Ber.* **1980**, *113*, 1663; Tolbert, L.M.; Ali, M.B. *J. Am. Chem. Soc.* **1981**, *103*, 2104.

²²⁹⁰ For an example of a study of a reaction that is concerted but asynchronous, see Avalos, M.; Babiano, R.; Clemente, F.R.; Cintas, P.; Gordillo, R.; Jiménez, J.L.; Palacios, J.C. *J. Org. Chem.* **2000**, *65*, 8251.

²²⁹¹ Houk, K.N.; Loncharich, R.J.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1989**, *111*, 9172; Lehd, M.; Jensen, F. *J. Org. Chem.* **1990**, *55*, 1034.

²²⁹² See Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *J. Org. Chem.* **2003**, *68*, 3884.

²²⁹³ de Echagüen, C.O.; Ortuño, R.M. *Tetrahedron Lett.* **1995**, *36*, 749. See Li, Y.; Padias, A.B.; Hall, Jr., H.K. *J. Org. Chem.* **1993**, *58*, 7049 for a discussion of diradicals in concerted *Diels–Alder reactions*.

²²⁹⁴ Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* **1962**, *1*, 269.

²²⁹⁵ Boger, D.L.; Patel, M. *Prog. Heterocycl. Chem.* **1989**, *1*, 30. Also see, Pugnaud, S.; Masure, D.; Hallé, J.-C.; Chaquin, P. *J. Org. Chem.*, **1997**, *62*, 8687; Wan, Z.-K.; Snyder, J.K. *Tetrahedron Lett.* **1998**, *39*, 2487.

²²⁹⁶ For a mechanistic study, see Gomez-Bengoa, E.; Helm, M.D.; Plant, A.; Harrity, J.P.A. *J. Am. Chem. Soc.* **2007**, *129*, 2691.

²²⁹⁷ Fleming, I. *Pericyclic Reactions* Oxford University Press, Oxford, **1999**, pp. 31–56; Gilchrist, T.L.; Storr, R. *C. Organic Reactions and Orbital Symmetry* 2nd ed., Cambridge University Press, Cambridge, **1979**; Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley, NY, **1976**; Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, **1970** [the text of this book also appears in *Angew. Chem. Int. Ed.* **1969**, *8*, 781]; Simonetta, M. *Top. Curr. Chem.* **1973**, *42*, 1; Houk, K.N. *Surv. Prog. Chem.* **1973**, *6*, 113; Gill, G.B. *Q. Rev. Chem. Soc.* **1968**, *22*, 338; Miller, S.I. *Adv. Phys. Org. Chem.* **1968**, *6*, 185; Miller, S.I. *Bull. Soc. Chim. Fr.* **1966**, 4031.

²²⁹⁸ Chattaraj, P.K.; Fuentealba, P.; Gómez, B.; Contreras, R. *J. Am. Chem. Soc.* **2000**, *122*, 348.

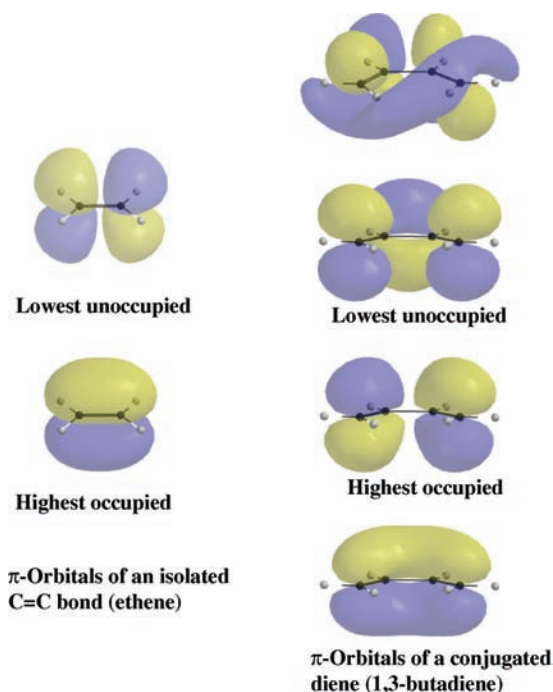


FIG. 15.2. Schematic drawings of the π orbitals of an isolated C=C bond and a conjugated diene explain these reactions. There are several ways of applying the orbital-symmetry principle to cycloaddition reactions, three of which are used more frequently than others.²²⁹⁹ Of these three, two will be discussed: the FMO and the Möbius–Hückel method. The third, called the correlation-diagram method,²³⁰⁰ is less convenient to apply than the other two.

The Frontier-Orbital Method²³⁰¹

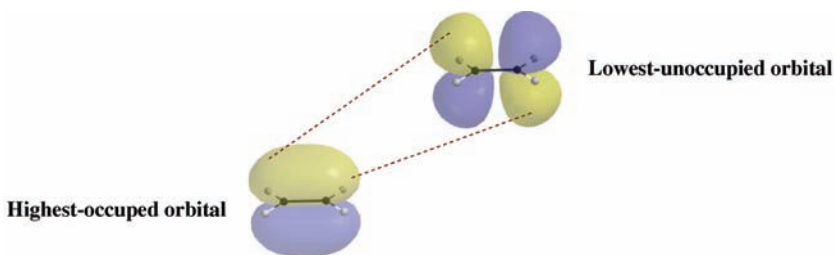
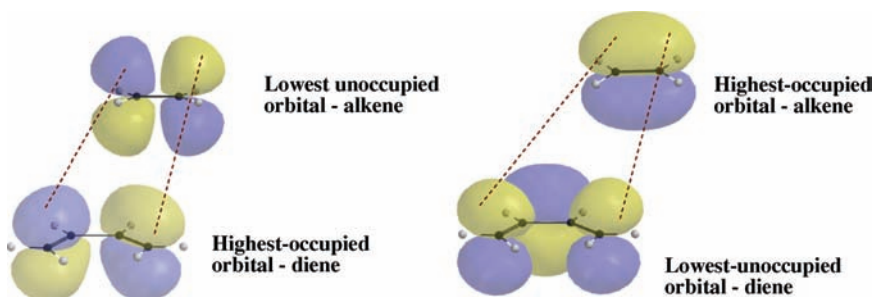
As applied to cycloaddition reactions, the rule is that *reactions are allowed only when all overlaps between the HOMO of one reactant and the LUMO of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe*.²³⁰² Recall that monoalkenes have two π molecular orbitals (Sec. 1.D) and that conjugated dienes have four (Sec. 2.C), as shown in Fig. 15.2. A concerted cyclization of two monoalkenes (a [2 + 2] reaction) is not allowed because it would require that a positive lobe overlap with a negative lobe (Fig. 15.3). On the other

²²⁹⁹ See Epiotis, N.D. *Theory of Organic Reactions*, Springer, NY, **1978**; Ponec, R. *Collect. Czech. Chem. Commun.* **1984**, 49, 455; **1985**, 50, 1121; Hua-ming, Z.; De-xiang, W. *Tetrahedron* **1986**, 42, 515; Bernardi, F.; Olivucci, M.; Robb, M.A. *Res. Chem. Intermed.* **1989**, 12, 217; *Acc. Chem. Res.* **1990**, 23, 405.

²³⁰⁰ See Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, **1970**; *Angew. Chem. Int. Ed.* **1969**, 8, 781; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, **1984**, pp. 352–366; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, **1982**, pp. 378–389; Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, **1978**, pp. 263–276.

²³⁰¹ Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* **1967**, 40, 2018; **1969**, 42, 3399; Fukui, K. *Acc. Chem. Res.* **1971**, 4, 57; Houk, K.N. *Acc. Chem. Res.* **1975**, 8, 361. See Chu, S. *Tetrahedron* **1978**, 34, 645; Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, **1999**; Fukui, K. *Angew. Chem. Int. Ed.* **1982**, 21, 801.

²³⁰² For a discussion of molecules with small HOMO–LUMO gaps, see Perepichka, D.F.; Bryce, M.R. *Angew. Chem. Int. Ed.* **2005**, 44, 5370.

FIG. 15.3. Overlap of orbitals in a thermal $[2 + 2]$ -cycloadditionFIG. 15.4. Two ways for orbitals to overlap in a thermal $[4 + 2]$ -cycloaddition

hand, the *Diels–Alder reaction* (a $[4 + 2]$ reaction) is allowed, when considered from either direction (Fig. 15.4).

These considerations are reversed when the ring closures are photochemically induced, since in such cases an electron is promoted to a vacant orbital before the reaction occurs. Obviously, the $[2 + 2]$ reaction is now allowed (Fig. 15.5) and the $[4 + 2]$ -reaction is disallowed. The reverse reactions follow the same rules, by the principle of microscopic reversibility. In fact, *Diels–Alder* adducts are usually cleaved quite readily, while cyclobutanes, despite the additional strain, require more strenuous conditions.

The Möbius–Hückel Method²³⁰³

In this method, the orbital symmetry rules are related to the *Hückel aromaticity* rule discussed in Chapter 2.²³⁰⁴ *Hückel's rule*, which states that a cyclic system of electrons is aromatic (hence, stable) when it consists of $4n + 2$ electrons, applies of course to molecules in their ground states. In applying the orbital symmetry principle, we are not concerned with ground states, but with transition states. In the present method, do not examine the molecular orbitals themselves, but rather the *p* orbitals before they overlap to form the molecular orbitals. Such a set of *p* orbitals is called a *basis set* (Fig. 15.6). In investigating the possibility of a concerted reaction, the basis sets are put into the position they would occupy in the transition state. Figure 15.7 shows this for both the $[2 + 2]$ and the $[4 + 2]$ ring closures, looking for *sign inversions*. In Fig. 15.7, there are no sign inversions in either case. That is, the dashed line connects only lobes with a minus sign. Systems with *zero or*

²³⁰³ Zimmerman, H.E. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, 1977, pp. 53–107; *Acc. Chem. Res.* **1971**, 4, 272; Dewar, M.J.S. *Angew. Chem. Int. Ed.* **1971**, 10, 761; Jefford, C.W.; Burger, U. *Chimia*, **1971**, 25, 297; Herndon, W.C. *J. Chem. Educ.* **1981**, 58, 371.

²³⁰⁴ See Morao, I.; Cossío, F.P. *J. Org. Chem.* **1999**, 64, 1868.

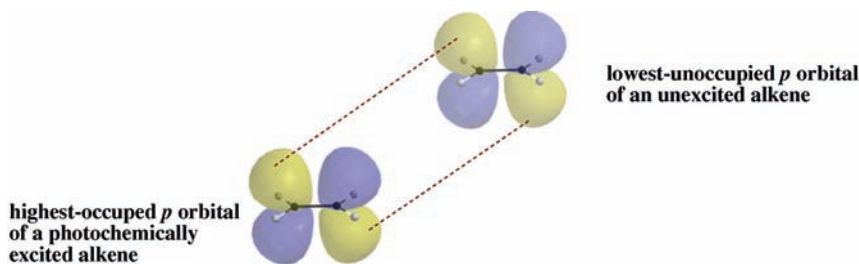
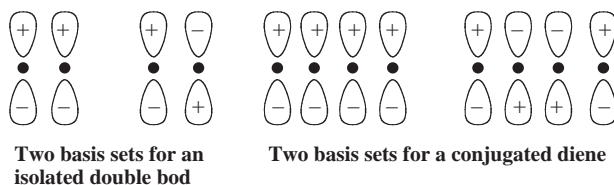
FIG. 15.5. Overlap of orbitals in a photochemical $[2+2]$ -cycloaddition

FIG. 15.6. Some basis sets

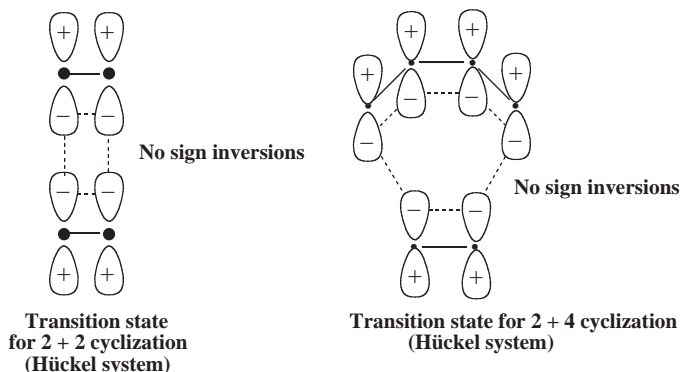


FIG. 15.7. Transition states illustrating Hückel–Möbius rules for cycloaddition reactions

an even number of sign inversions are called *Hückel systems*. Because they have no sign inversions, both of these systems are Hückel systems. Systems with an odd number of sign inversions are called *Möbius systems* (because of the similarity to the Möbius strip, which is a mathematical surface, shown in Fig. 15.8).²³⁰⁵ Möbius systems do not enter into either of these reactions, but an example of such a system is shown in Reaction 18.-28, B. Double-twist *Möbius* aromaticity has been invoked in the *Diels–Alder* transition state for the reaction of a 5,6-di-*tert*-butyl substituted decapentaene.²³⁰⁶

The rule may then be stated: A thermal pericyclic reaction involving a Hückel system is allowed only if the total number of electrons is $4n+2$. A thermal pericyclic reaction involving a Möbius system is allowed only if the total number of electrons is $4n$. For photochemical reactions, these rules are reversed. Since both the $[4+2]$ - and $[2+2]$ -cycloadditions are *Hückel* systems, the *Möbius–Hückel method* predicts that the $[4+2]$ -reaction, with

²³⁰⁵ See Hennigar, K.H.R.; Langler, R.F. *Austr. J. Chem.* **2010**, 63, 490.

²³⁰⁶ Rzepa, H.S. *Chem. Commun.* **2005**, 5220.



FIG. 15.8. A Möbius strip. Such a strip is easily constructed by twisting a thin strip of paper 180° and fastening the ends together

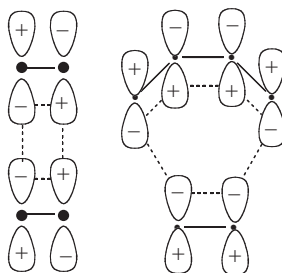


FIG. 15.9. Transition states of $[2+2]$ - and $[4+2]$ -cyclizations involving other basis sets

6 electrons, is thermally allowed, but the $[2+2]$ -reaction is not. On the other hand, the $[2+2]$ -reaction is allowed photochemically, while the $[4+2]$ -reaction is forbidden.

Note that both the $[2+2]$ and $[4+2]$ transition states are *Hückel* systems no matter what basis sets were chosen. For example, Fig. 15.9 shows other basis sets we might have chosen. In every case there will be zero or an even number of sign inversions.

Thus, the FMO and *Hückel-Möbius* methods (and the correlation-diagram method as well) lead to the same conclusions: Thermal $[4+2]$ -cycloadditions and photochemical $[2+2]$ -cycloadditions (and the reverse ring openings) are allowed, while photochemical $[4+2]$ - and thermal $[2+2]$ -ring closings (and openings) are forbidden.

Application of the same procedures to other ring closures shows that $[4+4]$ - and $[2+6]$ -ring closures and openings require photochemical induction while the $[4+6]$ - and $[2+8]$ -reactions can take place only thermally (see Reaction 15-53). In general, cycloaddition reactions allowed thermally are those with $4n+2$ electrons, while those allowed photochemically have $4n$ electrons.

It must be emphasized once again that the rules apply only to cycloaddition reactions that take place by cyclic mechanisms, which is where two σ bonds are formed (or broken) at about the same time.²³⁰⁷ The rule does not apply to cases where one bond is clearly formed (or broken) before the other. It must further be emphasized that the fact that the thermal *Diels-Alder reaction* (mechanism *a*) is allowed by the principle of conservation of orbital symmetry does not constitute proof that any given *Diels-Alder reaction* proceeds by this mechanism. The principle merely says the mechanism is allowed, not that it must go by this pathway. However, the principle does say that thermal $[2+2]$ -cycloadditions in

²³⁰⁷ See Lehr, R.E.; Marchand, A.P. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 1, Academic Press, NY, 1977, pp. 1-51.

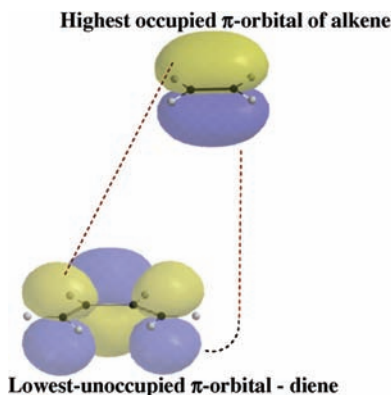
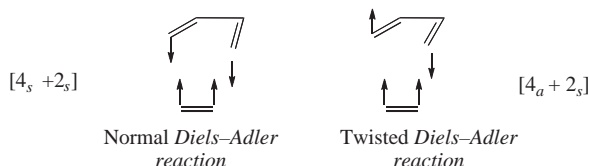


FIG. 15.10. Overlap of orbitals in an antarafacial thermal $[4+2]$ -cycloaddition

which the molecules assume a face-to-face geometry cannot²³⁰⁸ take place by a cyclic mechanism because their activation energies would be too high (however, see below). In Reaction 15-62 it will be seen that such reactions largely occur by two-step mechanisms. Similarly, $[4+2]$ -photochemical cycloadditions are also known, but the fact that they are not stereospecific indicates that they also take place by the two-step diradical mechanism (mechanism *b*).²³⁰⁹

In all of the above discussions, it has been assumed that a given molecule forms both the new σ bonds from the same face of the π system. This manner of bond formation, called *suprafacial*, is certainly most reasonable and almost always takes place. The subscript *s* is used to designate this geometry, and a normal *Diels–Alder reaction* would be called a $[\pi 2_s + \pi 4_s]$ -cycloaddition (the subscript π indicates that π electrons are involved in the cycloaddition). However, there is another approach in which the newly forming bonds of the diene lie on *opposite* faces of the π system, that is, they point in opposite directions. This type of orientation of the newly formed bonds is called *antarafacial*, and the reaction would be a $[\pi 2_s + \pi 4_a]$ -cycloaddition (*a* stands for antarafacial). The FMO method shows that this reaction (and consequently the reverse ring-opening reactions) are thermally forbidden and photochemically allowed. Thus in order for a $[\pi 2_s + \pi 4_a]$ reaction to proceed, overlap between the highest-occupied π orbital of the alkene and the lowest-unoccupied π orbital of the diene would have to occur as shown in Fig. 15.10, with a +lobe overlapping a –lobe. Since like signs are no



²³⁰⁸ See Baldwin, J.E.; Andrist, A.H.; Pinschmidt, Jr., R.K. *Acc. Chem. Res.* **1972**, 5, 402; Berson, J.A. *Acc. Chem. Res.* **1972**, 5, 406; Baldwin, J.E. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, **1977**, pp. 273–302.

²³⁰⁹ See Sieber, W.; Heimgartner, H.; Hansen, H.; Schmid, H. *Helv. Chim. Acta* **1972**, 55, 3005; Bartlett, P.D.; Helgeson, R.; Wersel, O.A. *Pure Appl. Chem.* **1968**, 16, 187; Seeley, D.A. *J. Am. Chem. Soc.* **1972**, 94, 4378; Kaupp, G. *Angew. Chem. Int. Ed.* **1972**, 11, 313, 718.

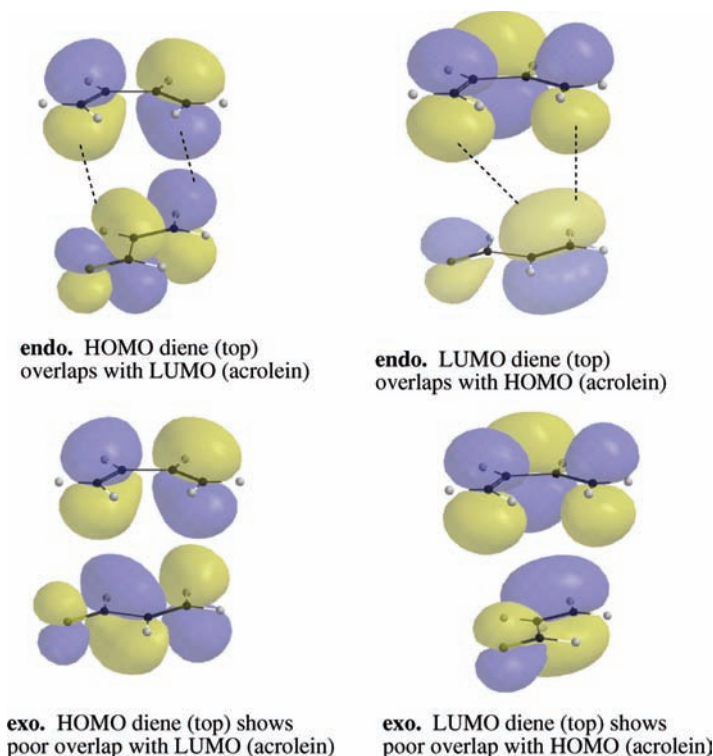


FIG. 15.11. Overlap of orbitals in $[4 + 2]$ -cycloaddition of 1,3-butadiene with acrolein

longer overlapping, the thermal reaction is now forbidden. Similarly, thermal $[\pi 4_s + \pi 2_a]$ and $[\pi 2_s + \pi 4_a]$ -cyclizations are forbidden, while thermal $[\pi 4_a + \pi 2_a]$ - and $[\pi 2_s + \pi 2_a]$ -cyclizations are allowed. These considerations are reversed for the corresponding photochemical processes. Of course, an antarafacial approach is highly unlikely in a $[4 + 2]$ -cyclization,²³¹⁰ but larger ring closures could take place by such a pathway, and $[2 + 2]$ -thermal cyclizations, where the $[\pi 2_s + \pi 2_s]$ -pathway is forbidden, can also do so in certain cases (see Reaction 15-63). Whether a given cycloaddition is allowed or forbidden depends on the geometry of approach of the two molecules involved.

Symmetry considerations have also been advanced to explain predominant endo addition.²³¹¹ In the case of $[4 + 2]$ -addition of butadiene to acrolein, the approach can be exo or endo. It can be seen (Fig. 15.11) that whether the HOMO of the diene overlaps with the LUMO of acrolein or vice versa, the endo orientation is stabilized by additional secondary overlap of orbitals²³¹² of like sign (dashed lines between heavy dots). Addition from the exo direction has no such stabilization since the sign of the orbitals do not match. Evidence for secondary orbital overlap as the cause of predominant endo orientation, at least in some cases, is that $[4 + 6]$ -cycloaddition is predicted by similar considerations to

²³¹⁰ A possible photochemical $[2 + 4]$ cycloaddition has been reported: Hart, H.; Miyashi, T.; Buchanan, D.N.; Sasson, S. *J. Am. Chem. Soc.* **1974**, *96*, 4857.

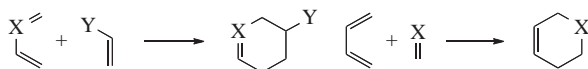
²³¹¹ Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* **1965**, *87*, 4388.

²³¹² See Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095; Gleiter, R.; Paquette, L.A. *Acc. Chem. Res.* **1983**, *16*, 328. See Singleton, D.A. *J. Am. Chem. Soc.* **1992**, *114*, 6563.

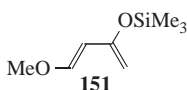
proceed with predominant exo orientation, and that is what is found.²³¹³ However, this explanation does not account for endo orientation in cases where the dienophile does not possess additional π orbitals, and a number of alternative explanations have been offered.²³¹⁴

OS **II**, 102; **III**, 310, 807; **IV**, 238, 738, 890, 964; **V**, 414, 424, 604, 985, 1037; **VI**, 82, 196, 422, 427, 445, 454; **VII**, 4, 312, 485; **VIII**, 31, 38, 298, 353, 444, 597; **IX**, 186, 722; **75**, 201; **81**, 171. For a reverse Diels–Alder reaction, see OS **VII**, 339.

15-61 Heteroatom Diels–Alder Reactions



Alkenes, alkynes, and dienes are not the only units that can participate in *Diels–Alder reactions*. Other double- and triple-bond compounds can be dienophiles and they give rise to heterocyclic compounds.²³¹⁵ Among these are $\text{N}\equiv\text{C}-$, $-\text{N}=\text{C}-$,²³¹⁶ iminium salts,²³¹⁷ $-\text{N}=\text{N}-$, $\text{O}=\text{N}-$,²³¹⁸ and $-\text{C}=\text{O}$ compounds,²³¹⁹ and even molecular oxygen (Reaction 15-62). Several catalysts can be used, depending on the nature of the heteroatoms incorporated into the alkene or diene.²³²⁰ Intramolecular cycloaddition with a diene–imine substrate leads to pyrrolidines.²³²¹



Aldehydes react with suitably functionalized dienes (e.g., **151**), known as *Danishefsky's diene*,²³²² and the reaction usually requires a Lewis acid catalyst (e.g., lanthanide compounds).²³²³ The *Diels–Alder reaction* of aldehydes with dienes can be catalyzed by many transition metal compounds, including Co ²³²⁴ and In ²³²⁵ catalysts. Aldehydes react using a chiral Ti ²³²⁶ or a Zr ²³²⁷ catalyst to give the dihydropyran with good

²³¹³ See Apeloig, Y.; Matzner, E. *J. Am. Chem. Soc.* **1995**, 117, 5375.

²³¹⁴ See Fox, M.A.; Cardona, R.; Kiwiet, N.J. *J. Org. Chem.* **1987**, 52, 1469.

²³¹⁵ See McCarrick, M.A.; Wu, Y.-D.; Houk, K.N. *J. Org. Chem.* **1993**, 58, 3330.

²³¹⁶ Anniyappan, M.; Muralidharan, D.; Perumal, P.T. *Tetrahedron Lett.* **2003**, 44, 3653. For a review see Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, 57, 6099.

²³¹⁷ Domingo, L.R. *J. Org. Chem.* **2001**, 66, 3211; Chou, S.-S.P.; Hung, C.-C. *Synth. Commun.* **2001**, 31, 1097.

²³¹⁸ Martin, S.F.; Hartmann, M.; Josey, J.A. *Tetrahedron Lett.* **1992**, 33, 3583.

²³¹⁹ Boger, D.L.; Weinreb, S.M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press, NY, **1987**; Weinreb, S.M.; Scola, P.M. *Chem. Rev.* **1989**, 89, 1525; Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* **1987**, 42, 245; Boger, D.L. *Tetrahedron* **1983**, 39, 2869; Weinreb, S.M.; Staib, R.R. *Tetrahedron* **1982**, 38, 3087; Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, 75, 651; Katritzky, A.R.; Dennis, N. *Chem. Rev.* **1989**, 89, 827; Schmidt, R.R. *Acc. Chem. Res.* **1986**, 19, 250; Boger, D.L. *Chem. Rev.* **1986**, 86, 781.

²³²⁰ See Molander, G.A.; Rzas, R.M. *J. Org. Chem.* **2000**, 65, 1215.

²³²¹ Amos, D.T.; Renslo, A.R.; Danhesier, R.L. *J. Am. Chem. Soc.* **2003**, 125, 4970.

²³²² See Danishefsky, S.; Schuda, P.F.; Kitahara, T. Etheredge, S.J. *J. Am. Chem. Soc.* **1977**, 99, 6066. Also see Sudo, Y.; Shirasaki, D.; Harada, S.; Nishida, A. *J. Am. Chem. Soc.* **2008**, 130, 12588.

²³²³ See Zhang, X.; Du, H.; Wang, Z.; Wu, Y.-D.; Ding, K. *J. Org. Chem.* **2006**, 71, 2862.

²³²⁴ Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2001**, 74, 1333.

²³²⁵ Ali, T.; Chauhan, K.K.; Frost, C.G. *Tetrahedron Lett.* **1999**, 40, 5621.

²³²⁶ Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* **2002**, 67, 2175.

²³²⁷ Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, 125, 3793.

enantioselectivity. Copper(I) catalysts have been used as well.²³²⁸ Note that the reaction of *Danishefsky's diene* with an imine,²³²⁹ formed *in situ* by reaction of an aryl aldehyde and an aniline derivative, proceeds without a Lewis acid.²³³⁰ Ketones also react with suitably functionalized dienes.²³³¹ Indium trichloride (InCl₃) is a good catalyst for imino-*Diels–Alder reactions*.²³³² Hetero-*Diels–Alder reactions* involving carbonyls have been done in water.²³³³ Ultrasound has been used to promote the *Diels–Alder reactions* of 1-azadienes.²³³⁴ Polymer-supported dienes have been used.²³³⁵

Hetero-*Diels–Alder reactions* that proceed with good-to-excellent asymmetric induction are well known.²³³⁶ Asymmetric *Diels–Alder reactions* of carbonyl compounds are well known.²³³⁷ Chiral 1-aza-dienes have been developed as substrates, for example.²³³⁸ Azadienes also react with chiral dienophiles.²³³⁹ Chiral catalysts have been developed.²³⁴⁰

Dienes related to **151** are known, and their reactivity has been examined. Amino-substituted dienes undergo what is known as hydrogen-bonding catalyzed reactions.²³⁴¹ Imines react with other substrates (e.g., allenes), to give tetrahydropyridine derivatives, with good enantioselectivity in the presence of a chiral ligand.²³⁴² Azo compounds (—N=N—) react as dienophiles in the presence of an Ag catalyst.²³⁴³ Iminium ions undergo *Diels–Alder cycloaddition*.²³⁴⁴

Azadienes undergo *Diels–Alder reactions* to form pyridine, dihydro- and tetrahydropyridine derivatives.²³⁴⁵ *Aza-Diels–Alder reactions* have been done in ionic liquids.²³⁴⁶ Similarly, acyl iminium salts (C=N(R)—C=O) react with alkenes via cycloaddition.²³⁴⁷ *N*-Vinyl lactim ethers undergo *Diels–Alder reactions* with a limited set of dienophiles.²³⁴⁸ Brønsted acids can catalyze inverse electron demand *aza-Diels–Alder reactions*.²³⁴⁹

Thioketones react with dienes to give *Diels–Alder cycloadducts*.²³⁵⁰ The carbonyl group of lactams has also been shown to be a dienophile.²³⁵¹ Certain heterocyclic aromatic

²³²⁸ Chen, I.-H.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 5151.

²³²⁹ In an ionic liquid, see Pégot, B.; Vo-Thanh, G. *Synlett* **2005**, 1409/

²³³⁰ Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309.

²³³¹ See Jørgensen, K.A. *Eur. J. Org. Chem.* **2004**, 2093.

²³³² Babu, G.; Perumal, P.T. *Tetrahedron* **1998**, *54*, 1627.

²³³³ Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. *Tetrahedron* **1994**, *50*, 10265.

²³³⁴ Villacampa, M.; Pérez, J.M.; Avendaño, C.; Menéndez, J.C. *Tetrahedron Lett.* **1994**, *50*, 10047.

²³³⁵ Pierres, C.; George, P.; van Hijfte, L.; Ducep, J.-B.; Hibert, M.; Mann, A. *Tetrahedron Lett.* **2003**, *44*, 3645.

²³³⁶ Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R.G.; Jørgensen, K.A. *J. Am. Chem. Soc.* **1998**, *120*, 8599.

²³³⁷ Pellissier, H. *Tetrahedron* **2009**, *65*, 2839.

²³³⁸ Beaudegnies, R.; Ghosez, L. *Tetrahedron Asymmetry* **1994**, *5*, 557.

²³³⁹ Wurz, R.P.; Fu, G.C. *J. Am. Chem. Soc.* **2005**, *127*, 12234.

²³⁴⁰ See He, M.; Struble, J.R.; Bode, J.W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

²³⁴¹ Jensen, K.H.; Sigman, M.S. *Angew. Chem. Int. Ed.* **2008**, *47*, 4748.

²³⁴² Wurz, R.P.; Fu, G.C. *J. Am. Chem. Soc.* **2005**, *127*, 12234.

²³⁴³ Kawasaki, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 16482.

²³⁴⁴ See Sarkar, N.; Banerjee, A.; Nelson, S.G. *J. Am. Chem. Soc.* **2008**, *130*, 9222.

²³⁴⁵ Jayakumar, S.; Ishar, M.P.S.; Mahajan, M.P. *Tetrahedron* **2002**, *58*, 379.

²³⁴⁶ Yadav, J.S.; Reddy, B.V.S.; Reddy, J.S.S.; Rao, R.S. *Tetrahedron* **2003**, *59*, 1599.

²³⁴⁷ Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J.-i. *Org. Lett.* **2003**, *5*, 945.

²³⁴⁸ Sheu, J.; Smith, M.B.; Matsumoto, K. *Synth. Commun.* **1993**, *23*, 253.

²³⁴⁹ Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070; Esquivias, J.; Arrayás, R.G.; Carretero, J.C. *J. Am. Chem. Soc.* **2007**, *129*, 1480.

²³⁵⁰ Schatz, J.; Sauer, J. *Tetrahedron Lett.* **1994**, *35*, 4767.

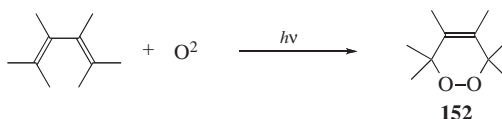
²³⁵¹ Degnan, A.P.; Kim, C.S.; Stout, C.W.; Kalivretenos, A.G. *J. Org. Chem.* **1995**, *60*, 7724.

rings (among them furans)²³⁵² can also behave as dienes in the Diels–Alder reaction. Some hetero dienes that give the reaction are —C=C—C=O , O=C—C=O , and N=C—C=N .²³⁵² Nitroso compounds of the type $t\text{-BuO}_2\text{C—N=O}$ react with dienes to give the corresponding 2-azadihydropyran.²³⁵³ Conjugated aldehydes react with vinyl ethers, with a chiral Cr catalyst, in an inverse electron demand cycloaddition that give a dihydropyran with good enantioselectivity.²³⁵⁴ Vinyl sulfilimines have been used in chiral *Diels–Alder reactions*.²³⁵⁵

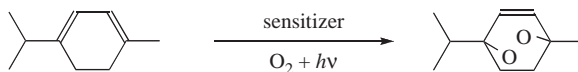
OS IV, 311; V, 60, 96; 80, 133. See also, OS VII, 326.

15-62 Photooxidation of Dienes (Addition of Oxygen, Oxygen)

[4 + 2] *OC,OC-cyclo-Peroxy-1/4/addition*



Conjugated dienes react with oxygen under the influence of light to give cyclic peroxides (**152**).²³⁵⁶ The reaction has mostly²³⁵⁷ been applied to cyclic dienes.²³⁵⁸ Cycloaddition of furan has been reported using singlet oxygen.²³⁵⁹ The scope extends to certain aromatic compounds (e.g., phenanthrene).²³⁶⁰ Besides those dienes and aromatic rings that can be photooxidized directly, there is a larger group that gives the reaction in the presence of a photosensitizer (see Sec. 7.A.vi, category 5; e.g., eosin, a red xanthene dye). Among these is α -terpinene, which is converted to ascaridole:



²³⁵² Katritzky, A.R.; Dennis, N. *Chem. Rev.* **1989**, 89, 827; Schmidt, R.R. *Acc. Chem. Res.* **1986**, 19, 250; Boger, D.L. *Chem. Rev.* **1986**, 86, 781. See Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2002**, 41, 4079.

²³⁵³ Bach, P.; Bols, M. *Tetrahedron Lett.* **1999**, 40, 3461.

²³⁵⁴ Gademann, K.; Chavez, D.E.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* **2002**, 41, 3059.

²³⁵⁵ Ruano, J.L.G.; Clemente, F.R.; Gutiérrez, L.G.; Gordillo, R.; Castro, A.M.M.; Ramos, J.H.R. *J. Org. Chem.* **2002**, 67, 2926.

²³⁵⁶ See Clennan, E.L. *Tetrahedron* **1991**, 47, 1343; *Adv. Oxygenated Processes* **1988**, 1, 85; Wasserman, H.H.; Ives, J.L. *Tetrahedron* **1981**, 37, 1825; Denny, R.W.; Nickon, A. *Org. React.* **1973**, 20, 133; Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, **1968**, pp. 382–397; Gollnick, K.; Schenck, G.O. in Hamer, J. *1,4-Cycloaddition Reactions*, Academic Press, NY, **1967**, pp. 255–344.

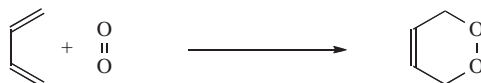
²³⁵⁷ Matsumoto, M.; Dobashi, S.; Kuroda, K.; Kondo, K. *Tetrahedron* **1985**, 41, 2147.

²³⁵⁸ See Saito, I.; Nittala, S.S. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, **1983**, pp. 311–374; Balci, M. *Chem. Rev.* **1981**, 81, 91; Adam, W.; Bloodworth, A.J. *Top. Curr. Chem.* **1981**, 97, 121.

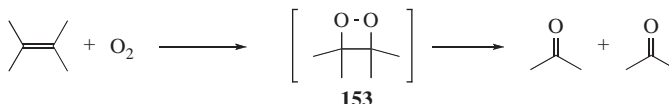
²³⁵⁹ Onitsuka, S.; Nishino, H.; Kurosawa, K. *Tetrahedron* **2001**, 57, 6003.

²³⁶⁰ See in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, **1979**, the articles by Wasserman, H.H.; Lipshutz, B.H. pp. 429–509; Saito, I.; Matsuura, T. pp. 511–574; Rigaudy, J. *Pure Appl. Chem.* **1968**, 16, 169.

As in Reaction 14-7, it is not the ground-state oxygen (the triplet), that reacts, but the excited singlet state,^{2361,2362} so the reaction is actually a *Diels–Alder reaction* (see Reaction 15-60) with singlet oxygen as dienophile:²³⁶³



Like Reaction 15-60, this reaction is reversible.



As previously discussed, the reaction of singlet oxygen with double-bond compounds gives hydroperoxides (Reaction 14-7), but singlet oxygen can also react with double bonds in another way to give a dioxetane intermediate²³⁶⁴ (Reaction 153), which usually cleaves to aldehydes or ketones,²³⁶⁵ but has been isolated.²³⁶⁶ Both the six-membered cyclic peroxides²³⁶⁷ and the four-membered **205**²³⁶⁸ have been formed from oxygenation reactions that do not involve singlet oxygen. If cyclic peroxides (e.g., **205**) are desired, better reagents²³⁶⁹ are triphenyl phosphite ozonide [(PhO)₃PO₃] and triethylsilyl hydrotrioxide [(Et₃SiOOOH)], but yields are not high.²³⁷⁰

15-63 [2 + 2]-Cycloadditions

[2 + 2]cyclo-Ethylene-1/2/addition



²³⁶¹ Frimer, A.A. *Singlet O₂*, 4 Vols., CRC Press, Boca Raton, FL, **1985**; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, **1979**. See Frimer, A.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, **1983**, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* **1981**, 10, 205; Ohloff, G. *Pure Appl. Chem.* **1975**, 43, 481; Kearns, D.R. *Chem. Rev.* **1971**, 71, 395; Wayne, R.P. *Adv. Photochem.* **1969**, 7, 311.

²³⁶² Turro, N.J.; Ramamurthy, V. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, **1980**, pp. 1–23; Murray, R.W. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, **1979**, pp. 59–114; Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*, Academic Press, NY, **1982**.

²³⁶³ Monroe, B.M. *J. Am. Chem. Soc.* **1981**, 103, 7253. See also, Hathaway, S.J.; Paquette, L.A. *Tetrahedron Lett.* **1985**, 41, 2037; O'Shea, K.E.; Foote, C.S. *J. Am. Chem. Soc.* **1988**, 110, 7167.

²³⁶⁴ Adam, W.; Cilento, G. *Angew. Chem. Int. Ed.* **1983**, 22, 529; Schaap, A.; Zaklika, K.A. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, **1979**, pp. 173–242; Bartlett, P.D. *Chem. Soc. Rev.* **1976**, 5, 149. For discussions of the mechanisms see Frimer, A.A. *Chem. Rev.* **1979**, 79, 359; Clennan, E.L.; Nagraba, K. *J. Am. Chem. Soc.* **1988**, 110, 4312.

²³⁶⁵ Kearns, D.R. *Chem. Rev.* **1971**, 71, 395, pp. 422–424; Foote, C.S. *Pure Appl. Chem.* **1971**, 27, 635.

²³⁶⁶ Adam, W. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, **1983**, pp. 829–920; Bartlett, P.D.; Landis, M.E. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, **1979**, pp. 243–286; Adam, W. *Adv. Heterocycl. Chem.* **1977**, 21, 437. See also, Adam, W.; Encarnación, L.A.A. *Chem. Ber.* **1982**, 115, 2592; Adam, W.; Baader, W.J. *Angew. Chem. Int. Ed.* **1984**, 23, 166.

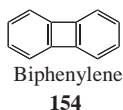
²³⁶⁷ See Nelson, S.F.; Teasley, M.F.; Kapp, D.L. *J. Am. Chem. Soc.* **1986**, 108, 5503.

²³⁶⁸ See Nelson, S.F. *Acc. Chem. Res.* **1987**, 20, 269.

²³⁶⁹ See Curci, R.; Lopez, L.; Troisi, L.; Rashid, S.M.K.; Schaap, A.P. *Tetrahedron Lett.* **1987**, 28, 5319.

²³⁷⁰ Posner, G.H.; Weitzberg, M.; Nelson, W.M.; Murr, B.L.; Seliger, H.H. *J. Am. Chem. Soc.* **1987**, 109, 278.

Two alkene molecules react under thermal conditions to give cyclobutane derivatives in what is known as a $[2 + 2]$ -cycloaddition. The cycloaddition occurs when the alkenes are the same or different, but the reaction is not general for all alkenes.²³⁷¹ Certain transition metal complexes can catalyze the cycloaddition.²³⁷² Benzyne undergo cycloaddition to give biphenylene derivatives (**154**),²³⁷³ activated alkenes (e.g., styrene, acrylonitrile, butadiene), and certain methylenecyclopropanes.²³⁷⁴ Alkenes react with alkynes²³⁷⁵ or with activated alkynes, with a Ru catalyst, to give cyclobutenes.²³⁷⁶ Dimerization of allenes leads to bis(alkylidene) cyclobutenes.²³⁷⁷ Substituted ketenes can dimerize to give cyclobutenone derivatives, although ketene itself dimerizes in a different manner, to give an unsaturated β -lactone (Reaction **16-95**).²³⁷⁸



Intramolecular $[2 + 2]$ -cycloadditions are common in which a diene is converted to a bicyclic compound with a four-membered ring fused to another ring. Transition metal catalyzed reactions have been reported, including the use of Fe complexes.²³⁷⁹ Heating *N*-vinyl imines, where the vinyl moiety is a silyl enol, gives β -lactams.²³⁸⁰ Apart from photochemical initiation of such reactions (see below), intramolecular cycloaddition of two conjugated ketone units, in the presence of PhMeSiH_2 and catalyzed by Co compounds, leads to the bicyclic compound with two ketone substituents.²³⁸¹ In a variation of this reaction, a diyne was treated with $\text{Ti}(\text{O}i\text{Pr})_4/2$ $i\text{PrMgCl}$ to generate a bicyclic cyclobutene with two vinylidene units.²³⁸²

Ketenes react with many alkenes to give cyclobutanone derivatives²³⁸³ and intermolecular cycloadditions are well known.²³⁸⁴ A typical reaction of dimethylketene and ethene gives 2,2-dimethylcyclobutanone, as shown.²³⁸⁵ Ketenes react with imines via

²³⁷¹ Carruthers, W. *Cycloaddition Reactions in Organic Synthesis* Pergamon, Elmsford, NY, **1990**; Reinhoudt, D.N. *Adv. Heterocycl. Chem.* **1977**, 21, 253; Roberts, J.D.; Sharts, C.M. *Org. React.* **1962**, 12, 1; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, 2nd ed., Cambridge University Press, Cambridge, **1979**, pp. 173–212; Dilling, W.L. *Chem. Rev.* **1983**, 83, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 546–647, 1341–1344.

²³⁷² See Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* **2004**, 69, 517.

²³⁷³ See Mariet, N.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2002**, 43, 5789.

²³⁷⁴ Dolbier, Jr., W.R.; Lomas, D.; Garza, T.; Harmon, C.; Tarrant, P. *Tetrahedron* **1972**, 28, 3185.

²³⁷⁵ López-Carrillo, V.; Echavarren, A.M. *J. Am. Chem. Soc.* **2010**, 132, 9292.

²³⁷⁶ Jordan, R.W.; Tam, W. *Org. Lett.* **2000**, 2, 3031.

²³⁷⁷ Saito, S.; Hirayama, K.; Kabuto, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, 122, 10776.

²³⁷⁸ Dehmlow, E.V.; Pickardt, J.; Slopianka, M.; Fastabend, U.; Drechsler, K.; Soufi, J. *Liebigs Ann. Chem.* **1987**, 377.

²³⁷⁹ Bouwkamp, M.W.; Bowman, A.C.; Lobkovsky, E.; Chirik, P.J. *J. Am. Chem. Soc.* **2006**, 128, 13340.

²³⁸⁰ Bandin, E.; Favi, G.; Martelli, G.; Panunzio, M.; Piersanti, G. *Org. Lett.* **2000**, 2, 1077.

²³⁸¹ Baik, T.-G.; Luis, A.L.; Wang, L.-C.; Krische, M.J. *J. Am. Chem. Soc.* **2001**, 123, 6716.

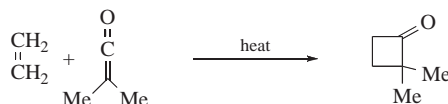
²³⁸² Delas, C.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **2001**, 42, 4147.

²³⁸³ See de Faria, A.R.; Matos, C.R.; Correia, C.R.D. *Tetrahedron Lett.* **1993**, 34, 27.

²³⁸⁴ Martin, P.; Greuter, H.; Bellus, D. *Helv. Chim. Acta.*, **1984**, 64, 64.

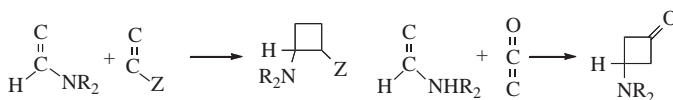
²³⁸⁵ Sustmann, R.; Ansmann, A.; Vahrenholt, F. *J. Am. Chem. Soc.* **1972**, 94, 8099; Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G.P. *Natural Product Synthesis Through Pericyclic Reactions*, American Chemical Society Washington, DC, **1983**, pp. 119–254, p. 39.

[2 + 2]-cycloaddition to produce β -lactams.²³⁸⁶ Cycloaddition of an imine with a conjugated ester in the presence of Et_3MeSiH and an Ir catalyst also gives a β -lactam.²³⁸⁷ See Reaction **19-66** for a discussion of reactions that give β -lactams.



Different alkenes combine as follows:

1. $\text{F}_2\text{C}=\text{CX}_2$ (X = F or Cl), especially $\text{F}_2\text{C}=\text{CF}_2$, form cyclobutanes with many alkenes. Compounds of this type even react with conjugated dienes to give four-membered rings rather than undergoing normal *Diels–Alder reactions*.²³⁸⁸
2. Allenes²³⁸⁹ and ketenes²³⁹⁰ react with activated alkenes and alkynes. Ketenes give 1,2-addition, even with conjugated dienes.²³⁹¹ Ketenes also add to unactivated alkenes if sufficiently long reaction times are used.²³⁹² Allenes and ketenes also add to each other.²³⁹³
3. Enamines²³⁹⁴ form four-membered rings with *Michael-type* alkenes²³⁹⁵ and ketenes.²³⁹⁶ In both cases, only enamines from aldehydes give stable four-membered rings:



Generating the ketene *in situ* from an acyl halide and a tertiary amine is a convenient way to carry out the reaction of enamines with ketenes.

²³⁸⁶ Brown, M.J. *Heterocycles* **1989**, 29, 2225; Isaacs, N.S. *Chem. Soc. Rev.* **1976**, 5, 181; Mukerjee, A.K.; Srivastava, R.C. *Synthesis* **1973**, 327; Sandhu, J.S.; Sain, B. *Heterocycles* **1987**, 26, 777.; Wack, H.; France, S.; Hafez, A.M.; Drury, III, W.J.; Weatherwax, A.; Lectka, T. *J. Org. Chem.* **2004**, 69, 4531.

²³⁸⁷ Townes, J.A.; Evans, M.A.; Queffelec, J.; Taylor, S.J.; Morken, J.P. *Org. Lett.* **2002**, 4, 2537.

²³⁸⁸ De Cock, C.; Piettre, S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* **1985**, 41, 4183.

²³⁸⁹ Schuster, H.F.; Coppola, G.M. *Allenenes in Organic Synthesis* Wiley, NY, **1984**, pp. 286–317; Hopf, H. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, **1982**, pp. 525–562; Ghosez, L.; O'Donnell, M.J. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions* Vol. 2, Academic Press, NY, **1977**, pp. 79–140; Luzung, M.R.; Mauleón, P.; Toste, F.D. *J. Am. Chem. Soc.* **2007**, 129, 12402.

²³⁹⁰ Ghosez, L.; O'Donnell, M.J. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reaction*, Vol. 2, Academic Press, NY, **1977**; Brady, W.T. *Synthesis* **1971**, 415; Snider, B.B. *Chem. Rev.* **1988**, 88, 793. See Ussing, B.R.; Hang, C.; Singleton, D.A. *J. Am. Chem. Soc.* **2006**, 128, 7594.

²³⁹¹ See Huisgen, R.; Feiler, L.A.; Otto, P. *Tetrahedron Lett.* **1968**, 4491; *Chem. Ber.* **1969**, 102, 3475; Corey, E.J.; Ravindranathan, T.; Terashima, S. *J. Am. Chem. Soc.* **1971**, 93, 4326. For a review of ketene equivalents, see Ranganathan, S.; Ranganathan, D.; Mehrotra, A.K. *Synthesis* **1977**, 289.

²³⁹² Bak, D.A.; Brady, W.T. *J. Org. Chem.* **1979**, 44, 107.

²³⁹³ Gras, J.; Bertrand, M. *Nouv. J. Chim.* **1981**, 5, 521.

²³⁹⁴ Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed.; Marcel Dekker, NY, **1988**, pp. 347–440.

²³⁹⁵ Brannock, K.C.; Bell, A.; Goodlett, V.W.; Thweatt, J.G. *J. Org. Chem.* **1964**, 29, 813.

²³⁹⁶ Hasek, R.H.; Gott, P.G.; Martin, J.C. *J. Org. Chem.* **1966**, 31, 1931.

4. Alkenes with electron-withdrawing groups may form cyclobutanes with alkenes containing electron-donating groups.²³⁹⁷ The enamine reactions, mentioned above, are examples of this, but it has also been accomplished with tetracyanoethylene and similar molecules, which give substituted cyclobutanes when treated with alkenes of the form $C=C-A$, where A may be OR,²³⁹⁸ SR (enol and thioenol ethers),²³⁹⁹ cyclopropyl,²⁴⁰⁰ or certain aryl groups.²⁴⁰¹

Enantioselective [2 + 2]-cycloaddition reactions are known. Chiral organocatalysts lead to chiral cyclobutane derivatives.²⁴⁰²

Solvents are not necessary for [2 + 2]-cycloadditions. They can be carried out at 100–225 °C under pressure, although the reactions in Group 4 occur under milder conditions. However, the choice of solvent can control the distribution of products in photochemical [2 + 2]-cycloaddition.²⁴⁰³

It has been found that certain [2 + 2]-cycloadditions that do not occur thermally can be made to take place without photochemical initiation using certain catalysts, usually transition metal compounds.²⁴⁰⁴ Among the catalysts used are Lewis acids²⁴⁰⁵ and phosphine–Ni complexes.²⁴⁰⁶ The role of the catalyst is not certain and may be different in each case. One possibility is that the presence of the catalyst causes a forbidden reaction to become allowed, through coordination of the catalyst to the π or s bonds of the substrate.²⁴⁰⁷ In such a case, the reaction would of course be a concerted [$2_s + 2_s$] process.²⁴⁰⁸ However, the available evidence is more consistent with nonconcerted mechanisms involving metal–carbon σ -bonded intermediates, at least in most cases.²⁴⁰⁹ For example, such an intermediate was isolated in the dimerization of norbornadiene, catalyzed by Ir complexes.²⁴¹⁰ Photochemical [$\pi 2 + s 2$]-cycloadditions have also been reported. Visible light mediates cycloaddition in the presence of a Rh catalyst.²⁴¹² Some reverse cyclobutane ring openings can also be catalytically induced (Reaction 18-38).

Thermal cycloadditions leading to four-membered rings can also take place between a cyclopropane ring and an alkene or alkyne²⁴¹³ bearing electron-withdrawing groups.²⁴¹⁴

²³⁹⁷ See Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668.

²³⁹⁸ Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 71–84.

²³⁹⁹ Williams, J.K., Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* **1962**, *84*, 2210.

²⁴⁰⁰ Nishida, S.; Moritani, I.; Teraji, T. *J. Org. Chem.* **1973**, *38*, 1878.

²⁴⁰¹ Nagata, J.; Shirota, Y.; Nogami, T.; Mikawa, H. *Chem. Lett.* **1973**, 1087; Shirota, Y.; Yoshida, K.; Nogami, T.; Mikawa, H. *Chem. Lett.* **1973**, 1271.

²⁴⁰² Canales, E.; Corey, E.J. *J. Am. Chem. Soc.* **2007**, *129*, 12686; Butenschön, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3492; Ishihara, K.; Fushimi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7532.

²⁴⁰³ Ng, S.M.; Bader, S.J.; Snapper, M.L. *J. Am. Chem. Soc.* **2006**, *128*, 7315.

²⁴⁰⁴ Treutwein, J.; Hilt, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6811.

²⁴⁰⁵ Yamazaki, S.; Fujitsuka, H.; Yamabe, S.; Tamura, H. *J. Org. Chem.* **1992**, *57*, 5610.

²⁴⁰⁶ Yoshikawa, S.; Aoki, K.; Kiji, J.; Furukawa, J. *Tetrahedron* **1974**, *30*, 405.

²⁴⁰⁷ See Mango, F.D. *Top. Curr. Chem.* **1974**, *45*, 39; *Tetrahedron Lett.* **1973**, 1509.

²⁴⁰⁸ See Bachrach, S.M.; Gilbert, J.C. *J. Org. Chem.* **2004**, *69*, 6357; Ozkan, I.; Kinal, A. *J. Org. Chem.* **2004**, *69*, 5390.

²⁴⁰⁹ See Grubbs, R.H.; Miyashita, A.; Liu, M.M.; Burk, P.L. *J. Am. Chem. Soc.* **1977**, *99*, 3863.

²⁴¹⁰ Fraser, A.R.; Bird, P.H.; Bezman, S.A.; Shapley, J.R.; White, R.; Osborn, J.A. *J. Am. Chem. Soc.* **1973**, *95*, 597.

²⁴¹¹ See Prinzbach, H.; Sedelmeier, G.; Martin, H. *Angew. Chem. Int. Ed.* **1977**, *16*, 103.

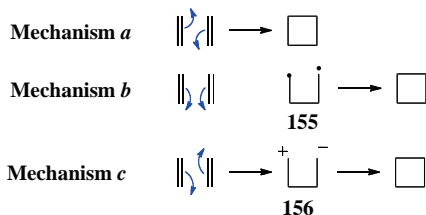
²⁴¹² Ischay, M.A.; Anzovino, M.E.; Du, J.; Yoon, T.P. *J. Am. Chem. Soc.* **2008**, *130*, 12886.

²⁴¹³ Gassman, P.G.; Mansfield, K.T. *J. Am. Chem. Soc.* **1968**, *90*, 1517, 1524.

²⁴¹⁴ For a review, see Gassman, P.G. *Acc. Chem. Res.* **1971**, *4*, 128.

These reactions are $[\pi 2 + {}_s 2]$ -cycloadditions. Ordinary cyclopropanes do not undergo the reaction, but it has been accomplished with strained systems (e.g., bicyclo[1.1.0]butanes²⁴¹⁵ and bicyclo[2.1.0]pentanes). For example, bicyclo[2.1.0]pentane reacts with maleonitrile (or fumaronitrile) to give all three isomers of 2,3-dicyanonorbornane, as well as four other products.²⁴¹⁶ The lack of stereospecificity and the negligible effect of solvent on the rate indicate a diradical mechanism.

If dienes are involved in the reaction, the *Diels–Alder reaction* may compete, although most alkenes react with a diene either entirely by 1,2- or entirely by 1,4-addition. Three mechanisms have been proposed for $[2 + 2]$ -cycloaddition.²⁴¹⁷



Mechanism *a* is a concerted pericyclic process, and mechanisms *b* and *c* are two-step reactions involving, respectively, a diradical (**155**) and a diion (**156**) intermediate. As in Reaction **15-60**, a diradical intermediate must be a singlet. In searching for ways to tell which mechanism is operating in a given case, mechanism *c* is expected to be sensitive to changes in solvent polarity, while mechanisms *a* and *b* should be insensitive. Mechanism *a* is expected to be stereospecific, while mechanisms *b* and *c* probably would not be stereospecific. However, if the second step of these processes takes place very rapidly, before **155** or **156** have a chance to rotate about the newly formed single bond, stereospecificity might be observed. Because of entropy considerations, such rapid ring closure might be more likely here than in a $[4 + 2]$ -cycloaddition.

There is evidence that the reactions can take place by all three mechanisms, depending on the structure of the reactants. A thermal $[\pi 2_s + \pi 2_s]$ mechanism is ruled out for most of these substrates by the orbital symmetry rules, but a $[\pi 2_s + \pi 2_a]$ mechanism is allowed (see above), and there is much evidence that ketenes and certain other linear molecules²⁴¹⁸ in which the steric hindrance to such an approach is minimal can and often do react by this mechanism. In a $[\pi 2_s + \pi 2_a]$ cycloaddition, the molecules must approach each other in such a way (Fig. 15.12*a*) that the HOMO–LUMO overlap requires that the groups of one molecule project *into* the plane of the other. This does not happen with ordinary alkenes,²⁴¹⁹ but if one molecule is a ketene (Fig. 15.12*b*), a group on the carbon of the C=C unit is missing (relative to an alkene) and the $[\pi 2_s + \pi 2_a]$ -reaction can take place.

²⁴¹⁵ Cairncross, A.; Blanchard, E.P. *J. Am. Chem. Soc.* **1966**, 88, 496.

²⁴¹⁶ Gassman, P.G.; Mansfield, K.T.; Murphy, T.J. *J. Am. Chem. Soc.* **1969**, 91, 1684.

²⁴¹⁷ For a review, see Bartlett, P.D. *Q. Rev. Chem. Soc.* **1970**, 24, 473. See Check, C.E.; Gilbert, T.M. *J. Org. Chem.* **2005**, 70, 9828.

²⁴¹⁸ See Gilbert, J.C.; Baze, M.E. *J. Am. Chem. Soc.* **1984**, 106, 1885.

²⁴¹⁹ See Bartlett, P.D.; Cohen, G.M.; Elliott, S.P.; Hummel, K.; Minns, R.A.; Sharts, C.M.; Fukunaga, J.Y. *J. Am. Chem. Soc.* **1972**, 94, 2899.

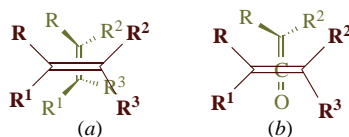
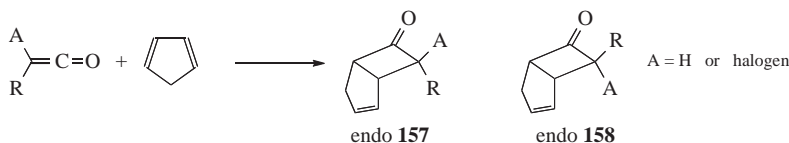


FIG. 15.12. Steric interactions in $[\pi 2_s + \pi 2_s]$ -cycloaddition between (a) two alkene molecules and (b) a ketene and an alkene

Among the evidence²⁴²⁰ for this mechanism²⁴²¹ is the following: (1) the reactions are stereospecific.²⁴²² (2) The isomer that forms is the *more hindered one*. Thus the reaction of methylketene plus cyclopentadiene gave only



the endo product (**157**, A = H, R = CH₃).²⁴²³ Even more remarkably, when haloalkyl ketenes $RXC=C=O$ were treated with cyclopentadiene, the endo/exo ratio of the product (**157**, **158**, A = halogen) actually *increased* substantially when R was changed from Me to *i*Pr to *t*-Bu!²⁴²⁴ One would expect preferential formation of the exo products (**158**) from $[\pi 2_s + \pi 2_s]$ -cycloadditions where the molecules approach each other face-to-face. However, a $[\pi 2_s + \pi 2_a]$ -process leads to endo products because the ketene molecule (which for steric reasons would approach with its smaller group, methyl in the figure, directed toward the alkene) must twist as shown in Fig. 15.13 (*tert*-butyl = larger; methyl = smaller group) in order for the π lobes to interact. This process swings the larger group (*tert*-butyl) into the endo position.²⁴²⁵ The experimental results in which the amount of endo isomer increases with the increasing size of the R group appears to be contrary to what would be expected from steric hindrance considerations (called *masochistic steric effects*), but they are just what is predicted for a $[\pi 2_s + \pi 2_a]$ reaction. (3) There is only moderate polar solvent acceleration.²⁴²⁶ (4) The rate of the reaction is not very sensitive to the presence of electron-withdrawing or electron-donating substituents.²⁴²⁷ Because cycloadditions involving allenes are often stereospecific, it has been suggested that these also take place

²⁴²⁰ Also see Gheorghiu, M.D.; Părvulescu, L.; Drăghici, C.; Elian, M. *Tetrahedron* **1981**, 37 Suppl., 143. See, however, Holder, R.W.; Graf, N.A.; Duesler, E.; Moss, J.C. *J. Am. Chem. Soc.* **1983**, 105, 2929.

²⁴²¹ See, however, Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* **1990**, 112, 1754; Bernardi, F.; Bottoni, A.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* **1990**, 112, 2106; Valentí, E.; Pericàs, M.A.; Moyano, A. *J. Org. Chem.* **1990**, 55, 3582.

²⁴²² Bertrand, M.; Gras, J.L.; Goré, J. *Tetrahedron* **1975**, 31, 857; Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* **1972**, 94, 2870; Huisgen, R.; Mayr, H. *Tetrahedron Lett.* **1975**, 2965, 2969.

²⁴²³ Rey, M.; Roberts, S.; Dieffenbacher, A.; Dreiding, A.S. *Helv. Chim. Acta* **1970**, 53, 417. See Rey, M.; Roberts, S.M.; Dreiding, A.S.; Roussel, A.; Vanlierde, H.; Toppet, S.; Ghosez, L. *Helv. Chim. Acta* **1982**, 65, 703.

²⁴²⁴ Brady, W.T.; Roe Jr., R. *J. Am. Chem. Soc.* **1970**, 92, 4618.

²⁴²⁵ Brook, P.R.; Harrison, J.M.; Duke, A.J. *Chem. Commun.* **1970**, 589

²⁴²⁶ Brady, W.T.; O'Neal, H.R. *J. Org. Chem.* **1967**, 32, 612; Huisgen, R.; Feiler, L.A.; Otto, P. *Tetrahedron Lett.* **1968**, 4485, *Chem. Ber.* **1969**, 102, 3444; Sterk, H. *Z. Naturforsch. Teil B* **1972**, 27, 143.

²⁴²⁷ Isaacs, N.S.; Stanbury, P. *J. Chem. Soc. Perkin Trans. 2*, **1973**, 166.

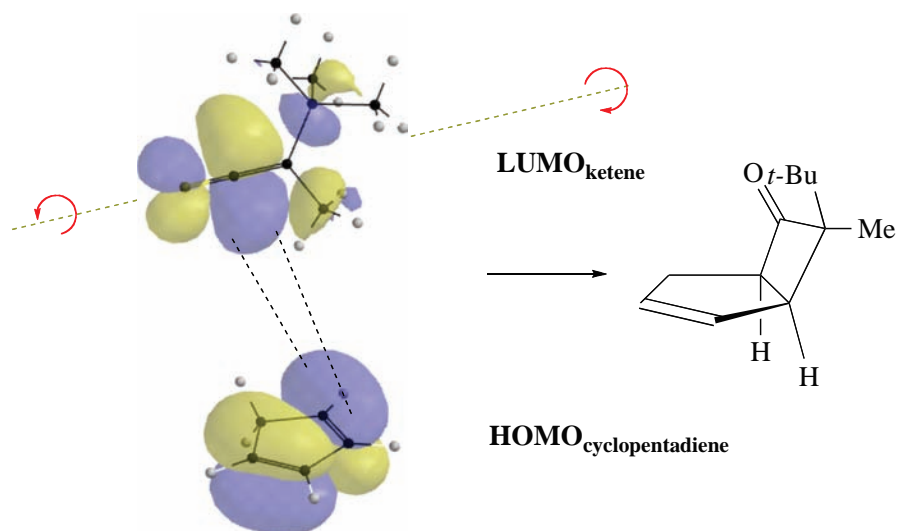
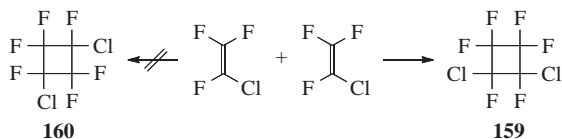


FIG. 15.13. Orbital overlap in the reaction of a ketene with cyclopentadiene. Here S and L represent small and large. [Reproduced from Brook, P.R.; Harrison, J.M.; Duke, A.J. *Chem. Commun.* **1970**, 589 with permission from the Royal Society of Chemistry]

by the $[\pi 2_s + \pi 2_a]$ mechanism,²⁴²⁸ but the evidence in these cases is more consistent with the diradical mechanism *b*.²⁴²⁹

The diradical mechanism *b* is most prominent in the reactions involving fluorinated alkenes.²⁴³⁰ These reactions are generally not stereospecific²⁴³¹ and are insensitive to solvent effects. Further evidence that a diion is not involved is that head-to-head coupling is found when an unsymmetrical molecule is dimerized. Thus dimerization of $F_2C=CFCl$ gives **159**, not **160**. If one pair of electrons moved before the other, the positive end of one molecule would be expected to attack the negative end of the other.²⁴³²



²⁴²⁸ See Baldwin, J.E.; Roy, U.V. *Chem. Commun.* **1969**, 1225; Moore, W.R.; Bach, R.D.; Ozretich, T.M. *J. Am. Chem. Soc.* **1969**, 91, 5918.

²⁴²⁹ Pasto, D.J.; Yang, S.H. *J. Org. Chem.* **1986**, 51, 1676; Dolbier, D.W.; Seabury, M. *J. Am. Chem. Soc.* **1987**, 109, 4393; Dolbier, Jr., W.R.; Weaver, S.L. *J. Org. Chem.* **1990**, 55, 711; Becker, D.; Denekamp, C.; Haddad, N. *Tetrahedron Lett.* **1992**, 33, 827.

²⁴³⁰ See, however, Roberts, D.W. *Tetrahedron* **1985**, 41, 5529.

²⁴³¹ Bartlett, P.D.; Hummel, K.; Elliott, S.P.; Minns, R.A. *J. Am. Chem. Soc.* **1972**, 94, 2898.

²⁴³² See De Cock, C.; Piettre, S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* **1985**, 41, 4183; Doering, W. von E.; Guyton, C.A. *J. Am. Chem. Soc.* **1978**, 100, 3229.

The diion mechanism²⁴³³ *c* has been reported for at least some of the reactions²⁴³⁴ in categories 3 and 4,²⁴³⁵ as well as some ketene dimerizations.²⁴³⁶ The rate of the reaction between 1,2-bis(trifluoromethyl)-1,2-dicyanoethene and ethyl vinyl ether, for example, was strongly influenced by changes in solvent polarity.²⁴³⁷ Some of these reactions are nonstereospecific, but others are stereospecific.²⁴³⁸ As previously indicated, it is likely that in the latter cases the diionic intermediate closes before rotation can take place. Such rapid ring closure is more likely for a diion than for a diradical because of the attraction between the opposite charges. Other evidence for the diion mechanism in these cases is that reaction rates are greatly dependent on the presence of electron-donating and electron-withdrawing groups and that it is possible to trap the diionic intermediates.

Whether a given alkene reacts by the diradical or diion mechanism depends, among other things, on the groups attached to it. For example, phenyl and vinyl groups at the α positions of **155** or **156** help to stabilize a diradical, while donors (e.g., oxygen and nitrogen) favor a diion (they stabilize the positively charged end).²⁴³⁹ A table in Ref. 2439 (see p. 451) shows which mechanism is more likely for [2 + 2]-cycloadditions of various pairs of alkenes.

Thermal cleavage of cyclobutanes²⁴⁴⁰ to give two alkene molecules (*cycloreversion*,²⁴⁴¹ the reverse of [2 + 2]-cycloaddition) operates by the diradical mechanism, and the [$\sigma 2_s + \sigma 2_a$]-pathway has not been found²⁴⁴² (the subscripts σ indicate that σ bonds are involved in this reaction).

In some cases, double bonds add to triple bonds to give cyclobutenes, apparently at about the same rate that they add to double bonds. The addition of triple bonds to triple bonds would give cyclobutadienes, and this has not been observed, except where these rearrange before they can be isolated (see Reaction **15-65**)²⁴⁴³ or in the presence of a suitable coordination compound, so that the cyclobutadiene is produced in the form of a complex (Sec. 2.K.ii).²⁴⁴⁴

Although thermal [2 + 2]-cycloaddition reactions are essentially limited to the cases described above, many (although by no means all) double-bond compounds react *when photochemically excited* (either directly or by a photosensitizer, see Sec. 7.A.vi,

²⁴³³ See Huisgen, R. *Acc. Chem. Res.* **1977**, *10*, 117, 199; Huisgen, R.; Schug, R.; Steiner, G. *Bull. Soc. Chim. Fr.* **1976**, 1813.

²⁴³⁴ See Gompper, R. *Angew. Chem. Int. Ed.* **1969**, *8*, 312.

²⁴³⁵ The reactions of ketenes with enamines are apparently not concerted but take place by the diionic mechanism: Otto, P.; Feiler, L.A.; Huisgen, R. *Angew. Chem. Int. Ed.* **1968**, *7*, 737.

²⁴³⁶ See Moore, H.W.; Wilbur, D.S. *J. Am. Chem. Soc.* **1978**, *100*, 6523.

²⁴³⁷ Proskow, S.; Simmons, H.E.; Cairns, T.L. *J. Am. Chem. Soc.* **1966**, *88*, 5254. See also, Huisgen, R. *Pure Appl. Chem.* **1980**, *52*, 2283.

²⁴³⁸ Huisgen, R.; Steiner, G. *J. Am. Chem. Soc.* **1973**, *95*, 5054, 5055.

²⁴³⁹ Hall Jr., H.K. *Angew. Chem. Int. Ed.* **1983**, *22*, 440.

²⁴⁴⁰ See Frey, H.M. *Adv. Phys. Org. Chem.* **1966**, *4*, 147, see pp. 170–175, 180–183.

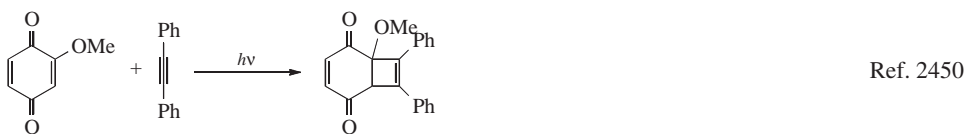
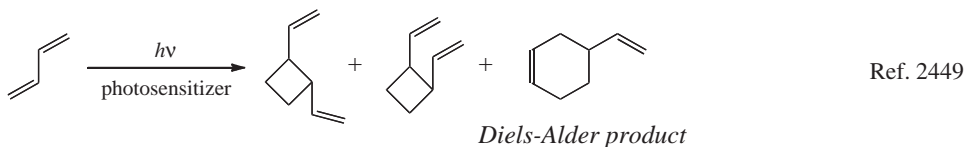
²⁴⁴¹ See Schaumann, E.; Ketcham, R. *Angew. Chem. Int. Ed.* **1982**, *21*, 225. See also, Reddy, G.D.; Wiest, O.; Hudlicky, T.; Schapiro, V.; Gonzalez, D. *J. Org. Chem.* **1999**, *64*, 2860.

²⁴⁴² See Paquette, L.A.; Carmody, M.J. *J. Am. Chem. Soc.* **1976**, *98*, 8175. See however Doering, W. von E.; Roth, W.R.; Breuckmann, R.; Figge, L.; Lennartz, H.; Fessner, W.; Prinzbach, H. *Chem. Ber.* **1988**, *121*, 1.

²⁴⁴³ See Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 435–442.

²⁴⁴⁴ D'Angelo, J.; Ficini, J.; Martinon, S.; Riche, C.; Sevin, A. *J. Organomet. Chem.* **1979**, *177*, 265. See Hogeveen, H.; Kok, D.M. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 2, Wiley, NY, **1983**, pp. 981–1013.

category 5), even if they are not in the above categories.²⁴⁴⁵ Simple alkenes absorb in the far-UV (Sec. 7.A.iii), which is difficult to reach experimentally, although this problem can sometimes be overcome by the use of suitable photosensitizers. The reaction has been applied to simple alkenes²⁴⁴⁶ (especially to strained compounds, e.g., cyclopropenes and cyclobutenes), but more often the double-bond compounds involved are conjugated dienes,²⁴⁴⁷ α,β -unsaturated ketones,²⁴⁴⁸ conjugated acids or acid derivatives, and quinones. Since these compounds, are conjugated, they absorb at longer wavelengths (Sec 7.A.iii). Both dimerizations and mixed additions are common. Some examples follow:



See also, Section 7.A.vii (Reaction 7-9). Photochemical [2 + 2]-cycloadditions can also take place intramolecularly if a molecule has two double bonds that are properly oriented.²⁴⁵¹ The cyclization of the quinone dimer shown above is one example. Other examples are



²⁴⁴⁵ Demuth, M.; Mikhail, G. *Synthesis* **1989**, 145; Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, **1989**, pp. 58–109; Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, 87, 433; Wender, P.A. in Coyle, J. D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, **1986**, pp. 163–188; Schreiber, S.L. *Science* **1985**, 227, 857; Baldwin, S.W. *Org. Photochem.* **1981**, 5, 123; Kricka, L.J.; Ledwith, A. *Synthesis* **1974**, 539; Herndon, W.C. *Top. Curr. Chem.* **1974**, 46, 141; Turro, N.J.; Dalton, J.C.; Weiss, D.S. *Org. Photochem.* **1969**, 2, 1; Trecker, D.J. *Org. Photochem.* **1969**, 2, 63.

²⁴⁴⁶ See Arnold, D.R.; Abraitys, V.Y. *Chem. Commun.* **1967**, 1053; Yamazaki, H.; Cvetanovic, R.J. *J. Am. Chem. Soc.* **1969**, 91, 520.

²⁴⁴⁷ See Dilling, W.L. *Chem. Rev.* **1969**, 69, 845.

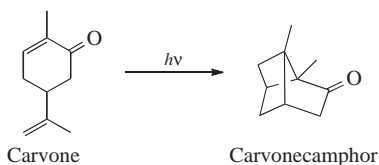
²⁴⁴⁸ Schuster, D.I.; Lem, G.; Kaprinidis, N.A. *Chem. Rev.* **1993**, 93, 3; Cossy, J.; Carrupt, P.; Vogel, P. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 2, Wiley, NY, **1989**, pp. 1369–1565; Weedon, A.C. in Horspool, W.M. *Synthetic Organic Photochemistry* Plenum, NY, **1984**, pp. 61–143; Bauslaugh, P.G. *Synthesis* **1970**, 287; Eaton, P.E. *Acc. Chem. Res.* **1968**, 1, 50; Erickson, J.A.; Kahn, S.D. *Tetrahedron* **1993**, 49, 9699.

²⁴⁴⁹ Liu, R.S.H.; Turro, N.J.; Hammond, G.S. *J. Am. Chem. Soc.* **1965**, 87, 3406; Cundall, R.B.; Griffiths, P.A. *Trans. Faraday Soc.* **1965**, 61, 1968; DeBoer, C.D.; Turro, N.J.; Hammond, G.S. *Org. Synth.* **V**, 528.

²⁴⁵⁰ Pappas, S.P.; Pappas, B.C. *Tetrahedron Lett.* **1967**, 1597.

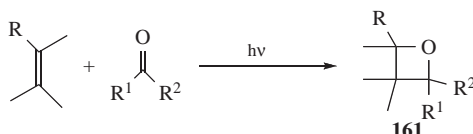
²⁴⁵¹ See Becker, D.; Haddad, N. *Org. Photochem.* **1989**, 10, 1-162; Crimmins, M.T. *Chem. Rev.* **1988**, 88, 1453; Oppolzer, W. *Acc. Chem. Res.* **1982**, 15, 135; Prinzbach, H. *Pure Appl. Chem.* **1968**, 16, 17.

²⁴⁵² Hammond, G.S.; Turro, N.J.; Fischer, A. *J. Am. Chem. Soc.* **1961**, 83, 4674; Dauben, W.G.; Cargill, R.L. *Tetrahedron* **1961**, 15, 197. See also, Cristol, S.J.; Snell, R.L. *J. Am. Chem. Soc.* **1958**, 80, 1950.



Ref. 2453

It is obvious that many molecules can be constructed in this way that would be difficult to make by other procedures. However, attempted cyclizations of this kind are not always successful. In many cases, polymeric or other side products are obtained instead of the desired product.



The photochemical cycloaddition of a carbonyl, generally from an aldehyde or ketone and an alkene, is called the *Paternò-Büchi reaction*.²⁴⁵⁴ This $[2 + 2]$ -cycloaddition gives an oxetane (**161**) and the reaction is believed to proceed via a diradical intermediate. Silyl enol ethers react with aldehydes under nonphotochemical conditions using ZnCl_2 at 25°C or SnCl_4 at -78°C .²⁴⁵⁵

It is possible that some of these photochemical cycloadditions take place by a $[\pi 2_s + \pi 2_s]$ -mechanism, which is of course allowed by orbital symmetry; when and if they do, one of the molecules must be in the excited singlet state (S_1) and the other in the ground state.²⁴⁵⁶ The nonphotosensitized dimerizations of *cis*- and *trans*-2-butene are stereospecific,²⁴⁵⁷ making it likely that the $[\pi 2_s + \pi 2_s]$ -mechanism is operating in these reactions. However, in most cases it is a triplet excited state that reacts with the ground-state molecule; in these cases the diradical (or in certain cases, the diionic) mechanism is taking place.²⁴⁵⁸ In one intramolecular case, the intermediate diradical has been trapped.²⁴⁵⁹ Photosensitized $[2\pi + 2\pi]$ -cycloadditions almost always involve the triplet state, and hence a diradical (or diionic) mechanism.

The photochemical diradical mechanism is not quite the same as the thermal diradical mechanism. In the thermal mechanism, the initially formed diradical must be a singlet, but in the photochemical process a triplet excited state is adding to a ground state, which is of course a singlet. Thus, in order to conserve spin,²⁴⁶⁰ the initially formed diradical must be a triplet; that is, the two electrons must have the same spin. Consequently, the second, or ring closing, step of the mechanism cannot take place at once, because a new bond cannot form

²⁴⁵³ Ciamician, G.; Silber, P. *Ber.* **1908**, *41*, 1928; Büchi, G.; Goldman, I.M. *J. Am. Chem. Soc.* **1957**, *79*, 4741.

²⁴⁵⁴ Paternò, E.; Chieffi, C. *Gazz. Chim. Ital.* **1909**, *39*, 341; Büchi, G.; Inman, C.G.; Lipinsky, E.S. *J. Am. Chem. Soc.* **1954**, *76*, 4327. See García-Expósito, E.; Bearpark, M.J.; Ortuño, R.M.; Robb, M.A.; Branchadell, V. *J. Org. Chem.* **2002**, *67*, 6070.

²⁴⁵⁵ Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* **1999**, *1*, 1197.

²⁴⁵⁶ Reactions between two excited molecules are extremely rare.

²⁴⁵⁷ Yamazaki, H.; Cvetanovic, R.J.; Irwin, R.S. *J. Am. Chem. Soc.* **1976**, *98*, 2198; Lewis, F.D.; Kojima, M. *J. Am. Chem. Soc.* **1988**, *110*, 8660.

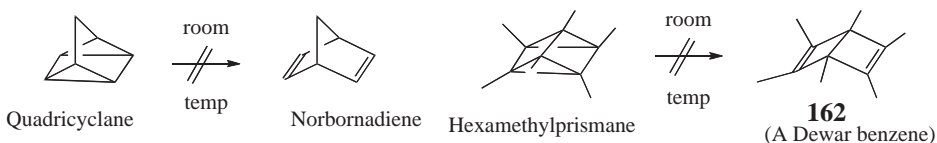
²⁴⁵⁸ Maradyn, D.J.; Weedon, A.C. *Tetrahedron Lett.* **1994**, *35*, 8107.

²⁴⁵⁹ Becker, D.; Haddad, N.; Sahali, Y. *Tetrahedron Lett.* **1989**, *30*, 2661.

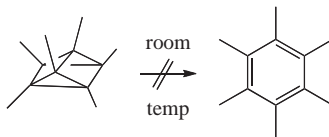
²⁴⁶⁰ This is an example of the *Wigner spin conservation rule* (Sec. 7.A.vi, category 5). Note that spin conservation is something entirely different from symmetry conservation.

from a combination of two electrons with the same spin, and the diradical has a reasonably long lifetime before collisions with molecules in the environment allow a spin inversion to take place and the diradical to cyclize. The prediction is nonstereospecificity, and that is what is found.²⁴⁶¹ It has been believed that at least some [2 + 2] photocycloadditions take place by way of exciplex intermediates²⁴⁶² [an *exciplex*²⁴⁶³ is an excited EDA complex (Sec. 7.A.vii) that is dissociated in the ground state; in this case one double bond is the donor and the other is the acceptor], but there is evidence against this.²⁴⁶⁴

In Reaction **15-60**, the principle of conservation of orbital symmetry was used to explain why certain reactions take place readily and others do not. The orbital-symmetry principle can also explain why certain molecules are stable although highly strained. Quadricyclane and hexamethylprismane²⁴⁶⁵ are thermodynamically much less stable (because they are much more strained), for example, than their corresponding isomeric dienes, norbornadiene and



hexamethylbicyclo[2.2.0]hexadiene (**162**).²⁴⁶⁶ Yet the former two compounds can be kept indefinitely at room temperature, although in the absence of orbital-symmetry considerations it is not easy to understand why the electrons simply do not move over to give the more stable diene isomers. The reason is that both these reactions involve the conversion of a cyclobutane ring to a pair of double bonds (a $s_2 + s_2$ process) and, as seen previously, a thermal process of this sort is forbidden by the *Woodward–Hoffmann rules*. The process is allowed photochemically, so both quadricyclane and hexamethylprismane are photochemically converted to the respective dienes at room temperature or below.²⁴⁶⁷ It is also possible to conceive of simple bond rearrangements whereby hexamethylprismane is converted to hexamethylbenzene (as shown below), which of course is far more stable than either hexamethylprismane or **162**. It has been calculated that hexamethylbenzene is at least 90 kcal mol^{-1} (380 kJ mol^{-1}) more stable than hexamethylprismane. A correlation diagram for this reaction²⁴⁶⁸ discloses that it too is a symmetry-forbidden process. All three of these “forbidden” reactions do take place when the compounds are heated, but the diradical mechanism is likely under these conditions.²⁴⁶⁸



²⁴⁶¹ See, for example, Kramer, B.D.; Bartlett, P.D. *J. Am. Chem. Soc.* **1972**, *94*, 3934.

²⁴⁶² See Caldwell, R.A.; Creed, D. *Acc. Chem. Res.* **1980**, *13*, 45; Mattes, S.L.; Farid, S. *Acc. Chem. Res.* **1982**, *15*, 80; Swapna, G.V.T.; Lakshmi, A.B.; Rao, J.M.; Kunwar, A.C. *Tetrahedron* **1989**, *45*, 1777.

²⁴⁶³ For a review of exciplexes, see Davidson, R.S. *Adv. Phys. Org. Chem.* **1983**, *19*, 1–130.

²⁴⁶⁴ Schuster, D.I.; Heibel, G.E.; Brown, P.B.; Turro, N.J.; Kumar, C.V. *J. Am. Chem. Soc.* **1988**, *110*, 8261.

²⁴⁶⁵ See Schäfer, W.; Criegee, R.; Askani, R.; Grüner, H. *Angew. Chem. Int. Ed.* **1967**, *6*, 78.

²⁴⁶⁶ See Schäfer, W.; Hellmann, H. *Angew. Chem. Int. Ed.* **1967**, *6*, 518.

²⁴⁶⁷ With transition metal catalysts: Landis, M.E.; Gremaud, D.; Patrick, T.B. *Tetrahedron Lett.* **1982**, *23*, 375; Maruyama, K.; Tamiaki, H. *Chem. Lett.* **1987**, 683.

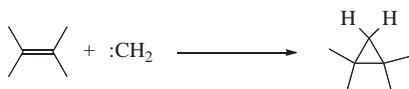
²⁴⁶⁸ See Oth, J.F.M. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1185.

Bicyclo[2.2.0]hexadienes and prismanes are *valence isomers* of benzenes.²⁴⁶⁹ These compounds actually have the structures that were proposed for benzenes in the nineteenth century. Prismanes have the Ladenburg formula, and bicyclo[2.2.0]hexadienes have the *Dewar* formula. Because of this, bicyclo[2.2.0]hexadiene is often called *Dewar benzene*. In the paragraph prior to Section 2.A, it was mentioned that Dewar formulas are canonical forms (although not very important) of benzenes. Yet they also exist as separate compounds in which the positions of the nuclei are different from those of benzenes.

OS V, 54, 235, 277, 297, 370, 393, 424, 459, 528; VI, 378, 571, 962, 1002, 1024, 1037; VII, 177, 256, 315; VIII, 82, 116, 306, 377; IX, 28, 275; 80, 160. For the reverse reaction, see OS V, 734.

15-64 The Addition of Carbenes and Carbenoids to Double and Triple Bonds

epi-Methylene-addition



Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives by what can be considered as a formal [1 + 2]-cycloaddition.²⁴⁷⁰ Many carbene derivatives [e.g., PhCH, ROCH,²⁴⁷¹ Me₂C=C, and C(CN)₂] have been added to double bonds, but the reaction is often performed with CH₂ itself, with halo and dihalocarbenes,²⁴⁷² and with carbalkoxycarbenes²⁴⁷³ (generated from diazoacetic esters). Alkylcarbenes (HCR) have been added to alkenes,²⁴⁷⁴ but more often these rearrange to give alkenes (Sec. 5.D.ii, category 4). The carbene can be generated in any of the ways normally used (Sec. 5.D.ii). However, most reactions in which a cyclopropane is formed by treatment of an alkene with a carbene “precursor” do not actually involve free carbene intermediates. In some cases, it is certain that free carbenes are not involved, and in other cases there is doubt. Because of this, the term *carbene transfer* is often used to cover all reactions in which a double bond is converted to a cyclopropane, whether a carbene or a carbenoid (Sec. 5.D.ii) is actually involved.

Carbene itself (:CH₂) is extremely reactive and gives many side reactions, especially insertion reactions (12-21), which greatly reduce yields. This competition is also true with Rh catalyzed diazoalkane cyclopropanations²⁴⁷⁵ (see below). When: CH₂ must be added for preparative purposes, a free carbene is not used, but the *Simmons–Smith procedure*

²⁴⁶⁹ Kobayashi, Y.; Kumadaki, I. *Adv. Heterocycl. Chem.* **1982**, 31, 169; *Acc. Chem. Res.* **1981**, 14, 76; van Tamelen, E.E. *Acc. Chem. Res.* **1972**, 5, 186; *Angew. Chem. Int. Ed.* **1965**, 4, 738; Schäfer, W.; Hellmann, H. *Angew. Chem. Int. Ed.* **1967**, 6, 518.

²⁴⁷⁰ See Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, Wiley, NY, **1987**, the reviews by Tsuji, T.; Nishida, S. pt. 1, pp. 307–373; Verhé, R.; De Kimpe, N. pt. 1, pp. 445–564; Marchand, A.P. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, pt. 1, Wiley, NY, **1977**, pp. 534–607, 625–635; Kirmse, W. *Carbene Chemistry* 2nd ed.; Academic Press, NY, **1971**, pp. 85–122, 267–406. For a review of certain intramolecular additions, see Burke, S.D.; Grieco, P.A. *Org. React.* **1979**, 26, 361. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 135–153.

²⁴⁷¹ See Schöllkopf, U. *Angew. Chem. Int. Ed.* **1968**, 7, 588.

²⁴⁷² See Parham, W.E.; Schweizer, E.E. *Org. React.* **1963**, 13, 55.

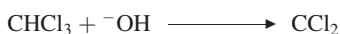
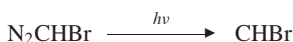
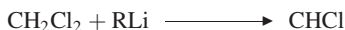
²⁴⁷³ See Dave, V.; Warnhoff, E.W. *Org. React.* **1970**, 18, 217.

²⁴⁷⁴ See Frey, H.M. *J. Chem. Soc.* **1962**, 2293.

²⁴⁷⁵ Doyle, M.P.; Phillips, I.M. *Tetrahedron Lett.* **2001**, 42, 3155. For a review, see Merlic, C.A.; Zechman, A.L. *Synthesis* **2003**, 1137.

(see **167**) or some other method that does not involve free carbenes is employed instead. Halocarbenes are less active than carbenes, and this reaction proceeds quite well, since insertion reactions do not interfere.²⁴⁷⁶ Vinyldiazolactone is a vinylcarbene precursor for a reaction with alkenes to give spirolactones.²⁴⁷⁷

The absolute rate constant for addition of selected alkoxychlorocarbene to butenes has been measured to range from 330 to $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.²⁴⁷⁸ Both entropy and enthalpy play a role in addition of some carbenes.²⁴⁷⁹ Shown are a few of the many ways²⁴⁸⁰ in which halocarbenes or carbenoids are generated,²⁴⁸¹ and most involve formal elimination (for the first two steps of the S_N1cB mechanism, see Sec. 10.G.iii):



The reaction between CHCl_3 and HO^- is often carried out under phase-transfer conditions.²⁴⁸⁵ It has been shown that the reaction between PhCHCl_2 and $t\text{-BuOK}$ produces a carbenoid, but when the reaction is run in the presence of a crown ether, the carbene $[\text{Ph}(\text{Cl})\text{C}:]$ is formed instead.²⁴⁸⁶ The reaction of iodoform and CrCl_2 leads to iodocyclopropanes upon reaction with alkenes.²⁴⁸⁷ Dihalocyclopropanes are very useful compounds²⁴⁸⁸ that can be reduced to cyclopropanes, treated with Mg or Na to give allenes (Reaction **18-3**), or converted to a number of other products.

²⁴⁷⁶ Moss, R.A. *Acc. Chem. Res.* **1989**, 22, 15; Kostikov, R.R.; Molchanov, A.P.; Khlebnikov, A.F. *Russ. Chem. Rev.* **1989**, 58, 654.

²⁴⁷⁷ Bykowski, D.; Wu, K.-H.; Doyle, M.P. *J. Am. Chem. Soc.* **2006**, 128, 16038.

²⁴⁷⁸ Moss, R.A.; Ge, C.-S.; Wlostowska, J.; Jang, E.G.; Jefferson, E.A.; Fan, H. *Tetrahedron Lett.* **1995**, 36, 3083.

²⁴⁷⁹ Moss, R.A.; Wang, L.; Zhang, M.; Skalit, C.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **2008**, 130, 5634.

²⁴⁸⁰ Seyferth, D.; Haas, C.K.; Dagani, D. *J. Organomet. Chem.* **1976**, 104, 9.

²⁴⁸¹ See also Kirmse, W. *Carbene Chemistry* 2nd ed., Academic Press, NY, **1971**, pp. 313–319; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 135–143.

²⁴⁸² See Seyferth, D. *Acc. Chem. Res.* **1972**, 5, 65; Larock, R.C. *Organomercurcury Compounds in Organic Synthesis* Springer, NY, **1985**, pp. 341–380.

²⁴⁸³ Seyferth, D. in Moss, R.A.; Jones, Jr., M. *Carbenes*, Vol. 2, Wiley, NY, **1975**, pp. 101–158; Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, **1969**, pp. 237–270.

²⁴⁸⁴ Léonel, E.; Paugam, J.P.; Condon-Gueugnot, S.; Nédélec, Y.-Y. *Tetrahedron* **1998**, 54, 3207.

²⁴⁸⁵ See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis* Academic Press, NY, **1978**, pp. 224–268; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, **1977**, pp. 18–43, 58–62. For a discussion of the mechanism, see Gol'dberg, Yu.Sh.; Shimanskaya, M.V. *J. Org. Chem. USSR* **1984**, 20, 1212.

²⁴⁸⁶ Moss, R.A.; Lawrynowicz, W. *J. Org. Chem.* **1984**, 49, 3828.

²⁴⁸⁷ Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R. *J. Am. Chem. Soc.* **2003**, 125, 12990.

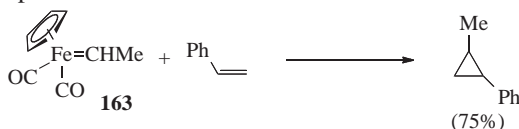
²⁴⁸⁸ Banwell, M.G.; Reum, M.E. *Adv. Strain Org. Chem.* **1991**, 1, 19–64; Kostikov, R.R.; Molchanov, A.P.; Hopf, H. *Top. Curr. Chem.* **1990**, 155, 41–80.

Alkenes of all types can be converted to cyclopropane derivatives by this reaction, but difficulty may be encountered with sterically hindered ones.²⁴⁸⁹ Even tetracyanoethylene, which responds very poorly to electrophilic attack, gives cyclopropane derivatives with carbenes.²⁴⁹⁰ Conjugated dienes give 1,2-addition to give a vinylcyclopropane.²⁴⁹¹ Addition of a second molar equivalent gives bicyclopentyl derivatives.²⁴⁹² 1,4-Addition is rare but has been reported in certain cases.²⁴⁹³ Carbene adds to ketene to give cyclopropanone.²⁴⁹⁴ Allenes react with carbenes to give cyclopropanes with exocyclic unsaturation.²⁴⁹⁵



A second equivalent gives spiropentanes. In fact, any size ring with an exocyclic double bond can be converted by a carbene to a spiro compound.²⁴⁹⁶

Free carbenes can also be avoided by using transition metal–carbene complexes ($L_nM=CRR'$, L = a ligand, M = a metal),²⁴⁹⁷ which add the group CRR' to double bonds.²⁴⁹⁸ An example is the reaction of iron carbene (**163**).²⁴⁹⁹ These complexes can be isolated in some cases; in others they are generated *in situ* from appropriate precursors, of which diazo compounds are among the most important. Chromium complexes have been used for the cyclopropanation of alkenes.²⁵⁰⁰



Diazo compounds, including CH_2N_2 and other diazoalkanes, react with metals or metal salts (Cu, Pd,²⁵⁰¹ Ag,²⁵⁰² La,²⁵⁰³ and Rh²⁵⁰⁴ are commonly used) to give the carbene complexes that add CRR' to double bonds.²⁵⁰⁵ Polymer-supported benzenesulfonyl azides

²⁴⁸⁹ Dehmlow, E.V.; Eulenberger, A. *Liebigs Ann. Chem.* **1979**, 1112.

²⁴⁹⁰ Cairns, T.L.; McKusick, B.C. *Angew. Chem.* **1961**, 73, 520.

²⁴⁹¹ Woodworth, R.C.; Skell, P.S. *J. Am. Chem. Soc.* **1957**, 79, 2542.

²⁴⁹² See Skattebøl, L. *J. Org. Chem.* **1964**, 29, 2951.

²⁴⁹³ See Hudlicky, T.; Seoane, G.; Price, J.D.; Gadamasetti, K.G. *Synlett* **1990**, 433; Lambert, J.B.; Ziemnicka-Merchant, B.T. *J. Org. Chem.* **1990**, 55, 3460.

²⁴⁹⁴ Rothgery, E.F.; Holt, R.J.; McGee Jr., H.A. *J. Am. Chem. Soc.* **1975**, 97, 4971; Wasserman, H.H.; Berdahl, D. R.; Lu, T. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, Wiley, NY, **1987**, pt. 2, pp. 1455–1532.

²⁴⁹⁵ Landor, S.R. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, **1982**, pp. 351–360; Binger, P.; Büch, H.M. *Top. Curr. Chem.* **1987**, 135, 77.

²⁴⁹⁶ See Krapcho, A.P. *Synthesis* **1978**, 77–126.

²⁴⁹⁷ Doyle, M.P.; McKervy, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, NY, **1998**.

²⁴⁹⁸ See Helquist, P. *Adv. Met.-Org. Chem.* **1991**, 2, 143; Brookhart, M.; Studabaker, W.B. *Chem. Rev.* **1987**, 87, 411; Syatkovskii, A.I.; Babitskii, B.D. *Russ. Chem. Rev.* **1984**, 53, 672.

²⁴⁹⁹ Brookhart, M.; Tucker, J.R.; Husk, G.R. *J. Am. Chem. Soc.* **1983**, 105, 258.

²⁵⁰⁰ Barluenga, J.; Aznar, F.; Gutiérrez, I.; García-Granda, S.; Llorca-Baragaño, M.A. *Org. Lett.* **2002**, 4, 4233.

²⁵⁰¹ Beaufort, L.; Demonceau, A.; Noels, A.F. *Tetrahedron* **2005**, 61, 9025. Also see Rodríguez-García, C.; Oliva, A.; Ortuño, R.M.; Branchadell, V. *J. Am. Chem. Soc.* **2001**, 123, 6157.

²⁵⁰² Thompson, J.L.; Davies, H.M.L. *J. Am. Chem. Soc.* **2007**, 129, 6090.

²⁵⁰³ Nishiyama, Y.; Tanimizu, H.; Tomita, T. *Tetrahedron Lett.* **2007**, 48, 6405,

²⁵⁰⁴ See Panne, P.; DeAngelis, A.; Fox, J.M. *Org. Lett.* **2008**, 10, 2987.

²⁵⁰⁵ See Adams, J.; Spero, D.M. *Tetrahedron* **1991**, 47, 1765; Maas, G. *Top. Curr. Chem.* **1987**, 137, 75; Doyle, M.P. *Chem. Rev.* **1986**, 86, 919; *Acc. Chem. Res.* **1986**, 19, 348; Heck, R.F. *Palladium Reagents in Organic Synthesis* Academic Press, NY, **1985**, pp. 401–407; Wulfsberg, D.S.; Poling, B. *React. Intermed. (Plenum)* **1980**, 1, 321; Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* **1966**, 7, 128.

have been developed as a safe diazo-transfer reagent.²⁵⁰⁶ Diazoketones and diazoesters react with alkenes to give the cyclopropane derivative, usually with a transition metal catalyst (e.g., a Cu complex).²⁵⁰⁷ The Ru catalyst reaction of diazoesters with an alkyne gives a cyclopropene.²⁵⁰⁸ An X-ray structure of an Os catalyst intermediate has been determined.²⁵⁰⁹ Electron-rich alkenes react faster than simple alkenes.²⁵¹⁰

Asymmetric cyclopropanation reactions are a growing area of interest,²⁵¹¹ and chiral complexes have been used for enantioselective cyclopropane synthesis.²⁵¹² Decomposition of diazoalkanes in the presence of chiral Rh²⁵¹³ Cu,²⁵¹⁴ Ir,²⁵¹⁵ Co,²⁵¹⁶ Au,²⁵¹⁷ or Ru²⁵¹⁸ complexes leads to optically active cyclopropanes. Diazosulfonate esters have been used in asymmetric cyclopropanations.²⁵¹⁹ The use of chiral additives or auxiliaries with a metal complex also leads to cyclopropanes enantioselectively.²⁵²⁰ An important chiral species is Rh₂(S-DOSP)₄,²⁵²¹ which leads to cyclopropanes with excellent enantioselectivity in carbene cyclopropanation reactions.²⁵²² Chiral organocatalysts have been used.²⁵²³ The Cu catalyzed diazoester cyclopropanation was reported in an ionic liquid.²⁵²⁴ Phosphonate esters have been incorporated into the diazo compound.²⁵²⁵ *Fischer carbene* compounds (see Reaction **15-58**) react with enolate anions to

²⁵⁰⁶ Green, G.M.; Peet, N.P.; Metz, W.A. *J. Org. Chem.* **2001**, *66*, 2509.

²⁵⁰⁷ Díaz-Requejo, M.M.; Belderráin, T.R.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* **2001**, *123*, 3167. See Bühl, M.; Terstegen, F.; Löffler, F.; Meynhardt, B.; Kierse, S.; Müller, M.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* **2001**, 2151.

²⁵⁰⁸ See Panne, P.; Fox, J.M. *J. Am. Chem. Soc.* **2007**, *129*, 22.

²⁵⁰⁹ Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2001**, *123*, 4843.

²⁵¹⁰ See Davies, H.M.L.; Xiang, B.; Kong, N.; Stafford, D.G. *J. Am. Chem. Soc.* **2001**, *123*, 7461.

²⁵¹¹ Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.

²⁵¹² Singh, V.K.; DattaGupta, A.; Sekar, G. *Synthesis* **1997**, 137; Davies, H.M.L.; Bruzinski, P.R.; Fall, M.J. *Tetrahedron Lett.* **1996**, *37*, 4133.

²⁵¹³ Davies, H.M.L.; Rusiniak, L. *Tetrahedron Lett.* **1998**, *39*, 8811; Haddad, N.; Galili, N. *Tetrahedron Asymmetry* **1997**, *8*, 3367; Ichianagi, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* **1997**, *53*, 9599; Fukuda, T.; Katsuki, T. *Tetrahedron* **1997**, *53*, 7201.

²⁵¹⁴ Bayardon, J.; Holczknecht, O.; Pozzi, G.; Sinou, D. *Tetrahedron Asymmetry* **2006**, *17*, 1568.

²⁵¹⁵ Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 10327.

²⁵¹⁶ Chen, Y.; Ruppel, J.V.; Zhang, X.P. *J. Am. Chem. Soc.* **2007**, *129*, 12074; Doyle, M.P. *Angew. Chem. Int. Ed.* **2009**, *48*, 850.

²⁵¹⁷ Prieto, A.; Fructos, M.R.; Díaz-Requejo, M.M.; Pérez, P.J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A.M. *Tetrahedron* **2009**, *65*, 1790.

²⁵¹⁸ Iwasa, S.; Takezawa, F.; Tuchiya, Y.; Nishiyama, H. *Chem. Commun.* **2001**, 59. For a discussion of the mechanism, see Oxgaard, J.; Goddard III, W.A. *J. Am. Chem. Soc.* **2004**, *126*, 442.

²⁵¹⁹ Ye, T.; Zhou, C. *New J. Chem.* **2005**, *29*, 1159.

²⁵²⁰ Ferreira, V.F.; Leão, R.A.C.; da Silva, F. de C.; Pinheiro, S.; Lhoste, P.; Sinou, D. *Tetrahedron Asymmetry* **2007**, *18*, 1217; Miller, J.A.; Gross, B.A.; Zhuravel, M.A.; Jin, W.; Nguyen, S.B.T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3885.

²⁵²¹ Doyle, M.P. *Pure Appl. Chem.* **1998**, *70* 1123; Davies, H.M.L.; Hansen, T.; Churchill, M.R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. See also, Davies, H.M.L.; Lee, G.H. *Org. Lett.* **2004**, *6*, 2117.

²⁵²² Davies, H.M.L.; Townsend, R.J. *J. Org. Chem.* **2001**, *66*, 6595.

²⁵²³ Johansson, C.C.C.; Bremeyer, N.; Ley, S.V.; Owen, D.R.; Smith, S.C.; Gaunt, M.J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6024.

²⁵²⁴ Fraile, J.M.; García, J.I.; Herrerías, C.I.; Mayoral, J.A.; Carrié, D.; Vaultier, M. *Tetrahedron Asymmetry* **2001**, *12*, 1891.

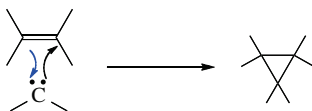
²⁵²⁵ Ferrand, Y.; Le Maux, P.; Simonneaux, G. *Org. Lett.* **2004**, *6*, 3211.

give cyclopropane derivatives.²⁵²⁶ A Cr promoted cyclopropanation of conjugated amides has been reported.²⁵²⁷

Asymmetric, intramolecular cyclopropanation reactions have been reported.²⁵²⁸ Note that the reaction of a diazoester with a chiral dirhodium catalyst leads to β -lactones with modest enantioselectivity.²⁵²⁹

Triple-bond compounds²⁵³⁰ react with carbenes to give cyclopropenes, except that in the case of acetylene itself, the cyclopropenes first formed cannot be isolated because they rearrange to allenes.²⁵³¹ Cyclopropenones (Sec. 2.K.i) are obtained by hydrolysis of dihalocyclopropenes.²⁵³²

Most carbenes are electrophilic, and, in accord with this, electron-donating substituents on the alkene increase the rate of the reaction, and electron-withdrawing groups decrease it,²⁵³³ although the range of relative rates is not very great.²⁵³⁴ As discussed in Section 5.D.i, carbenes in the singlet state, which is the most common state, react stereospecifically and syn,²⁵³⁵ probably by a one-step mechanism,²⁵³⁶ similar to mechanism *a* of Reactions **15-60** and **15-63**:



Infrared spectra of a carbene and the cyclopropane product have been observed in an Ar matrix at 12–45 K.²⁵³⁷ Carbenes in the triplet state react nonstereospecifically,²⁵³⁸ probably by a diradical mechanism, similar to mechanism *b* of Reactions **15-49** and **15-63**:



For carbenes or carbenoids of the type $R-C-R'$ there is another aspect of stereochemistry.²⁵³⁹ When these species are added to all but symmetrical alkenes, two isomers

²⁵²⁶ Barluenga, J.; Suero, M.G.; Pérez-Sánchez, I.; Flórez, J. *J. Am. Chem. Soc.* **2008**, *130*, 2708.

²⁵²⁷ Concellón, J.M.; Rodríguez-Solla, H.; Méjica, C.; Blanco, E.G.; García-Granda, S.; Diaz, M.R. *Org. Lett.* **2008**, *10*, 349.

²⁵²⁸ See Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860.

²⁵²⁹ Doyle, M.P.; May, E.J. *Synlett* **2001**, 967.

²⁵³⁰ See Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 427–434; Closs, G.L. *Adv. Alicyclic Chem.* **1966**, *1*, 53–127, see pp. 58–65.

²⁵³¹ Frey, H.M. *Chem. Ind. (London)* **1960**, 1266.

²⁵³² Vol'pin, M.E.; Koreshkov, Yu.D.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1959**, 535.

²⁵³³ Mitsch, R.A.; Rodgers, A.S. *Int. J. Chem. Kinet.* **1969**, *1*, 439.

²⁵³⁴ Moss, R.A. in Jones Jr., M.; Moss, R.A. *Carbenes*, Vol. 1, Wiley, NY, **1973**, pp. 153–304. See also, Cox, D.P.; Gould, I.R.; Hacker, N.P.; Moss, R.A.; Turro, N.J. *Tetrahedron Lett.* **1983**, *24*, 5313.

²⁵³⁵ Ando, W.; Hendrick, M.E.; Kulczycki, Jr., A.; Howley, P.M.; Hummel, K.F.; Malament, D.S. *J. Am. Chem. Soc.* **1972**, *94*, 7469.

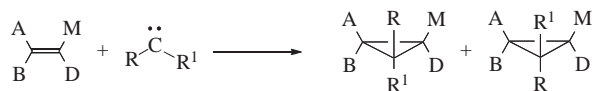
²⁵³⁶ See Giese, B.; Lee, W.; Neumann, C. *Angew. Chem. Int. Ed.* **1982**, *21*, 310.

²⁵³⁷ Nefedov, O.M.; Zuev, P.S.; Maltsev, A.K.; Tomilov, Y.V. *Tetrahedron Lett.* **1989**, *30*, 763.

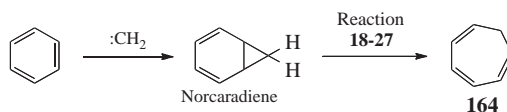
²⁵³⁸ Skell, P.S.; Klebe, J. *J. Am. Chem. Soc.* **1960**, *82*, 247. See also, Jones, Jr., M.; Tortorelli, V.J.; Gaspar, P.P.; Lambert, J.B. *Tetrahedron Lett.* **1978**, 4257.

²⁵³⁹ Moss, R.A. *Sel. Org. Transform.*, **1970**, *1*, 35–88; Closs, G.L. *Top Stereochem.* **1968**, *3*, 193–235. For a discussion of enantioselectivity in this reaction, see Nakamura, A. *Pure Appl. Chem.* **1978**, *50*, 37.

are possible, even if the four groups originally on the double-bond carbons maintain their configurations:



Which isomer is predominantly formed depends on R, R', and on the method by which the carbene or carbenoid is generated. Most studies have been carried out on monosubstituted species (R' = H), and in these studies it is found that aryl groups generally prefer the more substituted side (syn addition) while carbethoxy groups usually show antistereoselectivity. When R = halogen, free halocarbenes show little or no stereochemical preference, while halocarbenoids exhibit a preference for syn addition. Beyond this, it is difficult to make simple generalizations.



Carbenes are so reactive that they add to the “double bonds” of aromatic rings.²⁵⁴⁰ The products are usually unstable and rearrange to give ring expansion. Carbene reacts with benzene to give cycloheptatriene (**164**),²⁵⁴¹ but not all carbenes are reactive enough to add to benzene. The norcaradiene intermediate cannot be isolated in this case²⁵⁴² (it undergoes an electrocyclic rearrangement, Reaction **18-27**), although certain substituted norcaradienes, [e.g., the product of addition of $\text{:C}(\text{CN})_2$ to benzene],²⁵⁴³ have been isolated.²⁵⁴⁴ With :CH_2 , insertion is a major side reaction, and, for example, benzene gives toluene as well as cycloheptatriene. A method of adding :CH_2 to benzene rings without the use of free carbene is the catalytic decomposition of diazomethane (CH_2N_2) in the aromatic compound as a solvent with CuCl or CuBr.²⁵⁴⁵ By this method, better yields of cycloheptatrienes are obtained without insertion of side products. *Picosecond optical grating calorimetry* has been used to investigate the photochemical decomposition of diazomethane in benzene, and it appears that a transient is formed that is consistent with a weak complex between singlet methylene and benzene.²⁵⁴⁶ Chlorocarbene (:CHCl) is active enough to add to benzene, but dihalocarbenes do not add to benzene or toluene, only to rings with greater electron density. Pyrroles and indoles can be expanded, respectively, to pyridines and quinolines by treatment with halocarbenes²⁵⁴⁷ via the initially formed adduct **165** in the case of the indole. In such cases, a side reaction that sometimes occurs is expansion of the *six-membered* ring. Ring

²⁵⁴⁰ See Giese, C.M.; Hadad, C.M. *J. Org. Chem.* **2002**, 67, 2532.

²⁵⁴¹ Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* **1951**, 75, 297.

²⁵⁴² It has been detected by UV spectroscopy: Rubin, M.B. *J. Am. Chem. Soc.* **1981**, 103, 7791.

²⁵⁴³ Ciganek, E. *J. Am. Chem. Soc.* **1967**, 89, 1454.

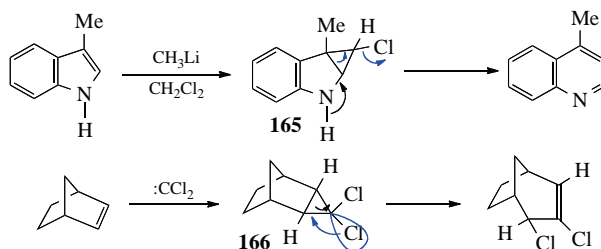
²⁵⁴⁴ See Kawase, T.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* **1987**, 26, 559.

²⁵⁴⁵ Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* **1961**, 650, 1; Müller, E.; Fricke, H. *Liebigs Ann. Chem.* **1963**, 661, 38; Müller, E.; Kessler, H.; Fricke, H.; Kiedaisch, W. *Liebigs Ann. Chem.* **1961**, 675, 63.

²⁵⁴⁶ Khan, M.I.; Goodman, J.L. *J. Am. Chem. Soc.* **1995**, 117, 6635.

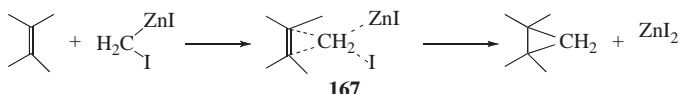
²⁵⁴⁷ See Rees, C.W.; Smithen, C.E. *Adv. Heterocycl. Chem.* **1964**, 3, 57–78.

expansion can occur even with nonaromatic compounds, when the driving force is supplied by relief of strain (see Reaction 166).²⁵⁴⁸



As previously mentioned, free carbene is not very useful for additions to double bonds since it gives too many side products. The *Simmons–Smith procedure* accomplishes the same result without a free carbene intermediate and without insertion of side products.²⁵⁴⁹ This is known as a *carbenoid* reaction. Intramolecular variations are known.²⁵⁵⁰ This procedure involves treatment of the double-bond compound with CH_2I_2 and a $\text{Zn}—\text{Cu}$ couple and leads to cyclopropane derivatives in good yields.²⁵⁵¹ The $\text{Zn}—\text{Cu}$ couple can be prepared in several ways,²⁵⁵² and heating Zn dust with CuCl in ether under nitrogen²⁵⁵³ is particularly convenient. The reaction has also been done with unactivated Zn and ultrasound.²⁵⁵⁴ When TiCl_4 is used along with Zn and CuCl , CH_2I_2 can be replaced by the cheaper CH_2Br_2 .²⁵⁵⁵

The actual attacking species is an organozinc intermediate, probably $(\text{ICH}_2)_2\text{Zn} \cdot \text{ZnI}_2$, which is stable enough for isolable solutions.²⁵⁵⁶ An X-ray crystallographic investigation of the intermediate, complexed with a diether, has been reported.²⁵⁵⁷ The addition is stereospecifically syn, and a concerted mechanism²⁵⁵⁸ is likely, perhaps involving **167**.²⁵⁵⁹ An iodomethylzinc phosphate has also been used for cyclopropanation reactions.²⁵⁶⁰ Diiodomethane gives cyclopropanes in a reaction mediated by indium.²⁵⁶¹



²⁵⁴⁸ Jefford, C.W.; Gunsher, J.; Hill, D.T.; Brun, P.; Le Gras, J.; Waegell, B. *Org. Synth.* **VI**, 142. For a review of the addition of halocarbenes to bridged bicyclic alkenes see Jefford, C.W. *Chimia*, **1970**, *24*, 357–363.

²⁵⁴⁹ See Simmons, H.E.; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.* **1973**, *20*, 1–131; Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* **1974**, *12*, 83–134, see pp. 84–103.

²⁵⁵⁰ Bull, J.A.; Charette, A.B. *J. Am. Chem. Soc.* **2010**, *132*, 1895.

²⁵⁵¹ Simmons, H.E.; Smith, R.D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.

²⁵⁵² LeGoff, E. *J. Org. Chem.* **1964**, *29*, 2048; Denis, J.M.; Girard, C.; Conia, J.M. *Synthesis* **1972**, 549.

²⁵⁵³ Rawson, R.J.; Harrison, I.T. *J. Org. Chem.* **1970**, *35*, 2057.

²⁵⁵⁴ Repic, O.; Lee, P.G.; Giger, U. *Org. Prep. Proced. Int.* **1984**, *16*, 25.

²⁵⁵⁵ Friedrich, E.C.; Lunetta, S.E.; Lewis, E.J. *J. Org. Chem.* **1989**, *54*, 2388.

²⁵⁵⁶ Blanchard, E.P.; Simmons, H.E. *J. Am. Chem. Soc.* **1964**, *86*, 1337. For an analysis of the reaction by density functional theory, see Fang, W.-H.; Phillips, D.L.; Wang, D.-q.; Li, Y.-L. *J. Org. Chem.* **2002**, *67*, 154.

²⁵⁵⁷ Denmark, S.E.; Edwards, J.P.; Wilson, S.R. *J. Am. Chem. Soc.* **1991**, *113*, 723.

²⁵⁵⁸ Dargel, T.K.; Koch, W. *J. Chem. Soc. Perkin Trans. 2*, **1996**, 877.

²⁵⁵⁹ Simmons, H.E.; Blanchard, E.P.; Smith, R.D. *J. Am. Chem. Soc.* **1964**, *86*, 1347. For the transition state and intermediate see Bernardi, F.; Bottoni, A.; Miscione, G.P. *J. Am. Chem. Soc.* **1997**, *119*, 12300.

²⁵⁶⁰ Lacasse, M.-C.; Poulard, C.; Charette, A.B. *J. Am. Chem. Soc.* **2005**, *127*, 12440.

²⁵⁶¹ Virender; Jain, S.L.; Sain, B. *Tetrahedron Lett.* **2005**, *46*, 37.

Asymmetric induction is possible when chiral additives are used.²⁵⁶² Chiral complexes also lead to enantioselectivity in the cyclopropanation reaction.²⁵⁶³ Organocatalysts have been used.²⁵⁶⁴

With the *Simmons–Smith procedure*, as with free carbenes, conjugated dienes give 1,2-addition,²⁵⁶⁵ and allenes give methylenecyclopropanes or spiropentanes.²⁵⁶⁶

An alternative way of carrying out the *Simmons–Smith reaction* is by treatment of the substrate with CH₂I₂ or another dihalomethane and Et₂Zn in ether.²⁵⁶⁷ This method can be adapted to the introduction of RCH and ArCH by the use of RCHI₂ or ArCHI₂ instead of the dihalomethane.²⁵⁶⁸ The reaction is compatible with other functionality in the carbenoid complex. The reaction of RCO₂CH₂I with diethyl zinc and an alkene under photolysis conditions give a cyclopropane.²⁵⁶⁹ In another method, CH₂I₂ or MeCHI₂ is used along with an alane (R₃Al) to transfer CH₂ or CHMe.²⁵⁷⁰ Titanium complexes have been used similarly.²⁵⁷¹ Samarium and CH₂I₂ has been used for the cyclopropanation of conjugated amides.²⁵⁷² For the conversion of enolate anions to cyclopropanols, CH₂I₂ has been used along with SmI₂.²⁵⁷³ Diodomethane in the presence of isopropylmagnesium chloride has been used to cyclopropanate allyl alcohols.²⁵⁷⁴

The *Simmons–Smith reaction* is the basis of a method for the indirect α methylation of a ketone.²⁵⁷⁵ The ketone (illustrated for cyclohexanone) is first converted to an enol ether, an enamine (Reaction 16-13) or silyl enol ether²⁵⁷⁶ (Reaction 12-17), and cyclopropanation via the *Simmons–Smith reaction* is followed by hydrolysis to give the α methylated ketone. A related procedure using diethylzinc and diiodomethane allows ketones to be chain-extended by one carbon.²⁵⁷⁷ In another variation, phenols can be ortho methylated in one laboratory step, by treatment with Et₂Zn and CH₂I₂.²⁵⁷⁸

Diazoesters react with amines with a Rh catalyst to give α -amino esters.²⁵⁷⁹ Diazoesters also react with aldehydes and a Rh catalyst. The product is an α,β -epoxy ester.²⁵⁸⁰

²⁵⁶² Balsells, J.; Walsh, P.J. *J. Org. Chem.* **2000**, 65, 5005; Du, H.; Long, J.; Shi, Y. *Org. Lett.* **2006**, 8, 2827; Long, J.; Du, H.; Li, K.; Shi, Y. *Tetrahedron Lett.* **2005**, 46, 2737.

²⁵⁶³ Song, Z.; Lu, T.; Hsung, R.P.; Al-Rashid, Z.F.; Ko, C.; Tang, Y. *Angew. Chem. Int. Ed.* **2007**, 46, 4069; Shitama, H.; Katsuki, T. *Angew. Chem. Int. Ed.* **2008**, 47, 2450; Zimmer, L.E.; Charette, A.B. *J. Am. Chem. Soc.* **2009**, 131, 15624.

²⁵⁶⁴ Long, J.; Xu, L.; Du, H.; Li, K.; Shi, Y. *Org. Lett.* **2009**, 11, 5226.

²⁵⁶⁵ Overberger, C.G.; Halek, G.W. *J. Org. Chem.* **1963**, 28, 867.

²⁵⁶⁶ Charette, A.B.; Jolicoeur, E.; Bydlinski, G.A.S. *Org. Lett.* **2001**, 3, 3293.

²⁵⁶⁷ See Zhao, C.; Wang, D.; Phillips, D.L. *J. Am. Chem. Soc.* **2002**, 124, 12903.

²⁵⁶⁸ Friedrich, E.C.; Biresaw, G. *J. Org. Chem.* **1982**, 47, 1615.

²⁵⁶⁹ Charette, A.B.; Beauchemin, A.; Fraancœur, S. *J. Am. Chem. Soc.* **2001**, 123, 8139.

²⁵⁷⁰ Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem.* **1985**, 50, 4412; *Org. Synth.* 67, 176.

²⁵⁷¹ Charette, A.B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, 123, 12168.

²⁵⁷² Concellón, J.M.; Rodríguez-Solla, H.; Gómez, C. *Angew. Chem. Int. Ed.* **2002**, 41, 1917.

²⁵⁷³ Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* **1987**, 28, 1307. See also, Molander, G.A.; Harring, L.S. *J. Org. Chem.* **1989**, 54, 3525.

²⁵⁷⁴ Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* **1997**, 38, 7349.

²⁵⁷⁵ See Wenkert, E.; Mueller, R.A.; Reardon, Jr., E.J.; Sathe, S.S.; Scharf, D.J.; Tosi, G. *J. Am. Chem. Soc.* **1970**, 92, 7428 for the enol ether procedure; Kuehne, M.E.; King, J.C. *J. Org. Chem.* **1973**, 38, 304 for the enamine procedure; Conia, J.M. *Pure Appl. Chem.* **1975**, 43, 317–326 for the silyl ether procedure.

²⁵⁷⁶ See Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, 41, 2073; *Org. Synth.* **VI**, 327.

²⁵⁷⁷ Brogan, J.B.; Zercher, C.K. *J. Org. Chem.* **1997**, 62, 6444.

²⁵⁷⁸ Lehnert, E.K.; Sawyer, J.S.; Macdonald, T.L. *Tetrahedron Lett.* **1989**, 30, 5215.

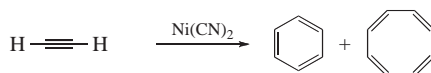
²⁵⁷⁹ Yang, M.; Wang, X.; Li, H.; Livant, P. *J. Org. Chem.* **2001**, 66, 6729.

²⁵⁸⁰ Doyle, M.P.; Hu, W.; Timmons, D.J. *Org. Lett.* **2001**, 3, 933.

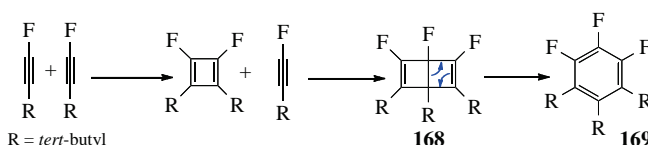
Diazoalkanes react similarly with aldehydes to give an alkene ($\text{Me}_3\text{SiCH}=\text{N}_2 + \text{ArCHO} \rightarrow \text{ArCH}=\text{CHOSiMe}_3$).²⁵⁸¹

OS V, 306, 855, 859, 874; VI, 87, 142, 187, 327, 731, 913, 974; VII, 12, 200, 203; VIII, 124, 196, 321, 467; IX, 422; 76, 86.

15-65 Trimerization and Tetramerization of Alkynes



Aromatic compounds can be prepared by cyclotrimerization of alkynes²⁵⁸² or triynes.²⁵⁸³ Cyclotrimerization is possible by heating to 450–600 °C with no catalyst.²⁵⁸³ The *spontaneous* (no catalyst) trimerization of *t*-BuC≡CF gave 1,2,3-tri-*tert*-butyl-4,5,6-trifluorobenzene (**169**), which the first time was three adjacent *tert*-butyl groups put onto a benzene ring.²⁵⁸⁴ The fact that this is a head-to-head joining allows formation of **169** from two alkynes. The fact that **168** (a *Dewar benzene*) was also isolated lends support to this scheme.²⁵⁸⁵



When acetylene is heated with nickel cyanide, other Ni(II) or Ni(0) compounds, or similar catalysts, it gives benzene and cyclooctatetraene.²⁵⁸⁶ It is possible to get more of either product by a proper choice of catalyst. Substituted acetylenes give substituted benzenes,²⁵⁸⁷ and this reaction has been used to prepare very crowded molecules. Dialkylalkynes were trimerized over $\text{CO}_2(\text{CO})_8$ ²⁵⁸⁸ and over $\text{Hg}[\text{Co}(\text{CO})_4]_2$ to give hexaisopropylbenzene.²⁵⁸⁹ The six isopropyl groups are not free to rotate, but are lined up perpendicular to the plane of the benzene ring. Highly substituted benzene derivatives have also been prepared via cyclotrimerization using a Rh,²⁵⁹⁰ Ni,²⁵⁹¹

²⁵⁸¹ Dias, E.L.; Brookhart, M.; White, P.S. *J. Am. Chem. Soc.* **2001**, 123, 2442.

²⁵⁸² For a review, see Rubin, M.; Sromek, A.W.; Gevorgyan, V. *Synlett* **2003**, 2265.

²⁵⁸³ Kociulek, M.G.; Johnson, R.P. *Tetrahedron Lett.* **1999**, 40, 4141.

²⁵⁸⁴ Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Valange, P. *Angew. Chem. Int. Ed.* **1964**, 3, 746; Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Senders, J.R.; Valange, P. *Angew. Chem. Int. Ed.* **1964**, 3, 755.

²⁵⁸⁵ See also, Wingert, H.; Regitz, M. *Chem. Ber.* **1986**, 119, 244.

²⁵⁸⁶ See Winter, M.J. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, **1985**, pp. 259–294; Vollhardt, K.P.C. *Angew. Chem. Int. Ed.* **1984**, 23, 539; Acc. Chem. Res. **1977**, 10, 1; Maitlis, P.M. *J. Organomet. Chem.* **1980**, 200, 161; Reppe, W.; Kutepow, N.V.; Magin, A. *Angew. Chem. Int. Ed.* **1969**, 8, 727; Schore, N.E. *Chem. Rev.* **1988**, 88, 1081. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 198–201.

²⁵⁸⁷ Sigman, M.S.; Fatland, A.W.; Eaton, B.E. *J. Am. Chem. Soc.* **1998**, 120, 5130; Larock, R.C.; Tian, Q. *J. Org. Chem.* **1998**, 63, 2002.

²⁵⁸⁸ Yong, L.; Butenschön, H. *Chem. Commun.* **2002**, 2852; Marchueta, I.; Olivella, S.; Solà, L.; Moyano, A.; Pericás, M.A.; Riera, A. *Org. Lett.* **2001**, 3, 3197. See also, Agenet, N.; Gandon, V.; Vollhardt, K.P.C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2007**, 129, 8860.

²⁵⁸⁹ See Hopff, H.; Gati, A. *Helv. Chim. Acta* **1965**, 48, 509.

²⁵⁹⁰ See Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. *Chem. Lett.* **2007**, 36, 998.

²⁵⁹¹ Mori, N.; Ikeda, S.-i.; Odashima, K. *Chem. Commun.* **2001**, 181.

Ti,²⁵⁹² Mo,²⁵⁹³ Ru,²⁵⁹⁴ Co,²⁵⁹⁵ or a Pd²⁵⁹⁶ catalyst. Alkynes react with allenes and a Ni catalyst to give highly substituted benzene derivatives.²⁵⁹⁷ Conjugated ketones react with internal alkynes with Me₃Al and a Ni catalyst²⁵⁹⁸ to give an aromatic ring fused to a cyclic ketone after reaction with DBU and air.²⁵⁹⁹ N-Aryl chloroimines react with alkynes and a Rh catalyst to give quinolines,²⁶⁰⁰ as do N-aryl alkynyl imines with a W complex.²⁶⁰¹

Intramolecular cyclotrimerizations have been reported by condensation of a diyne²⁶⁰² with an alkyne in the presence of a Pd,²⁶⁰³ Mo,²⁶⁰⁴ Ni,²⁶⁰⁵ Rh,²⁶⁰⁶ Ir,²⁶⁰⁷ Ag,²⁶⁰⁸ Co,²⁶⁰⁹ or Ru catalyst.²⁶¹⁰ Triynes have been similarly condensed with a Rh catalyst.²⁶¹¹ Note that this type of cyclization has been labeled as a [2 + 2 + 2]-cycloaddition reaction, which is discussed in Reaction **15-66**. The internal cyclotrimerization of a triyne, utilizing a siloxy tether and a Co catalyst has been reported.²⁶¹² Fused-ring aromatic compounds are prepared by this method. Similar results were obtained from diynes and allenes with a Ni catalyst.²⁶¹³ Solid-supported cyclotrimerizations have been reported.²⁶¹⁴ Endiynes are cyclized to bicyclic arenes using a Pd²⁶¹⁵ or Ru²⁶¹⁶ catalyst, as are yndienes with a Ru catalyst.²⁶¹⁷ Alkynyl biaryls are cyclized to phenanthrene derivatives using ICl.²⁶¹⁸ In the presence of PhMe₂SiH, CO, and a Rh catalyst, a nonconjugated triyne leads to a tricyclic compound in which a benzene ring is fused to two carbocyclic rings.²⁶¹⁹ Internal cyclotrimerization of an aryl alkynyl ketone where the aryl group has an *ortho*

²⁵⁹² Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 9682.

²⁵⁹³ Nishida, M.; Shiga, H.; Mori, M. *J. Org. Chem.* **1998**, *63*, 8606.

²⁵⁹⁴ Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712.

²⁵⁹⁵ Sugihara, T.; Wakabayashi, A.; Nagai, Y.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* **2002**, 576.

²⁵⁹⁶ Gevorgyan, V.; Quan, L.G.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 568. Also see Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 6836; Li, J.-H.; Xie, Y.-X. *Synth. Commun.* **2004**, *34*, 1737.

²⁵⁹⁷ Shanmugasundaram, M.; Wu, M.-S.; Cheng, C.-H. *Org. Lett.* **2001**, *3*, 4233.

²⁵⁹⁸ Ikeda, S.; Kondo, H.; Arai, T.; Odashima, K. *Chem. Commun.* **2002**, 2422.

²⁵⁹⁹ Mori, N.; Ikeda, S.-i.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2722.

²⁶⁰⁰ Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109.

²⁶⁰¹ Sangu, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* **2004**, *6*, 353.

²⁶⁰² See Kawathar, S.P.; Schreiner, P.R. *Org. Lett.* **2002**, *4*, 3643.

²⁶⁰³ Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835. See also, Tsukada, N.; Sugawara, S.; Nakaoka, K.; Inoue, Y. *J. Org. Chem.* **2003**, *68*, 5961.

²⁶⁰⁴ Hara, R.; Guo, Q.; Takahashi, T. *Chem. Lett.* **2000**, 140.

²⁶⁰⁵ Jeevanandam, A.; Korivi, R.P.; Huang, I.-w.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 807.

²⁶⁰⁶ Witulski, B.; Zimmermann, A. *Synlett* **2002**, 1855.

²⁶⁰⁷ Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382.

²⁶⁰⁸ Zhao, J.; Hughes, C.O.; Toste, F.D. *J. Am. Chem. Soc.* **2006**, *128*, 7436.

²⁶⁰⁹ Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474.

²⁶¹⁰ Yamamoto, Y.; Hattori, K.; Nishiyama, H. *J. Am. Chem. Soc.* **2006**, *128*, 8336.

²⁶¹¹ Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 7784.

²⁶¹² Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, *6*, 1519.

²⁶¹³ Shanmugasundaram, M.; Wu, M.-S.; Jegannathan, M.; Huang, C.-W.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 7724.

²⁶¹⁴ Young, D.D.; Senaiar, R.S.; Deiters, A. *Chemistry: European J.* **2006**, *12*, 5563.

²⁶¹⁵ Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 2653.

²⁶¹⁶ Odedra, A.; Wu, C.-J.; Pratap, T.B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406.

²⁶¹⁷ Lian, J.-J.; Odedra, A.; Wu, C.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 4186.

²⁶¹⁸ Yao, T.; Campo, M.A.; Larock, R.C. *J. Org. Chem.* **2005**, *70*, 3511.

²⁶¹⁹ Ojima, I.; Vu, A.T.; McCullagh, J.V.; Kinoshita, A. *J. Am. Chem. Soc.* **1999**, *121*, 3230.

trimethylsilylalkyne substituent gives a tetracyclic naphthalene derivative with a fused cyclopentanone unit.²⁶²⁰ Benzene derivatives with ortho alkyne units can be converted to naphthalene derivatives in aq NaOH with hydrazine, Te, NaBH₄ and sonication.²⁶²¹ Vinyl and alkyne substituents with a Ru catalyst lead to naphthalene derivatives.²⁶²² Cyclo-trimerization occurs with alkynyl boronic esters.²⁶²³

Imino and iodo substituents with a silyl alkyne and a Pd catalyst leads to an isoquinoline.²⁶²⁴ Benzene derivatives having ortho imine and alkyne substituents give an isoquinoline when treated with iodine²⁶²⁵ or with a Pd catalyst.²⁶²⁶ Diynes with nitriles and a Ru catalyst lead to isoquinolines.²⁶²⁷ Pyridines fused to carboxylic rings can be prepared by similar methodology using a cyanoamine and a Co catalyst.²⁶²⁸ An isocyanate (Ar—N=C=O) reacts with a diyne and a Ru catalyst to give a bicyclic pyridone.²⁶²⁹ Isocyanides and alkynes also react with a phosphine catalyst to give pyrroles.²⁶³⁰ Ortho alkynyl and epoxy substituents leads to β -naphthols using a Ru catalyst.²⁶³¹

Nitriles react with 2 molar equivalents of acetylene, in the presence of a Co catalyst, to give 2-substituted pyridines.²⁶³² Propargyl amines react with cyclohexanone derivatives and a Au complex to give tetrahydroquinolines.²⁶³³ Treatment of alkynes with Cp₂ZrEt₂ followed by reaction with acetonitrile and then a second alkyne with a Ni catalyst gives a highly substituted pyridine.²⁶³⁴ This reaction can be done intramolecularly using a photochemically induced reaction with a Co catalyst and *p*-TolCN to give pyridines incorporated into macrocycles.²⁶³⁵ Diynes react with *N*-heterocyclic carbenes in the presence of a Ni catalyst to give pyridines.²⁶³⁶ Alkynyl esters react with enamino esters with a ZnBr₂ catalyst to give substituted pyridines.²⁶³⁷ α -Halo oxime ethers react with alkynes and *Grignard reagents*, with a mixture of Pd and Cu catalysts, to give pyrimidines.²⁶³⁸ Triketones fix nitrogen gas in the presence of TiCl₄ and Li metal to form bicyclic pyrrole derivatives.²⁶³⁹

In contrast to the spontaneous reaction, the catalyzed process seldom gives the 1,2,3-trisubstituted benzene isomer from an acetylene (RC \equiv CH). The chief product is usually

²⁶²⁰ Atienza, C.; Mateo, C.; de Frutos, Ó.; Echavarren, A.M. *Org. Lett.* **2001**, 3, 153.

²⁶²¹ Landis, C.A.; Payne, M.M.; Eaton, D.L.; Anthony, J.E. *J. Am. Chem. Soc.* **2004**, 126, 1338.

²⁶²² Klumpp, D.A.; Beauchamp, P.S.; Sanchez, Jr., G.V.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* **2001**, 42, 5821.

²⁶²³ Gandon, V.; Leca, D.; Aechtner, T.; Vollhardt, K.P.C.; Malacria, M.; Aubert, C. *Org. Lett.* **2004**, 6, 3405.

²⁶²⁴ Roesch, K.R.; Larock, R.C. *J. Org. Chem.* **2002**, 67, 86.

²⁶²⁵ Huang, Q.; Hunter, J.A.; Larock, R.C. *Org. Lett.* **2001**, 3, 2973.

²⁶²⁶ Dai, G.; Larock, R.C. *J. Org. Chem.* **2003**, 68, 920; Dai, G.; Larock, R.C. *Org. Lett.* **2002**, 4, 193.

²⁶²⁷ Varela, J.A.; Castedo, L.; Saá, C. *J. Org. Chem.* **2003**, 68, 8595.

²⁶²⁸ Boñaga, L.V.R.; Zhang, H.-C.; Maryanoff, B.E. *Chem. Commun.* **2004**, 2394.

²⁶²⁹ Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, 3, 2117.

²⁶³⁰ Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, 46, 2563.

²⁶³¹ Madhusaw, R.J.; Lin, M.-Y.; Shoel, S.Md.A.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, 126, 6895.

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²⁶³³ Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, 68, 6959.

²⁶³⁴ Takahashi, T.; Tsai, F.Y.; Kitora, M. *J. Am. Chem. Soc.* **2000**, 122, 4994.

²⁶³⁵ Moretto, A.F.; Zhang, H.-C.; Maryanoff, B.E. *J. Am. Chem. Soc.* **2001**, 123, 3157.

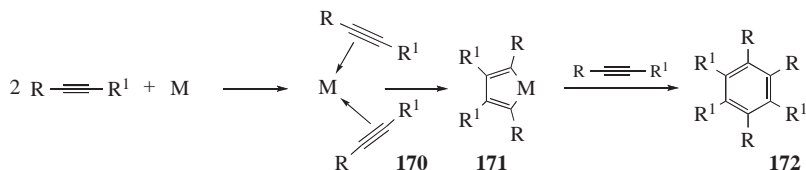
²⁶³⁶ McCormick, M.M.; Duong, H.A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, 127, 5030.

²⁶³⁷ Bagley, M.C.; Dale, J.W.; Hughes, D.D.; Ohnesorge, M.; Philips, N.G.; Bower, J. *Synlett* **2001**, 1523.

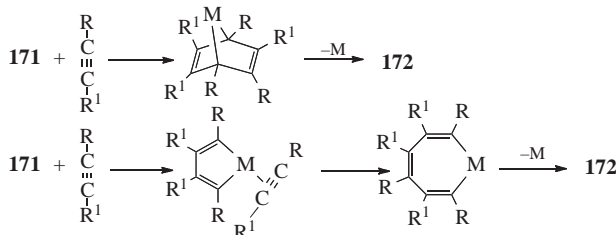
²⁶³⁸ Kikiya, H.; Yagi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, 124, 9032.

²⁶³⁹ Mori, M.; Hori, M.; Sato, Y. *J. Org. Chem.* **1998**, 63, 4832; Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. *Angew. Chem. Int. Ed.* **1998**, 37, 636.

the 1,2,4-isomer,²⁶⁴⁰ with lesser amounts of the 1,3,15-isomer also generally obtained, but little if any of the 1,2,3-isomer. The mechanism of the catalyzed



reaction to form benzenes²⁶⁴¹ is believed to go through a species **170** in which two molecules of alkyne coordinate with the metal, and another species (**171**), a five-membered heterocyclic intermediate.²⁶⁴² Such intermediates (where M = Rh, Ir, Zr,²⁶⁴³ or Ni) have been isolated and are shown to give benzenes (**172**) when treated with alkynes.²⁶⁴⁴ Note that this pathway accounts for the predominant formation of the 1,2,4-isomer. Two possibilities for the last step are a *Diels–Alder reaction*, and a ring expansion, each followed by extrusion of the metal.²⁶⁴⁵



In at least one case, the mechanism is different, going through a cyclobutadiene–nickel complex (see Sec. 2.K.ii), which has been isolated.²⁶⁴⁶ Similar results were obtained with a Ti complex.²⁶⁴⁷ Using a mixture of PdCl₂ and CuCl₂, however, aliphatic alkynes are converted to the 1,3,5-trialkyl benzene derivative.²⁶⁴⁸

Alkoxy chromium carbenes (*Fischer carbene complexes*, see Reaction **15-58**) react with phenylalkynes to give naphthalene derivatives.²⁶⁴⁹ These Cr carbenes react with

²⁶⁴⁰ See Saito, S.; Kawasaki, T.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **2001**, 66, 796.

²⁶⁴¹ See Colborn, R.E.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* **1986**, 108, 5470; Lawrie, C.J.; Gable, K.P.; Carpenter, B.K. *Organometallics* **1989**, 8, 2274.

²⁶⁴² Colborn, R.E.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* **1981**, 103, 6259; Kochi, J.K. *Organometallic Mechanisms and Catalysis* Academic Press, NY, **1978**, pp. 428–432; Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry* University Science Books, Mill Valley, CA **1987**, pp. 870–877; Eisch, J.J.; Sexsmith, S.R. *Res. Chem. Intermed.* **1990**, 13, 149–192.

²⁶⁴³ Takahashi, T.; Ishikawa, M.; Huo, S. *J. Am. Chem. Soc.* **2002**, 124, 388.

²⁶⁴⁴ See Eisch, J.J.; Galle, J.E. *J. Organomet. Chem.* **1975**, 96, C23; McAlister, D.R.; Bercaw, J.E.; Bergman, R.G. *J. Am. Chem. Soc.* **1977**, 99, 1666.

²⁶⁴⁵ See, however, Bianchini, C.; Caulton, K.G.; Chardon, C.; Eisenstein, O.; Folting, K.; Johnson, T.J.; Meli, A.; Peruzzini, M.; Raucher, D.J.; Streib, W.E.; Vizza, F. *J. Am. Chem. Soc.* **1991**, 113, 5127.

²⁶⁴⁶ Mauret, P.; Alphonse, P. *J. Organomet. Chem.* **1984**, 276, 249. See also, Pepermans, H.; Willem, R.; Gielen, M.; Hoogzand, C. *Bull. Soc. Chim. Belg.* **1988**, 97, 115.

²⁶⁴⁷ Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, 123, 7925.

²⁶⁴⁸ Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* **2001**, 66, 3627.

²⁶⁴⁹ Jackson, T.J.; Herndon, J.W. *Tetrahedron* **2001**, 57, 3859.

alkynyl boronates, cerium(IV) compounds, and then PhBr and a Pd catalyst to give a naphthoquinone.²⁶⁵⁰ Diynes react to give cyclotrimerization.²⁶⁵¹ Note that vinyl Chromium carbenes react directly with alkynes to give spirocyclic compounds (spiro [4.4]nona-1,3,6-trienes).²⁶⁵² Benzofurans can be prepared using methoxy carbenes.²⁶⁵³ Amino-substituted chromium carbenes react with alkynes and then silica to give substituted benzene derivatives that have an aminoalkyl ($-\text{NR}_2$) substituent.²⁶⁵⁴ Imino-substituted Chromium carbenes react with alkynes to give pyrrole derivatives.²⁶⁵⁵ Fischer carbene complexes react with alkynes to give the *Dötz benzannulation*,²⁶⁵⁶ giving *p*-alkoxyphenol derivatives. Modification of this basic technique can lead to eight-membered ring carbocycles (see Reaction 15-66).²⁶⁵⁷

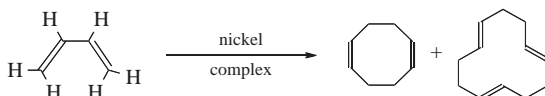
When benzene, in the gas phase, was adsorbed onto a surface of 10% rhodium-on-alumina, the reverse reaction took place, and acetylene was formed.²⁶⁵⁸

Heating ketones in the presence of TiCl_3OTf leads to 1,3,5-trisubstituted arenes.²⁶⁵⁹ Heating acetophenone with TiCl_4 gives 1,3,5-triphenylbenzene.²⁶⁶⁰

OS VII, 256; IX, 1; 80, 93.

15-66 Other Cycloaddition Reactions

cyclo-[But-2-en-1,4-diyl]-1/4/addition, and so on



Cycloaddition reactions other than $[4 + 2]$, $[3 + 2]$, or $[2 + 2]$ are possible, often providing synthetically useful routes to cyclic compounds. Conjugated dienes can be dimerized or trimerized at the 1,4-positions (formally, $[4 + 4]$ and $[4 + 4 + 4]$ cycloadditions) by treatment with certain complexes or other transition metal compounds.²⁶⁶¹ Thus butadiene gives 1,5-cyclooctadiene and 1,5,9-cyclododecatriene.²⁶⁶² The relative amount of each product can be controlled by use of the proper catalyst. For example, $\text{Ni:P}(\text{OC}_6\text{H}_4\text{-}o\text{-Ph})_3$ gives predominant dimerization, while $\text{Ni}(\text{cyclooctadiene})_2$ gives mostly trimerization. The products arise, not by direct 1,4 to 1,4 attack, but by stepwise

²⁶⁵⁰ Davies, M.W.; Johnson, C.N.; Harrity, J.P.A. *J. Org. Chem.* **2001**, 66, 3525.

²⁶⁵¹ Jiang, M.X.-W.; Rawat, M.; Wulff, W.D. *J. Am. Chem. Soc.* **2004**, 126, 5970.

²⁶⁵² Schirmer, H.; Flynn, B.L.; de Meijere, A. *Tetrahedron* **2000**, 56, 4977.

²⁶⁵³ Herndon, J.W.; Zhang, Y.; Wang, H.; Wang, K. *Tetrahedron Lett.* **2000**, 41, 8687.

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²⁶⁵⁷ Barluenga, J.; Aznar, F.; Palomero, M.A. *Angew. Chem. Int. Ed.* **2000**, 39, 4346.

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²⁶⁶¹ Wilke, G. *Angew. Chem. Int. Ed.* **1988**, 27, 186; Heimbach, P.; Schenkluhn, H. *Top. Curr. Chem.* **1980**, 92, 45; Baker, R. *Chem. Rev.* **1973**, 73, 487, see pp. 489–512; Semmelhack, M.F. *Org. React.* **1972**, 19, 115, pp. 128–143; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2 Academic Press, NY, **1974**, pp. 159–163; Heck, R.F. *Organotransition Metal Chemistry* Academic Press, NY, **1974**, pp. 157–164.

²⁶⁶² See Rona, P. *Intra-Sci. Chem. Rep.* **1971**, 5, 105.

mechanisms involving metal–alkene complexes.²⁶⁶³ The Rh catalyzed intramolecular cycloaddition of a furan with a conjugated diazoester gives a [3 + 4]-cycloadduct.²⁶⁶⁴ The suprafacial thermal addition of an allylic cation to a diene (a [4 + 3] cycloaddition) is allowed by the *Woodward–Hoffmann rules* (this reaction would be expected to follow the same rules as the *Diels–Alder reaction*²⁶⁶⁵). Pyrroles react with allylic diazo compounds, in the presence of a Rh catalyst, to give bicyclic amines in a [4 + 3]-cycloaddition.²⁶⁶⁶ A different [4 + 3]-cycloaddition involves the intramolecular reaction of a diene with an alkylidenecyclopropane unit, in the presence of a Pd catalyst, to give a seven-membered ring as part of a bicyclic system.²⁶⁶⁷ A [3 + 2 + 2]-cycloaddition was reported with an alkyne and an alkene–alkylidenecyclopropane substrate, in the presence of a Rh catalyst.²⁶⁶⁸ Reaction with a chiral Rh catalyst converts dienes and diazo compounds to cycloheptadienes.²⁶⁶⁹ Chiral cations have been used in [4 + 3] cycloadditions.²⁶⁷⁰ A [5 + 2]-cycloaddition of vinylcyclopropanes and alkenes, in the presence of a Rh catalyst, leads to seven-membered rings.²⁶⁷¹ The reaction of a conjugated carbonyl compound with a diazo ester, in the presence of a Cu catalyst, leads to a dihydropyran in what is labeled a [4 + 1]-cycloaddition.²⁶⁷² Dienes react with nitriles in a Ti mediated [4 + 1]-cycloaddition.²⁶⁷³ Cycloheptatriene reacts with terminal alkynes, using a complex catalyst involves Co and Zn compounds, to give a bicyclic triene via a [6 + 2]-cycloaddition.²⁶⁷⁴

As seen in Reaction **15-60**, the *Woodward–Hoffmann rules* allow suprafacial concerted cycloadditions to take place thermally if the total number of electrons is $4n + 2$ and photochemically if the number is $4n$. Furthermore, forbidden reactions become allowed if one molecule reacts antarafacially. It would thus seem that syntheses of many large rings could easily be achieved. However, when the newly formed ring is eight membered or greater, concerted mechanisms, although allowed by orbital symmetry for the cases stated, become difficult to achieve. Due to the entropy factor the two ends of one system must simultaneously encounter the two ends of the other, unless one or both components are cyclic, in which case the molecule has many fewer possible conformations. There have been a number of reports of cycloaddition reactions leading to eight membered and larger rings, some thermally and some photochemically induced, but (apart from the dimerization and trimerization of butadienes mentioned above, which are known not to involve direct

²⁶⁶³ See Graham, G.R.; Stephenson, L.M. *J. Am. Chem. Soc.* **1977**, *99*, 7098.

²⁶⁶⁴ Davies, H.M.L.; Calvo, R.L.; Townsend, R.-J.; Ren, P.; Churchill, R.M. *J. Org. Chem.* **2000**, *65*, 4261. For reviews of [3 + 4] cycloadditions see Mann, J. *Tetrahedron* **1986**, *42*, 4611; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* **1984**, *23*, 1; **1973**, *12*, 819; Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61.

²⁶⁶⁵ Garst, M.E.; Roberts, V.A.; Houk, K.N.; Rondan, N.G. *J. Am. Chem. Soc.* **1984**, *106*, 3882.

²⁶⁶⁶ Reddy, R.P.; Davies, H.M.L. *J. Am. Chem. Soc.* **2007**, *129*, 10312.

²⁶⁶⁷ Gulías, M.; Durán, J.; López, F.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* **2007**, *129*, 11026.

²⁶⁶⁸ Evans, P.A.; Inglesby, P.A. *J. Am. Chem. Soc.* **2008**, *130*, 12838.

²⁶⁶⁹ Deng, L.; Giessert, A.J.; Gerlitz, O.O.; Dai, X.; Diver, S.T.; Davies, H.M.L. *J. Am. Chem. Soc.* **2005**, *127*, 1342.

²⁶⁷⁰ Huang, J.; Hsung, R.P. *J. Am. Chem. Soc.* **2005**, *127*, 50. See Harmata, M. *Chem. Commun.* **2010**, 8886, 8904.

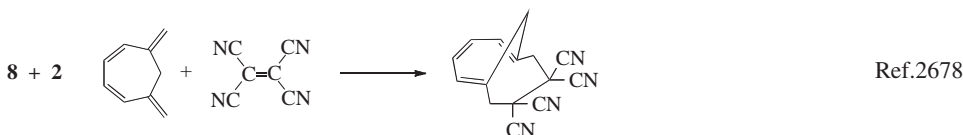
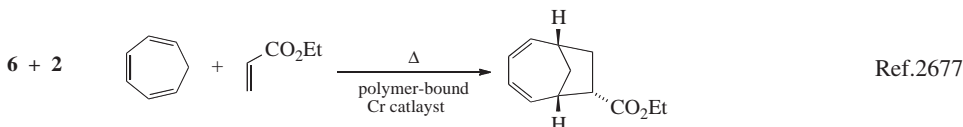
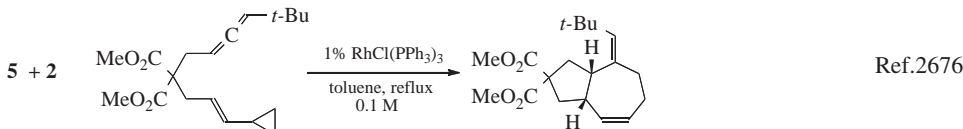
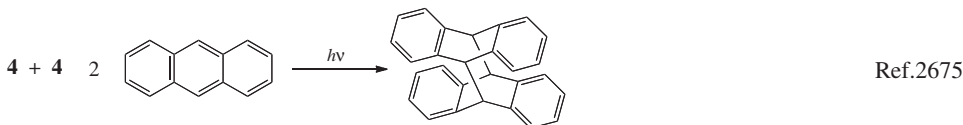
²⁶⁷¹ Wender, P.A.; Haustedt, L.O.; Lim, J.; Love, J.A.; Williams, T.J.; Yoon, J.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 6302.

²⁶⁷² Son, S.; Fu, G.C. *J. Am. Chem. Soc.* **2007**, *129*, 1046.

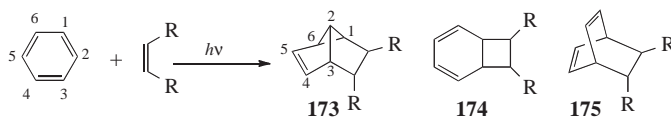
²⁶⁷³ Laroche, C.; Bertus, P.; Szymoniak, J. *Chem. Commun.* **2005**, 3030.

²⁶⁷⁴ Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* **2005**, *7*, 2353.

[4 + 4]- or [4 + 4 + 4]-cycloaddition) in most cases evidence is lacking to indicate whether they are concerted or stepwise processes. Some examples follows:



Benzene rings can undergo photochemical cycloaddition with alkenes.²⁶⁷⁹ The major product is usually the 1,3 addition product (**173**, in which a three-membered ring has also been formed), although some of the 1,2-product (**174** Reaction **15-63**) is sometimes formed as well. Compound **174** is usually the main product where the alkene bears electron-withdrawing groups and the aromatic compound electron-donating groups, or vice versa. The 1,4-product (**175**) is rarely formed. The reaction has also been run with benzenes substituted with alkyl, halo, OR, CN, and other groups, and with acyclic and cyclic alkenes bearing various groups.²⁶⁸⁰



²⁶⁷⁵ Shönberg, A. *Preparative Organic Photochemistry* Springer, NY, **1968**, pp. 97–99. Also see Zhu, M.; Qiu, Z.; Hiel, G.P.; Sieburth, S.Mc.N. *J. Org. Chem.* **2002**, *67*, 3487.

²⁶⁷⁶ Wender, P.A.; Gamber, G.G.; Scanio, M.J.C. *Angew. Chem. Int. Ed.* **2001**, *40*, 3895; Wender, P.A.; Pedersen, T.M.; Scanio, M.J.C. *J. Am. Chem. Soc.* **2002**, *124*, 15154; Wender, P.A.; Love, J.A.; Williams, T.J. *Synlett* **2003**, 1295.

²⁶⁷⁷ Rigby, J.H.; Mann, L.W.; Myers, B.J. *Tetrahedron Lett.* **2001**, *42*, 8773. See Rigby, J.H.; Ateeq, H.S.; Charles, N.R.; Henshilwood, J.A.; Short, K.M.; Sugathapala, P.M. *Tetrahedron* **1993**, *49*, 5495.

²⁶⁷⁸ Farrant, G.C.; Feldmann, R. *Tetrahedron Lett.* **1970**, 4979.

²⁶⁷⁹ See Wender, P.A.; Ternansky, R.; deLong, M.; Singh, S.; Olivero, A.; Rice, K. *Pure Appl. Chem.* **1990**, *62*, 1597; Gilbert, A. in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, **1984**, pp. 1–60. For a review of this and related reactions, see McCullough, J.J. *Chem. Rev.* **1987**, *87*, 811.

²⁶⁸⁰ See the table in Wender, P.A.; Siggel, L.; Nuss, J.M. *Org. Photochem.* **1989**, *10*, 357, pp. 384–415.

[2 + 2 + 2]-Cycloaddition reactions are known²⁶⁸¹ (also see Reaction **15-65**), usually with diynes, enynes, or intermolecular reactions of alkynes or alkenes with an alkyne, and facilitated by Ni²⁶⁸² Ru,²⁶⁸³ or a Co catalyst.²⁶⁸⁴ A mechanistic density functional study has been reported for this reaction.²⁶⁸⁵ With a Co catalyst, an intramolecular [2 + 2 + 2]-cycloaddition of diynes with nitriles leads to bicyclic pyridines.²⁶⁸⁶ Alkenyl isocyanates and alkynes react via [2 + 2 + 2]-cycloaddition, in the presence of a Ru catalyst, to form bicyclic conjugated lactams.²⁶⁸⁷ Pyridines can also be prepared by metal-catalyzed [2 + 2 + 2]-cycloaddition.²⁶⁸⁸ Alkynes and isocyanates react with CO in the presence of a Ru catalyst to give imides,²⁶⁸⁹ and other [2 + 2 + 1]-cycloadditions are known.²⁶⁹⁰ A Co catalyst is used for a [4 + 2 + 2]-cycloaddition of 1,3-butadiene and bicyclo[2.2.2]octa-2,5-diene.²⁶⁹¹ Eight-membered rings are produced by a Rh catalyzed [4 + 2 + 2] cycloaddition.²⁶⁹² Yne-dienes undergo [4 + 2 + 1]-cycloaddition in the presence of a Ni catalyst.²⁶⁹³ Chromium catalysts are available for [6 + 4]-cycloadditions.²⁶⁹⁴ Ene-diynes undergo [2 + 2 + 2 + 1]-cycloaddition to form seven-membered ring ketones, in the presence of CO and a Rh catalyst.²⁶⁹⁵ Nickel catalyzed [2 + 2 + 2 + 2]-cycloadditions of alkynes lead to eight-membered rings.²⁶⁹⁶

Allenenes and vinylcyclopropanes undergo [5 + 2]- and [5 + 2 + 1]-cycloadditions in the presence of a Rh catalyst.²⁶⁹⁷ A reductive elimination step determines the selectivity for various substrates in Rh catalyzed catalyzed [5 + 2]-cycloadditions.²⁶⁹⁸

OS VI, 512; VII, 485; X, 1, 336.

²⁶⁸¹ For a review, see Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741.

²⁶⁸² Louie, J.; Gibby, J.E.; Farnsworth, M.V.; Tekavec, T.N. *J. Am. Chem. Soc.* **2002**, *124*, 15188.

²⁶⁸³ Cadierno, V.; García-Garrido, S.E.; Gimeno, J. *J. Am. Chem. Soc.* **2006**, *128*, 15094; Tanaka, D.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2007**, *129*, 7730; Mallagaray, Á.; Medina, S.; Domínguez, G.; Pérez-Castells, J. *Synlett* **2010**, 2114.

²⁶⁸⁴ Hilt, G.; Paul, A.; Harms, K. *J. Org. Chem.* **2008**, *73*, 5187.

²⁶⁸⁵ Varela, J.A.; Rubín, S.G.; Castedo, L.; Saá, C. *J. Org. Chem.* **2008**, *73*, 1320.

²⁶⁸⁶ Boñaga, L.V.R.; Zhang, H.-C.; Moretto, A.F.; Ye, H.; Gauthier, D.A.; Li, J.; Leo, G.C.; Maryanoff, B.E. *J. Am. Chem. Soc.* **2005**, *127*, 3473.

²⁶⁸⁷ Yu, R.T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782; Yu, R.T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370.

²⁶⁸⁸ Varela, J.A.; Saá, C. *Synlett* **2008**, 2571.

²⁶⁸⁹ Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T.-a. *J. Am. Chem. Soc.* **2006**, *128*, 14816.

²⁶⁹⁰ Knölker, H.-J.; Braier, A.; Bröcher, D.J.; Jones, P.G.; Piotrowski, H. *Tetrahedron Lett.* **1999**, *40*, 8075; Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160.

²⁶⁹¹ Kiattansakul, R.; Snyder, J.K. *Tetrahedron Lett.* **1999**, *40*, 1079.

²⁶⁹² Gilbertson, S.R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784; Wender, P.A.; Christy, J.P. *J. Am. Chem. Soc.* **2006**, *128*, 5354. For a computational study, see Baik, M.-H.; Baum, E.W.; Burland, M.C.; Evans, P.A. *J. Am. Chem. Soc.* **2005**, *127*, 1602.

²⁶⁹³ Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 2609.

²⁶⁹⁴ Kündig, E.P.; Robvieux, F.; Kondratenko, M. *Synthesis* **2002**, 2053.

²⁶⁹⁵ Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I. *J. Am. Chem. Soc.* **2005**, *127*, 17756.

²⁶⁹⁶ Wender, P.A.; Christy, J.P. *J. Am. Chem. Soc.* **2007**, *129*, 13402.

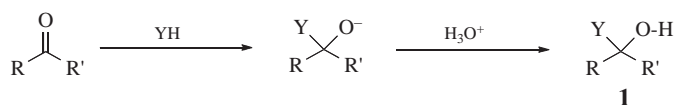
²⁶⁹⁷ Wegner, H.A.; de Meijere, A.; Wender, P.A. *J. Am. Chem. Soc.* **2005**, *127*, 6530; Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P.A.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 10060.

²⁶⁹⁸ Yu, Z.X.; Cheong, P.h.-Y.; Liu, P.; Legault, C.Y.; Wender, P.A.; Houk, K.N. *J. Am. Chem. Soc.* **2008**, *130*, 2378.

Addition to Carbon–Hetero Multiple Bonds

16.A. MECHANISM AND REACTIVITY

The reactions considered in this chapter involve addition to the carbon–oxygen, carbon–nitrogen, and carbon–sulfur double bonds, as well as the carbon–nitrogen triple bond. The mechanistic study of these reactions is much simpler than that of the additions to carbon–carbon multiple bonds considered in Chapter 15.¹ Since C=O, C=N, and C≡N bonds are strongly polar, with the carbon always the positive end (except for isocyanides, see Sec. 16.B.iv), there is never any doubt about the *orientation* of unsymmetrical addition to these bonds (the regiochemical preference). Nucleophilic attacking species always go to the carbon and electrophilic species to the oxygen or nitrogen. Additions to C=S bonds are much less common,² but in these cases the addition is sometimes in the other direction (reaction at sulfur is called *thiophilic addition* and addition to the carbon is called *carbophilic addition*).³ For example, the reaction of phenyllithium with thiobenzophenone (Ph₂C=S) gives, after hydrolysis, benzhydryl phenyl sulfide (Ph₂CHSPh).⁴



The normal acyl addition of YH to a ketone gives an alkoxide, and hydrolysis gives **1**. Note that the product has a stereogenic carbon, but unless there is chirality in R or R', or YH is optically active, the product must be a racemic mixture because there is no facial bias for addition to the carbonyl. The same holds true for C=N and C=S bonds. The stereochemistry of addition of a single YH to the carbon–nitrogen triple bond could be investigated, since the product can exist in (*E*) and (*Z*) forms (Sec. 4.K.i), but these reactions generally give imine products that undergo further reaction. Of course, if R or R' is chiral, a mixture of diastereomers

¹ See Jencks, W.P. *Prog. Phys. Org. Chem.* **1964**, 2, 63

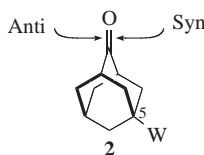
² See Schaumann, E. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 2, Wiley, NY, **1989**, pp. 1269–1367; Ohno, A. in Oae, S. *Organic Chemistry of Sulfur*, Plenum, NY, **1977**, pp. 189–229; Mayer, R. in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, **1967**, pp. 219–240; Campaigne, E. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, **1966**, pp. 917–959.

³ See Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, **1985**, pp. 219–338, pp. 261–267.

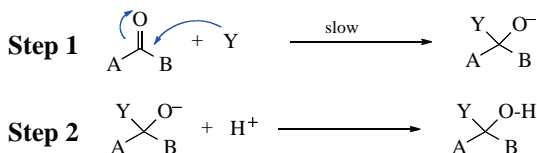
⁴ See Metzner, P.; Vialle, J.; Vibet, A. *Tetrahedron* **1978**, 34, 2289.

will result, and the stereochemistry of addition can be studied in such cases. *Cram's rule* or the *Felkin–Anh model* (Sec. 4.H) allows the direction of attack of Y to be predicted in many cases.⁵ However, the relative directions of attack of Y and H are not determined, but only the direction of attack of Y with respect to the rest of the substrate molecule.

In Section 15.B.iii, electronic effects were shown to play a part in determining which face of a carbon–carbon double bond is attacked. The same applies to additions to carbonyl groups. For example, in 5-substituted adamantanones (**2**) electron-withdrawing (–I) groups W cause the attack to come from the syn face, while electron-donating groups cause it to come from the anti face.⁶ In 5,6-disubstituted norborn-2-en-7-one systems, the carbonyl appears to tilt away from the π bond, with reduction occurring from the more hindered face.⁷ An *ab initio* study of nucleophilic addition to 4-*tert*-butylcyclohexanones attempted to predict π -facial selectivity.⁸



The mechanistic picture is further simplified by the fact that free radical additions to carbon–heteroatom double bonds are not as prevalent (but see Reaction **16-31**).⁹ In most cases, the nucleophile forms the first new bond to carbon, and these reactions are regarded as *nucleophilic additions*, which can be represented as:



The electrophile shown in step 2 is the proton. In almost all the reactions considered in this chapter the electrophilic atom is either hydrogen or carbon. Note that step 1 is exactly the same as step 1 of the tetrahedral mechanism of nucleophilic substitution at a carbonyl carbon (Sec. 16.A.i), but carbon groups (A, B = H, alkyl aryl, etc.) are poor leaving groups so that substitution does not compete with addition. For carboxylic acid derivatives, there are leaving groups (B = Cl, OR, NH₂, etc.) and acyl substitution predominates (Sec. 16.A.i). *The nature of A and B determines whether a nucleophilic attack at a carbon–heteroatom multiple bond will lead to substitution or addition.*

Both acids and bases can catalyze many of these reactions.¹⁰ Bases catalyze the reaction by converting a reagent YH to the more powerful nucleophile Y[–] (see Sec. 10.G.ii). Acids

⁵ See Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, **1962**, pp. 68–74. Also see Bartlett, P.A. *Tetrahedron* **1980**, 36, 2, 22; Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* **1975**, 75, 521.

⁶ See Laube, T.; Stilz, H.U. *J. Am. Chem. Soc.* **1987**, 109, 5876.

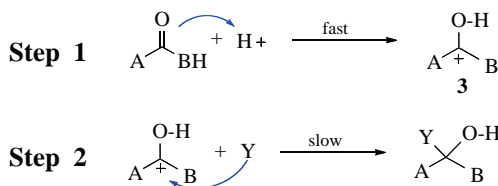
⁷ Kumar, V.A.; Venkatesan, K.; Ganguly, B.; Chandrasekhar, J.; Khan, F.A.; Mehta, G. *Tetrahedron Lett.* **1992**, 33, 3069.

⁸ Yadav, V.K.; Jeyaraj, D.A. *J. Org. Chem.* **1998**, 63, 3474. For a discussion of models, see Priyakumar, U.D.; Sastry, G.N.; Mehta, G. *Tetrahedron* **2004**, 60, 3465.

⁹ See Beckwith, A.L.J.; Hay, B.P. *J. Am. Chem. Soc.* **1989**, 111, 2674; Clerici, A.; Porta, O. *J. Org. Chem.* **1989**, 54, 3872; Cossy, J.; Pete, J.P.; Portella, C. *Tetrahedron Lett.* **1989**, 30, 7361.

¹⁰ See Jencks, W.P.; Gilbert, H.F. *Pure Appl. Chem.* **1977**, 49, 1021.

catalyze it by converting the substrate to an heteroatom-stabilized cation (oxocarbenium ion **3** from C=O) in step 1, thus making it more attractive to nucleophilic attack and making the reverse reaction somewhat less favorable. Similar catalysis can also be achieved with metallic ions (e.g., Ag^+), which act as Lewis acids.¹¹



In step 1 of the acid-catalyzed mechanism, the carbonyl reacts as a base with the proton to give **3**, which is known as an *oxocarbenium ion*. In Section 5.A.ii, it was pointed out that oxocarbenium ions are comparatively stable carbocations because the positive charge is delocalized on the oxygen by resonance.¹² Intermediate **3** then reacts with the nucleophile in step 2 to give the acyl addition product. The rate-determining step is usually the one involving nucleophilic attack. If one heteroatom (e.g., oxygen) stabilizes an adjacent carbocation, as in **3**, a second heteroatom (X) will stabilize an oxocarbenium ion ($-\text{X}-\text{C}^+-\text{X}-$) to a greater extent.¹³

Reactivity factors for carbon–heteroatom multiple bonds are similar to those for the tetrahedral mechanism of nucleophilic substitution.¹⁴ If A and/or B are electron-donating groups (e.g., alkyl groups), rates are decreased. Electron-attracting substituents increase rates. This means that aldehydes are more reactive than ketones. Aryl groups are somewhat deactivating compared to alkyl, because of resonance that stabilizes the substrate molecule, but is lost on going to the intermediate. Double bonds in conjugation with the carbon–heteroatom multiple bond also lower addition rates, for similar reasons but, more important, may provide competition from 1,4-addition (Sec. 15.A.ii). Steric factors are also quite important and contribute to the decreased reactivity of ketones compared with aldehydes. Highly hindered ketones like hexamethylacetone and dineopentyl ketone either do not undergo many of these reactions or require extreme conditions.

16.A.i. Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism

All the mechanisms discussed in previous chapters for substitution take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. Substitution at a carbonyl group (or the corresponding nitrogen and sulfur analogues) most often proceeds by a second-order mechanism, which in this book is called the *tetrahedral*¹⁵ *mechanism*.¹⁶

¹¹ Toromanoff, E. *Bull. Soc. Chim. Fr.* **1962**, 1190.

¹² See Brada, B.; Bundhoo, D.; Engels, B.; Hiberty, P.C. *Org. Lett.* **2008**, 10, 1951.

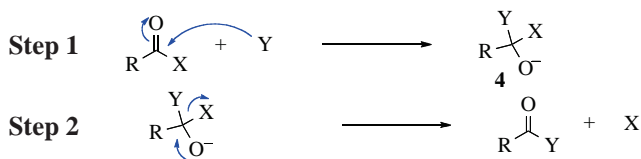
¹³ Chamberland, S.; Ziller, J.W.; Woerpel, K.A. *J. Am. Chem. Soc.* **2005**, 127, 5322.

¹⁴ For a review of the reactivity of nitriles, see Schaefer, F.C. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 239–305.

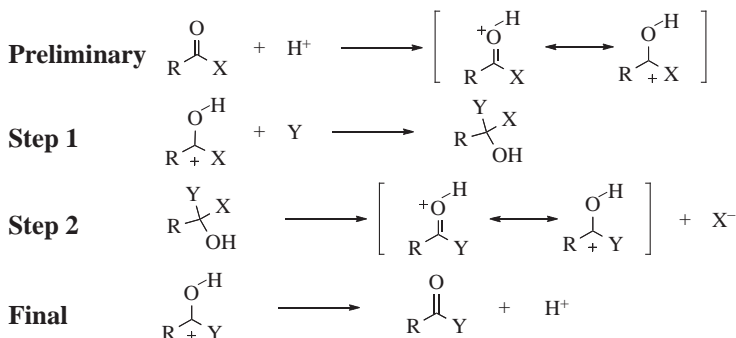
¹⁵ This mechanism has also been called the "addition–elimination mechanism".

¹⁶ See Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, **1972**, pp. 209–223; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, **1969**, pp. 463–554; Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, **1969**, pp. 375–452; Johnson, S.L. *Adv. Phys. Org. Chem.* **1967**, 5, 237.

The IUPAC designation is $A_N + D_N$. The S_N1 mechanisms, involving carbocations, are sometimes found with these substrates, especially with essentially ionic substrates (e.g., $\text{RCO}^+ \text{BF}_4^-$; there is evidence that in certain cases simple S_N2 mechanisms can take place, especially with a very good leaving group (e.g., Cl^-);¹⁷ and an SET mechanism has also been reported.¹⁸ However, the tetrahedral mechanism is by far the most prevalent. Although this mechanism displays second-order kinetics, it is not the same as the S_N2 mechanism discussed in Section 10.A.i. In the tetrahedral mechanism, first Y attacks to give an intermediate containing both X and Y (**4**), and then X leaves. This sequence, impossible at a saturated carbon, is possible at an unsaturated one because the central carbon can release a pair of electrons to the oxygen and so preserve its octet:



When reactions are carried out in acid solution, there may also be a preliminary and a final step:



The hydrogen ion is a catalyst. The reaction rate is increased because it is easier for the nucleophile to attack the carbon when the electron density of the latter has been decreased.¹⁹

Evidence for the existence of the tetrahedral mechanism is as follows:²⁰

1. The kinetics are first order each in the substrate and in the nucleophile, as predicted by the mechanism.
2. There is other kinetic evidence in accord with a tetrahedral intermediate. For example, the rate “constant” for the reaction between acetamide and hydroxylamine is not constant, but decreases with increasing hydroxylamine concentration.²¹ This

¹⁷ Williams, A. *Acc. Chem. Res.* **1989**, 22, 387. See Bentley, T.W.; Koo, I.S. *J. Chem. Soc. Perkin Trans. 2* **1989**, 1385. See, however, Buncel, E.; Um, I.H.; Hoz, S. *J. Am. Chem. Soc.* **1989**, 111, 971.

¹⁸ Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Ortega, F. *J. Am. Chem. Soc.* **1990**, 112, 9336.

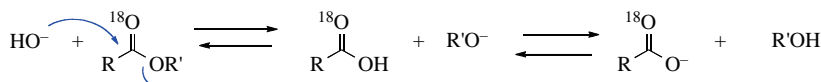
¹⁹ See Jencks, W.P. *Acc. Chem. Res.* **1976**, 9, 425; *Chem. Rev.* **1972**, 72, 705.

²⁰ Also see Guthrie, J.P. *J. Am. Chem. Soc.* **1978**, 100, 5892; Kluger, R.; Chin, J. *J. Am. Chem. Soc.* **1978**, 100, 7382; O’Leary, M.H.; Marlier, J.F. *J. Am. Chem. Soc.* **1979**, 101, 3300.

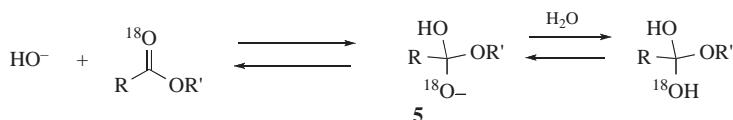
²¹ Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* **1964**, 86, 5616.

is not a smooth decrease; there is a break in the curve. A straight line is followed at low hydroxylamine concentration and another straight line at high concentration. This means that the identity of the rate-determining step is changing. Obviously, *this cannot happen if there is only one step: there must be two steps, and hence an intermediate*. Similar kinetic behavior has been found in other cases as well;²² in particular, plots of rate against pH are often bell-shaped.

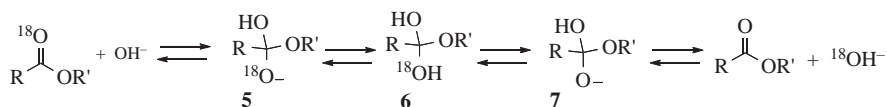
3. Basic hydrolysis has been carried out on carboxylic esters labeled with ^{18}O in the carbonyl group.²³ If this reaction proceeded by the normal $\text{S}_{\text{N}}2$ mechanism, all the ^{18}O would remain in the carbonyl group, even if, in an equilibrium process, some of the carboxylic acid formed went back to the starting material:



On the other hand, if the tetrahedral mechanism operates



then the intermediate **5** reacts with an acid (e.g., water) and is converted to the conjugate acid, symmetrical intermediate **6**. In this intermediate, the OH groups are equivalent, and (except for the small $^{18}\text{O}/^{16}\text{O}$ isotope effect) either one can lose a proton with equal facility:



The intermediates **5** and **7** can now lose OR' to give the carboxylic acid (not shown in the equations given), or they can lose OH to regenerate the carboxylic ester. If **5** reverts back to an ester, the ester will still be labeled, but if **7** reverts to an ester, the ^{18}O will be lost. A test of the two possible mechanisms is to stop the reaction before completion and to analyze the recovered ester for ^{18}O . Experiments by Bender²⁴ found that in alkaline hydrolysis of methyl, ethyl, and isopropyl benzoates, the esters had lost ^{18}O . A similar experiment carried out for acid-catalyzed hydrolysis of ethyl benzoate showed that here too the ester lost ^{18}O . However, alkaline hydrolysis of substituted benzyl benzoates showed *no* ^{18}O loss.²⁴ This result does not necessarily mean that no tetrahedral intermediate is involved in this case. If **5** and **7** do not revert to an ester, but go entirely to an acid, no ^{18}O loss will be found even with a tetrahedral intermediate. In the case of benzyl benzoates, this may very well be happening, because formation of the acid relieves steric strain. Another possibility is that **5** loses OR' before it can become

²² Kevill, D.N.; Johnson, S.L. *J. Am. Chem. Soc.* **1965**, 87, 928; Leinhard, G.E.; Jencks, W.P. *J. Am. Chem. Soc.* **1965**, 87, 3855; Schowen, R.L.; Jayaraman, H.; Kershner, L.D. *J. Am. Chem. Soc.* **1966**, 88, 3373.

²³ Bender, M.L.; Thomas, R.J. *J. Am. Chem. Soc.* **1961**, 83, 4183, 4189.

²⁴ Bender, M.L.; Matsui, H.; Thomas, R.J.; Tobey, S.W. *J. Am. Chem. Soc.* **1961**, 83, 4193. See also, Shain, S.A.; Kirsch, J.F. *J. Am. Chem. Soc.* **1968**, 90, 5848.

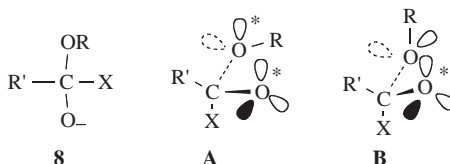
protonated to **6**.²⁵ Even the experiments that *do* show ^{18}O loss do not *prove* the existence of the tetrahedral intermediate, since it is possible that ^{18}O is lost by some independent process not leading to ester hydrolysis. To deal with this possibility, Bender and Heck²⁶ measured the rate of ^{18}O loss in the hydrolysis of ethyl trifluorothioacetate- ^{18}O :



This reaction had previously been shown²⁷ to involve an intermediate by the kinetic methods mentioned above. Bender and Heck²⁶ showed that the rate of ^{18}O loss and the value of the partitioning ratio k_2/k_3 as determined by the oxygen-exchange technique were exactly in accord with these values as previously determined by kinetic methods. Thus the original ^{18}O exchange measurements showed that there is a tetrahedral species present, but not necessarily on the reaction path, while the kinetic experiments showed that there is some intermediate present, but not necessarily tetrahedral. Bender and Heck's²⁶ results demonstrate that there is a tetrahedral intermediate and that it lies on the reaction pathway.

4. In some cases, tetrahedral intermediates have been isolated²⁸ or detected spectrally.²⁹

Several studies have been made of the directionality of approach by the nucleophile.³⁰ Menger³⁰ has proposed for reactions in general, and specifically for those that proceed by the tetrahedral mechanism, that there is no single definable preferred transition state, but rather a "cone" of trajectories. All approaches within this cone lead to reaction at comparable rates; it is only when the approach comes outside of the cone that the rate falls.



Directionality has also been studied for the second step. Once the tetrahedral intermediate (**4**) is formed, it loses Y (giving the product) or X (reverting to the starting compound). Deslongchamps has proposed that one of the factors affecting this choice is the conformation of the intermediate; more specifically, the positions of the lone pairs. In this view, a leaving group X or Y can depart only if the other two atoms on the carbon both have an orbital antiperiplanar to the C—X or C—Y bond. For example, consider an intermediate **8** formed by attack of ^-OR on a substrate $\text{R}'\text{COX}$. Cleavage of the C—X bond with loss of X can take place from conformation **A**, because the two lone-pair orbitals

²⁵ For evidence for this possibility, see McClelland, R.A. *J. Am. Chem. Soc.* **1984**, 106, 7579.

²⁶ Bender, M.L.; Heck, H. d'A. *J. Am. Chem. Soc.* **1967**, 89, 1211.

²⁷ Fedor, L.R.; Bruice, T.C. *J. Am. Chem. Soc.* **1965**, 87, 4138.

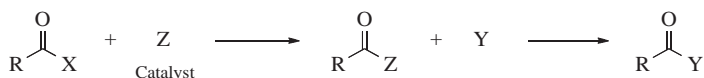
²⁸ See Khouri, F.F.; Kaloustian, M.K. *J. Am. Chem. Soc.* **1986**, 108, 6683.

²⁹ See Capon, B.; Dosunmu, M.I.; Sanchez, M. de N de M. *Adv. Phys. Org. Chem.* **1985**, 21, 37; McClelland, R.A.; Santry, L.J. *Acc. Chem. Res.* **1983**, 16, 394; Capon, B.; Ghosh, A.K.; Grieve, D.M.A. *Acc. Chem. Res.* **1981**, 14, 306. See also, van der Wel, H.; Nibbering, N.M.M. *Recl. Trav. Chim. Pays-Bas* **1988**, 107, 479, 491.

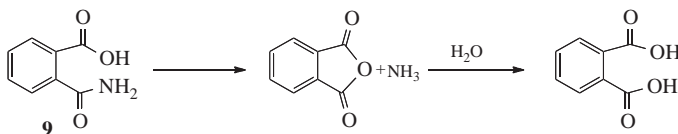
³⁰ See Menger, F.M. *Tetrahedron* **1983**, 39, 1013; Liotta, C.L.; Burgess, E.M.; Eberhardt, W.H. *J. Am. Chem. Soc.* **1984**, 106, 4849.

marked * are antiperiplanar to the C—X bond, but not from **B** because only the O[−] has such an orbital. If the intermediate is in conformation **B**, the OR may leave (if X has a lone-pair orbital in the proper position) rather than X. This factor is called *stereoelectronic control*.³¹ Free rotation in acyclic intermediates leads to many conformations, but some are preferred, and cleavage reactions may take place faster than rotation, so stereoelectronic control can be a factor in some situations. Much evidence has been presented for this concept.³² More generally, the term *stereoelectronic effects* refers to any case in which orbital position requirements affect the course of a reaction. The backside attack in the S_N2 mechanism is an example of a stereoelectronic effect.

Some nucleophilic substitutions at a carbonyl carbon are *catalyzed* by nucleophiles.³³ There occur, in effect, two tetrahedral mechanisms:



(For an example, see Reaction 16-58). When this happens internally, it is a neighboring-group mechanism at a carbonyl carbon.³⁴ For example, the hydrolysis of phthalamic acid (**9**) takes place as follows:



Evidence comes from comparative rate studies.³⁵ Thus **9** was hydrolyzed $\sim 10^5$ times faster than benzamide (PhCONH₂) at about the same concentration of hydrogen ions. That this enhancement of rate was not caused by the resonance or field effects of COOH (an electron-withdrawing group) was shown by the fact both *o*-nitrobenzamide and terephthalamic acid (the para isomer of **9**) were hydrolyzed more slowly than benzamide. Other examples of neighboring-group participation at a carbonyl carbon have been reported.³⁶ It is likely that nucleophilic catalysis is involved in enzyme catalysis of ester hydrolysis.

The attack of a nucleophile on a carbonyl group can result in substitution or addition, depending on the substituents, but the first step of each mechanism is the same. The main factor that determines the product is the identity of the group X in RCOX. When X is alkyl or hydrogen, addition usually takes place. When X is halogen, OCOR, NH₂, and so on, the

³¹ It has also been called the “antiperiplanar lone-pair hypothesis (ALPH)”. For a reinterpretation of this factor in terms of the principle of least nuclear motion (see Reaction 15-10), see Hosie, L.; Marshall, P.J.; Sinnott, M.L. *J. Chem. Soc. Perkin Trans. 2* **1984**, 1121; Sinnott, M.L. *Adv. Phys. Org. Chem.* **1988**, 24, 113.

³² Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, **1983**; Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, NY, **1983**. See Sinnott, M.L. *Adv. Phys. Org. Chem.* **1988**, 24, 113; Gorenstein, D.G. *Chem. Rev.* **1987**, 87, 1047; Deslongchamps, P. *Heterocycles* **1977**, 7, 1271. Also see Ndiwami, A.; Deslongchamps, P. *Can. J. Chem.* **1986**, 64, 1788; Hegarty, A.F.; Mullane, M. *J. Chem. Soc. Perkin Trans. 2* **1986**, 995. For evidence against the theory, see Perrin, C. L.; Nuñez, O. *J. Am. Chem. Soc.* **1986**, 108, 5997; **1987**, 109, 522.

³³ See Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, **1971**, pp. 147–179; Johnson, S.L. *Adv. Phys. Org. Chem.* **1967**, 5, 271. For a review where Z = a tertiary amine, see Cherkasova, E.M.; Bogatkov, S.V.; Golovina, Z.P. *Russ. Chem. Rev.* **1977**, 46, 246.

³⁴ Kirby, A.J.; Fersht, A.R. *Prog. Bioorg. Chem.* **1971**, 1, 1; Capon, B. *Essays Chem.* **1972**, 3, 127.

³⁵ Bender, M.L.; Chow, Y.; Chloupek, F.J. *J. Am. Chem. Soc.* **1958**, 80, 5380.

³⁶ See Page, M.I.; Render, D.; Bernáth, G. *J. Chem. Soc. Perkin Trans. 2* **1986**, 867.

usual reaction is substitution. When $X = OH$, protonation to generate OH_2^+ is usually required before the group can be lost.

In both the S_N1 and S_N2 mechanisms, the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways: (1) By altering the electron density at the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X , the greater the partial positive charge on C and the more rapid the attack by a nucleophile. (2) The nature of the leaving group affects the *position of equilibrium*. In the intermediate **4**, there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y , then Y will preferentially leave and **4** will revert to the starting compounds. Thus there is a partitioning factor between **4** going on to product (loss of X) or back to starting compound (loss of Y). The sum of these two factors causes the sequence of reactivity to be $RCOCl > RCOOCOR' > RCOOAr > RCOOR' > RCONH_2 > RCONR'_2 > RCOO^-$.³⁷ Note that this order is approximately the order of decreasing stability of the leaving-group anion. If the leaving group is bulky, it may exert a steric effect and retard the rate for this reason.

For a list of some of the more important reactions that operate by the tetrahedral mechanism, see Table 16.1, which shows the main reactions that proceed by the tetrahedral mechanism.

TABLE 16.1 The More Important Synthetic Reactions That Take Place by the Tetrahedral Mechanism.^a

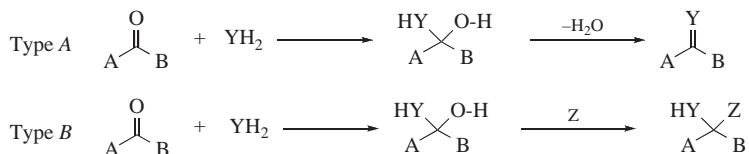
Reaction Number	Reaction
16-57	$RCOX + H_2O \longrightarrow RCOOH$
16-58	$RCOOCOR' + H_2O \longrightarrow RCOOH + R'COOH$
16-59	$RCO_2R' + H_2O \longrightarrow RCOOH + R'OH$
16-59	$RCONR'_2 + H_2O \longrightarrow RCOOH + R'_2NH$ ($R' = H, \text{alkyl, aryl}$)
16-61	$RCOX + R'OH \longrightarrow RCO_2R'$
16-62	$RCOOCOR + R'OH \longrightarrow RCO_2R'$
16-63	$RCOOH + R'OH \longrightarrow RCO_2R'$
16-64	$RCO_2R' + R''OH \longrightarrow RCO_2R'' + R'OH$
16-66	$RCOX + R'COO^- \longrightarrow RCOOCOR'$
10-21	$RCOX + H_2O_2 \longrightarrow RCO_3H$
16-69	$RCOX + R'SH \longrightarrow RCOSR'$
16-72	$RCOX + NHR'_2 \longrightarrow RCONR'_2$ ($R' = H, \text{alkyl, aryl}$)
16-73	$RCOOCOR + NHR'_2 \longrightarrow RCONR'_2$ ($R' = H, \text{alkyl, aryl}$)
16-74	$RCOOH + NHR'_2 \xrightarrow[\text{agent}]{\text{coupling}} RCONR'_2$ ($R' = H, \text{alkyl, aryl}$)
16-75	$RCO_2R' + NHR^2 \xrightarrow{\text{agent}} RCONR^2$ ($R^2 = H, \text{alkyl, aryl}$)
16-79	$RCOOH + SOCl_2 \longrightarrow RCOCl$
19-39	$RCOX + LiAlH(O-t-Bu)_3 \longrightarrow RCHO$
19-41	$RCONR'_2 + LiAlH_4 \longrightarrow RCHO$
16-81	$RCOX + R_2CuLi \longrightarrow RCOR'$
16-85	$2RCH_2CO_2R' \longrightarrow RCH_2COCHR'CO_2R'$

^aCatalysts are not shown.

³⁷ The compound $RCOOH$ would belong in this sequence just after $RCOOAr$, but it fails to undergo many reactions for a special reason. Many nucleophiles, instead of attacking the $C=O$ group, are basic enough to take a proton from the acid, converting it to the unreactive $RCOO^-$.

16.B. REACTIONS

Many of the reactions in this chapter are simple additions to carbon–hetero multiple bonds, with the reaction ending when the two groups have been added. But in many other cases subsequent reactions take place. There are generally two types:



In type A, the initially formed adduct loses water (or, in the case of addition to $\text{C}=\text{NH}$, ammonia, etc.), and the net result of the reaction is the substitution of $\text{C}=\text{Y}$ for $\text{C}=\text{O}$ (or $\text{C}=\text{NH}$, etc.). In type B there is a rapid substitution, and the OH (or NH_2 , etc.) is replaced by another group Z, which is often another YH moiety. This substitution is nucleophilic in most cases: Y usually has an unshared pair and $\text{S}_{\text{N}}1$ reactions occur very well on this type of compound (Sec. 10.G.i, category 2), even when the leaving group is as poor as OH or NH_2 . In this chapter, reactions will be classified according to what is initially adding to the carbon–heteroatom multiple bond, even if subsequent reactions take place so rapidly that it is impossible to isolate the initial adduct.

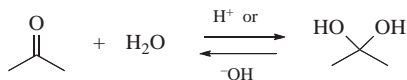
Most of the reactions considered in this chapter can be reversed. In many cases, we will consider the reverse reactions with the forward ones, in the same section. The reverse of some of the other reactions are considered in other chapters. In still other cases, one of the reactions in this chapter is the reverse of another (e.g., 16-2 and 16-13). For reactions that are reversible, the principle of microscopic reversibility (Sec. 6.H) applies.

First, reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the heteroatom will be discussed. Second, reactions in which carbon adds to the heteroatom will be discussed. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isocyanides, which are different in character, follow. Acyl substitution reactions that proceed by the tetrahedral mechanism, which mostly involve derivatives of carboxylic acids, are treated at the end.

16.B.i. Reactions in which Hydrogen or a Metallic Ion Adds to the Heteroatom

A. Attack by OH (Addition of H_2O)

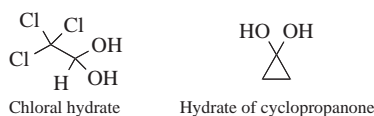
16-1 The Addition of Water to Aldehydes and Ketones: Formation of Hydrates

O-Hydro-*C*-hydroxy-addition

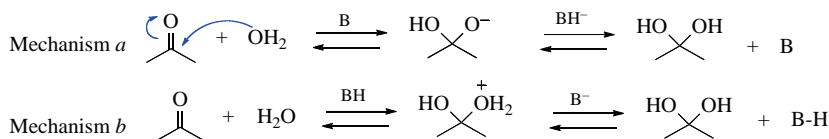
The adduct formed upon addition of water to an aldehyde or ketone is called a hydrate or *gem*-diol.³⁸ These compounds are usually stable only in water solution and decompose on

³⁸ See Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, 1973, pp. 183–187; *Adv. Phys. Org. Chem.* 1966, 4, 1; Le Hénaff, P. *Bull. Soc. Chim. Fr.* 1968, 4687.

distillation; that is, the equilibrium shifts back toward the carbonyl compound, usually via formation of an enol and tautomerization to the carbonyl. The position of the equilibrium is greatly dependent on the structure of the hydrate. Thus, formaldehyde in water at 20 °C exists 99.99% in the hydrated form, while for acetaldehyde this figure is 58%, and for acetone the hydrate concentration is negligible.³⁹ It has been found, by exchange with ¹⁸O, that the reaction with acetone is quite rapid when catalyzed by acid or base, but the equilibrium lies on the side of acetone and water.⁴⁰ Since methyl, a +I group, inhibits hydrate formation, it may be expected that electron-attracting groups would have the opposite effect, and this is indeed the case. The hydrate of chloral (trichloroacetaldehyde)⁴¹ is a stable crystalline substance. In order for it to revert to chloral, ⁻OH or H₂O must leave. This is made difficult by the electron-withdrawing character of the Cl₃C group and by the absence of a proton on the α carbon, which is required for loss of water to form an enol. Some other⁴² polychlorinated and polyfluorinated aldehydes and ketones⁴³ and α-keto aldehydes also form stable hydrates, as do cyclopropanones.⁴⁴ In the last case,⁴⁵ formation of the hydrate relieves some of the I strain (Sec. 9.B) of the parent ketone.



The reaction is subject to both general-acid and general-base catalysis; the following mechanisms can be written for basic (B) and acidic (BH) catalysis, respectively:⁴⁶



In mechanism *a*, as the H₂O attacks, the base pulls off a proton, and the net result is addition of ⁻OH. This can happen because the base is already hydrogen bonded to the H₂O molecule before the attack. In mechanism *b*, because HB is already hydrogen bonded to the oxygen of the carbonyl group, it gives up a proton to the oxygen as the water attacks. In this way, B and HB accelerate the reaction even beyond the extent that they form ⁻OH or H₃O⁺ by reaction with water. Reactions in which the catalyst donates a proton to the electrophilic reagent (in this case the aldehyde or ketone) in one direction and removes it in the other are called class e reactions. Reactions in which the catalyst does the same to the nucleophilic reagent are called class n reactions.⁴⁷ Thus the acid-catalyzed process here is a class e reaction, while the base-catalyzed process is a class n reaction.

³⁹ Bell, R.P.; Clunie, J.C. *Trans. Faraday Soc.* **1952**, 48, 439. See also, Bell, R.P.; McDougall, A.O. *Trans. Faraday Soc.* **1960**, 56, 1281.

⁴⁰ Cohn, M.; Urey, H.C. *J. Am. Chem. Soc.* **1938**, 60, 679.

⁴¹ For a review of chloral, see Luknitskii, F.I. *Chem. Rev.* **1975**, 75, 259.

⁴² Schulman, E.M.; Bonner, O.D.; Schulman, D.R.; Laskovics, F.M. *J. Am. Chem. Soc.* **1976**, 98, 3793.

⁴³ For a review of addition to fluorinated ketones, see Gambaryan, N.P.; Rokhlin, E.M.; Zeifman, Yu.V.; Ching-Yun, C.; Knunyants, I.L. *Angew. Chem. Int. Ed.* **1966**, 5, 947.

⁴⁴ See Krois, D.; Lehner, H. *Monatsh. Chem.* **1982**, 113, 1019.

⁴⁵ Turro, N.J.; Hammond, W.B. *J. Am. Chem. Soc.* **1967**, 89, 1028. For a review of cyclopropanone chemistry, see Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* **1974**, 47, 73.

⁴⁶ Sørensen, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* **1987**, 109, 4675; Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, **1987**, pp. 662–680. A theoretical treatment is in Wolfe, S.; Kim, C.-K.; Yang, K.; Weinberg, N.; Shi, Z. *J. Am. Chem. Soc.* **1995**, 117, 4240.

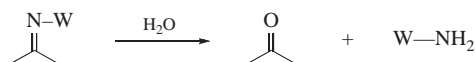
⁴⁷ Jencks, W.P. *Acc. Chem. Res.* **1976**, 9, 425.

For the reaction between ketones and H_2O_2 , see 17-37.

There are no OS references, but see OS VIII, 597, for the reverse reaction.

16-2 Hydrolysis of the Carbon–Nitrogen Double Bond⁴⁸

Oxo-de-alkylimino-bisubstitution, and so on



Compounds containing carbon–nitrogen double bonds can be hydrolyzed to the corresponding aldehydes or ketones.⁴⁹ For imines ($\text{W} = \text{R}$ or H) the hydrolysis is easy and can be carried out with water. When $\text{W} = \text{H}$, the imine is seldom stable enough for isolation, and in aqueous media hydrolysis usually occurs *in situ*, without isolation. The hydrolysis of *Schiff bases* ($\text{W} = \text{Ar}$) is more difficult and requires acid or base catalysis. Oximes ($\text{W} = \text{OH}$), arylhydrazones ($\text{W} = \text{NHAr}$), and, most easily, semicarbazones ($\text{W} = \text{NHCONH}_2$) can also be hydrolyzed. Often a reactive aldehyde (e.g., formaldehyde), is added to combine with the liberated amine.

A number of reagents⁵⁰ have been used to cleave $\text{C}=\text{N}$ bonds, especially those not easily hydrolyzable with acidic or basic catalysts or those that contain other functional groups that are attacked under these conditions.

Oximes have been converted to the corresponding aldehyde or ketone⁵¹ by treatment with aq phosphoric acid without an organic cosolvent,⁵² periodic acid,⁵³ DABCO– Br_2 ,⁵⁴ NBS in water,⁵⁵ Chloramine-T⁵⁶ HCO_2H on SiO_2 with microwave irradiation,⁵⁷ and 20% I_2 in water containing SDS (sodium dodecyl sulfate)⁵⁸ or in an ionic liquid on SiO_2 .⁵⁹ Transition metal compounds have been used, including those of Sb,⁶⁰ Co,⁶¹ Hg,⁶² Bi,⁶³ Cu,⁶⁴ or Zn.⁶⁵ Oxidizing agents can be quite effective, including KMnO_4 on Al_2O_3 ,⁶⁶ tetraalkylammonium permanganates,⁶⁷ and quinolinium dichromate.⁶⁸ Alkaline H_2O_2 ⁶⁹ has also been used.

⁴⁸ For a review, see Khoei, S.; Ruoho, A.E. *Org. Prep. Proceed. Int.* **2003**, 35, 527.

⁴⁹ For proton affinities of imines, see Hammerum, S.; Sølling, T.I. *J. Am. Chem. Soc.* **1999**, 121, 6002.

⁵⁰ For a list of reagents, with references, see Ranu, B.C.; Sarkar, D.C. *J. Org. Chem.* **1988**, 53, 878.

⁵¹ For a review, see Corsaro, A.; Chiacchio, U.; Pistrà, V. *Synthesis* **2001**, 1903.

⁵² Bhar, S.; Guha, S. *Synth. Commun.* **2005**, 35, 1183.

⁵³ Li, Z.; Ding, R.-B.; Xing, Y.-L.; Shi, S.-Y. *Synth. Commun.* **2005**, 35, 2515.

⁵⁴ Heravi, M.M.; Derikvand, F.; Ghassemzadeh, M. *Synth. Commun.* **2006**, 36, 581.

⁵⁵ Bandgar, B.P.; Makone, S.S. *Org. Prep. Proceed. Int.* **2000**, 32, 391.

⁵⁶ Padmavathi, V.; Reddy, K.V.; Padmaja, A.; Venugopalan, P. *J. Org. Chem.* **2003**, 68, 1567.

⁵⁷ A solvent-free reaction. See Zhou, J.-F.; Tu, S.-J.; Feng, J.-C. *Synth. Commun.* **2002**, 32, 959.

⁵⁸ Gogoi, P.; Hazarika, P.; Konwar, D. *J. Org. Chem.* **2005**, 70, 1934.

⁵⁹ Li, D.; Shi, F.; Guo, S.; Deng, Y. *Tetrahedron Lett.* **2004**, 45, 265.; Li, D.; Shi, F.; Deng, Y. *Tetrahedron Lett.* **2004**, 45, 6791.

⁶⁰ Narsaiah, A.V.; Nagaiah, K. *Synthesis* **2003**, 1881.

⁶¹ Mukai, C.; Nomura, I.; Kataoka, O.; Hanaoka, M. *Synthesis* **1999**, 1872.

⁶² De, S.K. *Synth. Commun.* **2004**, 34, 2289.

⁶³ See Arnold, J.N.; Hayes, P.D.; Kohaus, R.L.; Mohan, R.S. *Tetrahedron Lett.* **2003**, 44, 9173.

⁶⁴ Hashemi, M.M.; Beni, Y.A. *Synth. Commun.* **2001**, 31, 295; Tamami, B.; Kiasat, A.R. *Synth. Commun.* **2000**, 30, 4129.

⁶⁵ Tamami, B.; Kiasat, A.R. *Synth. Commun.* **2000**, 30, 4129.

⁶⁶ See Imanzadeh, G.H.; Hajipour, A.R.; Mallakpour, S.E. *Synth. Commun.* **2003**, 33, 735.

⁶⁷ Hajipour, A.R.; Mallakpour, S.E.; Khoei, E. *Synth. Commun.* **2002**, 32, 9.

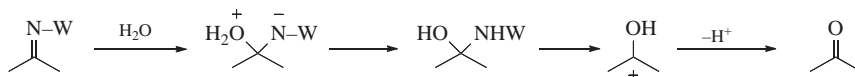
⁶⁸ Sadeghi, M.M.; Mohammadpour-Baltork, I.; Azarm, M.; Mazidi, M.R. *Synth. Commun.* **2001**, 31, 435. See also, Zhang, G.-S.; Yang, D.-H.; Chen, M.-F. *Org. Prep. Proceed. Int.* **1998**, 30, 713.

⁶⁹ Ho, T. *Synth. Commun.* **1980**, 10, 465.

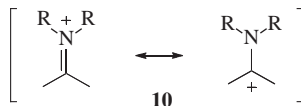
Phenylhydrazones can be converted to a ketone using Oxone and KHCO_3 ,⁷⁰ polymer-bound iodonium salts,⁷¹ or KMnO_4 on wet SiO_2 .⁷² Dimethylhydrazones have been converted to ketones with $\text{FeSO}_4 \cdot 7 \text{H}_2\text{O}$ in chloroform,⁷³ and $\text{Me}_3\text{SiCl}/\text{NaI}$ in acetonitrile with 1% water.⁷⁴ Hydrazones (e.g., RAMP or SAMP, Reaction **10-68**, category 4) can be hydrolyzed with aq CuCl_2 .⁷⁵ Tosylhydrazones can be hydrolyzed to the corresponding ketones with aq acetone and BF_3 –etherate,⁷⁶ as well as with other reagents.⁷⁷

Semicarbazones have been cleaved with ammonium chlorochromates on alumina⁷⁸ ($\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$,⁷⁹ $\text{Mg}(\text{HSO}_4)_2$ on wet silica,⁸⁰ or by SbCl_3 with microwave irradiation.⁸¹

The hydrolysis of carbon–nitrogen double bonds involves initial addition of water and elimination of a nitrogen moiety:



It is thus an example of reaction type A (see above). The sequence shown is generalized.⁸² In specific cases, there are variations in the sequence of the steps, depending on acid or basic catalysis or other conditions.⁸³ Which step is rate determining also depends on acidity and on the nature of W and of the groups connected to the carbonyl.⁸⁴



Iminium ions (**10**)⁸⁵ would be expected to undergo hydrolysis quite readily, since there is a resonance contributor with a positive charge on the carbon. Indeed, they react with water at room temperature.⁸⁶ Acid-catalyzed hydrolysis of enamines (the last step of the *Stork enamine reaction*, **10-69**, involves conversion to iminium ions).⁸⁷

⁷⁰ Hajipour, A.R.; Mahboubghah, N. *Org. Prep. Proceed. Int.* **1999**, 31, 112.

⁷¹ Chen, D.-J.; Cheng, D.-P.; Chen, Z.-C. *Synth. Commun.* **2001**, 31, 3847.

⁷² Hajipour, A.R.; Adibi, H.; Ruoho, A.E. *J. Org. Chem.* **2003**, 68, 4553.

⁷³ Nasreen, A.; Adapa, S.R. *Org. Prep. Proceed. Int.* **1999**, 31, 573.

⁷⁴ Kamal, A.; Ramana, K.V.; Arifuddin, M. *Chem. Lett.* **1999**, 827.

⁷⁵ Enders, D.; Hundertmark, T.; Lazny, R. *Synth. Commun.* **1999**, 29, 27.

⁷⁶ Sacks, C.E.; Fuchs, P.L. *Synthesis* **1976**, 456.

⁷⁷ See Chandrasekhar, S.; Reddy, Ch.R.; Reddy, M.V. *Chem. Lett.* **2000**, 430; Jiricny, J.; Orere, D.M.; Reese, C.B. *Synthesis* **1970**, 919.

⁷⁸ Zhang, G.-S.; Gong, H.; Yang, D.-H.; Chen, M.-F. *Synth. Commun.* **1999**, 29, 1165; Gong, H.; Zhang, G.-S. *Synth. Commun.* **1999**, 29, 2591.

⁷⁹ Chen, F.-E.; Liu, J.-P.; Fu, H.; Peng, Z.-Z.; Shao, L.-Y. *Synth. Commun.* **2000**, 30, 2295.

⁸⁰ Shirini, F.; Zolfigol, M.A.; Mallakpour, B.; Mallakpour, S.E.; Hajipour, A.R.; Baltork, I.M. *Tetrahedron Lett.* **2002**, 43, 1555.

⁸¹ Mitra, A.K.; De, A.; Karchaudhuri, N. *Synth. Commun.* **2000**, 30, 1651.

⁸² For reviews of the mechanism, see Bruylants, A.; Feytmants-de Medicis, E. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 465–504; Salomaa, P. in Patai, S. *The Chemistry of the Carbonyl Group* pt. 1, Wiley, NY, **1966**, pp. 199–205.

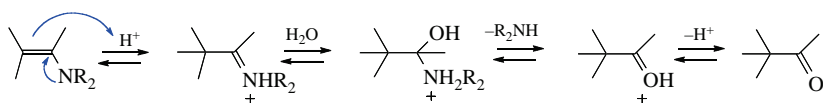
⁸³ See Sayer, J.M.; Conlon, E.H. *J. Am. Chem. Soc.* **1980**, 102, 3592.

⁸⁴ Cordes, E.H.; Jencks, W.P. *J. Am. Chem. Soc.* **1963**, 85, 2843.

⁸⁵ For a review of iminium ions, see Böhme, H.; Haake, M. *Adv. Org. Chem.* **1976**, 9, pt. 1, 107.

⁸⁶ Hauser, C.R.; Lednicer, D. *J. Org. Chem.* **1959**, 24, 46. For a study of the mechanism, see Gopalakrishnan, G.; Hogg, J.L. *J. Org. Chem.* **1989**, 54, 768.

⁸⁷ Sollenberger, P.Y.; Martin, R.B. *J. Am. Chem. Soc.* **1970**, 92, 4261. For a review of enamine hydrolysis see Stamhuis, E.J.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, **1988**, pp. 165–180.



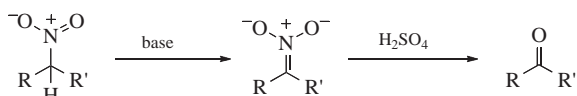
The mechanism of enamine hydrolysis is thus similar to that of vinyl ether hydrolysis (Reaction 10-6).

OS I, 217, 298, 318, 381; II, 49, 223, 234, 284, 310, 333, 395, 519, 522; III, 20, 172, 626, 818; IV, 120; V, 139, 277, 736, 758; VI, 1, 358, 640, 751, 901, 932; VII, 8; 65, 108, 183; 67, 33; 76, 23.

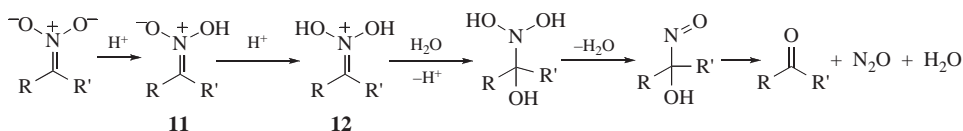
OS II, 24; IV, 819; V, 273; VI, 910.

16-3 Hydrolysis of Aliphatic Nitro Compounds

Oxo-de-hydro,nitro-bisubstitution



Primary or secondary aliphatic nitro compounds can be hydrolyzed, respectively, to aldehydes or ketones, by treatment of their conjugate bases with sulfuric acid. This is called the *Nef reaction*.⁸⁸ Tertiary aliphatic nitro compounds do not give the reaction because they cannot be converted to their conjugate bases. Like 16-2, this reaction involves hydrolysis of a C=N double bond. A possible mechanism involves initial formation of the *aci form* of the nitro compound (11):⁸⁹



Intermediates of type 12 have been isolated in some cases.⁹⁰

The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions by several alternative methods.⁹¹ Among these are treatment of the nitro compound with basic H_2O_2 in an ionic liquid,⁹² or 30% H_2O_2 — K_2CO_3 ,⁹³ DBU in acetonitrile,⁹⁴ or CAN.⁹⁵

When *primary* nitro compounds are treated with sulfuric acid without previous conversion to the conjugate bases, they give carboxylic acids. Hydroxamic acids are intermediates and can be isolated, so that this is also a method for their preparation.⁹⁶ Both the *Nef reaction* and the hydroxamic acid process involve the *aci form*; the difference in products arises from

⁸⁸ See Pinnick, H.W. *Org. React.* **1990**, 38, 655; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1988**, pp. 220–231, 416–419.

⁸⁹ Hawthorne, M.F. *J. Am. Chem. Soc.* **1957**, 79, 2510. Also see van Tamelen, E.E.; Thiede, R.J. *J. Am. Chem. Soc.* **1952**, 74, 2615; Sun, S.F.; Folliard, J.T. *Tetrahedron* **1971**, 27, 323.

⁹⁰ Feuer, H.; Spinicelli, L.F. *J. Org. Chem.* **1977**, 42, 2091.

⁹¹ For a review, see Ballini, R.; Petrini, M. *Tetrahedron* **2004**, 60, 1017.

⁹² Bortolini, O.; De Nino, A.; Garofalo, A.; Maiuolo, L.; Russo, B. *Synth. Commun.* **2010**, 40, 2483.

⁹³ Olah, G.A.; Arvanaghi, M.; Vankar, Y.D.; Prakash, G.K.S. *Synthesis* **1980**, 662.

⁹⁴ Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, 43, 5233.

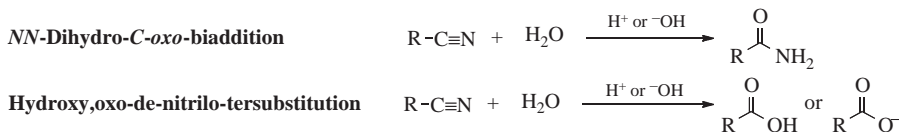
⁹⁵ Olah, G.A.; Gupta, B.G.B. *Synthesis* **1980**, 44.

⁹⁶ See Sosnovsky, G.; Krogh, J.A. *Synthesis* **1980**, 654.

higher acidity. For example, a difference in sulfuric acid concentration from 2 to 15.5 M changes the product from the aldehyde to the hydroxamic acid.⁹⁷ The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, it may be that the protonated *aci form* of the nitro compound is further protonated.

OS VI, 648; VII, 414. See also, OS IV, 573.

16-4 Hydrolysis of Nitriles



Nitriles can be hydrolyzed to give either amides or carboxylic acids.⁹⁸ The amide is formed initially, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is readily formed. When the acid is desired,⁹⁹ the reagent of choice is aq NaOH containing ~6–12% H₂O₂, but acid-catalyzed hydrolysis is also carried out. The reaction of nitriles with TFA–acetic acid–sulfuric acid, followed by treatment with water gives the corresponding amide.¹⁰⁰ A Rh catalyzed hydrolysis with aq isopropyl alcohol leads to the amide.¹⁰¹ A "dry" hydrolysis of nitriles has been reported.¹⁰² Enzymatic hydrolysis to give the amide was reported with nitrilase (ZmNIT2).¹⁰³ Nitriles can be hydrolyzed to the carboxylic acids without disturbing carboxylic ester functions also present, by the use of tetrachloro- or tetrafluorophthalic acid.¹⁰⁴

Hydrolysis of cyanohydrins [RCH(OH)CN] is usually carried out under acidic conditions, because basic solutions cause competing reversion of the cyanohydrin to the aldehyde and CN[–]. However, cyanohydrins have been hydrolyzed under basic conditions with borax or alkaline borates.¹⁰⁵

There are a number of procedures for stopping at the amide stage,¹⁰⁶ among them the use of concentrated H₂SO₄; 2 molar equivalents of chlorotrimethylsilane followed by H₂O,¹⁰⁷ aq NaOH with PEG-400 and microwave irradiation,¹⁰⁸ heating on neutral alumina,¹⁰⁹ or dry HCl followed by H₂O. The same result can also be obtained by use

⁹⁷ Kornblum, N.; Brown, R.A. *J. Am. Chem. Soc.* **1965**, 87, 1742. See also, Edward, J.T.; Tremaine, P.H. *Can J. Chem.* **1971**, 49, 3483, 3489, 3493.

⁹⁸ See Zil'berman, E.N. *Russ. Chem. Rev.* **1984**, 53, 900; Compagnon, P.L.; Miocque, M. *Ann. Chim. (Paris)* **1970**, [14] 5, 11, 23.

⁹⁹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1986–1987.

¹⁰⁰ Moorthy, J.N.; Singhal, N. *J. Org. Chem.* **2005**, 70, 1926.

¹⁰¹ Goto, A.; Endo, K.; Saito, S. *Angew. Chem. Int. Ed.* **2008**, 47, 3607.

¹⁰² Chemat, F.; Poux, M.; Berlan, J. *J. Chem. Soc. Perkin Trans. 2* **1996**, 1781; **1994**, 2597.

¹⁰³ Mukherjee, C.; Zhu, D.; Biehl, E.R.; Parmar, R.R.; Hua, L. *Tetrahedron* **2006**, 62, 6150. Also see Black, G.W.; Gregson, T.; McPake, C.B.; Perry, J.J.; Zhang, M. *Tetrahedron Lett.* **2010**, 51, 1639.

¹⁰⁴ Rounds, W.D.; Eaton, J.T.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* **1988**, 29, 6557.

¹⁰⁵ Jammot, J.; Pascal, R.; Commeyras, A. *Tetrahedron Lett.* **1989**, 30, 563.

¹⁰⁶ See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 119–125. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1988–1990.

¹⁰⁷ Basu, M.K.; Luo, F.-T. *Tetrahedron Lett.* **1998**, 39, 3005.

¹⁰⁸ Bendale, P.M.; Khadilkar, B.M. *Synth. Commun.* **2000**, 30, 1713.

¹⁰⁹ Wligus, C.P.; Downing, S.; Molitor, E.; Bains, S.; Pagni, R.M.; Kabalka, G.W. *Tetrahedron Lett.* **1995**, 36, 3469.

of water and certain metal ions or complexes¹¹⁰ including an In,¹¹¹ Au,¹¹² or a Ru catalyst.¹¹³ Other reagents include MnO₂/SiO₂ with microwave irradiation,¹¹⁴ or Hg(OAc)₂ in HOAc.¹¹⁵ The reaction of ferric nitrate and an amine generates the amide.¹¹⁶

Nitriles are converted to thioamides [ArC(=S)NH₂] with ammonium sulfide [(NH₄)₂S] in methanol, with microwave irradiation.¹¹⁷ Thioamides are also prepared using phosphorus pentasulfide.¹¹⁸

Thiocyanates are converted to thiocarbamates in a similar reaction:¹¹⁹ R—S—C≡N + H₂O → R—S—CO—NH₂. Hydrolysis of cyanamides gives amines, produced by the breakdown of the unstable carbamic acid intermediates: R₂NCN → [R₂NCOOH] → R₂NH.

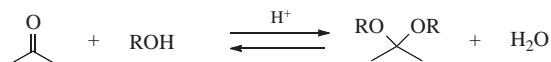
OS **I**, 21, 131, 201, 289, 298, 321, 336, 406, 436, 451; **II**, 29, 44, 292, 376, 512, 586 (see, however, **V**, 1054), 588; **III**, 34, 66, 84, 88, 114, 221, 557, 560, 615, 851; **IV**, 58, 93, 496, 506, 664, 760, 790; **V**, 239; **VI**, 932; **76**, 169. Also see, OS **III**, 609; **IV**, 359, 502; **66**, 142.

B. Attack by OR (Addition of ROH)

16-5 The Addition of Alcohols to Aldehydes and Ketones

Dialkoxy-de-oxo-bisubstitution

Dithioalkyl-de-oxo-bisubstitution



Acetals and ketals are formed by treatment of aldehydes and ketones, respectively, with alcohols in the presence of acid catalysts.¹²⁰ Lewis acid derivatives of Ti,¹²¹ Cu,¹²² In,¹²³ Ru,¹²⁴ or Co¹²⁵ can be used in conjunction with alcohols. Organocatalysts have been used for this conversion under acid-free conditions.¹²⁶ This reaction is reversible, and acetals and ketals can be hydrolyzed by treatment with acid.¹²⁷ With small unbranched aldehydes the equilibrium lies to the right. If ketals or acetals of larger molecules must be prepared the equilibrium must be shifted, usually by removal of water. This can be done by azeotropic distillation, ordinary distillation, or the use of a drying agent (e.g., Al₂O₃ or a molecular sieve).¹²⁸ The reaction is not

¹¹⁰ See McKenzie, C.J.; Robson, R. *J. Chem. Soc., Chem. Commun.* **1988**, 112.

¹¹¹ Kim, E.S.; Lee, H.S.; Kim, S.H.; Kim, J.N. *Tetrahedron Lett.* **2010**, 51, 1589.

¹¹² Ramón, R.S.; Marion, N.; Nolan, S.P. *Chemistry: Eur. J.* **2009**, 15, 8695.

¹¹³ See Polshettiwar, V.; Varma, R.S. *Chemistry: Eur. J.* **2009**, 15, 1582.

¹¹⁴ For a solvent-free reaction. See Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* **2002**, 32, 1731.

¹¹⁵ Plummer, B.F.; Menendez, M.; Songster, M. *J. Org. Chem.* **1989**, 54, 718.

¹¹⁶ Allen, C.L.; Lapkin, A.A.; Williams, J.M.J. *Tetrahedron Lett.* **2009**, 50, 4262.

¹¹⁷ Bagley, M.C.; Chapaneri, K.; Glover, C.; Merritt, E.A. *Synlett* **2004** 2615.

¹¹⁸ Kaboudin, B.; Elhamifar, D. *Synthesis* **2006**, 224.

¹¹⁹ Zil'berman, E.N.; Lazaris, A.Ya. *J. Gen. Chem. USSR* **1963**, 33, 1012.

¹²⁰ For reviews, see Meskens, F.A.J. *Synthesis* **1981**, 501; Schmitz, E.; Eichhorn, I. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, **1967**, pp. 309–351.

¹²¹ Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* **2001**, 57, 217.

¹²² Kumar, R.; Chakraborti, A.K. *Tetrahedron Lett.* **2005**, 46, 8319.

¹²³ Gregg, B.T.; Golden, K.C.; Quin, J.F. *Tetrahedron* **2008**, 64, 3287.

¹²⁴ De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* **2004**, 45, 8141.

¹²⁵ Velusamy, S.; Punniyamurthy, T. *Tetrahedron Lett.* **2004**, 45, 4917.

¹²⁶ Kotke, M.; Schreiner, P.R. *Tetrahedron* **2006**, 62, 434.

¹²⁷ See Heravi, M.M.; Tajbakhsh, M.; Habibzadeh, S.; Ghassemzadeh, M. *Monat. Chem.* **2001**, 132, 985.

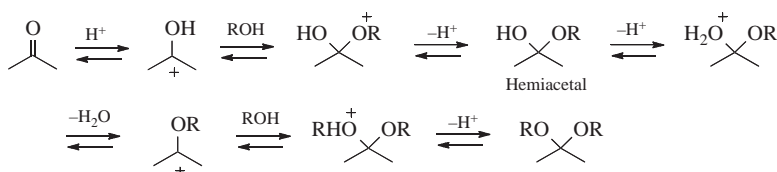
¹²⁸ For many examples of each of these methods, see Meskens, F.A.J. *Synthesis* **1981**, 501, pp. 502–505.

catalyzed in either direction by bases, so most acetals and ketals are quite stable to bases, though they are easily hydrolyzed by acids. This reaction is therefore a useful method of protection of aldehyde or ketone functions from attack by bases. The reaction is of wide scope.

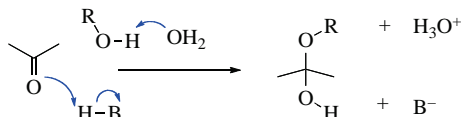
Most aldehydes are easily converted to acetals,¹²⁹ but the reaction with ketones is more difficult, presumably for steric reasons. While the reaction often fails, many ketals, especially from cyclic ketones, have been made in this manner.¹³⁰ Many functional groups may be present without being affected. 1,2- and 1,3-Diols form cyclic acetals and ketals (1,3-dioxolanes¹³¹ and 1,3-dioxanes,¹³² respectively), and these are often used to protect aldehydes and ketones. Chiral dioxolanes have been prepared from chiral diols.¹³³ Dioxolanes have been prepared from ketones in ionic liquids.¹³⁴ Ketones are converted with dimethyl ketals by electrolysis with NaBr in methanol.¹³⁵ Intramolecular reactions are possible in which a keto diol or an aldehyde diol generates a bicyclic ketal or acetal.

The conversion of acetals back to aldehydes or ketones is accomplished by many reagents, including aq acid. Heating with water under microwave irradiation converts acetals to the corresponding carbonyl compound.¹³⁶ Transition metal compounds of Bi¹³⁷ catalyze this conversion as well.

The mechanism for acetal/ketal formation involves initial formation of a *hemiacetal*,¹³⁸ and it is the reverse of that given for acetal hydrolysis:



In a study of the acid-catalyzed formation of the hemiacetal, Grunwald¹³⁹ showed that the data best fit a mechanism in which the three steps shown here are actually all concerted; that is, the reaction is simultaneously catalyzed by acid and base, with water acting as the base:¹⁴⁰



¹²⁹ For other methods, see Ott, J.; Tombo, G.M.R.; Schmid, B.; Venanzi, L.M.; Wang, G.; Ward, T.R. *Tetrahedron Lett.* **1989**, 30, 6151; Liao, Y.; Huang, Y.; Zhu, F. *J. Chem. Soc., Chem. Commun.* **1990**, 493.

¹³⁰ High pressure has been used to improve the results with ketones: Dauben, W.G.; Gerdes, J.M.; Look, G.C. *J. Org. Chem.* **1986**, 51, 4964. For other methods, see Otera, J.; Mizutani, T.; Nozaki, H. *Organometallics* **1989**, 8, 2063; Thurkauf, A.; Jacobson, A.E.; Rice, K.C. *Synthesis* **1988**, 233.

¹³¹ See Gopinath, R.; Haque, Sk.J.; Patel, B.K. *J. Org. Chem.* **2002**, 67, 5842.

¹³² Wu, H.-H.; Yang, F.; Cui, P.; Tang, J.; He, M.-Y. *Tetrahedron Lett.* **2004**, 45, 4963; Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* **2002**, 1296.

¹³³ Kurihara, M.; Hakamata, W. *J. Org. Chem.* **2003**, 68, 3413.

¹³⁴ See Li, D.; Shi, F.; Peng, J.; Guo, S.; Deng, Y. *J. Org. Chem.* **2004**, 69, 3582.

¹³⁵ Elinson, M.N.; Feducovich, S.K.; Dmitriev, D.E.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron Lett.* **2001**, 42, 5557.

¹³⁶ Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Tagarelli, A.; Sindona, G. *Tetrahedron Lett.* **2007**, 48, 8623.

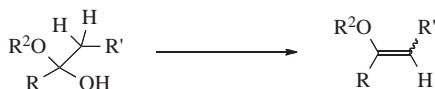
¹³⁷ Bailey, A.D.; Baru, A.R.; Tasche, K.K.; Mohan, R.S. *Tetrahedron Lett.* **2008**, 49, 691.

¹³⁸ For a review of hemiacetals, see Hurd, C.D. *J. Chem. Educ.* **1966**, 43, 527.

¹³⁹ Grunwald, E. *J. Am. Chem. Soc.* **1985**, 107, 4715.

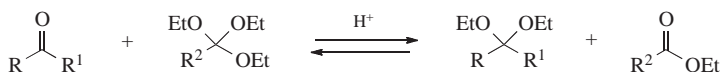
¹⁴⁰ See Grunwald, E. *J. Am. Chem. Soc.* **1985**, 107, 4710; Leussing, D.L. *J. Org. Chem.* **1990**, 55, 666.

Hemiacetals themselves are no more stable than the corresponding hydrates (Reaction 16-1). If the original aldehyde or ketone has an α hydrogen, it is possible to lose water from the hemiacetal, and enol ethers can be prepared in this manner:



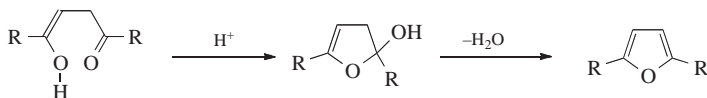
Similarly, treatment with an anhydride and a catalyst can give an enol ester (see Reaction 16-6).¹⁴¹ As with hydrates, it is noted that hemiacetals of cyclopropanones¹⁴² and of polychloro and polyfluoro aldehydes and ketones may be quite stable.

When acetals or ketals are treated with an alcohol of higher molecular weight than the one already there, transacetalation is possible (see Reaction 10-13). In another type of transacetalation, aldehydes or ketones can be converted to acetals or ketals by treatment with another acetal or ketal or with an ortho ester,¹⁴³ in the presence of an acid catalyst (shown for an ortho ester):



This method is useful for the conversion of ketones to ketals, since the direct reaction of a ketone with an alcohol often gives poor results. Alternatively, the substrate is treated with an alkoxy silane (ROSiMe_3) in the presence of trimethylsilyl trifluoromethanesulfonate.¹⁴⁴ Formic acid reacts with alcohols to give orthoformates.

1,4-Diketones give furans when treated with acids. This is actually an example of an intramolecular addition of an alcohol to a ketone, since it is the enol form that adds:



Similarly, 1,5-diketones give pyrans. Conjugated 1,4-diketones (e.g., 1,4-diphenylbut-2-en-1,4-dione) are converted to 2,5-diphenylfuran with formic acid, 5% Pd/C, PEG-200, and a sulfuric acid catalyst with microwave irradiation.¹⁴⁵ Note that alkynyl ketones are converted to furans with palladium(II) acetate.¹⁴⁶

OS I, 1, 298, 364, 381; II, 137; III, 123, 387, 502, 536, 644, 731, 800; IV, 21, 479, 679; V, 5, 292, 303, 450, 539; VI, 567, 666, 954; VII, 59, 149, 168, 177, 241, 271, 297; VIII, 357. Also see, OS IV, 558, 588; V, 25; VIII, 415.

¹⁴¹ For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, 1999, pp. 1484–1485.

¹⁴² See Salaun, J. *Chem. Rev.* 1983, 83, 619.

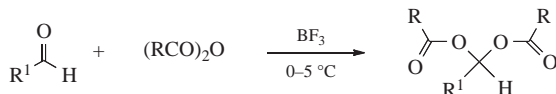
¹⁴³ See DeWolfe, R.H. *Carboxylic Ortho Ester Derivatives*, Academic Press, NY, 1970, pp. 154–164. See Karimi, B.; Ebrahimian, G.R.; Seradj, H. *Org. Lett.* 1999, 1, 1737; Leonard, N.M.; Oswald, M.C.; Freiberg, D.A.; Nattier, B.A.; Smith, R.C.; Mohan, R.S. *J. Org. Chem.* 2002, 67, 5202.

¹⁴⁴ Kato, J.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* 1985, 743. See also, Torii, S.; Takagishi, S.; Inokuchi, T.; Okumoto, H. *Bull. Chem. Soc. Jpn.* 1987, 60, 775.

¹⁴⁵ Rao, H.S.P.; Jothilingam, S. *J. Org. Chem.* 2003, 68, 5392.

¹⁴⁶ Jeevanandam, A.; Narkunan, K.; Ling, Y.-C. *J. Org. Chem.* 2001, 66, 6014. See Arcadi, A.; Cerichelli, G.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Tetrahedron Lett.* 2000, 41, 9195.

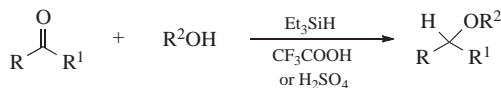
16-6 Acylation of Aldehydes and Ketones

O-Acyl-*C*-acyloxy-addition

Aldehydes can be converted to *acylals* by treatment with an anhydride in the presence of proton acids,¹⁴⁷ NBS,¹⁴⁸ ceric ammonium nitrate,¹⁴⁹ BF₃, LiBF₄,¹⁵⁰ and Lewis acid compounds of Fe,¹⁵¹ In,¹⁵² Cu,¹⁵³ Bi,¹⁵⁴ W,¹⁵⁵ or Zr.¹⁵⁶ *N*-Chlorosuccinimide with thiourea is a highly efficient catalyst.¹⁵⁷ Silica supported perchloric acid is useful for the preparation of acylals.¹⁵⁸ Conjugated aldehydes are converted to the corresponding acylal by reaction with acetic anhydride and a FeCl₃ catalyst.¹⁵⁹ The reaction cannot normally be applied to ketones, though an exception has been reported when the reagent is trichloroacetic anhydride, which gives acylals with ketones without a catalyst.¹⁶⁰

OS IV, 489.

16-7 Reductive Alkylation of Alcohols

C-Hydro-*O*-alkyl-addition

Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid¹⁶¹ or by hydrogenation in alcoholic acid in the presence of a Pt catalyst.¹⁶² The process can formally be regarded as addition of ROH to give a hemiacetal [RR'C(OH)OR²], followed by reduction of the OH. In this respect, it is similar to Reaction 16-17. Homoallylic ethers are formed by the Fe catalyzed reaction of acetals and aldehydes,¹⁶³ and by reactions in ionic liquids.¹⁶⁴ The In catalyzed reaction of aldehydes with allyltriethoxysilane leads to the corresponding ether.¹⁶⁵

¹⁴⁷ See Olah, G.A.; Mehrotra, A.K. *Synthesis* **1982**, 962.

¹⁴⁸ Karimi, B.; Seradj, H.; Ebrahimian, G.R. *Synlett* **2000**, 623.

¹⁴⁹ Roy, S.C.; Banerjee, B. *Synlett* **2002**, 1677.

¹⁵⁰ Yadav, J.S.; Reddy, B.V.S.; Venugopal, C.; Ramalingam, V.T. *Synlett* **2002**, 604.

¹⁵¹ Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* **2001**, 123, 3671; Wang, C.; Li, M. *Synth. Commun.* **2002**, 32, 3469.

¹⁵² Smith, B.M.; Graham, A.E. *Tetrahedron Lett.* **2006**, 47, 9317.

¹⁵³ Chandra, K.L.; Saravanan, P.; Singh, V.K. *Synlett* **2000**, 359.

¹⁵⁴ Aggen, D.H.; Arnold, J.N.; Hayes, P.D.; Smoter, N.J.; Mohan, R.S. *Tetrahedron* **2004**, 60, 3675.

¹⁵⁵ A solvent-free reaction. See Karimi, B.; Ebrahimian, G.-R.; Seradj, H. *Synth. Commun.* **2002**, 32, 669.

¹⁵⁶ Smitha, G.; Reddy, Ch.S. *Tetrahedron* **2003**, 59, 9571.

¹⁵⁷ Mei, Y.; Bentley, P.A.; Du, J. *Tetrahedron Lett.* **2009**, 50, 4199.

¹⁵⁸ Kamble, V.T.; Jamode, V.S.; Joshi, N.S.; Biradar, A.V.; Deshmukh, R.Y. *Tetrahedron Lett.* **2006**, 47, 5573.

¹⁵⁹ Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* **2001**, 123, 3671.

¹⁶⁰ Libman, J.; Sprecher, M.; Mazur, Y. *Tetrahedron* **1969**, 25, 1679.

¹⁶¹ Doyle, M.P.; DeBruyn, D.J.; Kooistra, D.A. *J. Am. Chem. Soc.* **1972**, 94, 3659.

¹⁶² Gooßen, L.J.; Linder, C. *Synlett* **2006**, 3489. For another method, see Loim, L.M.; Parnes, Z.N.; Vasil'eva, S.P.; Kursanov, D.N. *J. Org. Chem. USSR* **1972**, 8, 902.

¹⁶³ Spafford, M.J.; Anderson, E.D.; Lacey, J.R.; Palma, A.C.; Mohan, R.S. *Tetrahedron Lett.* **2007**, 48, 8665.

¹⁶⁴ Anzalone, P.W.; Mohan, R.S. *Synthesis* **2005**, 2661.

¹⁶⁵ Yang, M.-S.; Xu, L.-W.; Qiu, H.-Y.; Lai, G.-Q.; Jiang, J.-X. *Tetrahedron Lett.* **2008**, 49, 253.

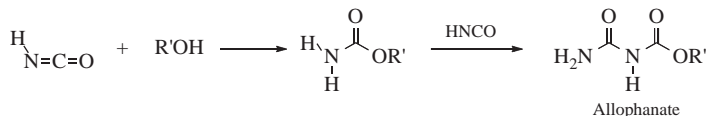
Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone \rightarrow dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.¹⁶⁶

16-8 The Addition of Alcohols to Isocyanates

N-Hydro-C-alkoxy-addition



The reaction of an isocyanate with alcohols gives a carbamate (a substituted urethane). This is an excellent reaction of wide scope that gives good yields. Isocyanic acid (HNCO) gives unsubstituted carbamates. Addition of a second equivalent of HNCO gives *allophanates*.



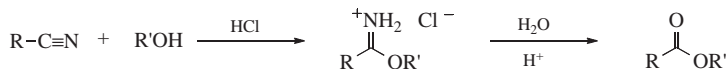
The isocyanate can be generated *in situ* by the reaction of an amine and oxalyl chloride, and subsequent reaction with HCl and then an alcohol gives the carbamate.¹⁶⁷ Combining compounds with two NCO groups with compounds containing two OH groups makes polyurethanes. Cyclic carbamates (e.g., 1,3-oxazine-2-ones), are generated by the reaction of an isocyanate with an oxetane, in the presence of a Pd catalyst.¹⁶⁸ Isothiocyanates similarly give thiocarbamates (RNHCSOR'),¹⁶⁹ but they react slower than the corresponding isocyanates. Isocyanates react with LiAlHSeH and then iodomethane to give the corresponding selenocarbonate (RNHCOSeMe).¹⁷⁰

The details of the mechanism are poorly understood,¹⁷¹ but the oxygen of the alcohol certainly attacks the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.¹⁷² Metallic compounds, can also catalyze the addition of ROH to isocyanates¹⁷³ by light,¹⁷⁴ or, for tertiary ROH, by lithium alkoxides¹⁷⁵ or *n*-butyllithium.¹⁷⁶

OS I, 140; V, 162; VI, 95, 226, 788, 795.

16-9 Alcoholysis of Nitriles

Alkoxy,oxo-de-nitrilo-tersubstitution



¹⁶⁶ Sassaman, M.B.; Kotian, K.D.; Prakash, G.K.S.; Olah, G.A. *J. Org. Chem.* **1987**, 52, 4314. See also, Kikugawa, Y. *Chem. Lett.* **1979**, 415.

¹⁶⁷ Oh, L.M.; Spoors, P.G.; Goodman, R.M. *Tetrahedron Lett.* **2004**, 45, 4769.

¹⁶⁸ Larksarp, C.; Alper, H. *J. Org. Chem.* **1999**, 64, 4152.

¹⁶⁹ See Walter, W.; Bode, K. *Angew. Chem. Int. Ed.* **1967**, 6, 281. See also, Wynne, J.H.; Jensen, S.D.; Snow, A.W. *J. Org. Chem.* **2003**, 68, 3733.

¹⁷⁰ Koketsu, M.; Ishida, M.; Takakura, N.; Ishihara, H. *J. Org. Chem.* **2002**, 67, 486.

¹⁷¹ See Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* **1975**, 4, 231.

¹⁷² See Donohoe, G.; Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1671 and references cited therein. See also, Sivakamasundari, S.; Ganesan, R. *J. Org. Chem.* **1984**, 49, 720.

¹⁷³ See Kim, Y.H.; Park, H.S. *Synlett* **1998**, 261; Duggan, M.E.; Imagire, J.S. *Synthesis* **1989**, 131.

¹⁷⁴ McManus, S.P.; Bruner, H.S.; Coble, H.D.; Ortiz, M. *J. Org. Chem.* **1977**, 42, 1428.

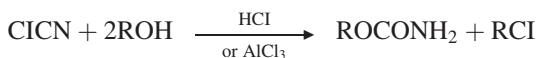
¹⁷⁵ Bailey, W.J.; Griffith, J.R. *J. Org. Chem.* **1978**, 43, 2690.

¹⁷⁶ Nikoiforov, A.; Jirovetz, L.; Buchbauer, G. *Liebigs Ann. Chem.* **1989**, 489.

The addition of dry HCl to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.¹⁷⁷ The salt can be converted to the free imino ester by treatment with a weak base (e.g., sodium bicarbonate) or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aq HCl can be used and the need for gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.¹⁷⁸

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group esterified and with no diester or diacid present.

Cyanogen chloride reacts with alcohols in the presence of an acid catalyst (e.g., dry HCl or AlCl₃), to give carbamates:¹⁷⁹

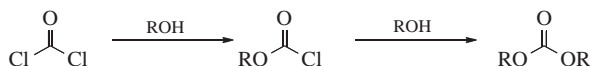


ROH can also be added to nitriles in another manner (Reaction **16-91**).

OS I, 5, 270; II, 284, 310; IV, 645; VI, 507; VIII, 415.

16-10 The Formation of Carbonates and Xanthates

Di-C-alkoxy-addition; S-Metallo-C-alkoxy-addition



The reaction of phosgene with an alcohol generates haloformic esters, and reaction with a second equivalent of alcohol gives a carbonate. This reaction is related to the acyl addition reactions of acyl chlorides in Reaction **16-98**. An important example is the preparation of carbobenzoxy chloride (PhCH₂OCOCI; CbzCl) from phosgene and benzyl alcohol. When CbzCl reacts with an amine, the product is the benzyl carbamate, *N*-Cbz, which is widely used for protection of amino groups during peptide synthesis. When an alcohol reacts with certain alkyl halides (e.g., benzyl chloride) and CO₂, in the presence of Cs₂CO₃ and tetrabutylammonium iodide, a mixed carbonate is formed.¹⁸⁰

The addition of alcohols to carbon disulfide (S=C=S) in the presence of a base produces xanthates.¹⁸¹ The base is often HO[−], but in some cases better results can be obtained by using methylsulfinyl carbanion (MeSOCH₂[−]).¹⁸² If an alkyl halide (RX) is present, the xanthate ester (ROCSSR') can be produced directly. In a similar manner, alkoxide ions add to CO₂ to give carbonate ester salts (ROCO₂[−]).

OS V, 439; VI, 207, 418; VII, 139.

¹⁷⁷ See Compagnon, P.L.; Miocque, M. *Ann. Chim. (Paris)* **1970**, [14] 5, 23, see pp. 24–26. Imino esters: see Neilson, D.G. in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, **1975**, pp. 385–489.

¹⁷⁸ Schaefer, F.C.; Peters, G.A. *J. Org. Chem.* **1961**, 26, 412.

¹⁷⁹ See Fuks, R.; Hartemink, M.A. *Bull. Soc. Chim. Belg.* **1973**, 82, 23.

¹⁸⁰ Kim, S.i.; Chu, F.; Dueno, E.E.; Jung, K.W. *J. Org. Chem.* **1999**, 64, 4578.

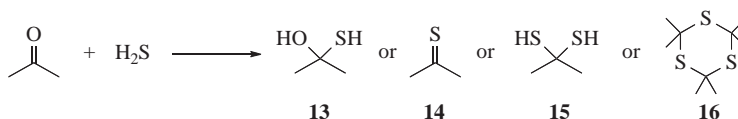
¹⁸¹ See Dunn, A.D.; Rudorf, W. *Carbon Disulphide in Organic Chemistry*, Ellis Horwood, Chichester, **1989**, pp. 316–367.

¹⁸² Meurling, P.; Sjöberg, B.; Sjöberg, K. *Acta Chem. Scand.* **1972**, 26, 279.

C. Sulfur Nucleophiles

16-11 The Addition of H₂S and Thiols to Carbonyl Compounds

O-Hydro-*C*-mercapto-addition, thioxo-de-oxo-bisubstitution, dimercapto-de-oxo-bisubstitution, and carbonyl-trithiane transformation



The addition of H₂S to an aldehyde or ketone can result in a variety of products. The most usual product is the trithiane **16**.¹⁸³ *gem*-Dithiols (**15**) are much more stable than the corresponding hydrates or α -hydroxy thiols.¹⁸⁴ They have been prepared by the treatment of ketones with H₂S under pressure¹⁸⁵ and under mild conditions with HCl as a catalyst.¹⁸⁶ A much more useful application is the addition of thiols to aldehydes and ketones to give hemi-mercaptals [CH(OH)SR] and dithioacetals [CH(SR)₂] (Reaction **16-5**). This reaction is generally not a good route to thioketones (**14**). α -Hydroxythiols (**13**) can be prepared from polychloro and polyfluoro aldehydes and ketones.¹⁸⁷ Apparently *gem*-hydroxy thiols (e.g., **13**) are rather unstable and quite difficult to prepare.

Thiols add to aldehydes and ketones to initially give hemi-mercaptals and dithioacetals. Hemi-mercaptals are ordinarily unstable,¹⁸⁸ but they are usually more stable than the corresponding hemiacetals and can be isolated in certain cases.¹⁸⁹ The isolated product of this reaction is most often the dithioacetal, which like the acetals obtained by reaction with an alcohol, are stable in the presence of base. However, a sufficiently strong base can remove a proton from the carbon between the sulfur atoms (—S—CHR—S—)¹⁹⁰ to form the corresponding carbanion (see Reaction **10-71**). The $\text{p}K_a$ of such protons is typically 31–37,¹⁹¹ requiring a strong base, and deprotonation is often quite slow. The reaction of aldehydes or ketones with thiols most commonly uses a Lewis acid catalyst (e.g., boron trifluoride etherate, BF₃•OEt₂)¹⁹² to give the dithioacetal¹⁹³ or dithioacetal. Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of TiCl₄,¹⁹⁴ SiCl₄,¹⁹⁵ LiBF₄,¹⁹⁶ Al(OTf)₃,¹⁹⁷ tosic acid on silica gel in dichloromethane,¹⁹⁸

¹⁸³ Campaigne, E.; Edwards, B.E. *J. Org. Chem.* **1962**, 27, 3760.

¹⁸⁴ For **15**, see Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* **1963**, 2, 370.

¹⁸⁵ Cairns, T.L.; Evans, G.L.; Larchar, A.W.; McKusick, B.C. *J. Am. Chem. Soc.* **1952**, 74, 3982.

¹⁸⁶ Campaigne, E.; Edwards, B.E. *J. Org. Chem.* **1962**, 27, 3760; Demuyne, M.; Vialle, J. *Bull. Soc. Chim. Fr.* **1967**, 1213.

¹⁸⁷ Harris Jr., J.F. *J. Org. Chem.* **1960**, 25, 2259.

¹⁸⁸ See, for example, Fournier, L.; Lamaty, G.; Nata, A.; Roque, J.P. *Tetrahedron* **1975**, 31, 809.

¹⁸⁹ For example, see Field, L.; Sweetman, B.J. *J. Org. Chem.* **1969**, 34, 1799.

¹⁹⁰ Truce, W.E.; Roberts, F.E. *J. Org. Chem.* **1963**, 28, 961.

¹⁹¹ Streitwieser Jr., A.; Caldwell, R.A.; Granger, M.R. *J. Am. Chem. Soc.* **1964**, 86, 3578; Streitwieser, Jr., A.; Maskornick, M.J.; Ziegler, G.R. *Tetrahedron Lett.* **1971**, 3927; Ward, H.R.; Lawler, R.G. *J. Am. Chem. Soc.* **1967**, 89, 5517.

¹⁹² Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1978**, 26, 3743; Corey, E.J.; Bock, M.G. *Tetrahedron Lett.* **1975**, 2643.

¹⁹³ See Samajdar, S.; Basu, M.K.; Becker, F.F.; Banik, N.K. *Tetrahedron Lett.* **2001**, 42, 4425.

¹⁹⁴ Kumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, 24, 1289.

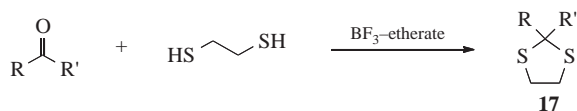
¹⁹⁵ Ku, B.; Oh, D.Y. *Synth. Commun.* **1989**, 433.

¹⁹⁶ This reaction is done neat, see Kazaraya, K.; Tsuji, S.; Sato, T. *Synlett* **2004**, 1640.

¹⁹⁷ A solvent-free reaction. Firouzabadi, H.; Iranpoor, N.; Kohmarch, G. *Synth. Commun.* **2003**, 33, 167.

¹⁹⁸ Ali, M.H.; Goretti Gomes, M. *Synthesis* **2005**, 1326.

and oxalic acid promotes the reaction.¹⁹⁹ Similarly reactions that use 1,2-ethanedithiol or 1,3-propanedithiol lead to 1,3-dithiolanes (**17**)²⁰⁰ or 1,3-dithianes.²⁰¹ 3-(1,3-Dithian-2-ylidene)pentane- 2,4-dione has been used as a thioacetalization reagent for reactions in water.²⁰²



Dithioacetals and dithioketals are used as protecting groups for aldehydes and ketones, and after subsequent reactions involving the R or R' group, deprotection regenerates the carbonyl.²⁰³ Simple hydrolysis is the most common method for converting thiocarbonyls to carbonyls, but there are a variety of reagents for this conversion.²⁰⁴ Lewis acids (e.g., aluminum chloride, AlCl₃) and mercuric salts are common reagents (the *Corey–Seebach procedure*).²⁰⁵ Other reagents include BF₃·OEt₂ in aq THF containing mercuric oxide (HgO),²⁰⁶ ceric ammonium nitrate [Ce(NH₄)₂(NO₃)₆],²⁰⁷ chlorotrimethylsilane and H₂O₂,²⁰⁸ PhI(OAc)₂ in aq acetone,²⁰⁹ and Cu salts.²¹⁰ When aldehydes and ketones react with mercapto–alcohols, mixed acetals or ketals are formed.

Thioamides are converted to amides with *Caro's acid* (H₂SO₅) on SiO₂.²¹¹ The use of 2-mercaptoethanol (HSCH₂CH₂OH), for example, leads to an oxathiolane²¹² and 3-mercaptopropanol (HSCH₂CH₂CH₂OH) leads to an oxathiane. Alternatively, the dithioketal can be desulfurized with Raney nickel (Reaction **14-27**), giving the overall conversion C=O → CH₂ (Reaction **19-70**).

Thioketones (**14**) can be prepared from certain ketones (e.g., diaryl ketones) by treatment with H₂S and an acid catalyst, usually HCl. They are often unstable and usually trimerize (to **16**) or react with air. Thioaldehydes²¹³ are even less stable and simple ones²¹⁴ apparently have never been isolated, although *tert*-BuCHS has been prepared in solution, where it exists for several hours at 20 °C.²¹⁵ A high-yield synthesis of thioketones involves

¹⁹⁹ Miyake, H.; Nakao, Y.; Sasaki, M. *Chem. Lett.* **2007**, 36, 104.

²⁰⁰ See Kamal, A.; Chouhan, G. *Synlett* **2002**, 474. For a review, see Olsen, R.K.; Currie, Jr., J.O. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, **1974**, pp. 521–532.

²⁰¹ See Laskar, D.D.; De, S.K. *Tetrahedron Lett.* **2004**, 45, 1035, 2339.

²⁰² Dong, D.; Ouyang, Y.; Yu, H.; Liu, Q.; Liu, J.; Wang, M.; Zhu, J. *J. Org. Chem.* **2005**, 70, 4535.

²⁰³ See Ganguly, N.C.; Datta, M. *Synlett* **2004**, 659.

²⁰⁴ Corsaro, A.; Pistarà, V. *Tetrahedron* **1998**, 54, 15027.

²⁰⁵ Seebach, D.; Corey, E.J. *J. Org. Chem.* **1975**, 40, 231; Seebach, D. *Synthesis* **1969**, 17.

²⁰⁶ Vedejs, E.; Fuchs, P.L. *J. Org. Chem.* **1971**, 36, 366.

²⁰⁷ Ho, T.-L.; Ho, H.C.; Wong, C.M. *J. Chem. Soc., Chem. Commun.* **1972**, 791a.

²⁰⁸ Bahrami, K.; Khodaei, M.M.; Tajik, M. *Synthesis* **2010**, 4282.

²⁰⁹ Shi, X.-X.; Wu, Q.-Q. *Synth. Commun.* **2000**, 30, 4081.

²¹⁰ Besra, R.C.; Rudrawar, S.; Chakraborti, A.K. *Tetrahedron Lett.* **2005**, 46, 6213; Oksdath-Mansilla, G.; Peñéory, A.B. *Tetrahedron Lett.* **2007**, 48, 6150.

²¹¹ Movassagh, B.; Lakouraj, M.M.; Ghodrati, K. *Synth. Commun.* **2000**, 30, 2353.

²¹² See Ballini, R.; Bosica, G.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G. *Synthesis* **2001**, 1826; Mondal, E.; Sahu, P.R.; Khan, A.T. *Synlett* **2002**, 463.

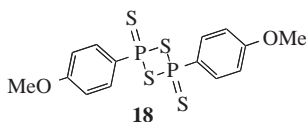
²¹³ See Usov, V.A.; Timokhina, L.V.; Voronkov, M.G. *Russ. Chem. Rev.* **1990**, 59, 378.

²¹⁴ See Muraoka, M.; Yamamoto, T.; Enomoto, K.; Takeshima, T. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1241, and references cited in these papers.

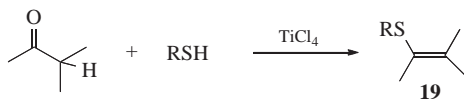
²¹⁵ Vedejs, E.; Perry, D.A. *J. Am. Chem. Soc.* **1983**, 105, 1683. See also, Baldwin, J.E.; Lopez, R.C.G. *J. Chem. Soc., Chem. Commun.* **1982**, 1029.

treatment of acyclic²¹⁶ ketones with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide²¹⁷ (**18**, known as *Lawesson's reagent*).²¹⁸ Thioketones can also be prepared by treatment of ketones with P_4S_{10} ,²¹⁹ P_4S_{10} and hexamethyldisiloxane,²²⁰ P_4S_{10} on alumina,²²¹ and from oximes or various types of hydrazone (overall conversion $C=N \rightarrow C=S$).²²² Reagent **18** converts the $C=O$ groups of amides and carboxylic esters²²³ to $C=S$ groups.²²⁴ Lactones react with **18** in the presence of hexamethyldisiloxane an microwave irradiation to give the thiolactone.²²⁵

Other reagents may be used for this transformation including $POCl_3$ followed by $S(TMS)_2$, which converts lactams to thiolactams.²²⁶ Treatment with triflic anhydride, and then H_2S ²²⁷ or aq $S(NH_4)_2$ ²²⁸ converts amides to thioamides, as does the microwave assisted reaction with $PSiCl_2/H_2O/Et_3N$, without solvent.²²⁹ Carboxylic acids ($RCOOH$) can be converted directly to dithiocarboxylic esters ($RCSSR'$),²³⁰ in moderate yield, with P_4S_{10} and a primary alcohol ($R'OH$).²³¹



If an aldehyde or ketone possesses an α hydrogen, it can be converted to the corresponding enol thioether (**19**) by treatment with a thiol in the presence of $TiCl_4$.²³² Aldehydes and ketones have been converted to sulfides by treatment with thiols and pyridine–borane, $RCOR' + R^2SH \rightarrow RR'CHSR^2$,²³³ in a reductive alkylation reaction, analogous to Reaction 16-7.



OS **II**, 610; **IV**, 927; **VI**, 109; **VII**, 124, 372. Also see, OS **III**, 332; **IV**, 967; **V**, 780; **VI**, 556; **VIII**, 302.

²¹⁶ Cyclopentanone and cyclohexanone gave different products: Scheibye, S.; Shabana, R.; Lawesson, S.; Rømming, C. *Tetrahedron* **1982**, 38, 993.

²¹⁷ See Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* **VII**, 372.

²¹⁸ See Jesberger, M.; Davis, T.P.; Barner, L. *Synthesis* **2003**, 1929. For a study of the mechanism, see Rauchfuss, T.B.; Zank, G.A. *Tetrahedron Lett.* **1986**, 27, 3445. See Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, 107, 5210. For reactions with fluoros Lawesson's reagent, see Kaleta, Z.; Makowski, B.T.; Soós, T.; Dembinski, R. *Org. Lett.* **2006**, 8, 1625.

²¹⁹ See Scheeren, J.W.; Ooms, P.H.J.; Nivard, R.J.F. *Synthesis* **1973**, 149.

²²⁰ Curphey, T.J. *J. Org. Chem.* **2002**, 67, 6461.

²²¹ Polshettiwar, V.; Kaushik, M.P. *Tetrahedron Lett.* **2004**, 45, 6255.

²²² See Okazaki, R.; Inoue, K.; Inamoto, N. *Tetrahedron Lett.* **1979**, 3673.

²²³ For a review of thiono esters $RC(=S)OR'$, see Jones, B.A.; Bradshaw, J.S. *Chem. Rev.* **1984**, 84, 17.

²²⁴ Yde, B.; Yousif, N.M.; Pedersen, U.S.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* **1984**, 40, 2047; Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* **VII**, 372.

²²⁵ Filippi, J.-J.; Fernandez, X.; Lizzani-Cuvelier, L.; Loiseau, A.-M. *Tetrahedron Lett.* **2003**, 44, 6647.

²²⁶ Smith, D.C.; Lee, S.W.; Fuchs, P.L. *J. Org. Chem.* **1994**, 59, 348.

²²⁷ Charette, A.B.; Chua, P. *Tetrahedron Lett.* **1998**, 39, 245.

²²⁸ Charette, A.B.; Grenon, M. *J. Org. Chem.* **2003**, 68, 5792.

²²⁹ Pathak, U.; Pandey, L.K.; Tank, R. *J. Org. Chem.* **2008**, 73, 2890.

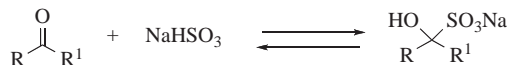
²³⁰ For a review of dithiocarboxylic esters, see Kato, S.; Ishida, M. *Sulfur Rep.*, **1988**, 8, 155.

²³¹ Davy, H.; Metzner, P. *Chem. Ind. (London)* **1985**, 824.

²³² Mukaiyama, T.; Saigo, K. *Chem. Lett.* **1973**, 479.

²³³ Kikugawa, Y. *Chem. Lett.* **1981**, 1157.

16-12 Formation of Bisulfite Addition Products

O-Hydro-*C*-sulfonato-addition

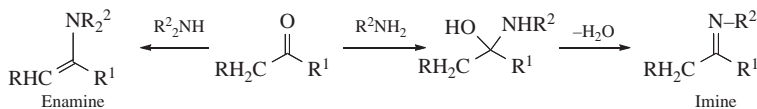
Bisulfite addition products are formed from aldehydes, methyl ketones, cyclic ketones (generally seven-membered and smaller rings), α -keto esters, and isocyanates, upon treatment with sodium bisulfite (NaHSO_3). Most other ketones do not undergo the reaction, probably for steric reasons. The reaction is reversible (by treatment of the addition product with either acid or base)²³⁴ and is useful for the purification of the starting compounds, since the addition products are soluble in water and many of the impurities are not.²³⁵

OS I, 241, 336; III, 438; IV, 903; V, 437.

D. Attack by NH_2 , NHR , or NR_2 (Addition of NH_3 , RNH_2 , R_2NH)

16-13 The Addition of Amines to Aldehydes and Ketones

Alkylimino-de-oxo-bisubstitution



The addition of ammonia²³⁶ to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be expected to be *hemiaminals*,²³⁷ but these compounds are generally unstable. In addition, many imines with a hydrogen on the nitrogen spontaneously polymerize.²³⁸

In contrast to ammonia, primary, secondary, and tertiary amines can add to aldehydes²³⁹ and ketones to give different kinds of products. Primary amines give imines²⁴⁰ and secondary amines give enamines (for reactions, see 10-69). Such imines are stable enough for isolation, but in some cases, especially with simple R groups, they rapidly decompose

²³⁴ For cleavage with ion-exchange resins, see Khosid, A.Kh.; Chizhova, N.V. *J. Org. Chem. USSR* **1985**, 21, 37. For a discussion of the mechanism, see Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* **1978**, 100, 1228.

²³⁵ The reaction has also been used to protect an aldehyde group in the presence of a keto group: Chihara, T.; Wakabayashi, T.; Taya, K. *Chem. Lett.* **1981**, 1657.

²³⁶ For a review of this reagent in organic synthesis, see Jeyaraman, R. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, **1983**, pp. 9–83.

²³⁷ These compounds have been detected by ^{13}C NMR: Chudek, J.A.; Foster, R.; Young, D. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1285.

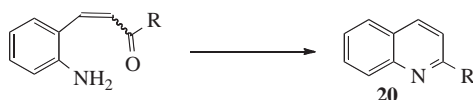
²³⁸ Methanimine $\text{CH}_2=\text{NH}$ is stable in solution for several hours at -95°C , but rapidly decomposes at -80°C : Braillon, B.; Lasne, M.C.; Ripoll, J.L.; Denis, J.M. *Nouv. J. Chim.*, **1982**, 6, 121. See also, Bock, H.; Dammel, R. *Chem. Ber.* **1987**, 120, 1961.

²³⁹ For a review of the reactions between amines and formaldehyde, see Farrar, W.V. *Rec. Chem. Prog.*, **1968**, 29, 85. For a synthesis of imines, see Kwon, M.S.; Kim, S.; Park, S.; Bosco, W.; Chidrala, R.K.; Park, J. *J. Org. Chem.* **2009**, 74, 2877; Kim, J.W.; He, J.; Yamaguchi, K.; Mizuno, N. *Chem. Lett.* **2009**, 38, 920.

²⁴⁰ See Dayagi, S.; Degani, Y. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 64–83; Reeves, R.L. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, **1966**, pp. 600–614. Also see Ku, Y.-Y.; Grieme, T.; Pu, Y.-M.; Bhatia, A.V.; King, S.A. *Tetrahedron Lett.* **2005**, 46, 1471; Guzen, K.P.; Guarezemini, A.S.; Órfão, A.T.G.; Cella, R.; Pereira, C.M.P.; Stefani, H.A. *Tetrahedron Lett.* **2007**, 48, 1845.

or polymerize unless there is at least one aryl group on the nitrogen or the carbon. When there is an aryl group, the compounds are quite stable. They are usually called *Schiff bases*, and this reaction is the best way to prepare them.²⁴¹ Even sterically hindered imines can be prepared.²⁴² The initial N-substituted hemiaminals²⁴³ lose water to give the stable *Schiff bases*.

In general, ketones react more slowly than aldehydes, and higher temperatures and longer reaction times are often required.²⁴⁴ In addition, the equilibrium must often be shifted, usually by removal of the water, either azeotropically by distillation, or with a drying agent (e.g., TiCl_4),²⁴⁵ or by addition of a molecular sieve.²⁴⁶ Imines have been formed from aldehydes and amines in an ionic liquid.²⁴⁷



The reaction is often used to effect ring closure.²⁴⁸ The *Friedländer quinoline synthesis*²⁴⁹ is an example where ortho alkenyl aniline derivatives give the quinoline (**20**).²⁵⁰ The alkene derivative can be prepared *in situ* from an aldehyde and a suitably functionalized ylid.²⁵¹ Pirylium ions react with ammonia or primary amines to give pyridinium ions²⁵² (see Reaction 10-57). Primary amines react with 1,4-diketones, with microwave irradiation, to give N-substituted pyrroles.²⁵³ Similar reactions in the presence of Montmorillonite KSF²⁵⁴ or by simply heating the components with tosic acid²⁵⁵ have been reported.

The reaction of secondary amines with ketones leads to enamines (see 10-69).²⁵⁶ When secondary amines are added to aldehydes or ketones, the initially formed N,N-disubstituted hemiaminals (**21**) cannot lose water in the same way since the iminium ion intermediate does not have a proton on nitrogen, and in some cases it is possible to isolate them.²⁵⁷ However, they are generally unstable, and under the reaction conditions usually react further. If no α hydrogen is present, **21** is converted to the more stable *aminal* (**22**).²⁵⁸

²⁴¹ See Lai, J.T. *Tetrahedron Lett.* **2002**, 43, 1965.

²⁴² Love, B.E.; Ren, J. *J. Org. Chem.* **1993**, 58, 5556.

²⁴³ See Forlani, L.; Marianucci, E.; Todesco, P.E. *J. Chem. Res. (S)* **1984**, 126.

²⁴⁴ See Eisch, J.J.; Sanchez, R. *J. Org. Chem.* **1986**, 51, 1848.

²⁴⁵ Weingarten, H.; Chupp, J.P.; White, W.A. *J. Org. Chem.* **1967**, 32, 3246.

²⁴⁶ See Roelofsen, D.P.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1972**, 91, 605.

²⁴⁷ Andrade, C.K.Z.; Takada, S.C.S.; Alves, L.M.; Rodrigues, J.P.; Suarez, P.A.Z.; Branda, R.F.; Soares, V.C.D. *Synlett* **2004**, 2135.

²⁴⁸ For a review, see Katritzky, A.R.; Ostercamp, D.L.; Yousaf, T.I. *Tetrahedron* **1987**, 43, 5171.

²⁴⁹ See Cheng, C.; Yan, S. *Org. React.* **1982**, 28, 37.

²⁵⁰ See Yadav, J.S.; Reddy, B.V.S.; Premalatha, K. *Synlett* **2004**, 963.

²⁵¹ Hsiao, Y.; Rivera, N.R.; Yasuda, N.; Hughes, D.L.; Reider, P.J. *Org. Lett.* **2001**, 3, 1101.

²⁵² See Zvezdina, E.A.; Zhadonva, M.P.; Dorofeenko, G.N. *Russ. Chem. Rev.* **1982**, 51, 469.

²⁵³ Danks, T.N. *Tetrahedron Lett.* **1999**, 40, 3957.

²⁵⁴ Banik, B.K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, 69, 213.

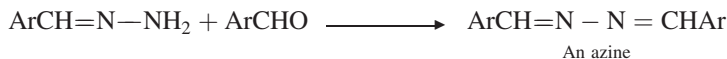
²⁵⁵ Klappa, J.J.; Rich, A.E.; McNeill, K. *Org. Lett.* **2002**, 4, 435.

²⁵⁶ See Hodgson, D.M.; Bray, C.D.; Kindon, N.D.; Reynolds, N.J.; Coote, S.J.; Um, J.M.; Houk, K.N. *J. Org. Chem.* **2009**, 74, 1019.

²⁵⁷ See Duhamel, P.; Cantacuzène, J. *Bull. Soc. Chim. Fr.* **1962**, 1843.

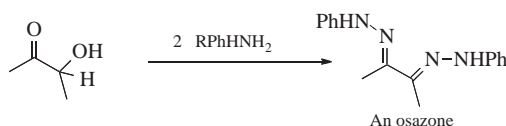
²⁵⁸ Duhamel, P. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, **1982**, pp. 849–907.

of product is especially important for aromatic aldehydes:

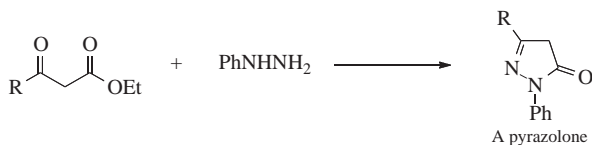


However, in some cases azines can be converted to hydrazones by treatment with excess hydrazine and NaOH.²⁷² Arylhydrazines, especially phenyl, *p*-nitrophenyl, and 2,4-dinitrophenyl,²⁷³ are used much more often and give the corresponding hydrazones with most aldehydes and ketones.²⁷⁴ Since these are usually solids, they make excellent derivatives and were commonly employed for this purpose in the past, before the advent of modern spectroscopy methods. Cyclic hydrazones are known,²⁷⁵ as are conjugated hydrazones.²⁷⁶ Azides react with *N,N*-dimethylhydrazine and ferric chloride to give the *N,N*-dimethylhydrazone.²⁷⁷ Alkenes react with CO/H₂, phenylhydrazine and a diphosphine catalyst to give a regioisomeric mixture of phenylhydrazones that favored “anti-Markovnikov” addition.²⁷⁸ Oximes are converted to hydrazones with water and hydrazine in refluxing ethanol.²⁷⁹

α -Hydroxy aldehydes and ketones and α -dicarbonyl compounds give *osazones*, in which two adjacent carbons have carbon–nitrogen double bonds:



Osazones are particularly important in carbohydrate chemistry, and the *osazone test*²⁸⁰ with phenylhydrazine is used to test for the presence of sugars with an adjacent stereogenic carbon. In contrast to this behavior, β -diketones and β -keto esters give *pyrazoles* and *pyrazolones*, respectively (the latter is illustrated for β -keto esters). No azines are formed under these conditions.



Other hydrazine derivatives frequently used to prepare the corresponding hydrazone are semicarbazide (NH₂NHCONH₂), in which case the hydrazone is called a semicarbazone: *Girard's reagents T and P* are hydrazones that are water soluble because of the ionic group. Girard's reagents are often used for purification of carbonyl compounds.²⁸¹

²⁷² See Day, A.C.; Whiting, M.C. *Org. Synth.* **VI**, 10.

²⁷³ See Behforouz, M.; Bolan, J.L.; Flynt, M.S. *J. Org. Chem.* **1985**, *50*, 1186.

²⁷⁴ For a review of arylhydrazones, see Buckingham, J. *Q. Rev. Chem. Soc.* **1969**, *23*, 37.

²⁷⁵ Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* **1998**, *39*, 2157.

²⁷⁶ Palacios, F.; Aparicio, D.; de los Santos, J.M. *Tetrahedron Lett.* **1993**, *34*, 3481.

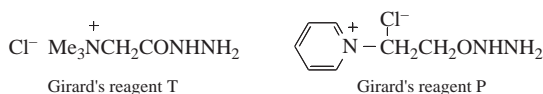
²⁷⁷ Barrett, I.C.; Langille, J.D.; Kerr, M.A. *J. Org. Chem.* **2000**, *65*, 6268.

²⁷⁸ Ahmed, M.; Jackstell, R.; Seayad, A.M.; Klein, H.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 869.

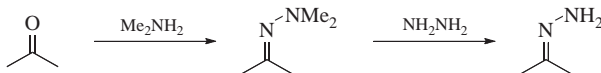
²⁷⁹ Pasha, M.A.; Nanjundaswamy, H.M. *Synth. Commun.* **2004**, *34*, 3827.

²⁸⁰ See Mester, L.; El Khadem, H.; Horton, D. *J. Chem. Soc., C* **1970**, 2567.

²⁸¹ See Stachissini, A.S.; do Amaral, L. *J. Org. Chem.* **1991**, *56*, 1419.



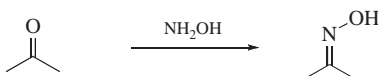
Simple *N*-unsubstituted hydrazones can be obtained by an exchange reaction. The *N,N*-dimethylhydrazone is prepared first and then treated with hydrazine:²⁸²



OS **II**, 395; **III**, 96, 351; **IV**, 351, 377, 536, 884; **V**, 27, 258, 747, 929; **VI**, 10, 12, 62, 242, 293, 679, 791; **VII**, 77, 438. Also see, OS **III**, 708; **VI**, 161; **VIII**, 597.

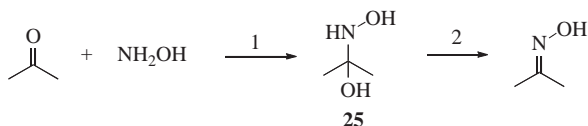
16-15 The Formation of Oximes

Hydroxyimino-de-oxo-bisubstitution



In a reaction very much like **16-14**, oximes can be prepared by the addition of hydroxylamine (NH_2OH) to aldehydes or ketones. Derivatives of hydroxylamine [e.g., $\text{H}_2\text{NOSO}_3\text{H}$ and $\text{HON}(\text{SO}_3\text{Na})_2$] have also been used. For hindered ketones (e.g., 2,2,4,4-tetramethyl-3-pentanone), high pressures (as high as 10,000 atm) may be necessary.²⁸³ The reaction of hydroxylamine with unsymmetrical ketones or with aldehydes leads to a mixture of (*E*)- and (*Z*)-isomers. For aromatic aldehydes, heating with K_2CO_3 led to the (*E*)- isomer, whereas heating with CuSO_4 gave the (*Z*)-hydroxylamine.²⁸⁴ Hydroxylamines react with ketones in ionic liquids²⁸⁵ and on silica gel.²⁸⁶

It has been shown²⁸⁷ that the rate of formation of oximes is at a maximum at a pH that depends on the substrate but is usually ~ 4 . The rate also decreases as the pH is either raised or lowered from this point (a bell-shaped curve). In Section 16.A.i, bell-shaped curves like this were shown to be caused by changes in the rate-determining step in many cases. In this case, at low pH values step 2 is rapid (because it is acid catalyzed), and



step 1 is slow (and rate determining), because under these acidic conditions most of the NH_2OH molecules have been converted to the conjugate $^+\text{NH}_3\text{OH}$ ions, which cannot attack the substrate. As the pH is slowly increased, the fraction of free NH_2OH molecules increases and consequently so does the reaction rate, until the maximum rate is reached at $\sim \text{pH } 4$. As the rising pH causes an increase in the rate of step 1, it also causes a *decrease* in

²⁸² Newkome, G.R.; Fishel, D.L. *J. Org. Chem.* **1966**, 31, 677.

²⁸³ Jones, W.H.; Tristram, E.W.; Benning, W.F. *J. Am. Chem. Soc.* **1959**, 81, 2151.

²⁸⁴ Sharghi, H.; Sarvari, M.H. *Synlett* **2001**, 99.

²⁸⁵ Ren, R.X.; Ou, W. *Tetrahedron Lett.* **2001**, 42, 8445.

²⁸⁶ Hajipour, A.R.; Mohammadpoor-Baltork, I.; Nikbaghat, K.; Imanzadeh, G. *Synth. Commun.* **1999**, 29, 1697.

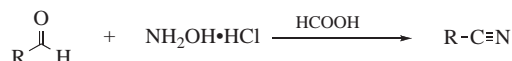
²⁸⁷ Jencks, W.P. *J. Am. Chem. Soc.* **1959**, 81, 475; *Prog. Phys. Org. Chem.* **1964**, 2, 63.

the rate of the acid-catalyzed step 2, although this latter process has not affected the overall rate since step 2 was still faster than step 1. However, when the pH goes above ~ 4 , step 2 becomes rate determining, and although the rate of step 1 is still increasing (as it will until essentially all the NH_2OH is unprotonated), it is now step 2 that determines the rate. This step is slowed by the decrease in acid concentration. Thus the overall rate decreases as the pH rises beyond ~ 4 . It is likely that similar considerations apply to the reaction of aldehydes and ketones with amines, hydrazines, and other nitrogen nucleophiles.²⁸⁸ There is evidence that when the nucleophile is 2-methylthiosemicarbazide, there is a second change in the rate-determining step: $> \text{pH} \sim 10$ basic catalysis of step 2 has increased the rate of this step to the point where step 1 is again rate determining.²⁸⁹ Still a third change in the rate-determining step has been found at $\sim \text{pH} 1$, showing that at least in some cases step 1 actually consists of two steps: formation of a zwitterion (e.g., $\text{HOH}_2\text{N}^+ - \text{C} - \text{O}^-$ in the case shown above) and conversion of this to **25**.²⁹⁰ The intermediate **25** has been detected by NMR in the reaction between NH_2OH and acetaldehyde.²⁹¹

OS I, 318, 327; II, 70, 204, 313, 622; III, 690, IV, 229; V, 139, 1031; VII, 149. See also, OS VI, 670.

16-16 The Conversion of Aldehydes to Nitriles

Nitrilo-de-hydro,oxo-tersubstitution



Aldehydes can be converted to nitriles in one step by treatment with hydroxylamine hydrochloride and either formic acid,²⁹² $\text{KF}-\text{Al}_2\text{O}_3$,²⁹³ or $\text{NaHSO}_4 \cdot \text{SiO}_2$ with microwave irradiation.²⁹⁴ Heating in *N*-methylpyrrolidinone (NMP) is also effective with aryl aldehydes²⁹⁵ and heating on dry alumina with aliphatic aldehyde.²⁹⁶ The reaction is a combination of **16-15** and **17-29**. Direct nitrile formation has also been accomplished with certain derivatives of NH_2OH , notably, $\text{NH}_2\text{OSO}_2\text{OH}$.²⁹⁷ Treatment with hydroxylamine and NaI ²⁹⁸ or certain carbonates²⁹⁹ also converts aldehydes to the nitrile. Another method involves treatment with hydrazoic acid, although the *Schmidt reaction* (**18-16**) may compete.³⁰⁰ Microwave irradiation has been used with $\text{NH}_2\text{OH} \cdot \text{HCl}$ and another reagent, which includes phthalic anhydride³⁰¹ or $\text{H}-\text{Y}$ zeolite.³⁰² The reaction of an aldehyde with hydroxylamine followed by diethyl

²⁸⁸ See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups, Supplement A*, pt. 1, Wiley, NY, **1977**, pp. 288–299; Sollenberger, P.Y.; Martin, R.B. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, **1968**, pp. 367–392. For isotope effect studies, see Rossi, M.H.; Stachissini, A.S.; do Amaral, L. *J. Org. Chem.* **1990**, *55*, 1300.

²⁸⁹ Sayer, J.M.; Jencks, W.P. *J. Am. Chem. Soc.* **1972**, *94*, 3262.

²⁹⁰ Sayer, J.M.; Edman, C. *J. Am. Chem. Soc.* **1979**, *101*, 3010.

²⁹¹ Cocivera, M.; Effio, A. *J. Am. Chem. Soc.* **1976**, *98*, 7371.

²⁹² Olah, G.A.; Keumi, T. *Synthesis* **1979**, 112.

²⁹³ Movassagh, B.; Shokri, S. *Tetrahedron Lett.* **2005**, *46*, 6923.

²⁹⁴ Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* **2000**, 1599.

²⁹⁵ Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Yadav, J.S. *Synthesis* **1999**, 586; Chakraborti, A.K.; Kaur, G. *Tetrahedron* **1999**, *55*, 13265.

²⁹⁶ Sharghi, H.; Sarvari, M.H. *Tetrahedron* **2002**, *58*, 10323.

²⁹⁷ Streith, J.; Fizet, C.; Fritz, H. *Helv. Chim. Acta* **1976**, *59*, 2786.

²⁹⁸ Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* **2003**, 1841.

²⁹⁹ Bose, D.S.; Goud, P.R. *Synth. Commun.* **2002**, *32*, 3621.

³⁰⁰ See Neunhoeffer, H.; Diehl, W.; Karafiat, U. *Liebigs Ann. Chem.* **1989**, 105.

³⁰¹ Veverková, E.; Toma, Š. *Synth. Commun.* **2000**, *30*, 3109.

³⁰² Srinivas, K.V.N.S.; Reddy, E.B.; Das, B. *Synlett* **2002**, 625.

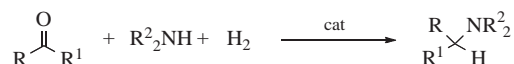
chlorophosphate (EtOPOCl₂) gives the nitrile.³⁰³ Heating with hydroxylamine in DMSO³⁰⁴ and using hydroxylamine and oxalyl chloride³⁰⁵ have been used. *tert*-Butanesulfinyl imines are also used for the conversion of aldehydes to nitriles.³⁰⁶ Other reagents include trimethylsilyl azide,³⁰⁷ hydroxylamine hydrochloride/MgSO₄/TsOH,³⁰⁸ or I₂ with aq ammonia.³⁰⁹ The reaction of a conjugated aldehyde with ammonia, CuCl, and 50% H₂O₂ gave the conjugated nitrile.³¹⁰ Aldehydes with IBX (*o*-iodoxybenzoic acid) and liquid ammonia gives the nitrile.³¹¹ Tetrabutylammonium tribromide in aq ammonia has also been used.³¹² Trichloroisocyanuric acid with a catalytic amount of TEMPO (Sec. 5.C.i) converts aldehydes to nitriles at 0 °C in dichloromethane.³¹³ Aromatic aldehydes are converted to the nitrile by heating 2.2 molar equivalents of NaN(SiMe₃)₂ in 1,3-dimethylimidazolidin-2-one, in a sealed tube.³¹⁴ The aldehydes employed had a hydroxy substituent.

In a related reaction, the reaction of primary alcohols with iodine in ammonia water gives the corresponding nitrile.³¹⁵ Upon treatment with 2 molar equivalents of dimethylaluminum amide (Me₂AlNH₂), carboxylic esters give nitriles: RCO₂R' → RCN.³¹⁶ This is likely a combination of Reaction 16-75 and 17-30 (see Reaction 19-5).

OS V, 656.

16-17 Reductive Alkylation of Ammonia or Amines

Hydro,dialkylamino-de-oxo-bisubstitution



When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen gas and an appropriate catalyst (e.g., Rh or Ir; heterogeneous or homogeneous),³¹⁷ *reductive alkylation* of ammonia or the amine (or *reductive amination* of the carbonyl compound) takes place.³¹⁸ The reaction can formally be regarded as occurring in the following manner (shown for a primary amine), which probably does correspond to the actual sequence of steps:³¹⁹ In this regard, the reaction of an aldehyde

³⁰³ Zhu, J.-L.; Lee, F.-Y.; Wu, J.-D.; Kuo, C.-W.; Shia, K.-S. *Synlett* **2007**, 1317.

³⁰⁴ Chill, S.T.; Mebane, R.C. *Synth. Commun.* **2009**, *39*, 3601.

³⁰⁵ Movassagh, B.; Fazeli, A. *Synth. Commun.* **2007**, *37*, 625.

³⁰⁶ Tanuwidjaja, J.; Peltier, H.M.; Lewis, J.C.; Schenkel, L.B.; Ellman, J.A. *Synthesis* **2007**, 3385.

³⁰⁷ Nishiyama, K.; Oba, M.; Watanabe, A. *Tetrahedron* **1987**, *43*, 693.

³⁰⁸ Ganboa, I.; Palomo, C. *Synth. Commun.* **1983**, *13*, 219.

³⁰⁹ Talukdar, S.; Hsu, J.-L.; Chou, T.-C.; Fang, J.-M. *Tetrahedron Lett.* **2001**, *42*, 1103.

³¹⁰ Erman, M.B.; Snow, J.W.; Williams, M.J. *Tetrahedron Lett.* **2000**, *41*, 6749.

³¹¹ Arote, N.D.; Bhalerao, D.S.; Akamanchi, K.G. *Tetrahedron Lett.* **2007**, *48*, 3651. Also see Zhu, C.; Ji, L.; Wei, Y. *Synthesis* **2010**, 3121.

³¹² Zhu, Y.-Z.; Cai, C. *Monat. Chemie* **2010**, *141*, 637.

³¹³ Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* **2003**, 2629.

³¹⁴ Hwu, J.R.; Wong, F.F. *Eur. J. Org. Chem.* **2006**, 2513.

³¹⁵ Mori, N.; Togo, H. *Synlett* **2005**, 1456. Also see Reddy, K.R.; Maheswari, C.U.; Venkateshwar, M.; Prashanthi, S.; Kantam, M.L. *Tetrahedron Lett.* **2009**, *50*, 2050.

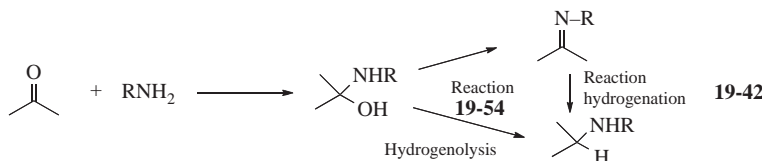
³¹⁶ Wood, J.L.; Khatri, N.A.; Weinreb, S.M. *Tetrahedron Lett.* **1979**, 4907.

³¹⁷ See Kadyrov, R.; Riermeier, T.H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067; Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120.

³¹⁸ See Rylander, P.N. *Hydrogenation Methods* Academic Press, NY, **1985**, pp. 82–93; Klyuev, M.V.; Khidekel, M.L. *Russ. Chem. Rev.* **1980**, *49*, 14; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals* Academic Press, NY, **1967**, pp. 291–303.

³¹⁹ See Le Bris, A.; Lefebvre, G.; Coussemant, F. *Bull. Soc. Chim. Fr.* **1964**, 1366, 1374, 1584, 1594.

with an amine to give an iminium salt (**16-31**) can be followed in a second chemical step of reduction of the C=N unit (**19-42**) using NaBH_4 or a variety of other reagents.³²⁰



Primary amines have been prepared from many aldehydes with at least five carbons and from many ketones by treatment with ammonia and a reducing agent. Smaller aldehydes are usually too reactive to permit isolation of the primary amine. Secondary amines have been prepared by both possible procedures: 2 molar equivalents of ammonia and 1 molar equivalent of aldehyde or ketone, and 1 molar equivalent of primary amine and 1 molar equivalent of carbonyl compound, the latter method being better for all but aromatic aldehydes. Tertiary amines can be prepared in three ways. In general, they are prepared from primary or secondary amines.³²¹ The method is seldom carried out with 3 molar equivalents of ammonia and 1 molar equivalent of carbonyl compound. When the reagent is ammonia, it is possible for the initial product to react again and for this product to react again, so that secondary and tertiary amines are usually obtained as side products. Similarly, primary amines give tertiary as well as secondary amines. In order to minimize this, the aldehyde or ketone is treated with an excess of ammonia or primary amine (unless of course the higher amine is desired).

For ammonia and primary amines there are two possible pathways, but when secondary amines are involved, only the hydrogenolysis pathway is possible. The reaction is compatible with amino acids, giving the N-alkylated amino acid.³²² Other reducing agents³²³ can be used instead of hydrogen and a catalyst, among them boranes,³²⁴ PhSiH_3 with 2% Bu_2SnCl_2 ,³²⁵ triethylsilane with an Ir³²⁶ or an In catalyst,³²⁷ zinc and HCl, or Zn (with formaldehyde for reductive methylation),³²⁸ and polymethylhydrosiloxane.³²⁹ Several hydride reducing agents can be used, including

³²⁰ See Bhattacharyya, S. *Synth. Commun.* **2000**, 30, 2001.

³²¹ Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines* Macmillan, NY, **1965**, pp. 44–52.

³²² Song, Y.; Sercel, A.D.; Johnson, D.R.; Colbry, N.L.; Sun, K.-L.; Roth, B.D. *Tetrahedron Lett.* **2000**, 41, 8225.

³²³ For a list of many of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 835–840.

³²⁴ Nugent, T.C.; El-Shazly, M.; Wakchaure, V.N. *J. Org. Chem.* **2008**, 73, 1297. For a reaction using ammonia-borane, see Ramachandran, P.V.; Gagare, P.D.; Sakavuyi, K.; Clark, P. *Tetrahedron Lett.* **2010**, 51, 3167. 1,2,3-Triazole-boranes have also been used: Liao, W.; Chen, Y.; Liu, Y.; Duan, H.; Petersen, J.L.; Shi, X. *Chem. Commun.* **2009**, 6436.

³²⁵ Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, 3, 1745. For a Mo-catalyzed reaction see Smith, C.A.; Cross, L.E.; Hughes, K.; Davis, R.E.; Judd, D.B.; Merritt, A.T. *Tetrahedron Lett.* **2009**, 50, 4906.

³²⁶ Mizuta, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, 70, 2195; Lee, O.-Y.; Law, K.-L.; Ho, C.-Y.; Yang, D. *J. Org. Chem.* **2008**, 73, 8829.

³²⁷ Lee, O.-Y.; Law, K.-L.; Yang, D. *Org. Lett.* **2009**, 11, 3302.

³²⁸ da Silva, R.A.; Estevam, I.H.S.; Bieber, L.W. *Tetrahedron Lett.* **2007**, 48, 7680.

³²⁹ Chandrasekhar, S.; Reddy, Ch.R.; Ahmed, M. *Synlett* **2000**, 1655.

NaBH_4 ,³³⁰ NaBH_4 with $\text{Ti}(\text{O}i\text{Pr})_4$,³³¹ or NiCl_2 ,³³² $\text{NaBH}_4/\text{H}_3\text{BO}_4$,³³³ BER,³³⁴ polymer-bound triethylammonium acetoxymethylborohydride,³³⁵ LiBH_4 ,³³⁶ ZnBH_4 -*N*-methylpiperidine,³³⁷ ZrBH_4 ,³³⁸ NaBH_3CN ,³³⁹ or sodium triacetoxymethylborohydride,³⁴⁰ Aldehydes and primary amines react with allylic halides, in the presence of Zn dust, to give a homoallylic secondary amine.³⁴¹ A *Hantzsch dihydropyridine* in conjunction with a Sc catalyst has been used,³⁴² and the use of a *Hantzsch ester* in a reductive amination is sometimes called a hydrogen-bond catalyzed reaction.³⁴³ The reaction of an aldehyde and an amine in isopropyl alcohol, in the presence of Ni nanoparticles, undergoes reductive amination via hydrogen transfer.³⁴⁴

Formic acid is an effective reagent for reductive amination³⁴⁵ in what is called the *Wallach reaction*. Secondary amines react with formaldehyde and NaH_2PO_3 to give the *N*-methylated tertiary amine³⁴⁶ and microwave irradiation has also been used.³⁴⁷ Conjugated aldehydes are converted to alkenyl-amines with the amine/silica gel followed by reduction with zinc borohydride.³⁴⁸ In the particular case where primary or secondary amines are reductively methylated with formaldehyde and formic acid, the method is called the *Eschweiler–Clarke procedure*. Heating with paraformaldehyde and oxalyl chloride has been used to give the same result.³⁴⁹ It is possible to use ammonium (or amine) salts of formic acid,³⁵⁰ or formamides, as a substitute for the *Wallach conditions*. This method is called the *Leuckart reaction*,³⁵¹ and in this case the products obtained are often the *N*-formyl derivatives of the amines instead of the free amines. A Rh catalyzed variation has been reported.³⁵²

³³⁰ Gribble, G.W.; Nutaitis, C.F. *Synthesis* **1987**, 709. For the use of an ionic liquid–water system, see Nagaiah, K.; Kumar, V.N.; Rao, R.S.; Reddy, B.V.S.; Narsaiah, A.V.; Yadav, J.S. *Synth. Commun.* **2006**, 36, 3345.

³³¹ Neidigh, K.A.; Avery, M.A.; Williamson, J.S.; Bhattacharyya, S. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2527; Bhattacharyya, S. *J. Org. Chem.* **1995**, 60, 4928.

³³² Saxena, I.; Borah, R.; Sarma, J.C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 503.

³³³ This is a solvent-free reaction. See Cho, B.T.; Kang, S.K. *Synlett* **2004**, 1484.

³³⁴ Yoon, N.M.; Kim, E.G.; Son, H.S.; Choi, J. *Synth. Commun.* **1993**, 23, 1595.

³³⁵ Bhattacharyya, S.; Rana, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* **2003**, 44, 4957.

³³⁶ Cabral, S.; Hulin, B.; Kawai, M. *Tetrahedron Lett.* **2007**, 48, 7134.

³³⁷ Alinezhad, H.; Tajbakhsh, M.; Zamani, R. *Synlett* **2006**, 431.

³³⁸ Heydari, A.; Khaksar, S.; Esfandyari, M.; Tajbakhsh, M. *Tetrahedron* **2007**, 63, 3363.

³³⁹ Mattson, R.J.; Pham, K.M.; Leuck, D.J.; Cowen, K.A. *J. Org. Chem.* **1990**, 55, 2552. See also, Barney, C.L.; Huber, E.W.; McCarthy, J.R. *Tetrahedron Lett.* **1990**, 31, 5547. See Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* **1979**, 11, 201; Lane, C.F. *Synthesis* **1975**, 135. See also, Grenga, P.N.; Sumbler, B.L.; Beland, F.; Priefer, R. *Tetrahedron Lett.* **2009**, 50, 6658.

³⁴⁰ Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* **1996**, 61, 3849.

³⁴¹ Fan, R.; Pu, D.; Qin, L.; Wen, F.; Yao, G.; Wu, J. *J. Org. Chem.* **2007**, 72, 3149.

³⁴² Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* **2004**, 60, 6649.

³⁴³ Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2006**, 8, 741.

³⁴⁴ Alonso, F.; Riente, P.; Yus, M. *Synlett* **2008**, 1289.

³⁴⁵ For a microwave induced reaction see Torch, S.; Barbry, D. *J. Chem. Res. (S)* **2001**, 292.

³⁴⁶ Davis, B.A.; Durden, D.A. *Synth. Commun.* **2000**, 30, 3353.

³⁴⁷ Barbry, D.; Torch, S. *Synth. Commun.* **1996**, 26, 3919.

³⁴⁸ Ranu, B.C.; Majee, A.; Sarkar, A. *J. Org. Chem.* **1998**, 63, 370.

³⁴⁹ Rosenau, T.; Potthast, A.; Röhring, J.; Hofinger, A.; Sixxa, H.; Kosma, P. *Synth. Commun.* **2002**, 32, 457.

³⁵⁰ For a review of ammonium formate in organic synthesis, see Ram, S.; Ehrenkauf, R.E. *Synthesis* **1988**, 91. See Byun, E.; Hong, B.; De Castro, K.A.; Lim, M.; Rhee, H. *J. Org. Chem.* **2007**, 72, 9815.

³⁵¹ Moore, M.L. *Org. React.* **1949**, 5, 301; Awachie, P.I.; Agwada, V.C. *Tetrahedron* **1990**, 46, 1899 and references cited therein; Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J.M.; Domínguez, E.; Palomo, C. *Tetrahedron Lett.* **1996**, 37, 8177; Lejon, T.; Helland, I. *Acta Chem. Scand.* **1999**, 53, 76.

³⁵² Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* **2002**, 67, 8685. See Riermeier, T.H.; Dingerdissen, U.; Börner, A. *Org. Prep. Proceed. Int.* **2004**, 36, 99.

Allylic silanes react with aldehydes and carbamates, in the presence of Bi catalysts,³⁵³ or $\text{BF}_3 \cdot \text{OEt}_2$ ³⁵⁴ to give the corresponding allylic *N*-carbamoyl derivative. The reaction can be done with aromatic amines in the presence of vinyl ethers and a Cu complex to give β -amino ketones.³⁵⁵ Reductive amination of an aryl amine and an aryl aldehyde that contains an ortho conjugated ketone substituent gives the amine, which adds 1,4- (Reaction 15-AA) to the α,β -unsaturated ketone unit to give a bicyclic amine.³⁵⁶ Alternative methods of reductive alkylation have been developed. Alkylation of an imine formed *in situ* is also possible.³⁵⁷

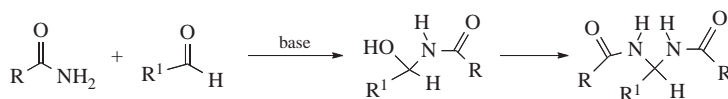
Enantioselective reductive amination reactions are known, generating chiral amines. Ketones and anilines react in the presence of an organocatalyst and a catalytic amount of a chiral phosphoric acid to give the chiral amine.³⁵⁸ The reaction of an aldehyde with a chiral amine initiated a reaction that gave a chiral primary amine.³⁵⁹ A Yb catalyzed reaction with a ketone gave a chiral secondary amine.³⁶⁰ Aldehydes react with *N*-diphenylphosphinoyl-imines and Et_2Zn , in the presence of a chiral Cu precatalyst, to give a chiral amine.³⁶¹ Asymmetric biocatalytic reductive amination reactions are known.³⁶² Asymmetric reductive amination has been attempted using a *Hantzsch ester* mediated reaction.³⁶³

Reductive alkylation has also been carried out on nitro, nitroso, azo, and other compounds that are reduced *in situ* to primary or secondary amines. Azo compounds react with aldehydes, in the presence of proline, and subsequent reduction with NaBH_4 gives the chiral hydrazine derivative.³⁶⁴

OS I, 347, 528, 531; II, 503; III, 328, 501, 717, 723; IV, 603; V, 552; VI, 499; VII, 27.

16-18 Addition of Amides to Aldehydes

Alkylamido-de-oxo-bisubstitution



Amides can add to aldehydes in the presence of bases (so the nucleophile is actually RCONH^-) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides.³⁶⁵ If the R' group contains an α hydrogen, water may split out.

³⁵³ Ollevier, T.; Ba, T. *Tetrahedron Lett.* **2003**, 44, 9003.

³⁵⁴ Billet, M.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2001**, 42, 631.

³⁵⁵ Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, 64, 6833.

³⁵⁶ Suwa, T.; Shibata, I.; Nishino, K.; Baba, A. *Org. Lett.* **1999**, 1, 1579.

³⁵⁷ See Choudary, B.M.; Jyothi, K.; Madhi, S.; Kantam, M.L. *Synlett* **2004**, 231; Yadav, J.S.; Reddy, B.V.S.; Raju, A.K. *Synthesis* **2003**, 883.

³⁵⁸ Storer, R.I.; Carrera, D.E.; Ni, Y.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2006**, 128, 84. See Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, 128, 13074.

³⁵⁹ Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, 128, 11038.

³⁶⁰ Nugent, T.C.; El-Shazly, M.; Wakchaure, V.N. *J. Org. Chem.* **2008**, 73, 1297.

³⁶¹ Côté, A.; Charette, A.B. *J. Org. Chem.* **2005**, 70, 10864.

³⁶² Koszelewski, D.; Lavandera, I.; Clay, D.; Guebitz, G.M.; Rozzell, D.; Kroutil, W. *Angew. Chem. Int. Ed.* **2008**, 47, 9337.

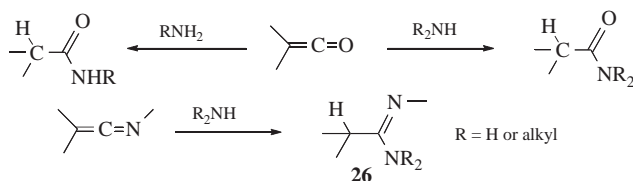
³⁶³ Wakchaure, V.N.; Nicoletti, M.; Ratjen, L.; List, B. *Synlett* **2010**, 2708.

³⁶⁴ List, B. *J. Am. Chem. Soc.* **2002**, 124, 5656; Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K.A. *J. Am. Chem. Soc.* **2002**, 124, 6254.

³⁶⁵ Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 754–759; Zaugg, H.E.; Martin, W.B. *Org. React.* **1965**, 14, 52, pp. 91–95, 104–112; Gilbert, E.E. *Synthesis* **1972**, 30.

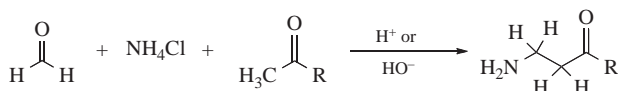
Sulfonamides add to aldehydes to give the *N*-sulfonyl imine. Benzaldehyde reacts with TsNH₂ (e.g., with trifluoroacetic anhydride, TFAA) in CH₂Cl₂ at reflux,³⁶⁶ or with TiCl₄ in refluxing dichloroethane,³⁶⁷ to give the *N*-tosylimine (Ts–N=CHPh). In a similar manner, the reaction of TolSO₂Na + PhSO₂Na with an aldehyde in aq formic acid gives the *N*-phenylsulfonyl imine.³⁶⁸ The reaction of an aldehyde with Ph₃P=NTs and a ruthenium catalyst gives the *N*-tosyl imine.³⁶⁹

Primary and secondary amines add to ketenes to give, respectively, *N*-substituted and *N*, *N*-disubstituted amides:³⁷⁰ and to ketenimines to give amidines, (**26**).³⁷¹



16-19 The Mannich Reaction

Acyl,amino-de-oxo-bisubstitution, and so on



In the *Mannich reaction*, formaldehyde (or sometimes another aldehyde) is condensed with ammonia, in the form of its salt, and a compound containing an active hydrogen.³⁷² This can formally be considered as an addition of ammonia to give H₂NCH₂OH, followed by a nucleophilic substitution. The reaction can be carried out with salts of primary or secondary amines,³⁷³ or with amides³⁷⁴ rather than ammonia, in which cases the product is substituted on the nitrogen with R, R², and RCO, respectively. The product is referred to as a *Mannich base*. The imine can be generated *in situ*, and the reaction of a ketone, formaldehyde, and diethylamine with microwave irradiation gave the *Mannich* product, a β-amino ketone.³⁷⁵ Many active hydrogen compounds give the reaction, including ketones and aldehydes, esters, nitroalkanes,³⁷⁶ and nitriles as well as ortho-carbon atoms of phenols, the carbon of terminal alkynes, the oxygen of alcohols and the sulfur of thiols.³⁷⁷

³⁶⁶ Lee, K.Y.; Lee, C.G.; Kim, J.N. *Tetrahedron Lett.* **2003**, *44*, 1231.

³⁶⁷ Ram, R.N.; Khan, A.A. *Synth. Commun.* **2001**, *31*, 841.

³⁶⁸ Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75.

³⁶⁹ Jain, S.L.; Sharma, V.B.; Sain, B. *Tetrahedron Lett.* **2004**, *45*, 4341.

³⁷⁰ Tidwell, T.T. *Acc. Chem. Res.* **1990**, *23*, 273; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* **1975**, *4*, 231. For an enantioselective reaction, see Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* **2002**, *124*, 10006.

³⁷¹ Stevens, C.L.; Freeman, R.C.; Noll, K. *J. Org. Chem.* **1965**, *30*, 3718.

³⁷² Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791; Gevorgyan, G.A.; Tramontini, M. *Synthesis* **1973**, 703; House, H.O. *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin, NY, **1972**, pp. 654–660; Gevorgyan, G.A.; Agababyan, A.G.; Mndzhoyan, O.L. *Russ. Chem. Rev.* **1985**, *54*, 495.

³⁷³ Agababyan, A.G.; Gevorgyan, G.A.; Mndzhoyan, O.L. *Russ. Chem. Rev.* **1982**, *51*, 387.

³⁷⁴ Hellmann, H. *Angew. Chem.* **1957**, *69*, 463; *Newer Methods Prep. Org. Chem.* **1963**, *2*, 277.

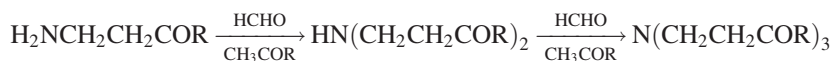
³⁷⁵ Gadhwal, S.; Baruah, M.; Prajapati, D.; Sandhu, J.S. *Synlett* **2000**, 341.

³⁷⁶ Qian, C.; Gao, F.; Chen, R. *Tetrahedron Lett.* **2001**, *42*, 4673. See Baer, H.H.; Urbas, L., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Wiley, NY, **1970**, pp. 117–130.

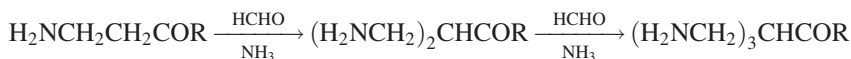
³⁷⁷ see Massy, D.J.R. *Synthesis* **1987**, 589; Dronov, V.I.; Nikitin, Yu.E. *Russ. Chem. Rev.* **1985**, *54*, 554

Arylamines do not normally give the reaction, but hydrazines can be used.³⁷⁸ Vinylogous *Mannich reactions* are known³⁷⁹ (see Sec. 6.B for vinylogy).

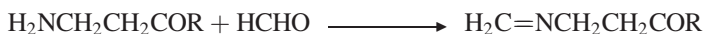
The *Mannich base* product can react further in three ways. If it is a primary or secondary amine, it may condense with one or two additional molecules of aldehyde and an active compound, for example,



If the active hydrogen compound has two or three active hydrogen atoms, the *Mannich base* may condense with one or two additional molecules of aldehyde and ammonia or amine, for example,



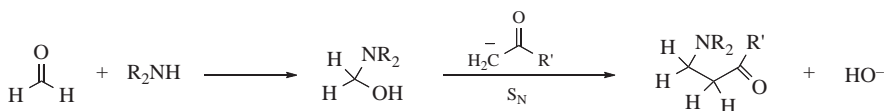
Another reaction consists of condensation of the *Mannich base* with excess formaldehyde:



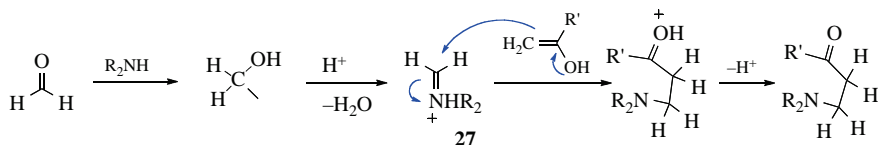
Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times, they are side products.

When the *Mannich base* contains an amino group β to a carbonyl (and it usually does), ammonia is easily eliminated. This is a route to α,β -unsaturated aldehydes, ketones, esters, and so on.

Studies of the reaction kinetics have led to the following proposals for the mechanism of the *Mannich reaction*.³⁸⁰ The base-catalyzed reaction:



The acid-catalyzed reaction:



According to this mechanism, it is the free amine, not the salt that reacts, even in acid solution; and the active-hydrogen compound (in the acid-catalyzed process) reacts as the enol when that is possible. This latter step is similar to what happens in Reaction 12-4. There is kinetic evidence for the intermediacy of the iminium ion (27).³⁸¹

When an unsymmetrical ketone is used as the active-hydrogen component, two products are possible. Regioselectivity has been obtained by treatment of the ketone with

³⁷⁸ El Kaim, L.; Grimaud, L.; Perroux, Y.; Tirla, C. *J. Org. Chem.* **2003**, 68, 8733.

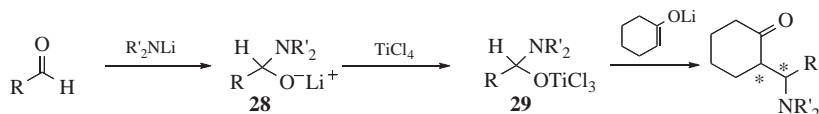
³⁷⁹ Bur, S.; Martin, S.F. *Tetrahedron* **2001**, 57, 3221; Martin, S.F. *Acc. Chem. Res.* **2002**, 35, 895.

³⁸⁰ Cummings, T.F.; Shelton, J.R. *J. Org. Chem.* **1960**, 25, 419.

³⁸¹ Benkovic, S.J.; Benkovic, P.A.; Comfort, D.R. *J. Am. Chem. Soc.* **1969**, 91, 1860.

preformed iminium ions:³⁸² the use of $\text{Me}_2\text{N}^+=\text{CH}_2$ CF_3COO^- in CF_3COOH gives substitution at the more highly substituted position, while with $(i\text{Pr})_2\text{N}^+=\text{CH}_2$ ClO_4^- the reaction takes place at the less highly substituted position.³⁸³ The preformed iminium compound dimethyl(methylene)ammonium iodide ($\text{CH}_2=\text{N}^+\text{Me}_2 \text{I}^-$), called an *Eschenmoser's salt*,³⁸⁴ has also been used in *Mannich reactions*.³⁸⁵ The analogous chloride salt has been condensed with an imine to give a β,β' -dimethylamino ketone after acid hydrolysis.³⁸⁶

Another type of preformed reagent (**29**) has been used to carry out diastereoselective *Mannich reactions*. The lithium salts (**28**) are treated with TiCl_4 to give **29**, which is then treated with the enolate anion of a ketone.³⁸⁷ The Pd catalyzed Mannich reaction of enol ethers to imines is also known.³⁸⁸ The reaction of silyl enol ethers and imines³⁸⁹ is catalyzed by HBF_4 in aq methanol.³⁹⁰ Similarly, silyl enol ethers react with aldehydes and aniline in the presence of InCl_3 to give the β -amino ketone.³⁹¹



Enantioselective *Mannich reactions* are known.³⁹² Chiral catalysts are commonly used,³⁹³ including proline,³⁹⁴ proline derivatives, or proline analogues,³⁹⁵ a Pybox-La catalyst,³⁹⁶ chiral aminosulfonamides,³⁹⁷ or Cinchona alkaloids,³⁹⁸ and other chiral amines.³⁹⁹ Chiral

³⁸² See Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* **1971**, *10*, 330.

³⁸³ Jasor, Y.; Luche, M.; Gaudry, M.; Marquet, A. *J. Chem. Soc., Chem. Commun.* **1974**, 253; Gaudry, M.; Jasor, Y.; Khac, T.B. *Org. Synth.* **VI**, 474.

³⁸⁴ Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* **1971**, *10*, 330.

³⁸⁵ See Bryson, T.A.; Bonitz, G.H.; Reichel, C.J.; Dardis, R.E. *J. Org. Chem.* **1980**, *45*, 524, and references cited therein.

³⁸⁶ Arend, M.; Risch, N. *Tetrahedron Lett.* **1999**, *40*, 6205.

³⁸⁷ Seebach, D.; Schiess, M.; Schweizer, W.B. *Chimia* **1985**, *39*, 272. See also, Katritzky, A.R.; Harris, P.A. *Tetrahedron* **1990**, *46*, 987.

³⁸⁸ See Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450.

³⁸⁹ See Fujisawa, H.; Takahashi, E.; Mukaiyama, T. *Chemistry: European J.* **2006**, *12*, 5082.

³⁹⁰ Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **2001**, *42*, 4025.

³⁹¹ Loh, T.-P.; Wei, L.L. *Tetrahedron Lett.* **1998**, *39*, 323.

³⁹² See Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102; Marques, M.M.B. *Angew. Chem. Int. Ed.* **2006**, *45*, 348; Ibrahim, I.; Córdova, A. *Chem. Commun.* **2006**, 1760; Amedjkouh, M.; Brandberg, M. *Chem. Commun.* **2008**, 3043.

³⁹³ See Rodríguez, B.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2888.

³⁹⁴ List, B.; Pojarliev, P.; Biller, W.T.; Martin, H.J. *J. Am. Chem. Soc.* **2004**, *124*, 827; Ibrahim, I.; Casas, J.; Córdova, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 6528; Yang, J.W.; Stadler, M.; List, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 609.

³⁹⁵ Mitsumori, S.; Zhang, H.; Cheong, P.H.-Y.; Houk, K.N.; Tanaka, F.; Barbas, III, C.F. *J. Am. Chem. Soc.* **2006**, *128*, 1040; Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, III, C.F. *J. Am. Chem. Soc.* **2006**, *128*, 9630. See also, Hayashi, Y.; Aratake, S.; Imai, Y.; Hibino, K.; Chen, Q.-Y.; Yamaguchi, J.; Uchimar, T. *Chemistry: Asian J.* **2008**, *3*, 225.

³⁹⁶ Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588; Cutting, G.A.; Stainforth, N.E.; John, M.P.; Kociok-Köhn, G.; Willis, M.C. *J. Am. Chem. Soc.* **2007**, *129*, 10632.

³⁹⁷ Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408; Kano, T.; Hato, Y.; Yamamoto, A.; Maruoka, K. *Tetrahedron* **2008**, *64*, 1197.

³⁹⁸ Lou, S.; Taoka, B.M.; Ting, A.; Schaus, S.E. *J. Am. Chem. Soc.* **2005**, *127*, 11256; Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048.

³⁹⁹ Haurena, C.; LeGall, E.; Sengmany, S.; Martens, T. *Tetrahedron* **2010**, *66*, 9902.

Brønsted acids are also used as catalysts,⁴⁰⁰ as well as chiral ammonium salts.⁴⁰¹ Chiral diamine⁴⁰² or phosphine-imine⁴⁰³ ligands have been used, and chiral dinuclear zinc compounds.⁴⁰⁴ Chiral auxiliaries on the carbonyl fragment can be used.⁴⁰⁵ Chiral imines, in the form of chiral hydrazones, have been used with silyl enol ethers and a Sc catalyst.⁴⁰⁶ Chiral amines react with aldehydes, with silyl enol ethers and an InCl_3 catalyst in ionic liquids, to give the *Mannich* product with good enantioselectivity.⁴⁰⁷ A chiral thiourea catalyst has been used with a vinylogous *Mannich reaction*⁴⁰⁸ (see Sec. 6.B for vinylogy).

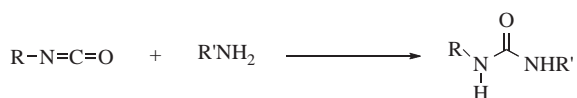
The reaction of nitroalkanes and amines, usually in the presence of a metal catalyst (e.g., CuBr),⁴⁰⁹ has been called the nitro-*Mannich reaction*.⁴¹⁰ An asymmetric nitro-*Mannich reaction* used a Cu—Sm catalyst,⁴¹¹ a Cu catalyst,⁴¹² or a chiral thiourea catalyst.⁴¹³

Also See, **11-22**.

OS **III**, 305; **IV**, 281, 515, 816; **VI**, 474, 981, 987; **VII**, 34. See also, OS **VIII**, 358.

16-20 The Addition of Amines to Isocyanates

N-Hydro-*C*-alkylamino-addition



Ammonia and primary and secondary amines can be added to isocyanates⁴¹⁴ to give substituted ureas.⁴¹⁵ Isothiocyanates give thioureas.⁴¹⁶ This is an excellent method for the preparation of ureas and thioureas. These compounds are often used as derivatives for primary and secondary amines. Isocyanic acid (HNCO) also gives the reaction; usually its salts (e.g., NaNCO) are used. Wöhler's famous synthesis of urea involved the addition of ammonia to a salt of this acid.⁴¹⁷

OS **II**, 79; **III**, 76, 617, 735; **IV**, 49, 180, 213, 515, 700; **V**, 555, 801, 802, 967; **VI**, 936, 951; **VIII**, 26.

⁴⁰⁰ Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790; Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756; Rueping, M.; Sugiono, E.; Schoepke, F. *R. Synlett* **2007**, 1441.

⁴⁰¹ Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878.

⁴⁰² Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640; Trost, B.M.; Terrell, C.R. *J. Am. Chem. Soc.* **2003**, *125*, 338.

⁴⁰³ Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500.

⁴⁰⁴ Trost, B.M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778.

⁴⁰⁵ Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.-i.; Tomioka, K. *Org. Lett.* **2004**, *6*, 1721.

⁴⁰⁶ Jacobsen, M.F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* **2004**, *69*, 4792.

⁴⁰⁷ Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* **2003**, *44*, 2409.

⁴⁰⁸ Liu, T.-Y.; Cui, J.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878.

⁴⁰⁹ Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672.

⁴¹⁰ Anderson, J.C.; Blake, A.J.; Howell, G.P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549.

⁴¹¹ Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900.

⁴¹² Anderson, J.C.; Howell, G.P.; Lawrence, R.M.; Wilson, C.S. *J. Org. Chem.* **2005**, *70*, 5665.

⁴¹³ Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606.

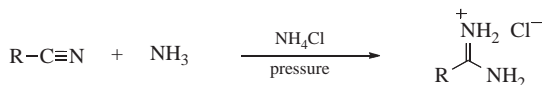
⁴¹⁴ For a review of the mechanism, see Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* **1975**, *4*, 231.

⁴¹⁵ See Vishnyakova, T.P.; Golubeva, I.A.; Glebova, E.V. *Russ. Chem. Rev.* **1985**, *54*, 249.

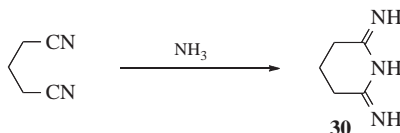
⁴¹⁶ Herr, R.J.; Kuhler, J.L.; Meckler, H.; Opalka, C.J. *Synthesis* **2000**, 1569.

⁴¹⁷ See Shorter, J. *Chem. Soc. Rev.* **1978**, *7*, 1. See also, Williams, A.; Jencks, W.P. *J. Chem. Soc. Perkin Trans. 2* **1974**, 1753, 1760; Hall, K.J.; Watts, D.W. *Aust. J. Chem.* **1977**, *30*, 781, 903.

16-21 The Addition of Ammonia or Amines to Nitriles

N-Hydro-*C*-amino-addition

Unsubstituted amidines (in the form of their salts) can be prepared by addition of ammonia to nitriles.⁴¹⁸ Many amidines have been made in this way. Dinitriles of suitable chain length can give imidines (30).⁴¹⁹

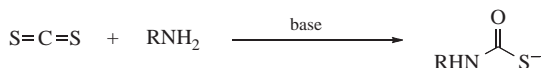


Primary and secondary amines can be used instead of ammonia, to give substituted amidines, but only if the nitrile contains electron-withdrawing groups; for example, Cl₃CCN gives the reaction. Ordinary nitriles do not react, and, in fact, acetonitrile is often used as a solvent in this reaction.⁴²⁰ Ordinary nitriles can be converted to amidines by treatment with an alkylchloroaluminum amide [MeAl(Cl)NR₂; R = H or Me].⁴²¹ The addition of ammonia to cyanamide (NH₂CN) gives guanidine [(NH₂)₂C=NH]. Guanidines can also be formed from amines.⁴²²

If water is present, in the presence of a Ru⁴²³ or a Pt catalyst,⁴²⁴ the addition of a primary or secondary amine to a nitrile gives an amide: RCN + R¹NHR² + H₂O → RCONR¹R² + NH₃ (R² may be H). When benzonitrile reacts with H₂PO₃Se[−] in aq methanol, a selenoamide [Ph(C=Se)NH₂], is formed after treatment with aq potassium carbonate.⁴²⁵

OS I, 302 [but also see, OS V, 589]; IV, 245, 247, 515, 566, 769. See also, OS V, 39.

16-22 The Addition of Amines to Carbon Disulfide and Carbon Dioxide

S-Metallo-*C*-alkylamino-addition

Salts of dithiocarbamic acid can be prepared by the addition of primary or secondary amines to carbon disulfide.⁴²⁶ This reaction is similar to 16-10. Hydrogen sulfide can be eliminated from the product, directly or indirectly, to give isothiocyanates (RNCS). Isothiocyanates can be obtained directly by the reaction of primary amines and CS₂ in

⁴¹⁸ For reviews of amidines, see Granik, V.G. *Russ. Chem. Rev.* **1983**, 52, 377; Gautier, J.; Miocque, M.; Farnoux, C.C. in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, **1975**, pp. 283–348.

⁴¹⁹ Elvidge, J.A.; Linstead, R.P.; Salaman, A.M. *J. Chem. Soc.* **1959**, 208.

⁴²⁰ Grivas, J.C.; Taurins, A. *Can. J. Chem.* **1961**, 39, 761.

⁴²¹ Garigipati, R.S. *Tetrahedron Lett.* **1990**, 31, 1969.

⁴²² Dräger, G.; Solodenko, W.; Messinger, J.; Schön, U.; Kirschning, A. *Tetrahedron Lett.* **2002**, 43, 1401.

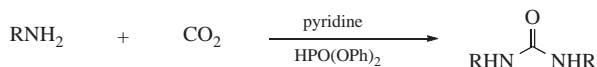
⁴²³ Murahashi, S.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* **1986**, 108, 7846.

⁴²⁴ Cobley, C.J.; van den Heuvel, M.; Abbadi, A.; de Vries, J.G. *Tetrahedron Lett.* **2000**, 41, 2467.

⁴²⁵ Kamiński, R.; Glass, R.S.; Skowrońska, A. *Synthesis* **2001**, 1308.

⁴²⁶ Dunn, A.D.; Rudolf, W. *Carbon Disulfide in Organic Chemistry*, Ellis Horwood, Chichester, **1989**, pp. 226–315; Katritzky, A.R.; Faïd-Allah, H.; Marson, C.M. *Heterocycles* **1987**, 26, 1657; Yokoyama, M.; Imamoto, T. *Synthesis* **1984**, 797, see pp. 804–812; Katritzky, A.R.; Marson, C.M.; Faïd-Allah, H. *Heterocycles* **1987**, 26, 1333.

pyridine in the presence of dicyclohexylcarbodiimide.⁴²⁷ A tosyl chloride mediated preparation of isothiocyanates is also known.⁴²⁸ Aniline derivatives react with CS₂ and NaOH, and then ethyl chloroformate to give the aryl isothiocyanate.⁴²⁹ In the presence of diphenyl phosphite and pyridine, primary amines add to CO₂ and to CS₂ to give, respectively, symmetrically substituted ureas and thioureas:⁴³⁰ Isoselenoureas [R₂NC(=NR¹)SeR²] can also be formed.⁴³¹

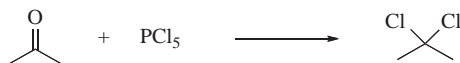


OS I, 447; **III**, 360, 394, 599, 763; **V**, 223.

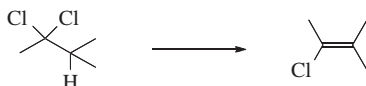
E. Halogen Nucleophiles

16-23 The Formation of *gem*-Dihalides from Aldehydes and Ketones

Dihalo-de-oxo-bisubstitution



Aliphatic aldehydes and ketones can be converted to *gem*-dichlorides⁴³² by treatment with PCl₅. The reaction fails for perhalo ketones.⁴³³ If the aldehyde or ketone has an α hydrogen, elimination of HCl may follow and a vinylic chloride is a frequent side product, as shown,⁴³⁴ or even the main product.⁴³⁵ Phosphorus pentabromide (PBr₅) does not give good yields of *gem*-dibromides,⁴³⁶ but these can be obtained from aldehydes, by the use of Br₂, and triphenyl phosphite.⁴³⁷ *gem*-Dichlorides can be prepared by reacting an aldehyde with BiCl₃.⁴³⁸



The mechanism of *gem*-dichloride formation involves initial attack on PCl₄⁺, which is present in solid PCl₅, by the carbonyl oxygen, followed by addition of Cl[−] to the carbon:⁴³⁹



⁴²⁷ Jochims, J.C. *Chem. Ber.* **1968**, 101, 1746.; Molina, P.; Alajarin, M.; Arques, A. *Synthesis* **1982**, 596.

⁴²⁸ Wong, R.; Dolman, S.J. *J. Org. Chem.* **2007**, 72, 3969.

⁴²⁹ Li, Z.; Qian, X.; Liu, Z.; Li, Z.; Song, G. *Org. Prep. Proceed. Int.* **2000**, 32, 571.

⁴³⁰ Fournier, J.; Bruneau, C.; Dixneuf, P.H.; Lécolier, S. *J. Org. Chem.* **1991**, 56, 4456. See Chiarotto, I.; Feroci, M. *J. Org. Chem.* **2003**, 68, 7137; Lemoucheux, L.; Rouden, J.; Ibazizene, M.; Sobrio, F.; Lasne, M.-C. *J. Org. Chem.* **2003**, 68, 7289.

⁴³¹ Asanuma, Y.; Fujiwara, S.-i.; Shi-ike, T.; Kambe, N. *J. Org. Chem.* **2004**, 69, 4845.

⁴³² For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 719–722.

⁴³³ Farah, B.S.; Gilbert, E.E. *J. Org. Chem.* **1965**, 30, 1241.

⁴³⁴ See Nikolenko, L.N.; Popov, S.I. *J. Gen. Chem. USSR* **1962**, 32, 29.

⁴³⁵ See Newman, M.S.; Fraenkel, G.; Kirn, W.N. *J. Org. Chem.* **1963**, 28, 1851.

⁴³⁶ See Napolitano, E.; Fiaschi, R.; Mastroianni, E. *Synthesis* **1986**, 122.

⁴³⁷ Hoffmann, R.W.; Bovicelli, P. *Synthesis* **1990**, 657. See also, Lansinger, J.M.; Ronald, R.C. *Synth. Commun.* **1979**, 9, 341.

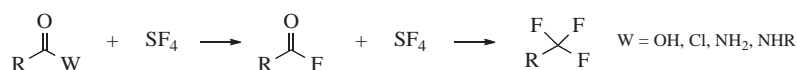
⁴³⁸ Kabalka, G.W.; Wu, Z. *Tetrahedron Lett.* **2000**, 41, 579.

⁴³⁹ Newman, M.S. *J. Org. Chem.* **1969**, 34, 741.

This chloride ion may come from PCl_6^- , which is also present in solid PCl_5 . There follows a two-step $\text{S}_{\text{N}}1$ process. Alternatively, **31** can be converted to the product without going through the chlorocarbenium ion, by an $\text{S}_{\text{N}}i$ process.

This reaction has sometimes been performed on carboxylic esters, though these compounds very seldom undergo any addition to the $\text{C}=\text{O}$ bond. An example is the conversion of F_3CCOOPh to $\text{F}_3\text{CCCl}_2\text{OPh}$.⁴⁴⁰ However, formates commonly give the reaction.

Many aldehydes and ketones have been converted to *gem*-difluoro compounds with sulfur tetrafluoride (SF_4),⁴⁴¹ including quinones, which give 1,1,4,4-tetrafluorocyclohexadiene derivatives. With ketones, yields can be raised and the reaction temperature lowered, by the addition of anhydrous HF .⁴⁴² Carboxylic acids, acyl chlorides, and amides react with SF_2 to give 1,1,1-trifluorides. In these cases, the first product is the acyl fluoride, which then undergoes the *gem*-difluorination reaction:



The acyl fluoride can be isolated. Carboxylic esters also give trifluorides, but more vigorous conditions are required. In this case, the carbonyl group of the ester is attacked first, and $\text{RCF}_2\text{OR}'$ can be isolated from $\text{RCO}_2\text{R}'$ ⁴⁴³ and then converted to the trifluoride. Anhydrides can react in either manner. Both types of intermediate are isolable under the right conditions, and SF_4 even converts CO_2 to CF_4 . A disadvantage of reactions with SF_4 is that they require a pressure vessel lined with stainless steel. Selenium tetrafluoride (SeF_4) gives similar reactions, but atmospheric pressure and ordinary glassware can be used.⁴⁴⁴ Another reagent that is often used to convert aldehydes and ketones to *gem*-difluorides is the commercially available diethylaminosulfur trifluoride (**DAST**, Et_2NSF_3), and CF_2Br_2 in the presence of zinc.⁴⁴⁵ The mechanism with SF_4 is probably similar in general nature, if not in specific detail, to that with PCl_5 . Some dithianes can be converted to *gem*-difluorides with a mixture of fluorine and iodine in acetonitrile.⁴⁴⁶ Oximes give *gem*-difluorides with NO^+BF_4^- and pyridinium polyhydrogen fluoride.⁴⁴⁷

Treatment with hydrazine to give the hydrazone, and then $\text{CuBr}_2/t\text{-BuOLi}$, generated the *gem*-dibromide.⁴⁴⁸ Oximes give *gem*-dichlorides upon treatment with chlorine and $\text{BF}_3\cdot\text{OEt}_2$, and then HCl .⁴⁴⁹

In a related process, α -halo ethers can be prepared by treatment of aldehydes and ketones with an alcohol and HX . The reaction is applicable to aliphatic aldehydes and ketones and to primary and secondary alcohols. The addition of HX to an aldehyde or

⁴⁴⁰ Clark, R.F.; Simons, J.H. *J. Org. Chem.* **1961**, 26, 5197.

⁴⁴¹ Wang, C.J. *Org. React.* **1985**, 34, 319; Boswell, Jr., G.A.; Ripka, W.C.; Scribner, R.M.; Tullock, C.W. *Org. React.* **1974**, 21, 1.

⁴⁴² Muratov, N.N.; Mohamed, N.M.; Kunshenko, B.V.; Burmakov, A.I.; Alekseeva, L.A.; Yagupol'skii, L.M. *J. Org. Chem. USSR* **1985**, 21, 1292.

⁴⁴³ See Bunnelle, W.H.; McKinnis, B.R.; Narayanan, B.A. *J. Org. Chem.* **1990**, 55, 768.

⁴⁴⁴ Olah, G.A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* **1974**, 96, 925.

⁴⁴⁵ Hu, C.-M.; Qing, F.-L.; Shen, C.-X. *J. Chem. Soc. Perkin Trans. 1* **1993**, 335.

⁴⁴⁶ Chambers, R.D.; Sandford, G.; Atherton, M. *J. Chem. Soc., Chem. Commun.* **1995**, 177.

⁴⁴⁷ York, C.; Prakash, G.K.S.; Wang, Q.; Olah, G.A. *Synlett* **1994**, 425.

⁴⁴⁸ Takeda, T.; Sasaki, R.; Nakamura, A.; Yamauchi, S.; Fujiwara, T. *Synlett* **1996**, 273.

⁴⁴⁹ Tordeux, M.; Boumizane, K.; Wakselman, C. *J. Org. Chem.* **1993**, 58, 1939.

ketone gives α -halo alcohols, which are usually unstable, although exceptions are known, especially with perfluoro and perchloro species.⁴⁵⁰

OS II, 549; V, 365, 396, 1082; VI, 505, 845; VIII, 247. Also see, OS I, 506. For α -haloethers, see OS I, 377; IV, 101 (see, however, OS V, 218), 748; VI, 101.

F. Attack at Carbon by Organometallic Compounds⁴⁵¹

16-24 The Addition of Grignard Reagents and Organolithium Reagents to Aldehydes and Ketones

O-Hydro-C-alkyl-addition



Organomagnesium compounds, commonly known as *Grignard reagents* (RMgX), are formed by the reaction of alkyl, vinyl, or aryl halides with magnesium metal, usually in ether solvents (e.g., diethyl ether or THF; Reaction 12-38). Halogen–Mg exchange can generate a *Grignard reagent* by reaction of aryl halides with reactive aliphatic *Grignard reagents*.⁴⁵² Microwave irradiation has been used to facilitate the formation of *Grignard reagents* from aryl chlorides that are slow to react otherwise.⁴⁵³

The addition of *Grignard reagents* to aldehydes and ketones⁴⁵⁴ is known as the *Grignard reaction*.⁴⁵⁵ The initial product of reaction with a carbonyl is a magnesium alkoxide, requiring a hydrolysis step to generate the final alcohol product. Formaldehyde gives primary alcohols; other aldehydes give secondary alcohols; and ketones give tertiary alcohols. The reaction is of very broad scope. In many cases, the hydrolysis step is carried out with dilute HCl or H₂SO₄, but this cannot be done for tertiary alcohols in which at least one R group is alkyl because such alcohols are easily dehydrated under acidic conditions (Reaction 17-1). In such cases (and often for other alcohols as well), an aqueous solution of ammonium chloride is used instead of a strong acid. *Grignard reagents* have been used in solid-phase synthesis.⁴⁵⁶ Ionic liquids have been used for the *Grignard reaction*.⁴⁵⁷

Transition metal catalysts can promote 1,2-addition of Grignard reagents to ketones. A catalytic amount of Zn(II) compounds promote the reaction, for example.⁴⁵⁸ In the presence of a catalytic amount of InCl₃, *Grignard reagents* react to give a mixture of 1,2- and 1,4-addition products with the 1,4-product predominating, but there was an increased 1,2-addition relative to the uncatalyzed reaction.⁴⁵⁹

⁴⁵⁰ For example, see Clark, D.R.; Emsley, J.; Hibbert, F. *J. Chem. Soc. Perkin Trans. 2* **1988**, 1107.

⁴⁵¹ See Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vols. 2–4, Wiley, NY, **1985–1987**.

⁴⁵² Song, J.J.; Yee, N.K.; Tan, Z.; Xu, J.; Kapadia, S.R.; Senanayake, C.H. *Org. Lett.* **2004**, 6, 4905.

⁴⁵³ Gold, H.; Larhed, M.; Nilsson, P. *Synlett* **2005**, 1596.

⁴⁵⁴ See Leung, S.S.-W.; Streitwieser, A. *J. Org. Chem.* **1999**, 64, 3390.

⁴⁵⁵ See Eicher, T. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, **1966**, pp. 621–693; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 138–528; Stowell, J.C. *Chem. Rev.* **1984**, 84, 409. For a computational study of this reaction, see Yamazaki, S.; Yamabe, S. *J. Org. Chem.* **2002**, 67, 9346.

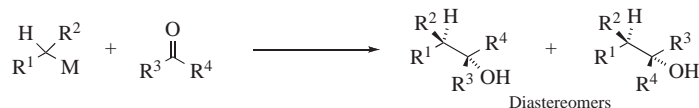
⁴⁵⁶ Franzén, R.G. *Tetrahedron* **2000**, 56, 685.

⁴⁵⁷ Handy, S.T. *J. Org. Chem.* **2006**, 71, 4659.

⁴⁵⁸ Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, 128, 9998; Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *J. Org. Chem.* **2010**, 75, 5008; Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *Chem. Commun.* **2010**, 2674.

⁴⁵⁹ Kelly, B.G.; Gilheany, D.G. *Tetrahedron Lett.* **2002**, 43, 887.

Diastereoselective addition⁴⁶⁰ has been carried out with achiral reagents and chiral substrates,⁴⁶¹ similar to the reduction shown in Reaction 19-36.⁴⁶² Because the attacking atom in this case is carbon, diastereoselective addition is possible with an achiral substrate and an optically active reagent.⁴⁶³ The use of suitable reactants creates, in the most general case, two new stereogenic centers, so the product can exist as two pairs of enantiomers, as shown. Even if the organometallic compound is racemic, it still may be possible to get a diastereoselective reaction; that is, one pair of enantiomers is formed in greater amount than the other.⁴⁶⁴



Asymmetric *Grignard reactions* are possible under certain circumstances.⁴⁶⁵ Chiral ligands with a chiral Cu catalyst⁴⁶⁶ or a chiral Ti complex⁴⁶⁷ give alcohols with good enantioselectivity. An interesting method formed using an alkylmagnesium halide, dibutylmagnesium (Bu₂Mg) and a chiral diamine, and subsequent reaction with an aldehyde led to the alcohol derived from acyl addition of a butyl group with good enantioselectivity.⁴⁶⁸ N-Heterocyclic carbenes have been used as organocatalysts for asymmetric *Grignard reactions*.⁴⁶⁹ Aryl iodides undergo halogen–magnesium exchange when pretreated with PhMgCl, and subsequent reaction with an aldehyde gives the alcohol.⁴⁷⁰

The reaction of aldehydes or ketones with alkyl and aryl *Grignard reagents* was done in the earliest work without preliminary formation of RMgX, by mixing RX, the carbonyl compound, and magnesium metal in an ether solvent. This approach preceded Grignard's work, and is now known as the *Barbier reaction*.⁴⁷¹ The organolithium analogue of this process is also known.⁴⁷² Yields were generally satisfactory. Carboxylic ester, nitrile, and imide groups in the R are not affected by the reaction conditions.⁴⁷³ Modern versions of the

⁴⁶⁰ Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. Also see Tomoda, S.; Senju, T. *Tetrahedron* **1999**, *55*, 3871. See Schulze, V.; Nell, P.G.; Burton, A.; Hoffmann, R.W. *J. Org. Chem.* **2003**, *68*, 4546.

⁴⁶¹ See Reetz, M.T. *Angew. Chem. Int. Ed.* **1984**, *23*, 556. See also, Keck, G.E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

⁴⁶² See Soai, K.; Niwa, S.; Hatanaka, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2129. Also see Hoffmann, R.W.; Dresely, S.; Hildebrandt, B. *Chem. Ber.* **1988**, *121*, 2225; Paquette, L.A.; Learn, K.S.; Romine, J.L.; Lin, H. *J. Am. Chem. Soc.* **1988**, *110*, 879; Brown, H.C.; Bhat, K.S.; Randad, R.S. *J. Org. Chem.* **1989**, *54*, 1570.

⁴⁶³ See Denmark, S.E.; Weber, E.J. *J. Am. Chem. Soc.* **1984**, *106*, 7970. See Greeves, N.; Pease, J.E. *Tetrahedron Lett.* **1996**, *37*, 5821; Zweifel, G.; Shoup, T.M. *J. Am. Chem. Soc.* **1988**, *110*, 5578.

⁴⁶⁴ See Masuyama, Y.; Takahara, J.P.; Kurusu, Y. *Tetrahedron Lett.* **1989**, *30*, 3437.

⁴⁶⁵ Luderer, M.R.; Bailey, W.F.; Luderer, M.R.; Fair, J.D.; Dancer, R.J.; Sommer, M.B. *Tetrahedron Asymm.* **2009**, *20*, 981.

⁴⁶⁶ Cotton, H.K.; Norinder, J.; Bäckvall, J.-E. *Tetrahedron* **2006**, *62*, 5632; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 4435; López, F.; van Zijl, A.W.; Minnaard, A.J.; Feringa, B.L. *Chem. Commun.* **2006**, 409.

⁴⁶⁷ Muramatsu, Y.; Harada, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 1088.

⁴⁶⁸ Yong, K.H.; Taylor, N.J.; Chong, J.M. *Org. Lett.* **2002**, *4*, 3553.

⁴⁶⁹ Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew. Chem. Int. Ed.* **2010**, *49*, 3037.

⁴⁷⁰ Sapountzis, I.; Dube, H.; Lewis, R.; Gommernann, N.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2445.

⁴⁷¹ Barbier, P. *Compt. Rend.*, **1899**, *128*, 110. See Blomberg, C.; Hartog, F.A. *Synthesis* **1977**, *18*; Molle, G.; Bauer, P. *J. Am. Chem. Soc.* **1982**, *104*, 3481. For a list of Barbier-type reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1125–1134.

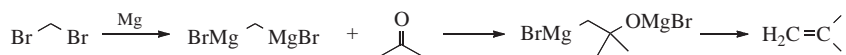
⁴⁷² Guijarro, A.; Yus, M. *Tetrahedron Lett.* **1993**, *34*, 3487; de Souza-Barboza, J.D.; Pétrier, C.; Luche, J. *J. Org. Chem.* **1988**, *53*, 1212.

⁴⁷³ Yeh, M.C.P.; Knochel, P.; Santa, L.E. *Tetrahedron Lett.* **1988**, *29*, 3887.

Barbier reaction employ other metals and/or reaction conditions, and will be discussed in Reaction **16-25**. However, *Mg–Barbier reactions* are catalyzed by other metal complexes (e.g., Cu compounds).⁴⁷⁴ Some transition metal compounds are stable in water, so some *Grignard–Barbier reactions* can be done in water.⁴⁷⁵ A *retro-Barbier reaction* has been reported in which a cyclic tertiary alcohol was treated to an excess of bromine and potassium carbonate to give 6-bromo-2-hexanone from 1-methylcyclopentanol.⁴⁷⁶

The reaction of RMgX or RLi with α,β -unsaturated aldehydes or ketones can proceed via 1,4-addition as well as normal 1,2-addition (see *Michael addition* in Reaction **15-25**).⁴⁷⁷ In general, alkyl lithium reagents give less 1,4 addition than the corresponding *Grignard reagents*.⁴⁷⁸ In a compound containing both an aldehyde and a ketone, it is possible to add RMgX chemoselectively to the aldehyde without significantly disturbing the carbonyl of the ketone group⁴⁷⁹ (see also, Reaction **16-24**). *Grignard reagents* have been shown to add to some conjugated cyclic ketones with an α,β -OTf group via 1,2-addition, followed by cleavage to give an alkynyl ketone.⁴⁸⁰

In some cases, a *Grignard reaction* can be performed intramolecularly.⁴⁸¹ For example, treatment of 5-bromo-2-pentanone with magnesium and a small amount of mercuric chloride in THF produced 1-methyl-1-cyclobutanol in 60% yield.⁴⁸² Other four- and five-membered ring compounds were also prepared by this procedure. Similar closing of five- and six-membered rings was achieved by treatment of a δ - or ϵ -halocarbonyl compound, not with a metal, but with a dianion derived from nickel tetraphenylporphyrine⁴⁸³ (see Reaction 16-25).



The gem-disubstituted Mg compounds formed from CH_2Br_2 or CH_2I_2 (Reaction **12-38**) react with aldehydes or ketones to give alkenes in moderate-to-good yields.⁴⁸⁴ *Wittig-type reactions* also produce alkenes and are discussed in Reaction **16-44**. The reaction could not be extended to other *gem*-dihalides. Similar reactions with *gem*-dimetallic compounds prepared with metals other than magnesium also have produced alkenes.⁴⁸⁵

Organolithium reagents (RLi), prepared from alkyl halides and Li metal or by exchange of an alkyl halide with a reactive organolithium (Reaction **12-38**) react with aldehydes and ketones by acyl addition to give the alcohol,⁴⁸⁶ after hydrolysis. Organolithium reagents are more basic than the corresponding *Grignard reagent*, which leads to problems of

⁴⁷⁴ Erdik, E.; Koçoğlu, M. *Tetrahedron Lett.* **2007**, 48, 4211.

⁴⁷⁵ Li, C.-J. *Tetrahedron* **1996**, 52, 5643.

⁴⁷⁶ Zhang, W.-C.; Li, C.-J. *J. Org. Chem.* **2000**, 65, 5831.

⁴⁷⁷ For a discussion of the mechanism of this reaction, see Holm, T. *Acta Chem. Scand.* **1992**, 46, 985.

⁴⁷⁸ An example was given in Reaction **15-25**.

⁴⁷⁹ Vaskan, R.N.; Kovalev, B.G. *J. Org. Chem. USSR* **1973**, 9, 501.

⁴⁸⁰ Kamijo, S.; Dudley, G.B. *J. Am. Chem. Soc.* **2005**, 127, 5028.

⁴⁸¹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1134–1135.

⁴⁸² Leroux, Y. *Bull. Soc. Chim. Fr.* **1968**, 359.

⁴⁸³ Corey, E.J.; Kuwajima, I. *J. Am. Chem. Soc.* **1970**, 92, 395. For another method, see Molander, G.A.; McKie, J. A. *J. Org. Chem.* **1991**, 56, 4112, and references cited therein.

⁴⁸⁴ Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G. *Tetrahedron* **1970**, 26, 1281.

⁴⁸⁵ See Piotrowski, A.M.; Malpass, D.B.; Boleslawski, M.P.; Eisch, J.J. *J. Org. Chem.* **1988**, 53, 2829; Tour, J.M.; Bedworth, P.V.; Wu, R. *Tetrahedron Lett.* **1989**, 30, 3927; Lombardo, L. *Org. Synth.* 65, 81.

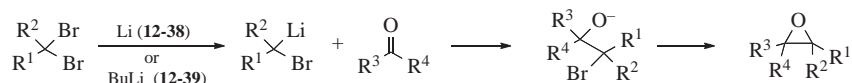
⁴⁸⁶ For a study of *Hammett* ρ values, see Maclin, K.M.; Richey, Jr., H.G. *J. Org. Chem.* **2002**, 67, 4370.

deprotonation in some cases. Organolithium reagents are generally more nucleophilic, however, and can add to hindered ketones with relative ease when compared to the analogous *Grignard reagent*.⁴⁸⁷ These reagents tend to form aggregates, which influences the reactivity and selectivity of the addition reaction.⁴⁸⁸ The addition of lithium amide–butyllithium mixed aggregates has been studied.⁴⁸⁹

Alkyl, vinyl,⁴⁹⁰ and aryl organolithium reagents can be prepared and undergo acyl addition. Structural variations are also possible, including enantioselective 1,2-addition.⁴⁹¹ 1-Bromo-1-lithioethene was prepared, and reacts with an aldehyde to give an allylic alcohol bearing a vinyl bromide unit.⁴⁹² An interesting variation of the fundamental acyl addition reaction of organolithium reagents treated an aldehyde with an acyl-lithio amide [LiC(=O)N(Me)CH₂Me] to give an α -hydroxy amide derivative.⁴⁹³

As with the reduction of aldehydes and ketones (Reaction 19-36), the addition of organometallic compounds to these substrates can be carried out enantioselectively and diastereoselectively.⁴⁹⁴ Chiral secondary alcohols have been obtained with high enantioselectivity by addition of *Grignard* and organolithium compounds to aromatic aldehydes, in the presence of optically active amino alcohols as ligands.⁴⁹⁵

An interesting variation is the reaction of methyllithium and CH₂I₂ with an aliphatic aldehyde to give an epoxide.⁴⁹⁶ A lithio-epoxide was formed by treating an epoxide with *sec*-butyllithium in the presence of sparteine,⁴⁹⁷ or with *n*-butyllithium/TMEDA,⁴⁹⁸ and subsequent reaction with an aldehyde led to an epoxy alcohol. Alkylidene oxetanes react with lithium, and then with an aldehyde to give a conjugated ketone.⁴⁹⁹ The reaction of *gem*-dihalides with a carbonyl compound and Li or BuLi give epoxides⁵⁰⁰ (see also, Reaction 16-46).



In other uses of *gem*-dihalo compounds, aldehydes and ketones add the CH₂I group [R₂CO \rightarrow R₂C(OH)CH₂I] when treated with CH₂I₂ in the presence of SmI₂,⁵⁰¹ and the

⁴⁸⁷ Lecomte, V.; Stéphan, E.; Le Bideau, F.; Jaouen, G. *Tetrahedron* **2003**, 59, 2169.

⁴⁸⁸ See Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, 58, 4717.

⁴⁸⁹ Liu, J.; Li, D.; Sun, C.; Williard, P.G. *J. Org. Chem.* **2008**, 73, 4045.

⁴⁹⁰ For a discussion of selectivity, see Spino, C.; Granger, M.-C.; Tremblay, M.-C. *Org. Lett.* **2002**, 4, 4735.

⁴⁹¹ Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron Asymmetry* **2006**, 17, 2021.

⁴⁹² Novikov, Y.Y.; Sampson, P. *J. Org. Chem.* **2005**, 70, 10247.

⁴⁹³ Cunico, R.F. *Tetrahedron Lett.* **2002**, 43, 355.

⁴⁹⁴ See Solladié, G. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, **1983**, pp. 157–199, 158–183; Nógrádi, M. *Stereoselective Synthesis* VCH, NY, **1986**, pp. 160–193; Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* **1991**, 30, 49.

⁴⁹⁵ Schön, M.; Naef, R. *Tetrahedron Asymmetry* **1999**, 10, 169; Arvidsson, P.I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron Asymmetry* **1999**, 10, 527.

⁴⁹⁶ Concellón, J.M.; Cuervo, H.; Fernández-Fano, R. *Tetrahedron* **2001**, 57, 8983.

⁴⁹⁷ Hodgson, D.M.; Reynolds, N.J.; Coote, S.J. *Org. Lett.* **2004**, 6, 4187.

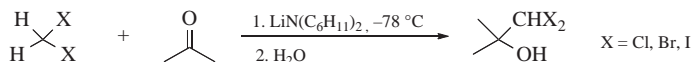
⁴⁹⁸ Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* **2004**, 6, 4191.

⁴⁹⁹ Hashemsadeh, M.; Howell, A.R. *Tetrahedron Lett.* **2000**, 41, 1855, 1859.

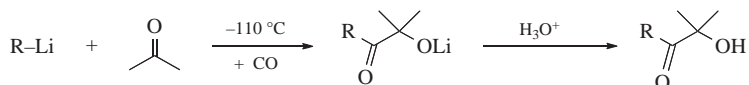
⁵⁰⁰ Cainelli, G.; Tangari, N.; Umami-Ronchi, A. *Tetrahedron* **1972**, 28, 3009, and references cited therein.

⁵⁰¹ Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* **1986**, 27, 3243.

CHX₂ group when treated with methylene halides and lithium dicyclohexylamide at low temperatures.⁵⁰²

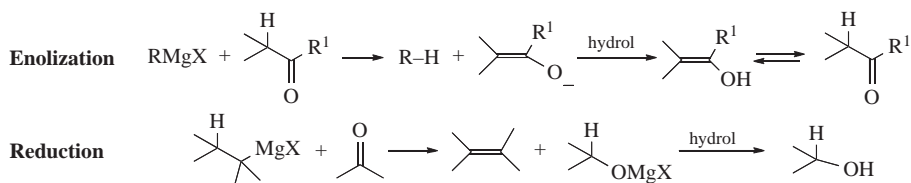


It is possible to add an acyl group to a ketone to give (after hydrolysis) an α-hydroxy ketone.⁵⁰³ This can be done by adding RLi and CO to the ketone at -110°C :⁵⁰⁴



When the same reaction is carried out with carboxylic esters (R'COOR²), α-diketones (RCOCOR') are obtained.⁵⁰³

Most aldehydes and ketones react with most *Grignard reagents*, but there are several potential side reactions⁵⁰⁵ that occur mostly with hindered ketones and with bulky *Grignard reagents*. The two most important of these are *enolization* and *reduction*. The former requires that the aldehyde or ketone have an α hydrogen, and the latter requires that the *Grignard reagent* have a β hydrogen:



Enolization is an acid–base reaction (**12-24**) in which a proton is removed from the α carbon by the *Grignard reagent*, which is a strong base. The carbonyl compound is converted to its enolate anion, which, on hydrolysis, gives the original ketone or aldehyde. Enolization is important not only for hindered ketones but also for those that have a relatively high percentage of enol (e.g., β-keto esters).

The carbonyl compound can be reduced to an alcohol (Reaction **16-24**) by the *Grignard reagent*, which itself undergoes elimination to give an alkene. The *Grignard reagent* must have a β-carbon that bears a hydrogen atom.

Two other side reactions are condensation (between enolate ion and excess ketone) and *Wurtz-type coupling* (**10-64**). Addition of *Grignard reagents* to ketones cannot be used to prepare highly hindered tertiary alcohols (e.g., triisopropylcarbinol, tri-*tert*-butylcarbinol, and diisopropylneopentylcarbinol) or they can be prepared only in extremely low yields, because reduction and/or enolization become prominent.⁵⁰⁶ However, these alcohols can

⁵⁰² Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1588.

⁵⁰³ See Seyferth, D.; Weinstein, R.M.; Wang, W.; Hui, R.C.; Archer, C.M. *Isr. J. Chem.* **1984**, *24*, 167.

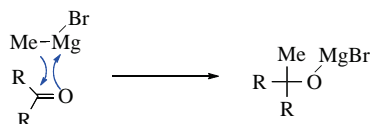
⁵⁰⁴ Seyferth, D.; Weinstein, R.M.; Wang, W. *J. Org. Chem.* **1983**, *48*, 1144; Seyferth, D.; Weinstein, R.M.; Wang, W.; Hui, R.C. *Tetrahedron Lett.* **1983**, *24*, 4907.

⁵⁰⁵ Lajis, N. H.; Khan, M.N.; Hassan, H.A. *Tetrahedron* **1993**, *49*, 3405.

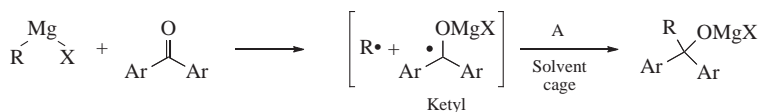
⁵⁰⁶ Whitmore, F.C.; George, R.S. *J. Am. Chem. Soc.* **1942**, *64*, 1239.

be prepared by the use of alkyllithium reagents at $-80\text{ }^{\circ}\text{C}$ ⁵⁰⁷ because enolization and reduction are much less important.⁵⁰⁸ Other methods of increasing the degree of addition at the expense of reduction include complexing the *Grignard reagent* with LiClO_4 or $\text{Bu}_4\text{N}^+\text{Br}^-$,⁵⁰⁹ or using benzene or toluene instead of ether as solvent.⁵¹⁰ Both reduction and enolization can be avoided by adding CeCl_3 to the *Grignard reagent*.⁵¹¹

There has been controversy regarding the mechanism of addition of *Grignard reagents* to aldehydes and ketones.⁵¹² The reaction is difficult to study because of the variable nature of the species present in the *Grignard* solution (Sec. 5.B.ii) and because the presence of small amounts of impurities in the Mg seems to have a great effect on the kinetics of the reaction, making reproducible experiments difficult.⁵¹³ There seem to be two basic mechanisms, depending on the reactants and the reaction conditions. In one of these, the R group is transferred to the carbonyl carbon with its electron pair. A detailed mechanism of this type has been proposed by Ashby *et al.*,⁵¹⁴ based on the discovery that this reaction proceeds by two paths: one first order in MeMgBr and the other first order in Me_2Mg .⁵¹⁵ According to this proposal, both MeMgBr and Me_2Mg add to the carbonyl carbon, though the exact nature of the step by which MeMgBr or Me_2Mg reacts with the substrate is not certain. One possibility is a four-centered cyclic transition state:⁵¹⁶



The other type of mechanism is a SET process⁵¹⁷ with a ketyl intermediate:⁵¹⁸



This mechanism, which has been mostly studied with diaryl ketones, is more likely for aromatic and other conjugated aldehydes and ketones than it is for strictly aliphatic ones.

⁵⁰⁷ Bartlett P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* **1968**, 90, 4421. See also, Lomas, J.S. *Nouv. J. Chim.*, **1984**, 8, 365; Molle, G.; Briand, S.; Bauer, P.; Dubois, J.E. *Tetrahedron* **1984**, 40, 5113.

⁵⁰⁸ Buhler, J.D. *J. Org. Chem.* **1973**, 38, 904.

⁵⁰⁹ Chastrette, M.; Amouroux, R. *Chem. Commun.* **1970**, 470; *Bull. Soc. Chim. Fr.* **1970**, 4348. See also, Richey, Jr., H.G.; DeStephano, J.P. *J. Org. Chem.* **1990**, 55, 3281.

⁵¹⁰ Canonne, P.; Foscolos, G.; Caron H.; Lemay, G. *Tetrahedron* **1982**, 38, 3563.

⁵¹¹ Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, 111, 4392.

⁵¹² See Holm, T. *Acta Chem. Scand. Ser. B* **1983**, 37, 567; Ashby, E.C. *Pure Appl. Chem.* **1980**, 52, 545; Ashby, E. C.; Laemmle, J.; Neumann, H.M. *Acc. Chem. Res.* **1974**, 7, 272. Also see Ashby, E.C.; Laemmle, J. *Chem. Rev.* **1975**, 75, 521; Solv'yanov, A.A.; Beletskaya, I.P. *Russ. Chem. Rev.* **1987**, 56, 465.

⁵¹³ See, for example, Ashby, E.C.; Neumann, H.M.; Walker, F.W.; Laemmle, J.; Chao, L. *J. Am. Chem. Soc.* **1973**, 95, 3330.

⁵¹⁴ Ashby, E.C.; Laemmle, J.; Neumann, H.M. *J. Am. Chem. Soc.* **1972**, 94, 5421.

⁵¹⁵ Ashby, E.C.; Laemmle, J.; Neumann, H.M. *J. Am. Chem. Soc.* **1971**, 93, 4601; Laemmle, J.; Ashby, E.C.; Neumann, H.M. *J. Am. Chem. Soc.* **1971**, 93, 5120.

⁵¹⁶ Ashby, E.C.; Yu, S.H.; Roling, P.V. *J. Org. Chem.* **1972**, 37, 1918. See also, Lasperas, M.; Perez-Rubalcaba, A.; Quiroga-Feijoo, M.L. *Tetrahedron* **1980**, 36, 3403.

⁵¹⁷ For a review, see Dagonneau, M. *Bull. Soc. Chim. Fr.* **1982**, II-269.

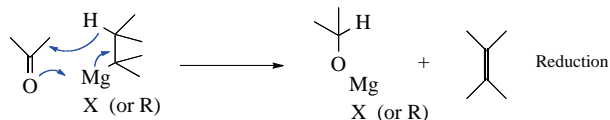
⁵¹⁸ See Walling, C. *J. Am. Chem. Soc.* **1988**, 110, 6846.

Among the evidence⁵¹⁹ for the SET mechanism are ESR spectra⁵²⁰ and the fact that $\text{Ar}_2\text{C}(\text{OH})\text{C}(\text{OH})\text{Ar}_2$ side products are obtained (from dimerization of the ketyl; see *pinacol coupling* in Reaction 19-76).⁵²¹ In the case of addition of RMgX to benzil (PhCOCOPh), ESR spectra of two different ketyl radicals were observed, both reported to be quite stable at room temperature.⁵²² Note that a separate study failed to observe freely diffusing radicals in the formation of *Grignard reagents*.⁵²³ Carbon isotope effect studies with $\text{Ph}^{14}\text{COPh}$ showed that the rate-determining step with most *Grignard reagents* is the carbon–carbon bond-forming step (marked A), although it is the initial electron-transfer step with allylmagnesium bromide.⁵²⁴ In the formation of *Grignard reagents* from bromocyclopropane, diffusing cyclopropyl radical intermediates were found.⁵²⁵ The concerted versus stepwise mechanism has been probed with chiral *Grignard reagents*.⁵²⁶

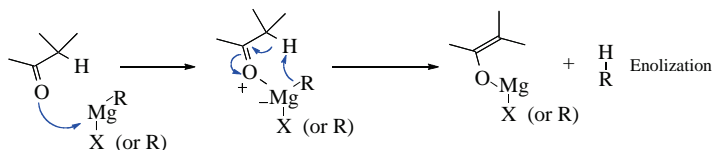
Note that there are similarities in reactivity for the $\text{S}_{\text{RN}}1$ (see Sec. 13.A.iv) and *Grignard mechanisms*.⁵²⁷ Experimental evidence from this work suggests a linear rather than a chain mechanism.

Mechanisms for the addition of organolithium reagents have been investigated much less.⁵²⁸ Addition of a cryptand that binds Li^+ inhibited the normal addition reaction, showing that the lithium is necessary for the reaction to take place.⁵²⁹

There is general agreement that the mechanism leading to reduction⁵³⁰ is usually as follows:



There is evidence that the mechanism leading to enolization is also cyclic, but involves prior coordination with magnesium:⁵³¹



⁵¹⁹ Also see Holm, T. *Acta Chem. Scand. Ser. B* **1988**, 42, 685; Liotta, D.; Saindane, M.; Waykole, L. *J. Am. Chem. Soc.* **1983**, 105, 2922; Yamataka, H.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* **1991**, 56, 2573.

⁵²⁰ Maruyama, K.; Katagiri, T. *Chem. Lett.* **1987**, 731, 735; *J. Phys. Org. Chem.* **1988**, 1, 21.

⁵²¹ See Holm, T.; Crossland, I. *Acta Chem. Scand.* **1971**, 25, 59.

⁵²² Maruyama, K.; Katagiri, T. *J. Am. Chem. Soc.* **1986**, 108, 6263; *J. Phys. Org. Chem.* **1989**, 2, 205. See also, Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* **1991**, 4, 158.

⁵²³ Walter, R.I. *J. Org. Chem.* **2000**, 65, 5014.

⁵²⁴ Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1989**, 111, 4912.

⁵²⁵ Garst, J.F.; Ungváry, F. *Org. Lett.* **2001**, 3, 605.

⁵²⁶ Hoffmann, R.W.; Hölzer, B. *Chem. Commun.* **2001**, 491.

⁵²⁷ Bodineau, N.; Mattalia, J.-M.; Hazimeh, H.; Handoo, K.L.; Timokhin, V.; Négrel, J.-C.; Chanon, M. *Eur. J. Org. Chem.* **2010**, 2476.

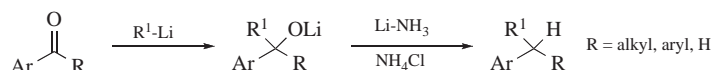
⁵²⁸ See Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* **1989**, 54, 4706.

⁵²⁹ Perraud, R.; Handel, H.; Pierre, J. *Bull. Soc. Chim. Fr.* **1980**, II-283.

⁵³⁰ See Cabaret, D.; Welvert, Z. *J. Organomet. Chem.* **1974**, 80, 199; Holm, T. *Acta Chem. Scand.* **1973**, 27, 1552; Morrison, J.D.; Tomaszewski, J.E.; Mosher, H.S.; Dale, J.; Miller, D.; Elsenbaumer, R.L. *J. Am. Chem. Soc.* **1977**, 99, 3167; Okuhara, K. *J. Am. Chem. Soc.* **1980**, 102, 244.

⁵³¹ Pinkus, A.G.; Sabesan, A. *J. Chem. Soc. Perkin Trans. 2* **1981**, 273.

Aromatic aldehydes and ketones can be alkylated and reduced in one reaction vessel by treatment with an alkyl- or aryllithium, followed by lithium and ammonia and then by ammonium chloride.⁵³²



A similar reaction has been carried out with *N,N*-disubstituted amides: $\text{RCONR}_2' \rightarrow \text{RR}^2\text{CHNR}_2'$.⁵³³

OS I, 188; II, 406, 606; III, 200, 696, 729, 757; IV, 771, 792; V, 46, 452, 608, 1058; VI, 478, 537, 542, 606, 737, 991, 1033; VII, 177, 271, 447; VIII, 179, 226, 315, 343, 386, 495, 507, 556; IX, 9, 103, 139, 234, 306, 391, 472; 75, 12; 76, 214; X, 200.

16-25 Addition of Other Organometallics to Aldehydes and Ketones

O -Hydro-*C*-alkyl-addition



A variety of organometallic reagents other than RMgX and RLi add to aldehydes and ketones. A simple example is formation of Na, or K alkyne anions (e.g., $\text{RC}\equiv\text{C-M}$, Reaction 16-38), which undergo acyl addition to ketones or aldehydes to give the propargylic alcohol.⁵³⁴ In the reaction with terminal acetylenes,⁵³⁵ sodium acetylides are the most common reagents (when they are used, While Na is the metal of choice for the addition of acetylenic groups, vinylic alanes (prepared as in Reaction 15-17) are the reagents of choice for the addition of vinylic groups.⁵³⁶ The reagent $\text{Me}_3\text{Al}/\text{C}\equiv\text{CH Na}^+$ also adds to aldehydes to give the ethynyl alcohol.⁵³⁷ A solvent-free reaction was reported that mixed a ketone, a terminal alkyne and potassium *tert*-butoxide.⁵³⁸ The reaction is often called the *Nef reaction*, but Li,⁵³⁹ Mg, and other metallic acetylides have also been used. A particularly convenient reagent is the lithium acetylide–ethylenediamine complex,⁵⁴⁰ a stable, free-flowing powder that is commercially available. Alternatively, the substrate may be treated with the alkyne itself in the presence of a base, so that the acetylide is generated *in situ*. This procedure is called the *Favorskii reaction*, not to be confused with the *Favorskii rearrangement* (18-7).⁵⁴¹ Zinc(II) chloride facilitates the addition of a terminal alkyne to an aldehyde to give a propargylic alcohol.⁵⁴² Zinc(II) triflate can also be

⁵³² Lipsky, S.D.; Hall, S.S. *Org. Synth.* **VI**, 537; McEnroe, F.J.; Sha, C.; Hall, S.S. *J. Org. Chem.* **1976**, *41*, 3465.

⁵³³ Hwang, Y.C.; Chu, M.; Fowler, F.W. *J. Org. Chem.* **1985**, *50*, 3885.

⁵³⁴ See Guillaume, S.; Plé, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* **2006**, *106*, 2355.

⁵³⁵ Ziegenbein, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 207–241; Ried, W. *Newer Methods Prep. Org. Chem.* **1968**, *4*, 95.

⁵³⁶ Newman, H. *Tetrahedron Lett.* **1971**, 4571. See Jacob, III, P.; Brown, H.C. *J. Org. Chem.* **1977**, *42*, 579.

⁵³⁷ Joung, M.J.; Ahn, J.H.; Yoon, N.M. *J. Org. Chem.* **1996**, *61*, 4472.

⁵³⁸ Miyamoto, H.; Yasaka, S.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 185.

⁵³⁹ See Midland, M.M. *J. Org. Chem.* **1975**, *40*, 2250, for the use of amine-free monolithium acetylide.

⁵⁴⁰ Beumel Jr., O.F.; Harris, R.F. *J. Org. Chem.* **1963**, *28*, 2775.

⁵⁴¹ See Kondrat'eva, L.A.; Potapova, I.M.; Grigina, I.N.; Glazunova, E.M.; Nikitin, V.I. *J. Org. Chem. USSR* **1976**, *12*, 948.

⁵⁴² Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 8323

used for alkyne addition to aldehydes,⁵⁴³ and in the presence of a chiral ligand leads to good enantioselectivity in the propargyl alcohol product.⁵⁴⁴

The reagents Et₃Al, Et₂Zn, and a terminal alkyne react with ketones, and in the presence of a cinchona alkaloid gives the alkynyl alcohol in moderate ee.⁵⁴⁵ Other enantioselective alkynylation reactions are known using various catalysts.⁵⁴⁶ Terminal alkynes add to aryl aldehydes in the presence of InBr₃ and NEt₃,⁵⁴⁷ SmI₂,⁵⁴⁸ or Me₂Zn.⁵⁴⁹ A Zn mediated reaction using iodoalkynes is known.⁵⁵⁰ Catalytically generated zinc acetylides add to aldehydes.⁵⁵¹ An In catalyzed addition of alkynes to aldehydes used a catalytic amount of BINOL and gave the alkynyl alcohol with high enantioselectivity.⁵⁵² Other enantioselective addition reactions of terminal alkynes are known.⁵⁵³ The reaction with In is compatible with the presence of a variety of other functional groups in the molecule, including phosphonate,⁵⁵⁴ propargylic sulfides.⁵⁵⁵

Many organometallic reagents have been reported for the addition of allylic groups,⁵⁵⁶ and there are enantioselective reactions.⁵⁵⁷ One of the most common methods is the *Barbier reaction* noted in Reaction 16-24, which includes metals and metal compounds other than Mg or Li, although the method is not limited to allylic compounds. Common reagents are allylic In compounds,⁵⁵⁸ which add to aldehydes or ketones in various solvents,⁵⁵⁹ Enantioselective In mediated *Barbier reactions* are known.⁵⁶⁰ Indium reacts with allylic bromides and ketones in water⁵⁶¹ and in aqueous media. The reaction of a

⁵⁴³ Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.

⁵⁴⁴ Boyall, D.; Frantz, D.E.; Carreira, E.M. *Org. Lett.* **2002**, *4*, 2605.; Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193; Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524. For an example using zinc(II) diflate, see Chen, Z.; Xiong, W.; Jiang, B. *Chem. Commun.* **2002**, 2098.

⁵⁴⁵ Liu, L.; Wang, R.; Kang, Y.-F.; Chen, C.; Xu, Z.-Q.; Zhou, Y.-F.; Ni, M.; Cai, H.-Q.; Gong, M.-Z. *J. Org. Chem.* **2005**, *70*, 1084.

⁵⁴⁶ See Li, H.; Huang, Y.; Jin, W.; Xue, F.; Wan, B. *Tetrahedron Lett.* **2008**, *49*, 1686; Mao, J.; Bao, Z.; Guo, J.; Ji, S. *Tetrahedron* **2008**, *64*, 9901; Yang, X.-F.; Hirose, T.; Zhang, G.-Y. *Tetrahedron Asymmetry* **2007**, *18*, 2668.

⁵⁴⁷ Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2003**, *44*, 4171.

⁵⁴⁸ Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* **2001**, 627.

⁵⁴⁹ Wolf, C.; Liu, S. *J. Am. Chem. Soc.* **2006**, *128*, 10996; Cozzi, P.G.; Rudolph, J.; Bolm, C.; Norrby, P.-O.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 5733.

⁵⁵⁰ Srihari, P.; Singh, V.K.; Bhunia, D.C.; Yadav, J.S. *Tetrahedron Lett.* **2008**, *49*, 7132.

⁵⁵¹ Downey, C.W.; Mahoney, B.D.; Lipari, V.R. *J. Org. Chem.* **2009**, *74*, 2904.

⁵⁵² Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760.

⁵⁵³ Ekström, J.; Zaitsev, S.B.; Adolfsson, H. *Synlett* **2006**, 885.

⁵⁵⁴ Ranu, B.C.; Samanta, S.; Hajra, A. *J. Org. Chem.* **2001**, *66*, 7519.

⁵⁵⁵ Mitzel, T.M.; Palomo, C.; Jendza, K. *J. Org. Chem.* **2002**, *67*, 136.

⁵⁵⁶ For a list of reagents and references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1156–1170. Also see Gajewski, J.J.; Bocian, W.; Brichford, N.L.; Henderson, J.L. *J. Org. Chem.* **2002**, *67*, 4236.

⁵⁵⁷ See Denmark, S.E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

⁵⁵⁸ For a review, see Cintas, P. *Synlett* **1995**, 1087.

⁵⁵⁹ Yi, X.-H.; Haberman, J.X.; Li, C.-J. *Synth. Commun.* **1998**, *28*, 2999; Lloyd-Jones, G.C.; Russell, T. *Synlett* **1998**, 903; Li, C.-J.; Lu, Y.-Q. *Tetrahedron Lett.* **1995**, *36*, 2721.

⁵⁶⁰ Hirayama, L.C.; Gamsey, S.; Kneuppel, D.; Steiner, D.; DeLaTorre, K.; Singaram, B. *Tetrahedron Lett.* **2005**, *46*, 2315; Haddad, T.D.; Hirayama, L.C.; Taynton, P.; Singaram, B. *Tetrahedron Lett.* **2008**, *49*, 508; Preite, M.D.; Pérez-Carvajal, A. *Synlett* **2006**, 3337. For an example in ionic liquids, see Teo, Y.-C.; Goh, E.-L.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 4573. For an example with propargylic halides, see Lacie, C. Hirayama, L.C.; Dunham, K.K.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 5173.

⁵⁶¹ Chan, T.H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228; Paquette, L.A.; Bennett, G.D.; Isaac, M.B.; Chhatriwalla, A. *J. Org. Chem.* **1998**, *63*, 1836; Li, X.-R.; Loh, T.-P. *Tetrahedron Asymmetry* **1996**, *7*, 1535.

propargyl halide, In, and an aldehyde in aq THF leads to an allenic alcohol.⁵⁶² When allyl iodide is mixed with In and TMSCl, reaction with a conjugated ketone proceed by 1,4-addition, but in the presence of 10% CuI, the major product is that of 1,2-addition.⁵⁶³ Allyl bromide reacts with Mn/TMSCl and an In catalyst in water to give the homoallylic alcohols from aldehydes.⁵⁶⁴ Indium metal is used for the acyl addition of allylic halides with a variety of aldehydes and ketones, including aliphatic aldehydes,⁵⁶⁵ aryl aldehydes,⁵⁶⁶ and α -keto esters.⁵⁶⁷ Elimination of the homoallylic alcohol to a conjugated diene can accompany the addition in some cases.⁵⁶⁸

Allyl bromide reacts with a ketone and Sm⁵⁶⁹ or SmI₂,⁵⁷⁰ to give the homoallylic alcohol. Other metals can be used with allylic halides to give homoallylic alcohols from aldehydes or ketones,⁵⁷¹ including Zn,⁵⁷² La,⁵⁷³ or Mg–Cd⁵⁷⁴ and compounds of Ti,⁵⁷⁵ Mn,⁵⁷⁶ Fe,⁵⁷⁷ Ga,⁵⁷⁸ Ge,⁵⁷⁹ Zr,⁵⁸⁰ Nb,⁵⁸¹ Cd,⁵⁸² Sb,⁵⁸³ Te,⁵⁸⁴ Ba,⁵⁸⁵ Ce,⁵⁸⁶ Nd,⁵⁸⁷ Hg,⁵⁸⁸ Bi,⁵⁸⁹ In,⁵⁹⁰ and Pb.⁵⁹¹

⁵⁶² Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042.

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⁵⁶⁵ Loh, T.-P.; Tan, K.-T.; Yang, J.-Y.; Xiang, C.-L. *Tetrahedron Lett.* **2001**, *42*, 8701.

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⁵⁶⁸ Kumar, V.; Chimni, S.; Kumar, S. *Tetrahedron Lett.* **2004**, *45*, 3409.

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⁵⁷⁰ Hélon, F.; Namy, J.-L. *J. Org. Chem.* **1999**, *64*, 2944.

⁵⁷¹ See Knochel, P.; Rao, S.A. *J. Am. Chem. Soc.* **1990**, *112*, 6146; Wada, M.; Ohki, H.; Akiba, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738; Marton, D.; Tagliavini, G.; Zordan, M.; Wardell, J.L. *J. Organomet. Chem.* **1990**, *390*, 127; Wang, W.; Shi, L.; Xu, R.; Huang, Y. *J. Chem. Soc. Perkin Trans. 1* **1990**, 424.

⁵⁷² Wang, J.-x.; Jia, X.; Meng, T.; Xin, L. *Synthesis* **2005**, 2838.

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⁵⁷⁵ See Bareille, L.; Le Gendre, P.; Moïse, C. *Chem. Commun.* **2005**, 775; Estévez, R.E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; García-Ruiz, J.M.; Robles, R.; Gansäuer, A.; Cuerva, J.M.; Oltra, J.E. *Chemistry: Eur. J.* **2009**, *15*, 2774.

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⁵⁷⁸ Wang, Z.; Yuan, S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5097.

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⁵⁸¹ Andrade, C.K.Z.; Azevedo, N.R.; Oliveira, G.R. *Synthesis* **2002**, 928.

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⁵⁸³ Li, L.-H.; Chan, T.H. *Can. J. Chem.* **2001**, *79*, 1536.

⁵⁸⁴ See Avilov, D.V.; Malasare, M.G.; Arslancan, E.; Dittmer, D.L. *Org. Lett.* **2004**, *6*, 2225.

⁵⁸⁵ Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130.

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⁵⁸⁸ Chan, T.H.; Yang, Y. *Tetrahedron Lett.* **1999**, *40*, 3863.

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In addition, $\text{BiCl}_3/\text{NaBH}_4$,⁵⁹² $\text{Mg}-\text{BiCl}_3$,⁵⁹³ and $\text{CrCl}_2/\text{NiCl}_2$,⁵⁹⁴ have been used. Allylic alcohols have been converted to organometallic reagents with diethylzinc and a Pd⁵⁹⁵ or a Ru catalyst,⁵⁹⁶ leading to the homoallylic alcohol upon reaction with an aldehyde. Allylic acetates add to aldehydes in the presence of a Ru catalyst.⁵⁹⁷

Enantioselective reactions are known.⁵⁹⁸ A Cu catalyzed reaction is known that proceeds with good enantioselectivity.⁵⁹⁹ Allylzinc bromide adds to aldehydes under solvent-free conditions.⁶⁰⁰ A chiral Cr–Mn complex has been used with allylic bromides in conjunction with trimethylsilyl chloride.⁶⁰¹ Reagents of the type $\text{R}-\text{Yb}$ have been prepared from RMgX .⁶⁰² The alkyl group of trialkyl aluminum compounds (e.g., AlEt_3) add to aldehydes, enantioselectively in the presence of chiral transition metal complexes.⁶⁰³ Furthermore, organotitanium reagents can be made to add chemoselectively to aldehydes in the presence of ketones.⁶⁰⁴ Organomanganese compounds are also chemoselective in this way.⁶⁰⁵ In a related reaction, organocerium reagents, generated from cerium chloride (CeCl_3 and a *Grignard reagent* or an organolithium reagent) gives an organometallic reagent that adds chemoselectively.⁶⁰⁶ Aryl halides that have a pendant ketone unit react with a Pd catalyst to give cyclization via acyl addition.⁶⁰⁷

As noted in Reaction 16-24, enolate formation and reduction complicate some *Grignard reactions*. One way to avoid complications is to add $(\text{RO})_3\text{TiCl}$, TiCl_4 ,⁶⁰⁸ $(\text{RO})_3\text{ZrCl}$, or $(\text{R}_2\text{N})_3\text{TiX}$ to the *Grignard* or organolithium reagent. This produces organotitanium or organozirconium compounds that are much more selective than *Grignard* or organolithium reagents.⁶⁰⁹ An important advantage of these reagents is that they do not react with NO_2 or CN functions that may be present in the substrate, as *Grignard* and organolithium reagents do. The reaction of a β -keto amide with TiCl_4 , for example, gives a complex that allows selective reaction of the ketone unit with $\text{MeMgCl}-\text{CeCl}_3$ to give the corresponding alcohol.⁶¹⁰ Premixing an allylic *Grignard reagent* with ScCl_3 prior to reaction with the

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⁶⁰⁵ Cahiez, G.; Figadere, B. *Tetrahedron Lett.* **1986**, 27, 4445. See Soai, K.; Watanabe, M.; Koyano, M. *Bull. Chem. Soc. Jpn.* **1989**, 62, 2124.

⁶⁰⁶ Bartoli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem. Int. Ed.* **1993**, 32, 1061; Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* **1994**, 35, 6713.

⁶⁰⁷ Quan, L.G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, 122, 4827.

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aldehyde gives direct acyl addition without allylic rearrangement as the major product, favoring the *trans*-alkene unit.⁶¹¹

Allyltin compounds readily add to aldehydes and ketones.⁶¹² Maleic acid promotes the reaction in aqueous media.⁶¹³ Allylic bromides react with Sn to generate the organo-metallic *in situ*, which then adds to aldehydes.⁶¹⁴ Allylic chlorides react with aldehydes in the presence of ditin compounds (e.g., Me₃Sn—SnMe₃ and a Pd catalyst).⁶¹⁵ Allyltrialkyltin compounds⁶¹⁶ and tetraallyltin react with aldehydes or ketones in the presence of BF₃—etherate,⁶¹⁷ or compounds of Cu,⁶¹⁸ Ce,⁶¹⁹ Bi,⁶²⁰ Pb,⁶²¹ Ag,⁶²² Cd,⁶²³ Cr,⁶²⁴ Pd,⁶²⁵ Re,⁶²⁶ Gd,⁶²⁷ Ti,⁶²⁸ Rh,⁶²⁹ Zr,⁶³⁰ Co,⁶³¹ or La.⁶³² Propargylic tin compounds react with aldehydes to give the alcohol, with good antiselectivity.⁶³³ Tetraallyltin reacts via 1,2-addition to conjugated ketones in refluxing methanol.⁶³⁴ Tetraallyltin reacts with aldehydes in ionic liquids⁶³⁵ and on wet silica.⁶³⁶ In addition, allyltributyltin adds to aldehydes in ionic liquids with InCl₃.⁶³⁷ Tetraallyltin adds to ketones or aldehydes to give homoallylic alcohols with good enantioselectivity in the presence of a chiral Ti complex⁶³⁸ or a chiral In

⁶¹¹ Matsukawa, S.; Funabashi, Y.; Imamoto, T. *Tetrahedron Lett.* **2003**, *44*, 1007.

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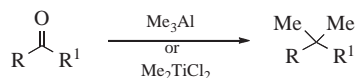
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complex.⁶³⁹ Allylic alcohols and homoallylic alcohols add to aldehydes in the presence of $\text{Sn}(\text{OTf})_2$ ⁶⁴⁰ In/InCl_3 ,⁶⁴¹ or with a Rh catalyst.⁶⁴²

The tin compound can be prepared *in situ* using an α -iodo ketone with an aldehyde and $\text{Bu}_2\text{SnI}_2\text{—LiI}$.⁶⁴³ A similar addition occurs with $(\text{allyl})_2\text{SnBr}_2$ in water.⁶⁴⁴ Asymmetric induction has been reported.⁶⁴⁵ The use of a chiral Rh⁶⁴⁶ or Ti⁶⁴⁷ catalyst leads to enantioselective addition of allyltributyltin to aldehydes. Allyltributyltin reacts with aldehydes in the presence of SiCl_4 and a chiral phosphoramidate to give the homoallylic alcohol with moderate enantioselectivity.⁶⁴⁸ Tetravinyltin adds to ketones in the presence of an In catalyst.⁶⁴⁹ Allenyl tin compounds ($\text{CH}_2=\text{C}=\text{CHSnBu}_3$) also react with aldehydes in the presence of $\text{BF}_3\cdot\text{OEt}_2$ to give a 2-dienyl alcohol.⁶⁵⁰ Selectfluor has been used to induce 1,2-addition of the allyl group of allyltributyltin to a conjugated aldehyde.⁶⁵¹

Both aluminum and titanium reagents have been used. Aluminum catalysts, (e.g., [methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)]), MABR), facilitate addition of allyltributyltin to aldehydes.⁶⁵² Triphenylaluminum reacts with aryl aldehydes in the presence of a Ti catalyst.⁶⁵³ Trimethylaluminum⁶⁵⁴ and dimethyltitanium dichloride⁶⁵⁵ exhaustively methylate ketones to give *gem*-dimethyl compounds⁶⁵⁶ (see also, Reaction 10-63):



The Ti reagent also dimethylates aromatic aldehydes.⁶⁵⁷ Triethylaluminum reacts with aldehydes, however, to give the mono-ethyl alcohol, and in the presence of a chiral additive the reaction proceeds with good asymmetric induction.⁶⁵⁸ A complex of $\text{Me}_3\text{Ti}\cdot\text{MeLi}$ has

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been shown to be selective for 1,2-addition with conjugated ketones, in the presence of nonconjugated ketones.⁶⁵⁹

Chiral amides react with aldehydes in the presence of TiCl_4 to give syn-selective addition products.⁶⁶⁰ Titanium-catalyzed enantioselective additions are also known.⁶⁶¹ High %ee values have been obtained with organometallics,⁶⁶² including organotitanium compounds (methyl, aryl, allylic) in which an optically active ligand is coordinated to the Ti,⁶⁶³ allylic boron compounds, and organozinc compounds. Chiral dendritic Ti catalysts have been used to give moderate enantioselectivity.⁶⁶⁴

Organozinc compounds add to aldehydes and ketones. An example is the reaction of an alkylzinc chloride (RZnCl) to give the corresponding alcohol.⁶⁶⁵ Enantioselective reaction of a carbonyl with a dialkylzinc is possible when chiral catalysts are employed,⁶⁶⁶ or when chiral ligands⁶⁶⁷ are employed.⁶⁶⁸ A comparison of the stereoselectivity for reactions of diphenylzinc and diethylzinc has been reported.⁶⁶⁹ Dialkylzinc reagents, in the presence of a chiral Ti complex⁶⁷⁰ a Zn complex,⁶⁷¹ an Al complex,⁶⁷² a chiral Cr complex,⁶⁷³ a chiral Schiff base,⁶⁷⁴ or a chiral bis(sulfonamide)⁶⁷⁵ and other chiral complexes⁶⁷⁶ react with aldehydes or ketones to give

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the corresponding alcohol with good enantioselectivity.⁶⁷⁷ High enantioselectivity was obtained from R_2Zn reagents ($R = \text{alkyl}$)⁶⁷⁸ and aromatic⁶⁷⁹ aldehydes by the use of a small amount of various catalysts.⁶⁸⁰ The enantioselectivity is influenced by additives (e.g., $LiCl$).⁶⁸¹ Silica-immobilized chiral ligands⁶⁸² can be used in conjunction with dialkylzinc reagents, and polymer-supported ligands have been used.⁶⁸³

Propargylic acetate adds to aldehydes with good antiselectivity in the presence of Et_2Zn and a Pd catalyst.⁶⁸⁴ With other organometallic compounds, active metals (e.g., alkylzinc reagents)⁶⁸⁵ are useful and compounds, such as alkylmercurys, do not react. Dimethylzinc and diethylzinc are probably the most common reagents. An intramolecular version is possible by reaction of an allene–aldehyde with dimethylzinc. Aryl halides react with Zn – Ni complexes to give acyl addition of the aryl group to an aldehyde.⁶⁸⁶ The reaction of an allylic halide and Zn ⁶⁸⁷ or $Zn/TMSCl$ ⁶⁸⁸ leads to acyl addition of aldehydes.

Organochromium compounds add to aldehydes or ketones.⁶⁸⁹ The reaction of an organochromium reagent with an aldehyde or ketone is known as the *Nozaki–Hiyama reaction*. In the original version, a $Cr(II)$ solution was prepared by reduction of chromic chloride by $LiAlH_4$. This product was subsequently treated with an aldehyde and an allylic halide.⁶⁹⁰ The coupling of allylic halides and aldehydes or ketones in the presence of a Cr catalyst and a chiral ligand gives products with good enantioselectivity.⁶⁹¹ Enantioselective coupling reactions catalyzed by Cr compounds are of increasing interest.⁶⁹² The organochromium reagent may be derived from vinyl halides, triflates, or aryl derivatives.⁶⁹³

⁶⁷⁷ See Braga, A.L.; Paixão, M.W.; Westermann, B.; Schneider, P.H.; Wessjohann, L.A. *J. Org. Chem.* **2008**, *73*, 2879.

⁶⁷⁸ See Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464.

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⁶⁸⁹ For a reaction of aliphatic halides, mediated by $Cr(II)$, see Wessjohann, L.A.; Schmidt, G.; Schrekker, H.S. *Tetrahedron* **2008**, *64*, 2134.

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⁶⁹¹ Miller, J.J.; Sigman, M.S. *J. Am. Chem. Soc.* **2007**, *129*, 2752; Hargaden, G.C.; O'Sullivan, T.P.; Guiry, P.J. *Org. Biomol. Chem.* **2008**, *6*, 562; Huang, X.-R.; Chen, C. *Tetrahedron Asymmetry* **2010**, *21*, 2999.

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Other metals facilitate addition of groups to an aldehyde, including the coupling of an alkene to an aldehyde using a Ni catalyst.⁶⁹⁴ Vinyl bromides react with $\text{NiBr}_2/\text{CrCl}_3/\text{TMSCl}$ to give a reagent that adds to aldehydes to give the allylic alcohol.⁶⁹⁵ Vinyl complexes generated from alkynes and SmI_2 add intramolecularly, and eight-membered rings have been formed in this way.⁶⁹⁶ Vinyl reagents are formed *in situ* via organozirconium compounds with Me_2Zn , Ti compounds, and terminal alkynes.⁶⁹⁷

Lithium dimethylcopper (Me_2CuLi) reacts with aldehydes⁶⁹⁸ and with certain ketones⁶⁹⁹ to give the expected alcohols. The $\text{RCu}(\text{CN})\text{ZnI}$ reagents also react with aldehydes, in the presence of BF_3 –etherate, to give secondary alcohols. Vinyltellurium compounds react with $\text{BF}_3\cdot\text{OEt}_2$ and cyanocuprates $[\text{R}(2\text{-thienyl})\text{CuCNLi}_2]$ to give a reagent that adds 1,2- to the carbonyl of a conjugated ketone.⁷⁰⁰ Vinyl tellurium compounds also react with *n*-butyllithium to give a reagent that adds to nonconjugated ketones.⁷⁰¹ In conjunction with BeCl_2 , organolithium reagents add to conjugated ketones. In THF, 1,4- addition is observed, but in diethyl ether the 1,2-addition product is formed.⁷⁰²

Alkenes and alkynes add to aldehydes or ketones via the π bond by conversion to a reactive organometallic. A radical-type addition is possible using alkenes with BEt_3 . Alkynes add to aldehydes elsewhere in the same molecule in the presence of BEt_3 and a Ni catalyst to give a cyclic allylic alcohol.⁷⁰³ Alkene aldehydes react similarly using Me_3SiOTf .⁷⁰⁴ In a similar manner, dienes⁷⁰⁵ or alkynes⁷⁰⁶ add to aldehydes in the presence of a Ni catalyst. Allenes add to aldehydes in the presence of a Ni catalyst, using a chiral imidazolynil carbene ligand, and the product is trapped as the triethylsilyl ether by addition of Et_3SiI .⁷⁰⁷ Ketenimines add to aldehydes, in the presence of SiCl_4 and an achiral ligand, to give the β -cyanohydrin with good enantioselectivity.⁷⁰⁸ Allylic acetates react with ketones to give the homoallylic alcohol under electrochemical conditions that include bipyridyl, tetrabutylammonium tetrafluoroborate, and FeBr_2 .⁷⁰⁹ Terminal alkynes react with Zr complexes and Me_2Zn to give an allylic tertiary alcohol.⁷¹⁰ Internal alkynes also give allylic alcohols in the presence of BEt_3 and a Ni catalyst.⁷¹¹ Reaction of an aldehyde containing a conjugated diene unit with diethylzinc and a Ni catalyst leads to cyclic

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⁷¹¹ Miller, K.M.; Jamison, T.F. *J. Am. Chem. Soc.* **2004**, *126*, 15342.

alcohols having a pendant allylic unit.⁷¹² A similar reaction was reported using a Cu catalyst.⁷¹³ The intramolecular addition of an alkene to an aldehyde leads to a saturated cyclic alcohol using PhSiH_3 and a Co catalyst.⁷¹⁴

Aryl halides react with a Ni complex under electrolytic conditions to add the aryl group to aldehydes.⁷¹⁵ The C position of an indole adds to aldehydes in the presence of a Pd catalyst.⁷¹⁶ The addition of trifluoromethyl to an aldehyde was accomplished photochemically using CF_3I and $(\text{Me}_2\text{N})_2\text{C}=\text{C}(\text{NMe}_2)_2$.⁷¹⁷ α -Iodo phosphonate esters react with aldehydes and SmI_2 to give a β -hydroxy phosphonate ester.⁷¹⁸ Addition to the allene in the presence of a Ni catalyst⁷¹⁹ or a CeCl_3 catalyst⁷²⁰ is followed by addition of the intermediate organometallic to the aldehyde to give the cyclic product.

Intramolecular addition of a conjugated ester (via the β -carbon) to an aldehyde generates a cyclic ketone.⁷²¹ This type of coupling has been called the *Stetter reaction*,⁷²² which actually involves the addition of aldehydes to activated double bonds (Reaction 15-34), mediated by a catalytic amount of thiazolium salt in the presence of a weak base. The intramolecular addition of the allene moiety to an aldehyde is catalyzed by a Pd complex in the presence of $\text{Me}_3\text{SiSnBu}_3$.⁷²³ A highly enantio- and diastereoselective intramolecular *Stetter reaction* has been developed.⁷²⁴ Alkynyl aldehydes react with silanes (e.g., Et_3SiH) and a nickel catalyst to give a cyclic compound having a silyl ether and an exocyclic vinylidene unit.⁷²⁵ Alkene-aldehydes give cyclic alcohols via intramolecular addition of the $\text{C}=\text{C}$ unit to the carbonyl under electrolytic conditions using a phase-transfer catalyst.⁷²⁶ A similar cyclization was reported using SnCl_4 .⁷²⁷ Vinylidene cycloalkanes react with aldehydes in the presence of a Pd catalyst to give a homoallylic alcohol where addition occurs at the carbon exocyclic to the ring.⁷²⁸ Allenes react with benzaldehyde using $\text{HCl}-\text{SnCl}_2$ with a Pd catalyst.⁷²⁹ Silyl allenenes react with aldehydes in the presence of a chiral Sc catalyst to give homopropargylic alcohols with good enantioselectivity.⁷³⁰ Intramolecular addition of an allene to aldehyde via addition of phenyl when treated with PhI and a Pd catalyst.⁷³¹ Allenes add to ketones to give homoallylic alcohols in the

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⁷²⁵ Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, 121, 6098.

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⁷³¹ Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, 67, 4376.

presence of SmI_2 and HMPA.⁷³² Alkenes having an allylic methyl group in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ add to formaldehyde to give a homoallylic alcohol.⁷³³ Conjugated dienes react with aldehyde via acyl addition of a terminal carbon of the diene, in the presence of $\text{Ni}(\text{acac})_2$ and Et_2Zn .⁷³⁴

Although organoboranes do not generally add to aldehydes and ketones,⁷³⁵ allylic boranes are exceptions.⁷³⁶ When they add, an allylic rearrangement always takes place. Allylic rearrangements may take place with the other reagents as well. The use of a chiral catalyst leads to asymmetric induction⁷³⁷ and chiral allylic boranes have been prepared.⁷³⁸ Addition of trialkylboranes to aldehydes is catalyzed by a Ni complex.⁷³⁹ Note that chloroboranes (R_2BCl) react with aldehydes via acyl addition of the alkyl group, giving the corresponding alcohol after treatment with water.⁷⁴⁰ Treatment with catecholborane gives addition to the conjugated ketone, and subsequent cyclization of the resulting organo-metallic at the nonconjugated ketone gives a cyclic alcohol with a pendant ketone unit, after treatment with methanol.⁷⁴¹ In the presence of Ru ,⁷⁴² Cu ,⁷⁴³ Ni ,⁷⁴⁴ or Pd ⁷⁴⁵ compounds, $\text{RB}(\text{OH})_2$ and arylboronic acids [$\text{ArB}(\text{OH})_2$, see Reaction 12-28] add to aldehydes to give the corresponding alcohol. Arylboronic acids add to aldehydes in the presence of a chiral ligand to give an alcohol with good enantioselectivity.⁷⁴⁶ An enantioselective intramolecular reaction of an arylboronic acid to a pendant ketone moiety used a Pd catalyst.⁷⁴⁷ Polymer-bound aryl borates add an aryl group to aldehydes in the presence of a Rh catalyst.⁷⁴⁸ An intramolecular version of the phenylboronic acid induced reaction is known, where a molecule with ketone and conjugated ketone units is converted to a cyclic alcohol using a chiral Rh catalyst.⁷⁴⁹ Allylic boronates add to aldehydes,⁷⁵⁰ and

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⁷³³ Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* **2002**, *4*, 1667.

⁷³⁴ Loh, T.-P.; Song, H.-Y.; Zhou, Y. *Org. Lett.* **2002**, *4*, 2715.

⁷³⁵ See Satoh, Y.; Tayano, T.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1989**, *30*, 5153.

⁷³⁶ See Hoffmann, R.W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem.* **1990**, *62*, 1993; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents* Academic Press, NY, **1988**, pp. 310–318; Bubnov, Yu.N. *Pure Appl. Chem.* **1987**, *21*, 895; Buynak, J.D.; Geng, B.; Uang, S.; Strickland, J.B. *Tetrahedron Lett.* **1994**, *35*, 985.

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⁷⁴⁵ Yamamoto, T.; Ohta, T.; Ito, Y. *Org. Lett.* **2005**, *7*, 4153.

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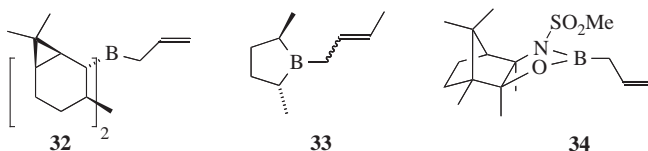
⁷⁴⁷ Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, *128*, 6504.

⁷⁴⁸ See Rudolph, J.; Schmidt, F.; Bolm, C. *Synthesis* **2005**, 840.

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⁷⁵⁰ See Gravel, M.; Lachance, H.; Lu, X.; Hall, D.G. *Synthesis* **2004**, 1290; Bouffard, J.; Itami, K. *Org. Lett.* **2009**, *11*, 4410.

there are enantioselective reactions.⁷⁵¹

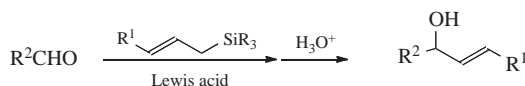


A number of optically active allylic boron compounds have been used, including⁷⁵² B-allylbis(2-isocaranyl)borane (**32**),⁷⁵³ (*E*)- and (*Z*)-crotyl-(*R,R*)-2,5-dimethylborolanes (**33**),⁷⁵⁴ and the borneol derivative **34**,⁷⁵⁵ all of which add an allyl group to aldehydes, with good enantioselectivity. A recyclable 10-TMS-9-borabicyclo[3.3.2]decane has been used for asymmetric allyl and crotyl addition to aldehydes.⁷⁵⁶ Where the substrate possesses an aryl group or a triple bond, using a metal carbonyl complex of the substrate enhances enantioselectivity.⁷⁵⁷

Potassium alkynyltrifluoroborates (Reaction **12-28**) react with aldehydes and a secondary amine, in an ionic liquid, to give a propargylic amine.⁷⁵⁸ Allylic trifluoroborates (Reaction **12-28**) react with aldehydes to give the homoallylic alcohol. The Pd catalyzed reaction of aryl aldehydes with PhBF₃K gave a diaryl alcohol.⁷⁵⁹ A Ru catalyzed reaction of aryltrifluoroborates led to sterically hindered diaryl ketones.⁷⁶⁰ Aliphatic aldehydes react with this reagent, in the presence of BF₃•OEt₂, to give the homoallylic alcohol with allylic rearrangement and a preference for the syn diastereomer.⁷⁶¹ Aryl aldehydes react as well.⁷⁶²

16-26 Addition of Trialkylallylsilanes to Aldehydes and Ketones

O-Hydro-*C*-alkyl-addition



Allylic trialkyl, trialkoxy, and trihalosilanes add to aldehydes to give the homoallylic alcohols in the presence of a Lewis acid⁷⁶³ (including TaCl₅⁷⁶⁴ and YbCl₃⁷⁶⁵), fluoride

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⁷⁵² See Roush, W.R.; Ando, K.; Powers, D.B.; Palkowitz, A.D.; Halterman, R.L. *J. Am. Chem. Soc.* **1990**, *112*, 6339; Brown, H.C.; Randad, R.S. *Tetrahedron Lett.* **1990**, *31*, 455; Stürmer, R.; Hoffmann, R.W. *Synlett* **1990**, 759.

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ion,⁷⁶⁶ proazaphosphatranes,⁷⁶⁷ or a catalytic amount of iodine.⁷⁶⁸ A Ru catalyst has been used in conjunction with an arylsilane and an aldehyde.⁷⁶⁹ Allyl(trimethoxy)silane adds an allyl group to aldehydes using a CdF_2 ⁷⁷⁰ catalyst or a chiral AgF complex.⁷⁷¹ Allyltrichlorosilanes have also been used in addition reactions with aldehydes.⁷⁷² Hünig's base ($i\text{Pr}_2\text{NEt}$) and a sulfoxide have also been used to facilitate the addition of an allyl group to an aldehyde from allyltrichlorosilane.⁷⁷³ The mechanism of this reaction has been examined.⁷⁷⁴

Allyltrichlorosilane reacts with aldehydes in the presence of certain additives to give the corresponding alcohol,⁷⁷⁵ and the reaction proceeds with good enantioselectivity by addition of a chiral additive.⁷⁷⁶ Other chiral additives have been used,⁷⁷⁷ as well as chiral catalysts,⁷⁷⁸ and chiral complexes of allyl silanes.⁷⁷⁹ Trimethoxyallylsilanes react with aldehydes in the presence of a Cu catalyst and a chiral ligand to give the chiral alcohol.⁷⁸⁰ Chiral allylic silyl derivatives add to aldehydes to give the chiral homoallylic alcohol.⁷⁸¹

Allylic silanes react with *gem*-diacetates in the presence of InCl_3 to give a homoallylic acetate⁷⁸² or with dimethyl acetals and TMSOTf in an ionic liquid to give the homoallylic methyl ether.⁷⁸³ Allylic alcohols can be treated with $\text{TMS}-\text{Cl}$ and NaI , and then Bi to give an organometallic reagent that adds to aldehydes.⁷⁸⁴

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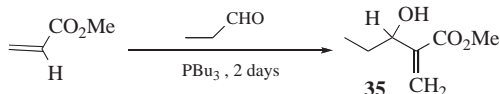
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16-27 Addition of Conjugated Alkenes to Aldehydes (the Baylis–Hillman Reaction)⁷⁸⁵*O*-Hydro-*C*-alkenyl-addition

In the presence of a base⁷⁸⁶ (1,4-diazabicyclo[2.2.2]octane, DABCO) or trialkylphosphines, conjugated carbonyl compounds (ketones, esters, including lactones)⁷⁸⁷ thioesters,⁷⁸⁸ and amides⁷⁸⁹) add to aldehydes via the α carbon to give α -alkenyl- β -hydroxy esters or amides. This sequence is called the *Baylis–Hillman reaction* (or *Morita–Baylis–Hillman*),⁷⁹⁰ and a simple example is the formation of **35**.⁷⁹¹ Mechanistic investigations of the reaction have been reported.⁷⁹² Methyl vinyl ketone gave other products in the *Baylis–Hillman reaction*, whereas conjugated esters do not.⁷⁹³ Methods that are catalytic in base have been developed for the *Baylis–Hillman reaction*.⁷⁹⁴ Both microwave irradiation⁷⁹⁵ and ultrasound⁷⁹⁶ have been used to induce the reaction.⁷⁹⁷ *Baylis–Hillman reactions* have been done in aqueous acidic media.⁷⁹⁸ There is a protein-catalyzed reaction.⁷⁹⁹ Under certain conditions, rate enhancements have been observed.⁸⁰⁰ The reaction has been done in ionic liquids⁸⁰¹ and PEG⁸⁰² or sulfolane,⁸⁰³ and without an organic solvent.⁸⁰⁴ Rate

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⁷⁸⁶ See Luo, S.; Mi, X.; Xu, H.; Wang, P.G.; Cheng, J.-P. *J. Org. Chem.* **2004**, 69, 8413.

⁷⁸⁷ See Karur, S.; Hardin, J.; Headley, A.; Li, G. *Tetrahedron Lett.* **2003**, 44, 2991.

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⁷⁸⁹ See Faltin, C.; Fleming, E.M.; Connon, S.J. *J. Org. Chem.* **2004**, 69, 6496.

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⁷⁹¹ Rafel, S.; Leahy, J.W. *J. Org. Chem.* **1997**, 62, 1521. Also see, Drewes, S.E.; Rohwer, M.B. *Synth. Commun.* **1997**, 27, 415.

⁷⁹² Robiette, R.; Aggarwal, V.K.; Jeremy N; Harvey, J.N. *J. Am. Chem. Soc.* **2007**, 129, 15513 (computational); Roy, D.; Sunoj, R.B. *Org. Lett.* **2007**, 9, 4873 (computational). Price, K.E.; Broadwater, S.J.; Walker, B.J.; McQuade, D.T. *J. Org. Chem.* **2005**, 70, 3980.

⁷⁹³ Shi, M.; Li, C.-Q.; Jiang, J.-K. *Chem. Commun.* **2001**, 833.

⁷⁹⁴ Pereira, S.I.; Adrio, J.; Silva, A.M.S.; Carretero, J.C. *J. Org. Chem.* **2005**, 70, 10175; Lin, Y.-S.; Liu, C.-W.; Tsai, T.Y.-R. *Tetrahedron Lett.* **2005**, 46, 1859; Zhao, S.-H.; Chen, Z.-B. *Synth. Commun.* **2005**, 35, 3045. For an ionic-liquid immobilized base, see Mi, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2005**, 70, 2338. See Aggarwal, V. K.; Emme, I.; Fulford, S.Y. *J. Org. Chem.* **2003**, 68, 692.

⁷⁹⁵ Kundu, M.K.; Mukherjee, S.B.; Balu, N.; Padmakumar, R.; Bhat, S.V. *Synlett* **1994**, 444.

⁷⁹⁶ Coelho, F.; Almeida, W.P.; Veronese, D.; Mateus, C.R.; Lopes, E.C.S.; Rossi, R.C.; Silveira, G.P.C.; Pavam, C. H. *Tetrahedron* **2002**, 58, 7437.

⁷⁹⁷ For improved procedures: Zhao, S.-H.; Bie, H.-Y.; Chen, Z.-B. *Org. Prep. Proceed. Int.* **2005**, 37, 231.

⁷⁹⁸ Caumul, P.; Hailes, H.C. *Tetrahedron Lett.* **2005**, 46, 8125.

⁷⁹⁹ Reetz, M.T.; Mondière, R.; Carballeira, J.D. *Tetrahedron Lett.* **2007**, 48, 1679.

⁸⁰⁰ See Rafel, S.; Leahy, J.W. *J. Org. Chem.* **1997**, 62, 1521; Luo, S.; Wang, P.G.; Cheng, J.-P. *J. Org. Chem.* **2004**, 69, 555; Cai, J.; Park, K.S.; Kim, J.; Choo, H.; Chong, Y. *Synlett* **2007**, 395. For a discussion of salt effects, see Kumar, A.; Pawar, S.S. *Tetrahedron* **2003**, 59, 5019.

⁸⁰¹ Rosa, J.N.; Afonso, C.A.M.; Santos, A.G. *Tetrahedron* **2001**, 57, 4189. For an example in a chiral ionic liquid, see Pégot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* **2004**, 45, 6425.

⁸⁰² Chandrasekhar, S.; Narsihmulu, Ch.; Saritha, B.; Sultana, S.S. *Tetrahedron Lett.* **2004**, 45, 5865.

⁸⁰³ Krishna, P.R.; Manjuvani, A.; Kannan, V.; Sharma, G.V.M. *Tetrahedron Lett.* **2004**, 45, 1183.

⁸⁰⁴ Asano, K.; Matsubara, S. *Synthesis* **2009**, 3219.

acceleration occurs with bis(arylthio)ureas in a DABCO promoted reaction.⁸⁰⁵ Transition metal compounds can facilitate the *Baylis–Hillman reaction*,⁸⁰⁶ and $\text{BF}_3 \cdot \text{OEt}_2$ has been used.⁸⁰⁷ A sila variation is known, involving the reaction of vinylsilanes and aldehydes.⁸⁰⁸ An *aza-Baylis–Hillman reaction* is discussed in Reaction 16-31.

An intramolecular version of the *Baylis–Hillman reaction* generated cyclopentenone derivatives from alkyne-aldehydes and a Rh catalyst.⁸⁰⁹ Other intramolecular cyclization reactions are known.⁸¹⁰ Cyclization of a conjugated ester using DABCO, where the “alcohol” group contained an aldehyde unit (an α -hydroxy aldehyde derivative) gave a lactone with a hydroxy unit at C-3 relative to the carbonyl and an α -vinylidene.⁸¹¹

Enantioselective *Baylis–Hillman reactions*⁸¹² are possible using a chiral auxiliary via an amide⁸¹³ or ester.⁸¹⁴ Organocatalysts can be used to give products with good enantioselectivity.⁸¹⁵ Sugars have been used as ester auxiliaries, and in reaction with aryl aldehydes and 20% DABCO gave the allylic alcohol with modest enantioselectivity.⁸¹⁶

Another variation is the *Rauhut–Currier cyclization* reaction,⁸¹⁷ which involves the reaction of a conjugated carbonyl with the allylic site of a second conjugated system. Intramolecular variations of this latter method are known.⁸¹⁸ With the boron trifluoride induced reaction between an aldehyde and a conjugated ketone, a saturated β -hydroxy ketone was formed with good antiselectivity.⁸¹⁹ The coupling of aldehydes with conjugated ketones used TiCl_4 ,⁸²⁰ dialkylaluminum halides,⁸²¹ and with (polymethyl)hydro-siloxane and a Cu catalyst.⁸²² Conjugated esters were coupled to aldehydes with DABCO and a La catalyst.⁸²³ Aldehydes are coupled to conjugated esters with a chiral quinuclidine catalyst and a Ti catalyst, as well as in the presence of tosylamine, the final product was the allylic *N*-tosylamine formed with modest enantioselectivity.⁸²⁴

⁸⁰⁵ Maher, D.J.; Connon, S.J. *Tetrahedron Lett.* **2004**, 45, 1301.

⁸⁰⁶ See Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, 9, 927.

⁸⁰⁷ Walsh, L.M.; Winn, C.L.; Goodman, J.M. *Tetrahedron Lett.* **2002**, 43, 8219.

⁸⁰⁸ Chuprakov, S.; Malyshev, D.A.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, 129, 14868.

⁸⁰⁹ Tanaka, K.; Fu, G.C. *J. Am. Chem. Soc.* **2001**, 123, 11492.

⁸¹⁰ Keck, G.E.; Welch, D.S. *Org. Lett.* **2000**, 4, 3687.

⁸¹¹ Krishna, P.R.; Kannan, V.; Sharma, G.V.M. *J. Org. Chem.* **2004**, 69, 6467.

⁸¹² See Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, 46, 4614; Also see, Markó, I.E.; Giles, P. R.; Hindley, N.J. *Tetrahedron* **1997**, 53, 1015.

⁸¹³ Brzezinski, L.J.; Rafel, S.; Leahy, J.W. *J. Am. Chem. Soc.* **1997**, 119, 4317.

⁸¹⁴ See Wei, H.-X.; Chen, D.; Xu, X.; Li, G.; Paré, P.W. *Tetrahedron Asymmetry* **2003**, 14, 971.

⁸¹⁵ Imbriglio, J.E.; Vasbinder, M.M.; Miller, S.J. *Org. Lett.* **2003**, 5, 3741. See also, Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, 7, 4293; Berkessel, A.; Roland, K.; Neudörfl, J.M. *Org. Lett.* **2006**, 8, 4195; Lattanzi, A. *Synlett* **2007**, 2106.

⁸¹⁶ Filho, E.P.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron Asymmetry* **2001**, 12, 847.

⁸¹⁷ Rauhut, M. M.; Currier, H. *U.S. Patent 3074999/19630122*, American Cyanamid Co., **1963**.

⁸¹⁸ Aroyan, C.E.; Miller, S.J. *J. Am. Chem. Soc.* **2007**, 129, 256.

⁸¹⁹ Chandrasekhar, S.; Narsihmulu, Ch.; Reddy, N.R.; Reddy, M.S. *Tetrahedron Lett.* **2003**, 44, 2583.

⁸²⁰ Li, G.; Wei, H.-X.; Gao, J.J.; Caputo, T.D. *Tetrahedron Lett.* **2000**, 41, 1; Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* **2000**, 2, 2397.

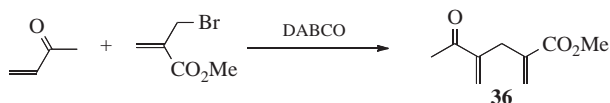
⁸²¹ Pei, W.; Wei, H.X.; Li, G. *Chem. Commun.* **2002**, 2412.

⁸²² Arnold, L.A.; Imbos, R.; Mandoli, A.; de Vries, A.H.M.; Naasz, R.; Feringa, B.L. *Tetrahedron* **2000**, 56, 2865.

⁸²³ Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem.* **2003**, 68, 915.

⁸²⁴ Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, 44, 2521.

Alkyl halides are coupled with conjugated carbonyls to give the alkylated derivative in what is known as *Morita–Baylis–Hillman alkylation*.⁸²⁵ α -Bromomethyl esters react with conjugated ketones and DABCO to give a coupling product, (**34**).⁸²⁶ A similar DBU induced reaction was reported using α -bromomethyl esters and conjugated nitro compounds.⁸²⁷

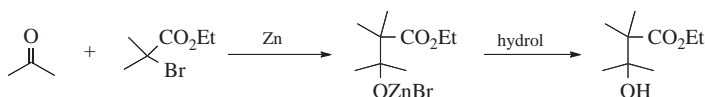


The reaction can be modified to give additional products, as with the reaction of *o*-hydroxybenzaldehyde and methyl vinyl ketone with DABCO, where the initial *Baylis–Hillman product* cyclized via conjugate addition of the phenolic oxygen to the conjugated ketone (Reaction **15-31**).⁸²⁸ Aldehydes and conjugated esters can be coupled with a sulfonamide to give an allylic amine.⁸²⁹

See OS **2010**, 87, 201

16-28 The Reformatsky Reaction

O-Hydro-*C*- α -ethoxycarbonylalkyl-addition



The *Reformatsky reaction*⁸³⁰ is very similar to Reaction **16-24**. An aldehyde or ketone is treated with Zn and a halide; the halide is usually an α -halo ester or a vinyllog (see Sec. 6. B) of an α -halo ester (e.g., $\text{RCHBrCH}=\text{CHCOOEt}$), although α -halo nitriles,⁸³¹ α -halo ketones,⁸³² and α -halo *N,N*-disubstituted amides have also been used. Especially high reactivity can be achieved with activated Zn,⁸³³ and with Zn and ultrasound.⁸³⁴ The reaction is catalytic in Zn in the presence of iodine and ultrasound.⁸³⁵ Metals other than Zn can be used, including In,⁸³⁶ Mn,⁸³⁷ low valent Ti,⁸³⁸ metal compounds of Ti,⁸³⁹ Sn,⁸⁴⁰

⁸²⁵ Krafft, M.E.; Haxell, T.F.M.; Seibert, K.A.; Abboud, K.A. *J. Am. Chem. Soc.* **2006**, 128, 4174; Krafft, M.E.; Haxell, T.F.N. *J. Am. Chem. Soc.* **2005**, 127, 10168; Krafft, M.E.; Seibert, K.A.; Haxell, T.F.N.; Hirose, C. *Chem. Commun.* **2005**, 5772.

⁸²⁶ Basavaiah, D.; Sharada, D.S.; Kumaragurubaran, N.; Reddy, R.M. *J. Org. Chem.* **2002**, 67, 7135.

⁸²⁷ Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Mignini, E.; Palmieri, A. *Tetrahedron* **2004**, 60, 4995.

⁸²⁸ Kaye, P.T.; Nocanda, X.W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1331.

⁸²⁹ Balan, D.; Adolfsson, H. *J. Org. Chem.* **2002**, 67, 2329.

⁸³⁰ See Fürstner, A. *Synthesis* **1989**, 571; Rathke, M.W. *Org. React.* **1975**, 22, 423; Gaudemar, M. *Organomet. Chem. Rev. Sect. A* **1972**, 8, 183; Ocampo, R.; Dolbier Jr., W.R. *Tetrahedron* **2004**, 60, 9325.

⁸³¹ Palomo, C.; Aizpurua, J.M.; López, M.C.; Aurekoetxea, N. *Tetrahedron Lett.* **1990**, 31, 2205; Zheng, J.; Yu, Y.; Shen, Y. *Synth. Commun.* **1990**, 20, 3277.

⁸³² See Huang, Y.; Chen, C.; Shen, Y. *J. Chem. Soc. Perkin Trans. 1* **1988**, 2855.

⁸³³ Rieke, R.D.; Uhm, S.J. *Synthesis* **1975**, 452; Bouhlel, E.; Rathke, M.W. *Synth. Commun.* **1991**, 21, 133.

⁸³⁴ Han, B.; Boudjouk, P. *J. Org. Chem.* **1982**, 47, 5030.

⁸³⁵ Ross, N.A.; Bartsch, R.A. *J. Org. Chem.* **2003**, 68, 360.

⁸³⁶ Araki, S.; Yamada, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1994**, 67, 1126.

⁸³⁷ Suh, Y.S.; Rieke, R.D. *Tetrahedron Lett.* **2004**, 45, 1807.

⁸³⁸ Aoyagi, Y.; Tanaka, W.; Ohta, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1225.

⁸³⁹ See Parrish, J.D.; SheHon, D.R.; Little, R.D. *Org. Lett.* **2003**, 5, 3615.

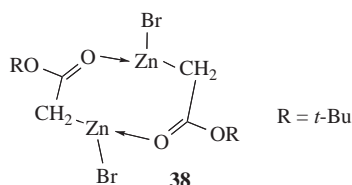
⁸⁴⁰ Shibata, I.; Kawasaki, M.; Yasuda, M.; Baba, A. *Chem. Lett.* **1999**, 689.

Sm⁸⁴¹ or Sc.⁸⁴² The use of additives (e.g., Ge⁸⁴³ or Me₂Zn)⁸⁴⁴ can lead to highly selective reactions.⁸⁴⁵ A combination of Zn and an α -bromo ester can be used in conjunction with BF₃·OEt₂, followed by reaction with dibenzoyl peroxide.⁸⁴⁶ The aldehyde or ketone can be aliphatic, aromatic, or heterocyclic, or contain various functional groups. Solvents used are generally ethers, including Et₂O, THF, and 1,4-dioxane, although the reaction can be done in water⁸⁴⁷ using dibenzoyl peroxide and MgClO₄.

With the use of chiral auxiliaries⁸⁴⁸ or chiral catalysts,⁸⁴⁹ good enantioselectivity⁸⁵⁰ can be achieved.

Dialkylzinc compounds are an alternative source of Zn in the *Reformatsky reaction*. The reaction of an α -bromo ester, an aldehyde, and diethylzinc in THF with a Rh catalyst, gave a β -hydroxy ester.⁸⁵¹

Formally, the reaction is somewhat analogous to the *Grignard reaction* (16-24), with EtO₂C—C—ZnBr (37) as an intermediate analogous to RMgX.⁸⁵² There is an intermediate derived from Zn and the ester, the structure of which has been shown to be 38, by X-ray crystallography of the solid intermediate prepared from *t*-BuOCOCH₂Br and Zn.⁸⁵³ As can be seen, it has some of the characteristics of 37.



After hydrolysis, the alcohol is the usual product, but sometimes (especially with aryl aldehydes) elimination follows directly and the product is an alkene. By the use of Bu₃P along with Zn, the alkene can be made the main product,⁸⁵⁴ making this an alternative to the *Wittig reaction* (16-44). The alkene is also the product when K₂CO₃/NaHCO₃ is used

⁸⁴¹ Utimoto, K.; Matsui, T.; Takai, T.; Matsubara, S. *Chem. Lett.* **1995**, 197; Arime, T.; Takahashi, H.; Kobayashi, S.; Yamaguchi, S.; Mori, N. *Synth. Commun.* **1995**, 25, 389; Park, H.S.; Lee, I.S.; Kim, Y.H. *Tetrahedron Lett.* **1995**, 36, 1673; Molander, G.A.; Etter, J.B. *J. Am. Chem. Soc.* **1987**, 109, 6556.

⁸⁴² Kagoshima, H.; Hashimoto, Y.; Saigo, K. *Tetrahedron Lett.* **1998**, 39, 8465.

⁸⁴³ Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, 63, 691.

⁸⁴⁴ Cozzi, P.G. *Angew. Chem. Int. Ed.* **2006**, 45, 2951.

⁸⁴⁵ Cozzi, P.G. *Angew. Chem. Int. Ed.* **2007**, 46, 2568.

⁸⁴⁶ Chattopadhyay, A.; Salaskar, A. *Synthesis* **2000**, 561.

⁸⁴⁷ Bieber, L.W.; Malvestiti, I.; Storch, E.C. *J. Org. Chem.* **1997**, 62, 9061.

⁸⁴⁸ See Orsini, F.; Sello, G.; Manzo, A.M.; Lucci, E.M. *Tetrahedron Asymmetry* **2005**, 16, 1913.

⁸⁴⁹ Kloetzing, R.J.; Thaler, T.; Knochel, P. *Org. Lett.* **2006**, 8, 1125; Shin, E.-k.; Kim, H.J.; Kim, Y.; Kim, Y.; Park, Y.S. *Tetrahedron Lett.* **2006**, 47, 1933; Emmerson, D.P.G.; Hems, W.P.; Davis, B.G. *Tetrahedron Asymmetry* **2005**, 16, 213; Fernández-Ibáñez, M.A.; Maciá, B.; Minnaard, A.J.; Feringa, B.L. *Angew. Chem. Int. Ed.* **2008**, 47, 1317; *Chem. Commun.* **2008**, 2571; Cozzi, P.G.; Mignogna, A.; Zoli, L. *Pure Appl. Chem.* **2008**, 80, 891.

⁸⁵⁰ See Ribeiro, C.M.R.; de S. Santos, E.; de O. Jardim, A.H.; Maia, M.P.; da Silva, F.C.; Moreira, A.P.D.; Ferreira, V.F. *Tetrahedron Asymmetry* **2002**, 13, 1703.

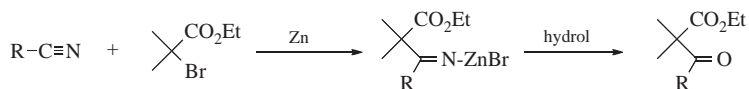
⁸⁵¹ Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, 2, 2549.

⁸⁵² See Maiz, J.; Arrieta, A.; Lopez, X.; Ugalde, J.M.; Cossio, F.P.; Fakultatea, K.; Unibertsitatea, E.H.; Lecea, B. *Tetrahedron Lett.* **1993**, 34, 6111.

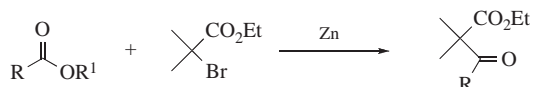
⁸⁵³ Dekker, J.; Budzelaar, P.H.M.; Boersma, J.; van der Kerk, G.J.M.; Spek, A.L. *Organometallics* **1984**, 3, 1403.

⁸⁵⁴ Shen, Y.; Xin, Y.; Zhao, J. *Tetrahedron Lett.* **1988**, 29, 6119. For another method, see Huang, Y.; Shi, L.; Li, S.; Wen, X. *J. Chem. Soc. Perkin Trans. 1* **1989**, 2397.

with 2% PEG–telluride.⁸⁵⁵ Since *Grignard reagents* cannot be formed from α -halo esters, the method is quite useful, but competing reactions sometimes lead to low yields. A similar reaction (called the *Blaise reaction*) has been carried out on nitriles⁸⁵⁶:



Carboxylic esters have also been used as substrates, but then, as might be expected (Sec. 16.A), the result is substitution and not addition:



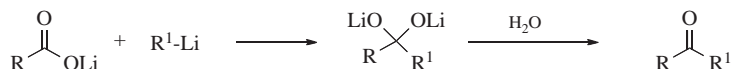
The product in this case is the same as with the corresponding nitrile, though the pathways are different. The reaction is compatible with amine substituents, and α -(*N,N*-dibenzyl) amino aldehydes have been used to prepare β -hydroxy- γ -(*N,N*-dibenzylamino) esters with good antiselectivity.⁸⁵⁷

For an alternative approach involving ester enolates, see Reaction 16-36.

OS 3, 408; 4, 120, 444; 6, 598; IX, 275.

16-29 The Conversion of Carboxylic Acid Salts to Ketones with Organometallic Compounds

Alkyl-de-oxido-substitution



Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkyl lithium reagent, followed by hydrolysis.⁸⁵⁸ The carboxylate salt is formed by reaction of the carboxylic acid with 1 molar equivalent of R^1Li . The R^1 group may be aryl or primary, secondary, or tertiary alkyl and R may be alkyl or aryl. The compounds MeLi and PhLi have been employed most often. Tertiary alcohols are side products. Lithium acetate can be used, but generally gives low yields. Using $\text{R}(\text{PrNH})\text{Mg}$, carboxylic acid salts react to form ketones.⁸⁵⁹

A variation of this transformation reacts the acid with lithium naphthalenide in the presence of 1-chlorobutane. The product is the ketone.⁸⁶⁰ A related reaction treats the lithium carboxylate with lithium metal and the alkyl halide, with sonication, to give the ketone.⁸⁶¹ Phenylboronic acid (Reaction 12-28) reacts with aryl carboxylic acids in the presence of a Pd catalyst and disuccinoyl carbonate to give a diaryl ketone.⁸⁶²

OS V, 775.

⁸⁵⁵ Huang, Z.-Z.; Ye, S.; Xia, W.; Yu, Y.-H.; Tang, Y. *J. Org. Chem.* **2002**, 67, 3096.

⁸⁵⁶ See Hannick, S.M.; Kishi, Y. *J. Org. Chem.* **1983**, 48, 3833.

⁸⁵⁷ Andrés, J.M.; Pedrosa, R.; Pérez, A.; Pérez-Encabo, A. *Tetrahedron* **2001**, 57, 8521.

⁸⁵⁸ See Jorgenson, M.J. *Org. React.* **1970**, 18, 1; Rubottom, G.M.; Kim, C. *J. Org. Chem.* **1983**, 48, 1550.

⁸⁵⁹ Ohki, M.; Asaoka, M. *Chem. Lett.* **2009**, 38, 856.

⁸⁶⁰ Alonso, F.; Lorenzo, E.; Yus, M. *J. Org. Chem.*, **1996**, 61, 6058.

⁸⁶¹ Aurell, M.J.; Danhui, Y.; Einhorn, J.; Einhorn, C.; Luche, J.L. *Synlett* **1995**, 459. Also see, Aurell, M.J.; Einhorn, C.; Einhorn, J.; Luche, J.L. *J. Org. Chem.* **1995**, 60, 8.

⁸⁶² Gooßen, L.J.; Ghosh, K. *Chem. Commun.* **2001**, 2084.

16-30 The Addition of Organometallic Compounds to CO₂ and CS₂**C-Alkyl-O-halomagnesio-addition**

Grignard reagents add to one C=O bond of CO₂ exactly as they do to an aldehyde or a ketone,⁸⁶³ but the product is the salt of a carboxylic acid. The reaction is usually performed by adding the *Grignard reagent* to dry ice. Many carboxylic acids have been prepared in this manner, and this constitutes an important way of increasing a carbon chain by one unit. Since labeled CO₂ is commercially available, this is a good method for the preparation of carboxylic acids labeled in the carboxyl group. Other organometallic compounds have also been used (RLi,⁸⁶⁴ RNa, RCaX, RBa,⁸⁶⁵ etc.), but much less often. The formation of the salt of a carboxylic acid after the addition of CO₂ to a reaction mixture is regarded as a positive test for the presence of a carbanion or of a reactive organometallic intermediate in that reaction mixture (see also, Reaction **16-42**).

Aryl organoboronates react with CO₂, in the presence of a Ru catalyst, to give the corresponding aryl carboxylic acid.⁸⁶⁶ Aryl and alkenyl boronic esters are carboxylated in the presence of a Cu catalyst.⁸⁶⁷ Vinyl halides react with CO and water, with a Pd catalyst in an ionic liquid, to give the conjugated carboxylic acid.⁸⁶⁸ Organozinc compounds are carboxylated with CO₂ and a Ni catalyst.⁸⁶⁹ Metal-free carboxylation of organozinc reagents is also known.⁸⁷⁰ In the presence of CO₂ and an organocatalyst, aromatic aldehydes are converted to the corresponding carboxylic acid.⁸⁷¹ Direct carboxylation of aryl bromides is possible using CO₂ and a Pd catalyst.⁸⁷² Allenes are converted to β,γ-unsaturated acids with CO₂ in the presence of Et₂Zn.⁸⁷³

When chiral additives (e.g., (–)-sparteine) have added to the initial reaction with the organolithium reagent, quenching with CO₂ produces carboxylic acids with good asymmetric induction.⁸⁷⁴

In a closely related reaction, *Grignard reagents* add to CS₂ to give salts of dithiocarboxylic acids.⁸⁷⁵ These salts can be trapped with amines to form thioamides.⁸⁷⁶ Two other reactions are worthy of note. (1) Lithium dialkylcopper reagents react with

⁸⁶³ See Volpin, M.E.; Kolomnikov, I.S. *Organomet. React.* **1975**, 5, 313; Sneed, R.P.A. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, **1969**, pp. 137–173; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 913–948. For a more general review, see Lapidus, A.L.; Ping, Y.Y. *Russ. Chem. Rev.* **1981**, 50, 63.

⁸⁶⁴ For a kinetic study, see Nudelman, N.S.; Doctorovich, F. *J. Chem. Soc. Perkin Trans. 2* **1994**, 1233.

⁸⁶⁵ Yanagisawa, A.; Yasue, K.; Yamamoto, H. *Synlett* **1992**, 593.

⁸⁶⁶ Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2006**, 128, 8706.

⁸⁶⁷ Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008**, 10, 2697.

⁸⁶⁸ Zhao, X.; Alper, H.; Yu, Z. *J. Org. Chem.* **2006**, 71, 3988.

⁸⁶⁹ Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, 10, 2681.

⁸⁷⁰ Kobayashi, K.; Kondo, Y. *Org. Lett.* **2009**, 11, 2035.

⁸⁷¹ Nair, V.; Varghese, V.; Paul, R.P.; Jose, A.; Sinu, C.R.; Menon, R.S. *Org. Lett.* **2010**, 12, 2653.

⁸⁷² Correa, A.; Martín, R. *J. Am. Chem. Soc.* **2009**, 131, 15974.

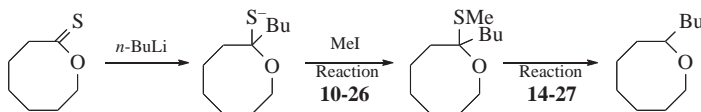
⁸⁷³ North, M. *Angew. Chem. Int. Ed.* **2009**, 48, 4104.

⁸⁷⁴ Park, Y.S.; Beak, P. *J. Org. Chem.* **1997**, 62, 1574.

⁸⁷⁵ See Ramadas, S.R.; Srinivasan, P.S.; Ramachandran, J.; Sastry, V.V.S.K. *Synthesis* **1983**, 605.

⁸⁷⁶ Katritzky, A.R.; Moutou, J.-L.; Yang, Z. *Synlett* **1995**, 99.

dithiocarboxylic esters to give tertiary thiols.⁸⁷⁷ (2) Thiono lactones can be converted to cyclic ethers,⁸⁷⁸ for example:



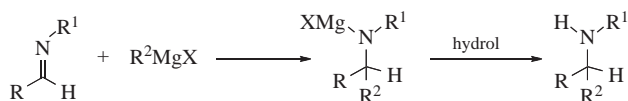
This is a valuable procedure because medium and large ring ethers are not easily made, while the corresponding thiono lactones can be prepared from the readily available lactones (see, e.g., Reaction 16-63) by reaction 16-11.

A terminal alkyne can be converted to the anion under electrolytic conditions, in the presence of CO_2 , to give propargylic acids ($\text{R}-\text{C}\equiv\text{C}-\text{CO}_2\text{H}$).⁸⁷⁹

OS I, 361, 524; II, 425; III, 413, 553, 555; V, 890, 1043; VI, 845; IX, 317.

16-31 The Addition of Organometallic Compounds to $\text{C}=\text{N}$ Compounds

N-Hydro-*C*-alkyl-addition



Aldimines can be converted to secondary amines by treatment with *Grignard reagents*.⁸⁸⁰ Ketimines generally react with *Grignard reagents* to give reduction instead of addition. However, organolithium compounds give the normal addition product with both aldimines and ketimines.⁸⁸¹ The solvent and the aggregation state of the organolithium play a role in the addition, however.⁸⁸² For the addition of an organometallic compound to an imine to give a primary amine, R' in $\text{RCH}=\text{NR}'$ would have to be H, and such compounds are seldom stable. However, the conversion has been done for $\text{R} = \text{aryl}$, by the use of the masked reagents $(\text{ArCH}=\text{N})_2\text{SO}_2$ [prepared from an aldehyde, RCHO , and sulfamide, $(\text{NH}_2)_2\text{SO}_2$]. Addition of R^2MgX or R^2Li to these compounds gives $\text{ArCHR}^2\text{NH}_2$ after hydrolysis.⁸⁸³ An intramolecular version of the addition of organolithium reagents is known that gave 2-phenylpyrrolidine.⁸⁸⁴ *Grignard reagents* add to imines in the presence of various transition metal catalysts, including $\text{Sc}(\text{OTf})_3$ ⁸⁸⁵ or Cp_2ZrCl_2 .⁸⁸⁶ Alkynes add to imines yielding propargylic amines.⁸⁸⁷

⁸⁷⁷ Bertz, S.H.; Dabbagh, G.; Williams, L.M. *J. Org. Chem.* **1985**, 50, 4414.

⁸⁷⁸ Nicolaou, K.C.; McGarry, D.G.; Somers, P.K.; Veale, C.A.; Furst, G.T. *J. Am. Chem. Soc.* **1987**, 109, 2504.

⁸⁷⁹ Köster, F.; Dinjus, E.; Duñach, E. *Eur. J. Org. Chem.* **2001**, 2507.

⁸⁸⁰ See Harada, K. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 266–272; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 1204–1227; Wang, D.-K.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett.* **1996**, 37, 4187; Bambridge, K.; Begley, M.J.; Simpkins, N.S. *Tetrahedron Lett.* **1994**, 35, 3391.

⁸⁸¹ Huet, J. *Bull. Soc. Chim. Fr.* **1964**, 952, 960, 967, 973.

⁸⁸² Qu, B.; Collum, D.B. *J. Am. Chem. Soc.* **2005**, 127, 10820; *J. Am. Chem. Soc.* **2006**, 128, 9355.

⁸⁸³ Davis, F.A.; Giangordano, M.A.; Starner, W.E. *Tetrahedron Lett.* **1986**, 27, 3957.

⁸⁸⁴ Yus, M.; Soler, T.; Foubelo, F. *J. Org. Chem.* **2001**, 66, 6207.

⁸⁸⁵ Saito, S.; Hatanaka, K.; Yamamoto, H. *Synlett* **2001**, 1859.

⁸⁸⁶ Gandon, V.; Bertus, P.; Szymoniak, J. *Eur. J. Org. Chem.* **2001**, 3677.

⁸⁸⁷ Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263.

When chiral additives are used in conjunction with the organolithium reagent, chiral amines are produced⁸⁸⁸ with good asymmetric induction.⁸⁸⁹ Chiral auxiliaries have been used in addition reactions of organometallic compounds to imines,⁸⁹⁰ and to oxime derivatives.⁸⁹¹ Transition metal asymmetric alkylation of imines uses metal compounds of Cu.⁸⁹² Chiral catalysts lead to enantioselective addition of alkynes to imines to give the amine.⁸⁹³ Chiral *N*-sulfinylimines reaction with lithium silanes give the α -silylsulfinylamine.⁸⁹⁴

Zinc metal reacts with allylic bromides to form an allylic zinc complex, which reacts with imines to give the homoallylic amine.⁸⁹⁵ This reaction is catalyzed by TMSCl.⁸⁹⁶ Dialkylzinc reagents add to functionalized imines to give the functionalized amine, often with transition metal catalysts (e.g., Ni compounds).⁸⁹⁷ Dialkylzinc reagents add to *N*-tosyl imines to give the alkylated tosylamine.⁸⁹⁸ In the presence of a chiral ligand, the metal-catalyzed reaction proceeds with good enantioselectivity.⁸⁹⁹ With a Cu catalyst and a chiral ligand the product is formed with good enantioselectivity.⁹⁰⁰ The reaction of imines (e.g., $\text{ArN}=\text{CHCO}_2\text{Et}$), where R = a chiral benzylic substituent and ZnBr_2 , followed by $\text{R}'\text{ZnBr}$ leads to a chiral α -amino ester.⁹⁰¹ Terminal alkynes add to imines using ZnCl_2 and TMSCl, and with a chiral ligand attached to nitrogen the reaction proceeds with some enantioselectivity.⁹⁰² Dimethylzinc has been used to mediate the addition of terminal alkynes to *N*-tosylimines.⁹⁰³

⁸⁸⁸ For a review see Enders, D.; Reinhold, U. *Tetrahedron Asymmetry*, **1997**, 8, 1895.

⁸⁸⁹ Denmark, S.E.; Stiff, C.M. *J. Org. Chem.* **2000**, 65, 5875; Chrzanowska, M.; Sokołowska, J. *Tetrahedron Asymmetry* **2001**, 12, 1435.

⁸⁹⁰ See Friestad, G.K.; Mathies, A.K. *Tetrahedron* **2007**, 63, 2541; Ferraris, D. *Tetrahedron* **2007**, 63, 9581.

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⁸⁹² Yamada, K.-i.; Tomioka, K. *Chem. Rev.* **2008**, 108, 2874.

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⁸⁹⁴ Ballweg, D.M.; Miller, R.C.; Gray, D.L.; Scheidt, K.A. *Org. Lett.* **2005**, 7, 1403.

⁸⁹⁵ Lee, C.-L.K.; Ling, H.-Y.; Loh, T.-P. *J. Org. Chem.* **2004**, 69, 7787. See van der Sluis, M.; Dalmolen, J.; de Lange, B.; Kaptein, B.; Kellogg, R.M.; Broxterman, Q.B. *Org. Lett.* **2001**, 3, 3943.

⁸⁹⁶ Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2003**, 68, 6444.

⁸⁹⁷ Xiao, X.; Wang, H.; Huang, Z.; Yang, J.; Bian, X.; Qin, Y. *Org. Lett.* **2006**, 8, 139; Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron* **2007**, 63, 1167.

⁸⁹⁸ See Dickstein, J.S.; Fennie, M.W.; Norman, A.L.; Paulose, B.J.; Kozłowski, M.C. *J. Am. Chem. Soc.* **2008**, 130, 15794; Gao, F.; Deng, M.; Qian, C. *Tetrahedron* **2005**, 61, 12238.

⁸⁹⁹ See Fu, P.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2008**, 130, 5530; Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Org. Lett.* **2006**, 8, 979; Basra, S.; Fennie, M.W.; Kozłowski, M.C. *Org. Lett.* **2006**, 8, 2659; Charette, A.B.; Boezio, A.A.; Côté, A.; Moreau, E.; Pytkowicz, J.; Desrosiers, J.-N.; Legault, C. *Pure Appl. Chem.* **2005**, 77, 1259.

⁹⁰⁰ Fujihara, H.; Nagai, K.; Yomioka, K. *J. Am. Chem. Soc.* **2000**, 122, 12055. See Wang, C.-J.; Shi, M. *J. Org. Chem.* **2003**, 68, 6229.

⁹⁰¹ Chiev, K.P.; Roland, S.; Mangeney, P. *Tetrahedron Asymmetry* **2001**, 13, 2205.

⁹⁰² Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2003**, 44, 6767.

⁹⁰³ Zani, L.; Alesi, S.; Cozzi, P.G.; Bolm, C. *J. Org. Chem.* **2006**, 71, 1558.

Other organometallic compounds add to aldimines,⁹⁰⁴ including Sn,⁹⁰⁵ Sm,⁹⁰⁶ Ge,⁹⁰⁷ Zr,⁹⁰⁸ Ga metal with ultrasound,⁹⁰⁹ Yb with Me₃SiCl,⁹¹⁰ and In.⁹¹¹ Catalytic amounts of the metal compound can be used with an allylic stannane.⁹¹² Catalytic enantioselective addition reactions with these organometallics are well known,⁹¹³ including reactions in an ionic liquid.⁹¹⁴ Aryltrialkylstannanes add the aryl group to *N*-tosyl imines using a Rh catalyst and sonication.⁹¹⁵ Allylic halides react with imines in the presence of In metal⁹¹⁶ or InCl₃⁹¹⁷ to give the homoallylic amine, and with *N*-sulfonyl imines to give the homoallylic sulfonamide.⁹¹⁸ In this latter reaction, antiselectivity was observed when the reaction was done in water, and syn selectivity when done in aq THF.⁹¹⁹ Aryl iodides add to *N*-aryl imines in the presence of a Rh catalyst.⁹²⁰ Arylation of *N*-tosyl ketimines proceeds with good enantioselectivity using a Rh catalyst.⁹²¹ Propargylic halides add to imines in the presence of In metal, in aq THF.⁹²²

Terminal alkynes react with aryl aldehydes and aryl amines to give propargylic amine without a catalyst.⁹²³ Alternatively, with an Ir⁹²⁴ or a Cu catalyst⁹²⁵ they also lead to a propargylic amine.⁹²⁶ Terminal alkynes add to *N*-substituted imines to give a propargylic amine with good enantioselectivity using a chiral Cu complex.⁹²⁷ Lithium alkyne anions add to chiral *N*-sulfinylimines, in the presence of Me₃Al, to give the chiral propargyl

⁹⁰⁴ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 847–863.

⁹⁰⁵ Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242; Kobayashi, S.; Iwamoto, S.; Nagayama, S. *Synlett* **1997**, 1099.

⁹⁰⁶ See Kim, B.; Han, R.; Park, R.; Bai, K.; Jun, Y.; Baik, W. *Synth. Commun.* **2001**, *31*, 2297.

⁹⁰⁷ Akiyama, T.; Iwai, J.; Onuma, Y.; Kagoshima, H. *Chem. Commun.* **1999**, 2191.

⁹⁰⁸ With a Cu catalyst, see Sato, A.; Ito, H.; Okada, M.; Nakamura, Y.; Taguchi, T. *Tetrahedron Lett.* **2005**, *46*, 8381.

⁹⁰⁹ Andrews, P.C.; Peatt, A.C.; Raston, C.L. *Tetrahedron Lett.* **2004**, *45*, 243.

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⁹¹¹ Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G.R.; Lloyd-Jones, G.C.; Shepperson, I.R. *J. Am. Chem. Soc.* **2007**, *129*, 3846. With a Cu catalyst, see Black, D.A.; Arndtsen, B.A. *Org. Lett.* **2006**, *8*, 1991.

⁹¹² **Al**: Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* **2003**, *125*, 3720. **La**: Aspinall, H.C.; Bissett, J.S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* **2002**, *43*, 323. **Nb**: Andrade, C.K.Z.; Oliveira, G.R. *Tetrahedron Lett.* **2002**, *43*, 1935; Akiyama, T.; Onuma, Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1157. **Pd**: Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 3562. **Ta**: Shibata, I.; Nose, K.; Sakamoto, K.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2004**, *69*, 2185. **Zr**: Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 1896.

⁹¹³ See Kobayashi, Sh.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

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⁹¹⁷ Under electrolysis conditions, see Hilt, G.; Smolko, K.I.; Waloch, C. *Tetrahedron Lett.* **2002**, *43*, 1437.

⁹¹⁸ Lu, W.; Chan, T.H. *J. Org. Chem.* **2000**, *65*, 8589.

⁹¹⁹ Lu, W.; Chan, T.H. *J. Org. Chem.* **2001**, *66*, 3467.

⁹²⁰ Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 12043.

⁹²¹ Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168.

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⁹²³ Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268.

⁹²⁴ Fischer, C.; Carreira, E.M. *Synthesis* **2004**, 1497.

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⁹²⁶ Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638.

⁹²⁷ See Colombo, F.; Benaglia, M.; Orlandi, S.; Uselli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064.

compound.⁹²⁸ Diynes add to *N*-sulfinyl imines in the presence of a chiral Rh catalyst to give the corresponding allylic sulfynylamine.⁹²⁹ Alkenes add to *N*-sulfinyl imines in the presence of a chiral Rh catalyst to give the alkylated sulfonamide.⁹³⁰

Triethylaluminum adds an ethyl group to an imine in the presence of a Eu catalyst. Reaction with PhSnMe₃ and *N*-tosylimines with a Rh catalyst leads to addition of a phenyl group to the carbon of the C=N bond.⁹³¹ Other *N*-sulfonyl imines react similarly to give the corresponding sulfonamide, and in the presence of a chiral ligand the reaction proceeds to good enantioselectivity.⁹³² *N*-Tosyl imines also react with dialkylzinc reagents, giving the sulfonamide with modest enantioselectivity.⁹³³ *N*-Sulfinyl imines [R₂CH=NS(=O)R']⁹³⁴ react with Grignard reagents at carbon to give the corresponding *N*-sulfynylamine.⁹³⁵ Furan derivatives add via C-2 with good enantioselectivity using a chiral phosphoric acid catalyst.⁹³⁶ Alkenes add to *N*-tosyl imines with a Yb catalyst⁹³⁷ and allenes add to *N*-carbamoyl imines in the presence of a V catalyst.⁹³⁸ *N*-Carbamoyl imines, formed *in situ*, react with allylic silanes in the presence of an iodine catalyst.⁹³⁹ *N*-Carbamoyl imines add acetonitrile (via carbon) using DBU and a Ru catalyst.⁹⁴⁰

Arylboronates (Reaction 12-28) add to *N*-sulfonyl imines in the presence of a Rh catalyst to give the corresponding sulfonamide.⁹⁴¹ Chiral Cu complexes have also been used for effective allylation of ketimines.⁹⁴² Aryl boronic acids (Reaction 12-28) add the aryl group to *N*-tosyl imines using a Rh⁹⁴³ or Pd⁹⁴⁴ catalyst. Arylboronic acids react similarly, and in the presence of a chiral Rh⁹⁴⁵ or Ir⁹⁴⁶ catalyst give a chiral sulfinamide or sulfonamide. Allylic boronates also add to aldehydes, and subsequent treatment with ammonia gives the homoallylic amine.⁹⁴⁷ Vinyl boronates add to nitrones in the presence of Me₂Zn, transferring the vinyl group to the C=N unit.⁹⁴⁸ Potassium allyltrifluoroborates react with *N*-tosylimines in the presence of a Pd catalyst.⁹⁴⁹

⁹²⁸ Patterson, A.W.; Ellman, J.A. *J. Org. Chem.* **2006**, 71, 7110.

⁹²⁹ Kong, J.-R.; Cho, C.-W.; Krische, M.J. *J. Am. Chem. Soc.* **2005**, 127, 11269.

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⁹³¹ Oi, S.; Moro, M.; Fukuhara, H.; Kawanishi, T.; Inoue, Y. *Tetrahedron Lett.* **1999**, 40, 9259.

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⁹³⁵ Tang, T.P.; Volkman, S.K.; Ellman, J.A. *J. Org. Chem.* **2001**, 66, 8772.

⁹³⁶ Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, 126, 11804. See also, Spanedda, M.V.; Ourévitich, M.; Crouse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2004**, 45, 5023.

⁹³⁷ Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **2003**, 68, 3112.

⁹³⁸ Trost, B.M.; Jonasson, C. *Angew. Chem. Int. Ed.* **2003**, 42, 2063.

⁹³⁹ Phukan, P. *J. Org. Chem.* **2004**, 69, 4005.

⁹⁴⁰ Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, 126, 13632.

⁹⁴¹ Ueda, M.; Saito, A.; Miyaoura, N. *Synlett* **2000**, 1637.

⁹⁴² Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, 128, 7687.

⁹⁴³ Duan, H.-F.; Jia, Y.-X.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, 8, 2567; Trincado, M.; Ellman, J.A. *Angew. Chem. Int. Ed.* **2008**, 47, 5623; Marelli, C.; Monti, C.; Gennari, C.; Piarulli, U. *Synlett* **2007**, 2213.

⁹⁴⁴ Zhang, Q.; Chen, J.; Liu, M.; Wu, H.; Cheng, J.; Qin, C.; Su, W.; Ding, J. *Synlett* **2008**, 935.

⁹⁴⁵ Weix, D.J.; Shi, Y.; Ellman, J.A. *J. Am. Chem. Soc.* **2005**, 127, 1092; Beenen, M.A.; Weix, D.J.; Ellman, J.A. *J. Am. Chem. Soc.* **2006**, 128, 6304; Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, 129, 5336.

⁹⁴⁶ Ngai, M.-Y.; Barchuk, A.; Krische, M.J. *J. Am. Chem. Soc.* **2007**, 129, 12644.

⁹⁴⁷ Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, 126, 7182.

⁹⁴⁸ Pandya, A.; Pinet, S.U.; Chavant, P.Y.; Vallée, Y. *Eur. J. Org. Chem.* **2003**, 3621.

⁹⁴⁹ Solin, N.; Wallner, O.A.; Szabó, K.J. *Org. Lett.* **2005**, 7, 689.

Allylic silanes (e.g., allyltrimethylsilane) add to *N*-substituted imines in the presence of a Pd catalyst to give the homoallylic amine.⁹⁵⁰ Similar results are obtained when the allylic silane and imine are treated with a catalytic amount of tetrabutylammonium fluoride.⁹⁵¹ Allylic trichlorosilanes add to hydrazones to give homoallylic hydrazine derivatives with excellent antiselectivity⁹⁵² and with good enantioselectivity using a chiral ligand.⁹⁵³ Chiral allylic silane derivatives have been developed, and add to hydrazones with good enantioselectivity.⁹⁵⁴

There is an *aza-Baylis–Hillman reaction* that converts imines and conjugated carbonyl derivatives to the α -amino conjugated derivative.⁹⁵⁵ *N*-Tosyl imines can be used in place of aldehydes, and the reaction of the imine, a conjugated ester and DABCO gave the allylic *N*-tosylimine.⁹⁵⁶ A “double *Baylis–Hillman*” reaction has also been reported using *N*-tosylimines and conjugated ketones.⁹⁵⁷ The use of chiral catalysts leads enantioselective product formation.⁹⁵⁸ An enantioselective *aza-Baylis–Hillman reaction*⁹⁵⁹ was reported using as chiral reaction medium.⁹⁶⁰ Aldehydes add via the α carbon using proline, to give β -amino aldehydes with good selectivity to give chiral β -amino aldehydes.⁹⁶¹

Silyl enol ethers add to hydrazones in the presence of ZnF_2 and a chiral ligand to give chiral β -hydrazino ketones.⁹⁶² Similar addition to imine derivatives was accomplished using ketene silyl acetals and Amberlyst-15.⁹⁶³ Alternatively, an imine is reacted first with $\text{Zn}(\text{OTf})_2$ and then with a ketene silyl acetal.⁹⁶⁴

Nitro compounds add to *N*-carbamoyl imines with a chiral diamine catalyst with some enantioselectivity.⁹⁶⁵ Nitro compounds add via carbon using a Cu catalyst, and with good enantioselectivity when a chiral ligand is used.⁹⁶⁶ The conjugate bases of nitro compounds (formed by treatment of the nitro compound with BuLi) react with Grignard reagents in the presence of $\text{ClCH}=\text{NMe}_2^+ \text{Cl}^-$ to give oximes: $\text{RCH}=\text{N}(\text{O})\text{OLi} + \text{R}'\text{MgX} \rightarrow \text{RR}'\text{C}=\text{NOH}$.⁹⁶⁷

⁹⁵⁰ Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614.

⁹⁵¹ See Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735.

⁹⁵² Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 9493.

⁹⁵³ Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610.

⁹⁵⁴ Berger, R.; Duff, K.; Leighton, J.L. *J. Am. Chem. Soc.* **2004**, *126*, 5686.

⁹⁵⁵ Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. See Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680; Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790; Gajda, A.; Gajda, T. *J. Org. Chem.* **2008**, *73*, 8643.

⁹⁵⁶ Xu, Y.-M.; Shi, M. *J. Org. Chem.* **2004**, *69*, 417.

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⁹⁵⁸ Qi, M.-J.; Ai, T.; Shi, M.; Li, G. *Tetrahedron* **2008**, *64*, 1181; Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas III, C.F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1878.

⁹⁵⁹ See Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614.

⁹⁶⁰ Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C.W.; Klankermayer, J.; Leitner, W. *Angew. Chem. Int. Ed.* **2006**, *45*, 3689.

⁹⁶¹ Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N.S.; Turner, J.M.; Thayumanavan, R.; Barbas, III, C.F. *J. Org. Chem.* **2003**, *68*, 9624; Chowdari, N.S.; Suri, J.T.; Barbas, III, C.F. *Org. Lett.* **2004**, *6*, 2507.

⁹⁶² Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7768. For a similar reaction using a Bi catalyst, see Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292.

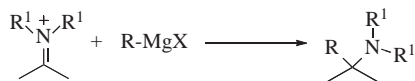
⁹⁶³ Shimizu, M.; Itoharu, S.; Hase, E. *Chem. Commun.* **2001**, 2318.

⁹⁶⁴ Ishimaru, K.; Kojima, T. *J. Org. Chem.* **2003**, *68*, 4959.

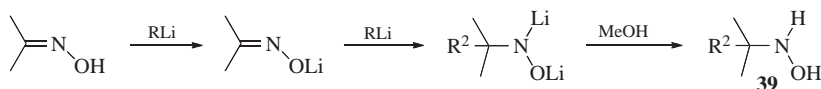
⁹⁶⁵ Nugent, B.M.; Yoder, R.A.; Johnston, J.N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

⁹⁶⁶ Nishiaki, N.; Knudson, K.R.; Gothelf, K.V.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992.

⁹⁶⁷ Fujisawa, T.; Kurita, Y.; Sato, T. *Chem. Lett.* **1983**, 1537.



Iminium salts⁹⁶⁸ give tertiary amines directly, via 1,2-addition to the C=N unit. Chloroiminium salts [ClCH=NR₂'Cl[−], generated *in situ* from an amide (HCONR₂') and phosgene (COCl₂)] react with 2 molar equivalents of a *Grignard reagent* RMgX, one adding to the C=N and the other replacing the Cl, to give tertiary amines R₂CHNR₂'.⁹⁶⁹



Many other C=N systems (phenylhydrazones, oxime ethers, etc.) give 1,2-addition when treated with *Grignard reagents*, while some gave reductions and others gave miscellaneous reactions. Organocerium reagents add to hydrazones.⁹⁷⁰ Indium metal promotes the addition of alkyl iodides to hydrazones.⁹⁷¹ A hydrazone can be formed *in situ* by reacting an aldehyde with a hydrazine derivative. In the presence of tetralyltin and a Sc catalysts, homoallylic hydrazine derivatives are formed.⁹⁷² Hydrazone derivatives react with iodoalkenes in the presence of InCl₃ and Mn₂(CO)₁₀ under photochemical conditions to give the hydrazine derivative.⁹⁷³ Ketene dithioacetals add to hydrazones using a chiral Zr catalyst to give a pyrazolidine.⁹⁷⁴ Oximes can be converted to hydroxylamines (**39**) by treatment with 2 molar equivalents of an alkyllithium reagent, followed by methanol.⁹⁷⁵ Oxime ethers add an allyl group upon reaction with allyl bromide and In metal in water.⁹⁷⁶ Nitrones [R₂C=N⁺(R')—O[−]] react with allylic bromides and Sm to give homoallylic oximes,⁹⁷⁷ and with terminal alkynes and a Zn catalyst to give propargylic oximes.⁹⁷⁸ *Grignard reagents* also add to nitrones.⁹⁷⁹ Nitrones react with CH₂=CHCH₂InBr in aq DMF to give the homoallylic oxime⁹⁸⁰ and silyl ketene acetals add in the presence of a chiral Ti catalyst to good enantioselectivity.⁹⁸¹

Allylic alcohols add to imines in the presence of a Pd catalyst to give the homoallylic amine.⁹⁸²

OS IV, 605; VI, 64. Also see, OS III, 329.

⁹⁶⁸ Paukstelis, J.V.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, **1988**, pp. 275–356.

⁹⁶⁹ Wieland, G.; Simchen, G. *Liebigs Ann. Chem.* **1985**, 2178.

⁹⁷⁰ Denmark, S.E.; Edwards, J.P.; Nicaise, O. *J. Org. Chem.* **1993**, 58, 569.

⁹⁷¹ Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, 60, 4227.

⁹⁷² Kobayashi, S.; Hamada, T.; Manabe, K. *Synlett* **2001**, 1140.

⁹⁷³ Friedstad, G.K.; Qin, J. *J. Am. Chem. Soc.* **2001**, 123, 9922.

⁹⁷⁴ Yamshita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, 126, 11279.

⁹⁷⁵ Richey Jr., H.G.; McLane, R.C.; Phillips, C.J. *Tetrahedron Lett.* **1976**, 233.

⁹⁷⁶ Bernardi, L.; Cerè, V.; Femoni, C.; Pollicino, S.; Ricci, A. *J. Org. Chem.* **2003**, 68, 3348.

⁹⁷⁷ Laskar, D.D.; Prajapati, D.; Sandu, J.S. *Tetrahedron Lett.* **2001**, 42, 7883.

⁹⁷⁸ Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* **1999**, 121, 11245. See Pinet, S.; Pandya, S.U.; Chavant, P.Y.; Ayling, A.; Vallee, Y. *Org. Lett.* **2002**, 4, 1463.

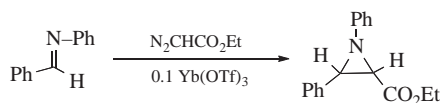
⁹⁷⁹ See Merino, P.; Tejero, T. *Tetrahedron* **2001**, 57, 8125.

⁹⁸⁰ Kumar, H.M.S.; Anjaneyulu, S.; Reddy, E.J.; Yadav, J.S. *Tetrahedron Lett.* **2000**, 41, 9311.

⁹⁸¹ Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* **2002**, 124, 2888.

⁹⁸² Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* **2005**, 7, 637.

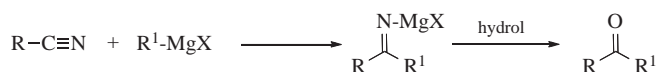
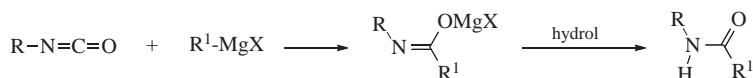
16-32 Addition of Carbenes and Diazoalkanes to C=N Compounds



In the presence of metal catalysts [e.g., Yb(OTf)_3], diazoalkanes add to imines to generate aziridines.⁹⁸³ The reaction is somewhat selective for the *cis*-diastereomer. The use of chiral additives in this reaction leads to aziridines enantioselectively.⁹⁸⁴ Imines can be formed by the reaction of an aldehyde and an amine, and subsequent treatment with Me_3SiI and butyllithium gives an aziridine.⁹⁸⁵ *N*-Tosyl imines react with diazoalkenes to form *N*-tosyl aziridines, with good *cis* selectivity⁹⁸⁶ and modest enantioselectivity in the presence of a chiral Cu catalyst,⁹⁸⁷ but give excellent enantioselectivity with a chiral Rh catalyst⁹⁸⁸ or with the use of an organocatalyst.⁹⁸⁹ Note that *N*-tosyl aziridines are formed by the reaction of an alkene with PhI=NTs and a Cu catalyst.⁹⁹⁰ *N*-Acylimines react with diazoesters via C—H insertion using a Pt catalyst.⁹⁹¹ The reaction of alkenes with diazo compounds is discussed in Reaction 15-53.

16-33 The Addition of Grignard Reagents to Nitriles and Isocyanates

Alkyl,oxo-de-nitrilo-tersubstitution (Overall transformation)

*N*-Hydro-C-alkyl-addition

Ketones can be prepared by addition of *Grignard reagents* to nitriles, followed by hydrolysis of the initially formed imine anion. Many ketones have been made in this manner, though when both R groups are alkyl, yields are not high.⁹⁹² Yields can be improved by the use of Cu(I) salts⁹⁹³ or by using benzene containing 1 equiv of ether as the

⁹⁸³ See Nagayama, S.; Kobayashi, S. *Chem Lett.* **1998**, 685. Also see, Rasmussen, K.G.; Jørgensen, K.A. *J. Chem. Soc., Chem. Commun.* **1995**, 1401.

⁹⁸⁴ See Janardanan, D.; Sunoj, R.B. *J. Org. Chem.* **2008**, 73, 8163.

⁹⁸⁵ Reetz, M.T.; Lee, W.K. *Org. Lett.* **2001**, 3, 3119.

⁹⁸⁶ Krumper, J.R.; Gerisch, M.; Suh, J.M.; Bergman, R.G.; Tilley, T.D. *J. Org. Chem.* **2003**, 68, 9705; Williams, A.L.; Johnston, J.N. *J. Am. Chem. Soc.* **2004**, 126, 1612.

⁹⁸⁷ Juhl, K.; Hazell, R.G.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293.

⁹⁸⁸ Aggarwal, V.K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* **2001**, 40, 1433.

⁹⁸⁹ Lu, Z.; Zhang, Y.; Wulff, W.D. *J. Am. Chem. Soc.* **2007**, 129, 7185. Also see Branco, P.S.; Raje, V.P.; Dourado, J.; Gordo, J. *Org. Biomol. Chem.* **2010**, 8, 2968.

⁹⁹⁰ Handy, S.T.; Czopp, M. *Org. Lett.* **2001**, 3, 1423.

⁹⁹¹ Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, 127, 9360.

⁹⁹² See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 767–845.

⁹⁹³ Weiberth, F.J.; Hall, S.S. *J. Org. Chem.* **1987**, 52, 3901.

solvent, rather than ether alone.⁹⁹⁴ In general, the ketimine salt does not react with *Grignard reagents*: Hence, tertiary alcohols or tertiary alkyl amines are not often side products.⁹⁹⁵ By careful hydrolysis of the salt, it is sometimes possible to isolate ketimines ($\text{RR}'\text{C}=\text{NH}$),⁹⁹⁶ especially when R and R' = aryl. The addition of *Grignard reagents* to the $\text{C}\equiv\text{N}$ group is normally slower than to the $\text{C}=\text{O}$ group, and cyano group containing aldehydes add the *Grignard reagent* without disturbing the CN group.⁹⁹⁷ Organolithium reagents add to nitriles, mediated by LiBr, to form N-acetyl enamines.⁹⁹⁸ Other metal compounds have been used, including Sm with allylic halides⁹⁹⁹ and organocerium compounds (e.g., MeCeCl_2).¹⁰⁰⁰ Allylic halides react with an excess of Zn metal in the presence of 40% AlCl_3 and in the presence of a nitrile, to give homoallylic ketones after hydrolysis.¹⁰⁰¹

Addition of *Grignard reagents*¹⁰⁰² or organolithium reagents¹⁰⁰³ to ω -halo nitriles leads to 2-substituted cyclic imines.

The *Blaise reaction* is the reaction of the organozinc reagent derived from a α -bromoester with Zn metal and a nitrile to give the corresponding β -ketoester.¹⁰⁰⁴

The following mechanism has been proposed for the reaction of the methyl *Grignard reagent* with benzonitrile¹⁰⁰⁵:



Arylboronic acids add to nitriles in the presence of a Pd catalyst.¹⁰⁰⁶ Aryl and alkenylboronic acids add to isocyanates in the presence of a Pd¹⁰⁰⁷ or Rh¹⁰⁰⁸ catalyst.

Arenes add to nitriles in the presence of a Pd catalyst in DMSO/trifluoroacetic acid to give a diaryl ketone.¹⁰⁰⁹

The addition of *Grignard reagents* to isocyanates gives, after hydrolysis, *N*-substituted amides.¹⁰¹⁰ This is a very good reaction and can be used to prepare derivatives of alkyl and aryl halides. The reaction has also been performed with alkyllithium compounds.¹⁰¹¹

⁹⁹⁴ Canonne, P.; Foscolos, G.B.; Lemay, G. *Tetrahedron Lett.* **1980**, 155.

⁹⁹⁵ See Gauthier, R.; Axiotis, G.P.; Chastrette, M. *J. Organomet. Chem.* **1977**, 140, 245.

⁹⁹⁶ Pickard, P.L.; Toblert, T.L. *J. Org. Chem.* **1961**, 26, 4886.

⁹⁹⁷ Cason, J.; Kraus, K.W.; McLeod, Jr., W.D. *J. Org. Chem.* **1959**, 24, 392.

⁹⁹⁸ Savarin, C.G.; Boice, G.N.; Murry, J.A.; Corley, E.; DiMichele, L.; Hughes, D. *Org. Lett.* **2006**, 8, 3903.

⁹⁹⁹ Yu, M.; Zhang, Y.; Guo, H. *Synth. Commun.* **1997**, 27, 1495.

¹⁰⁰⁰ Ciganek, E. *J. Org. Chem.* **1992**, 57, 4521.

¹⁰⁰¹ Lee, A.S.-Y.; Lin, L.-S. *Tetrahedron Lett.* **2000**, 41, 8803.

¹⁰⁰² Fry, D.F.; Fowler, C.B.; Dieter, R.K. *Synlett* **1994**, 836.

¹⁰⁰³ Gallulo, V.; Dimas, L.; Zezza, C.A.; Smith, M.B. *Org. Prep. Proceed. Int.* **1989**, 21, 297.

¹⁰⁰⁴ Blaise, E.E. *Compt. Rend.* **1901**, 132, 478; Rao, H.S.P.R.; Rafi, S.; Padmavathy, K. *Tetrahedron* **2008**, 64, 8037.

¹⁰⁰⁵ Ashby, E.C.; Chao, L.; Neumann, H.M. *J. Am. Chem. Soc.* **1973**, 95, 4896, 5186.

¹⁰⁰⁶ Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, 47, 6765.

¹⁰⁰⁷ Kianmehr, E.; Rajabi, A.; Ghanbari, M. *Tetrahedron Lett.* **2009**, 50, 1687.

¹⁰⁰⁸ Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 3577.

¹⁰⁰⁹ Zhou, C.; Larock, R.C. *J. Am. Chem. Soc.* **2004**, 126, 2302.

¹⁰¹⁰ See Screttas, C.G.; Steele, B.R. *Org. Prep. Proceed. Int.* **1990**, 22, 271.

¹⁰¹¹ Cooke, Jr., M.P.; Pollock, C.M. *J. Org. Chem.* **1993**, 58, 7474. For another method, see Einhorn, J.; Luche, J.L. *Tetrahedron Lett.* **1986**, 27, 501.

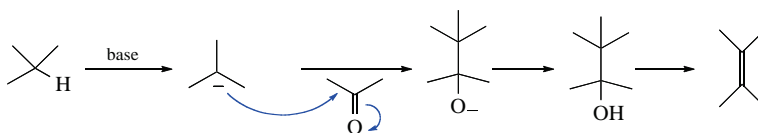
Isothiocyanates give *N*-substituted thioamides. Other organometallic compounds add to isocyanates. Vinyltin reagents lead to conjugate amides.¹⁰¹²

Note that terminal alkynes add to the carbon of an isonitrile in the presence of a uranium complex, giving a propargylic imine.¹⁰¹³

OSCV **III**, 26, 562; **V**, 120, 520.

G. Carbon Attack by Active Hydrogen Compounds

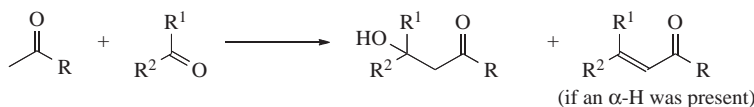
Reactions **16-34–16-50** are base-catalyzed condensations (although some of them are also catalyzed to acids).¹⁰¹⁴ In Reactions **16-34–16-44**, a base removes a C—H proton to give a carbanion, which then adds to a C=O. The oxygen acquires a proton, and the resulting alcohol may or may not be dehydrated, depending on whether an α hydrogen is present and on whether the new double bond would be in conjugation with double bonds already present:



The reactions differ in the nature of the active hydrogen component and the carbonyl component. Table 16.2 illustrates the differences. Reaction **16-50** is an analogous reaction involving addition to $C\equiv N$.

16-34 The Aldol Condensation¹⁰¹⁵

O-Hydro-*C*-(α -acylalkyl)-addition; α -Acylalkylidene-de-oxo-bisubstitution



In the *aldol reaction* or *aldol condensation*¹⁰¹⁶ the α carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another.¹⁰¹⁷ Although acid-catalyzed aldol reactions are known,¹⁰¹⁸ the most common form of the reaction uses a base. There is evidence that an SET mechanism can intervene when the substrate is an aromatic

¹⁰¹² Niestroj, M.; Neumann, W.P.; Thies, O. *Chem. Ber.* **1994**, 127, 1131.

¹⁰¹³ Barnea, E.; Andrea, T.; Kapon, M.; Berthet, J.-C.; Ephritikhine, M.; Eisen, M.S. *J. Am. Chem. Soc.* **2004**, 126, 10860.

¹⁰¹⁴ See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 629–682; Reeves, R.L. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, **1966**, pp. 567–619. See also, Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, **1979**.

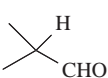
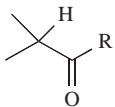
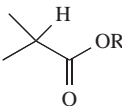
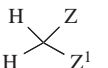
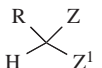
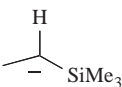
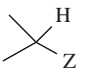
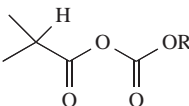
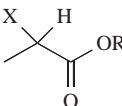
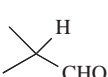
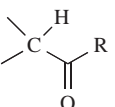
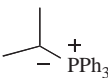
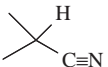
¹⁰¹⁵ See Mahrwald, R. *Modern Aldol Reactions*, 2 Volume Set, Wiley, NJ, **2004**; Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 816–823. For a treatise that discloses Aleksandr Borodin as the discoverer of the aldol condensation, see Podlech, J. *Angew. Chem. Int. Ed.* **2010**, 49, 6490.

¹⁰¹⁶ This reaction is also called the *aldol condensation*, although, strictly speaking, this term applies to the formation only of the α,β -unsaturated product, and not the aldol.

¹⁰¹⁷ See Thebtaranonth, C.; Thebtaranonth, Y. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, **1989**, pp. 199–280, 99–212; Hajos, Z.G. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1; Marcel Dekker, NY, **1979**; pp. 1–84; Nielsen, A.T.; Houlihan, W.J. *Org. React.* **1968**, 16, 1.

¹⁰¹⁸ See Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* **1998**, 120, 413.

TABLE 16.2 Base-Catalyzed Condensations Showing the Active-Hydrogen Components and the Carbonyl Compounds

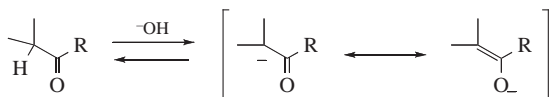
Reaction Number	Reaction	Active Hydrogen Component	Carbonyl Component	Subsequent Reaction
16-34	<i>Aldol</i>	 	Aldehyde, ketone	Dehydration may follow
16-36			Aldehyde, ketone (usually without α -hydrogens)	Dehydration may follow
16-38	<i>Knoevenagel</i>	 ,  and similar molecules	Aldehyde, ketone (usually without α -hydrogens)	Dehydration usually follows
16-41	<i>Peterson</i>		Aldehyde, ketone	Dehydration may follow
16-42		 $Z = \text{COR}, \text{COOR}, \text{NO}_2$	CO_2, CS_2	
16-39	<i>Perkin</i>		Aromatic aldehyde	Dehydration usually follows
16-40	<i>Darzen's</i>		Aldehyde, ketone	Epoxidation
16-43	<i>Tollen's</i>	 	Formaldehyde	Crossed-Cannizzaro reaction follows
16-44	<i>Wittig</i>		Aldehyde, ketone	Dehydration always follows
16-50	<i>Thorpe</i>		Nitrile	

ketone.¹⁰¹⁹ Although hydroxide was commonly used in early versions of this reaction, stronger bases [e.g., alkoxides (RO^-) or amides (R_2N^-)] are also common. Amine bases have been used to catalyze the aldol condensation.¹⁰²⁰ Hydroxide ion is not a strong

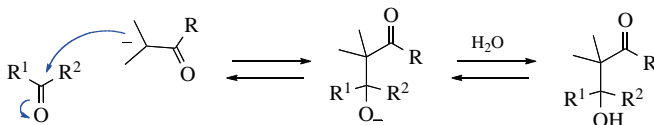
¹⁰¹⁹ Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* **1986**, 51, 472.

¹⁰²⁰ Markert, M.; Mulzer, M.; Schetter, B.; Mahrwald, R. *J. Am. Chem. Soc.* **2007**, 129, 7258. See Erkkilä, A.; Pihko, P.M. *J. Org. Chem.* **2006**, 71, 2538.

enough base to convert substantially all of an aldehyde or ketone molecule to the corresponding enolate ion; that is, the equilibrium lies well to the left, for both aldehydes



and ketones. Nevertheless, enough enolate ion is present for the reaction to proceed:



This equilibrium lies further to the right with alkoxide relative to hydroxide, but the equilibrium still lies predominantly to the left. With amide bases, and particularly with aprotic solvents, the equilibrium usually lies much more to the right when compared with alkoxides or hydroxide. Protic solvents, (e.g., water or alcohol) are acidic enough to react with the enolate anion and shift the equilibrium to the left. As noted, in an aprotic solvent (e.g., ether or THF), with a strong amide base (e.g., LDA, sec. Sec. 8.F, category 7), the equilibrium lies more to the right.¹⁰²¹ A variety of amide bases can be used to deprotonate the ketone or aldehyde, and in the case of an unsymmetrical ketone removal of the more acidic proton leads to the kinetic enolate anion.¹⁰²² Note that a polymer-bound amide base has been used¹⁰²³ and solid-phase chiral lithium amides are known.¹⁰²⁴ A polymer-supported phosphoramidate has been used as a catalyst for the aldol condensation.¹⁰²⁵

The product of an aldol condensation is a β -hydroxy aldehyde (called an *aldol*) or a β -hydroxy ketone, which in some cases is dehydrated during the course of the reaction. An aldol is readily isolated unless the substrate is an aromatic aldehyde or ketone when the reaction is done in aprotic solvents with a mild workup procedure. The aldol reaction has been done in ionic liquids.¹⁰²⁶ Even if the dehydration is not spontaneous, it can usually be done easily, since the new double bond is in conjugation with the $\text{C}=\text{O}$ bond; so that this is a method of preparing α,β -unsaturated aldehydes and ketones, as well as β -hydroxy aldehydes and ketones. One-pot procedures have been reported to give the conjugated product.¹⁰²⁷ The entire reaction is an equilibrium (including the dehydration step), and α,β -unsaturated and β -hydroxy aldehydes and ketones can be cleaved by treatment with ^-OH (the *retrograde aldol reaction*). The retro-aldol condensation has been exploited for crossed-aldol reactions.¹⁰²⁸ A vinylogous (Sec. 6.B) aldol reaction is known¹⁰²⁹ as is a

¹⁰²¹ See Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Tetrahedron Lett.* **2001**, 42, 7383.

¹⁰²² See Zhao, P.; Lucht, B.L.; Kenkre, S.L.; Collum, D.B. *J. Org. Chem.* **2004**, 69, 242; Zhao, P.; Condo, A.; Keresztes, I.; Collum, D.B. *J. Am. Chem. Soc.* **2004**, 126, 3113.

¹⁰²³ Seki, A.; Ishiwata, F.; Takizawa, Y.; Asami, M. *Tetrahedron* **2004**, 60, 5001.

¹⁰²⁴ Johansson, A.; Abrahamsson, P.; Davidsson, Ö. *Tetrahedron Asymmetry* **2003**, 14, 1261.

¹⁰²⁵ Flowers, II, R.A.; Xu, X.; Timmons, C.; Li, G. *Eur. J. Org. Chem.* **2004**, 2988.

¹⁰²⁶ Zheng, X.; Zhang, Y. *Synth. Commun.* **2003**, 161.

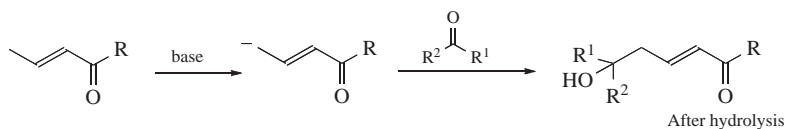
¹⁰²⁷ Kourouli, T.; Kefalas, P.; Ragoussis, N.; Ragoussis, V. *J. Org. Chem.* **2002**, 67, 4615.

¹⁰²⁸ See Simpura, I.; Nevalainen, V. *Angew. Chem. Int. Ed.* **2000**, 39, 3422.

¹⁰²⁹ See Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, 100, 1929; Casiraghi, G.; Zanardi, E.; Rassu, G. *Pure Appl. Chem.* **2000**, 72, 1645; Denmark, S.E.; Heemstra, Jr., J.R.; Beutner, G.L. *Angew. Chem. Int. Ed.* **2005**, 44, 4782.

‘double’ aldol.¹⁰³⁰ Enzyme-mediated aldol reactions have been reported using two aldehydes, including formaldehyde.¹⁰³¹

Under the principle of vinylogy (Sec. 6.B), the active hydrogen can be one in the γ position of an α,β -unsaturated carbonyl compound:



The scope of the aldol reaction may be discussed under five headings:

1. *Reaction between Two Molecules of the Same Aldehyde.* Homo-coupling. Hydroxide or alkoxide bases are used in protic solvents,¹⁰³² and the reaction is quite feasible. Nowadays, the use of dialkylamide bases in aprotic solvents (e.g., ether or THF) is more common. Many aldehydes have been converted to aldols and/or their dehydration products in this manner. The most effective catalysts are basic ion-exchange resins. Of course, the aldehyde must possess an α hydrogen.
2. *Reaction between Two Molecules of the Same Ketone.* Homo-coupling. With hydroxide or alkoxide bases in protic solvents the equilibrium lies well to the left,¹⁰³³ and the reaction is feasible only if the equilibrium can be shifted. This can often be done by allowing the reaction to proceed in a Soxhlet extractor (e.g., See OS I, 199). As with aldehydes, the use of dialkylamide bases (e.g., LDA or lithium hexamethyldisilazide, Sec. 8.F., category 7) in aprotic solvents (e.g., ether or THF) are more common. Unsymmetrical ketones condense on the side that has the most hydrogens with dialkylamide bases in aprotic solvents, but on the side with the fewest hydrogens with alkoxide bases in alcohol solvents.
3. *Reaction between Two Different Aldehydes.* Cross-coupling. In protic solvents with an alkoxide base, this will produce a mixture of four products (eight, if the alkenes are counted). However, if one aldehyde does not have an α hydrogen, only two aldols are possible, and in many cases the crossed product is the main one. The crossed-aldol reaction is often called the *Claisen–Schmidt reaction*.¹⁰³⁴ The crossed-aldol reaction is readily accomplished using amide bases in aprotic solvent. The first aldehyde is treated with LDA in THF at -78°C , for example, to form the enolate anion. Subsequent treatment with a second aldehyde leads to the mixed-aldol product. The crossed-aldol of two aldehydes has been done using potassium *tert*-butoxide and $\text{Ti}(\text{OBu})_4$.¹⁰³⁵
4. *Reaction between Two Different Ketones.* Cross-coupling. This is seldom attempted with hydroxide or alkoxide bases in protic solvents since similar considerations apply to those discussed for aldehydes. This reaction is commonly done with amide bases in aprotic solvents, but with somewhat more difficulty than with aldehydes.

¹⁰³⁰ See Abiko, A.; Inoue, T.; Masamune, S. *J. Am. Chem. Soc.* **2002**, *124*, 10759.

¹⁰³¹ Demir, A.S.; Ayhan, P.; Igdir, A.C.; Duygu, A.N. *Tetrahedron* **2004**, *60*, 6509.

¹⁰³² For discussions of equilibrium constants in aldol reactions, see Guthrie, J.P.; Wang, X. *Can. J. Chem.* **1991**, *69*, 339; Guthrie, J.P. *J. Am. Chem. Soc.* **1991**, *113*, 7249, and references cited therein.

¹⁰³³ The equilibrium concentration of the product from acetone in pure acetone was determined to be 0.01%: Maple, S.R.; Allerhand, A. *J. Am. Chem. Soc.* **1987**, *109*, 6609.

¹⁰³⁴ For an aqueous version, see Buonora, P.T.; Rosauer, K.G.; Dai, L. *Tetrahedron Lett.* **1995**, *36*, 4009.

¹⁰³⁵ Han, Z.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2000**, *41*, 4415.

5. *Reaction between an Aldehyde and a Ketone.* This is usually feasible with hydroxide or alkoxides bases in protic solvents when the aldehyde has no α hydrogen, since there is no competition from ketone condensing with itself.¹⁰³⁶ This is also called the *Claisen–Schmidt reaction*. Even when the aldehyde has an α hydrogen, it is generally the α carbon of the ketone that adds to the carbonyl of the aldehyde, not the other way around. Mixtures are usually produced, however. If the ketone or the aldehyde is treated with an amide base in aprotic solvents, a second aldehyde or ketone can be added to give the aldolate with high regioselectivity. The reaction can be also made regioselective by preparing an enol derivative of the ketone separately¹⁰³⁷ and then adding this to the aldehyde (or ketone). Other types of preformed derivatives that react with aldehydes and ketones are enamines (with a Lewis acid catalyst),¹⁰³⁸ and enol borinates ($R'CH=CR^2-OBR_2$),¹⁰³⁹ which can be synthesized by Reaction **15-27** or directly from an aldehyde or ketone¹⁰⁴⁰. Preformed metallic enolates are also used. For example, lithium enolates¹⁰⁴¹ (prepared by Reaction **12-23**) react with the substrate in the presence of $ZnCl_2$.¹⁰⁴² In this case, the aldol product is stabilized by chelation of its two oxygen atoms with the zinc ion.¹⁰⁴³ Other metallic enolates can be used for aldol reactions, either preformed or generated *in situ* with a catalytic amount of a metal compound. Compounds used for this purpose include metal complexes of Mg,¹⁰⁴⁴ Ti,¹⁰⁴⁵ Zr,¹⁰⁴⁶ Pd,¹⁰⁴⁷ In,¹⁰⁴⁸ Sn,¹⁰⁴⁹ La,¹⁰⁵⁰ and Sm,¹⁰⁵¹ all of which give products with moderate-to-excellent diastereoselectivity¹⁰⁵² and regioselectivity. α -Alkoxy ketones react with lithium enolates particularly fast.¹⁰⁵³ A bis(aldol) condensation has been reported with epoxy ketones and aldehydes using SmI_2 .¹⁰⁵⁴

There are discussions that relate to the transition state of the aldol condensation. There is experimental evidence for chair-like transition states in the aldol reactions of methyl

¹⁰³⁶ See Kad, G.L.; Kaur, K.P.; Singh, V.; Singh, J. *Synth. Commun.* **1999**, 29, 2583.

¹⁰³⁷ See Mukaiyama, T. *Isr. J. Chem.* **1984**, 24, 162; Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, **1979**, pp. 264–276.

¹⁰³⁸ Takazawa, O.; Kogami, K.; Hayashi, K. *Bull. Chem. Soc. Jpn.* **1985**, 58, 2427.

¹⁰³⁹ See Hooz, J.; Oudenes, J.; Roberts, J.L.; Benderly, A. *J. Org. Chem.* **1987**, 52, 1347; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, 29, 1041. For a review, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, pp. 324–333. For an *ab initio* study see Murga, J.; Falomir, E.; Carda, M.; Marco, J.A. *Tetrahedron* **2001**, 57, 6239.

¹⁰⁴⁰ See Brown, H.C.; Ganesan, K. *Tetrahedron Lett.* **1992**, 33, 3421.

¹⁰⁴¹ See Arnett, E.M.; Fisher, F.J.; Nichols, M.A.; Ribeiro, A.A. *J. Am. Chem. Soc.* **1990**, 112, 801.

¹⁰⁴² House, H.O.; Crumrine, D.S.; Teranishi, A.Y.; Olmstead, H.D. *J. Am. Chem. Soc.* **1973**, 95, 3310.

¹⁰⁴³ It has been contended that such stabilization is not required: Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* **1979**, 101, 7723.

¹⁰⁴⁴ Wei, H.-X.; Jasoni, R.L.; Shao, H.; Hu, J.; Paré, P.W. *Tetrahedron* **2004**, 60, 11829.

¹⁰⁴⁵ See Mahrwald, R.; Costisella, B.; Gündogan, B. *Synthesis* **1998**, 262.

¹⁰⁴⁶ Evans, D.A.; McGee, L.R. *Tetrahedron Lett.* **1980**, 21, 3975; *J. Am. Chem. Soc.* **1981**, 103, 2876.

¹⁰⁴⁷ Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, 111, 4126.

¹⁰⁴⁸ See Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* **2001**, 57, 4231.

¹⁰⁴⁹ Yanagisawa, A.; Kimura, K.; Nakatsuka, Y.; Yamamoto, H. *Synlett* **1998**, 958.

¹⁰⁵⁰ Kobayashi, S.; Hachiya, I.; Takahori, T. *Synthesis* **1993**, 371.

¹⁰⁵¹ Yokoyama, Y.; Mochida, K. *Synlett* **1996**, 445; Sasai, H.; Arai, S.; Shibasaki, M. *J. Org. Chem.* **1994**, 59, 2661. Also see, Bao, W.; Zhang, Y.; Wang, J. *Synth. Commun.* **1996**, 26, 3025.

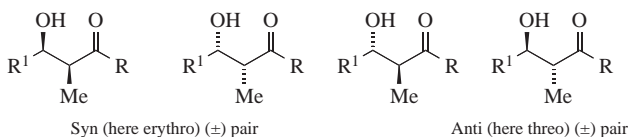
¹⁰⁵² For a review, see Mahrwald, R. *Chem. Rev.* **1999**, 99, 1095.

¹⁰⁵³ Das, G.; Thornton, E.R. *J. Am. Chem. Soc.* **1990**, 112, 5360.

¹⁰⁵⁴ Mukaiyama, T.; Arai, H.; Shiina, I. *Chem. Lett.* **2000**, 580.

ketone lithium enolate anions.¹⁰⁵⁵ A computational study gave the gas-phase activation energies for lithium enolate anions in an aldol-type reaction.¹⁰⁵⁶ There is a computational study of the mechanism for an aldol reaction in pure water.¹⁰⁵⁷

The reactions with pre-formed enol derivatives provide a way to control the stereoselectivity of the aldol reaction.¹⁰⁵⁸ As with the *Michael reaction* (15-24), the aldol reaction creates two new stereogenic centers. In the most general case, there are four stereoisomers of the aldol product (two racemic diastereomers), which can be represented as the syn and anti diastereomers shown. The reaction may be diastereoselective, however, if one is preferred over the other.



Among the preformed enol, derivatives used for diastereoselective aldol condensations have been enolates of Li,¹⁰⁵⁹ Mg, Ti,¹⁰⁶⁰ and Sn,¹⁰⁶¹ silyl enol ethers,¹⁰⁶² enol borinates,¹⁰⁶³ and enol borates [R'CH=CR²OB(OR)₂].¹⁰⁶⁴ The nucleophilicity of silyl enol ethers has been examined¹⁰⁶⁵ and reactions of these compounds are discussed in Reaction 16-35.

Base-induced formation of the enolate anion generally leads to a mixture of (*E*)- and (*Z*)-isomers, and dialkyl amide bases are used in most cases. The (*E/Z*) stereoselectivity depends on the structure of the lithium dialkylamide base, with the highest (*E/Z*) ratios obtained with LiTMP–butyllithium mixed aggregates in THF.¹⁰⁶⁶ The use of LiHMDS resulted in a reversal of the (*E/Z*) selectivity. In general, metallic (*Z*)-enolates give the syn (or erythro) pair, and this reaction is highly useful for the diastereoselective synthesis of these products.¹⁰⁶⁷ The (*E*) isomers generally react nonstereoselectively. However, anti-stereoselectivity has been achieved in a number of cases, with Ti enolates,¹⁰⁶⁸ with Mg

¹⁰⁵⁵ Liu, C.M.; Smith, III, W.J.; Gustin, D.J.; Roush, W.R. *J. Am. Chem. Soc.* **2005**, 127, 5770.

¹⁰⁵⁶ Pratt, L.M.; Nguen, NV.; Ramachandran, B. *J. Org. Chem.* **2005**, 70, 4279.

¹⁰⁵⁷ Zhang, X.; Houk, K.N. *J. Org. Chem.* **2005**, 70, 9712.

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¹⁰⁵⁹ Ertas, M.; Seebach, D. *Helv. Chim. Acta* **1985**, 68, 961.

¹⁰⁶⁰ Schetter, B.; Ziemer, B.; Schnakenburg, G.; Mahrwald, R. *J. Org. Chem.* **2008**, 73, 813; Mahrwald, R.; Schetter, B. *Org. Lett.* **2006**, 8, 281.

¹⁰⁶¹ Labadie, S.S.; Stille, J.K. *Tetrahedron* **1984**, 40, 2329; Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1986**, 187. See also, Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, 24, 3347.

¹⁰⁶² Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Am. Chem. Soc.* **1983**, 105, 6963; Sakurai, H.; Sasaki, K.; Hosomi, A. *Bull. Chem. Soc. Jpn.* **1983**, 56, 3195; Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1986**, 860.

¹⁰⁶³ Walker, M.A.; Heathcock, C.H. *J. Org. Chem.* **1991**, 56, 5747. For reviews, see Paterson, I. *Chem. Ind. (London)* **1988**, 390; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, p. 324.

¹⁰⁶⁴ Hoffmann, R.W.; Ditrich, K.; Fr6ch, S. *Liebigs Ann. Chem.* **1987**, 977.

¹⁰⁶⁵ Patz, M.; Mayr, H. *Tetrahedron Lett.* **1993**, 34, 3393.

¹⁰⁶⁶ Pratt, L. M.; Newman, A.; Cyr, J. S.; Johnson, H.; Miles, B.; Lattier, A.; Austin, E.; Henderson, S.; Hershey, B.; Lin, M.; Balamraju, Y.; Sammonds, L.; Cheramie, J.; Karnes, J.; Hymel, E.; Woodford, B.; Carter, C. *J. Org. Chem.* **2003**, 68, 6387.

¹⁰⁶⁷ See Paddon-Row, M.N.; Houk, K.N. *J. Org. Chem.* **1990**, 55, 481; Denmark, S.E.; Henke, B.R. *J. Am. Chem. Soc.* **1991**, 113, 2177.

¹⁰⁶⁸ See Nerz-Stormes, M.; Thornton, E.R. *J. Org. Chem.* **1991**, 56, 2489.

enolates,¹⁰⁶⁹ with certain enol borinates,¹⁰⁷⁰ and with lithium enolates at $-78\text{ }^{\circ}\text{C}$.¹⁰⁷¹ Enolization accounts for syn–anti isomerization of aldols.¹⁰⁷² In another variation, a β -keto *Weinreb amide* (see Reaction **16-82**) reacted with TiCl_4 and *Hünig's base* ($i\text{Pr}_2\text{NET}$) and then an aldehyde to give the β -hydroxy ketone.¹⁰⁷³

These reactions are enantioselective¹⁰⁷⁴ (in which case only one of the four isomers predominates)¹⁰⁷⁵ by using¹⁰⁷⁶ chiral enol derivatives,¹⁰⁷⁷ chiral aldehydes or ketones,¹⁰⁷⁸ or both.¹⁰⁷⁹ Chiral bases¹⁰⁸⁰ can be used (e.g., proline),¹⁰⁸¹ proline derivatives,¹⁰⁸² or chiral additives used in conjunction with an organobase.¹⁰⁸³ Indeed, chiral organocatalysts are increasingly important,¹⁰⁸⁴ including those that can be used in aqueous

¹⁰⁶⁹ Swiss, K.A.; Choi, W.; Liotta, D.; Abdel-Magid, A.F.; Maryanoff, C.A. *J. Org. Chem.* **1991**, *56*, 5978.

¹⁰⁷⁰ Danda, H.; Hansen, M.M.; Heathcock, C.H. *J. Org. Chem.* **1990**, *55*, 173. See also, Corey, E.J.; Kim, S.S. *Tetrahedron Lett.* **1990**, *31*, 3715.

¹⁰⁷¹ Hirama, M.; Noda, T.; Takeishi, S.; Itô, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2645; Majewski, M.; Gleave, D.M. *Tetrahedron Lett.* **1989**, *30*, 5681.

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¹⁰⁷³ Calter, M.A.; Guo, X.; Liao, W. *Org. Lett.* **2001**, *3*, 1499.

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¹⁰⁷⁵ For antiselective aldol reactions see Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321. For a “non-Evans” *syn*-aldol, see Yan, T.-H.; Lee, H.-C.; Tan, C.-W. *Tetrahedron Lett.* **1993**, *34*, 3559.

¹⁰⁷⁶ Klein, J. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, **1989**, pp. 567–677; Braun, M. *Angew. Chem. Int. Ed.* **1987**, *26*, 24.

¹⁰⁷⁷ Paterson, I.; Goodman, J.M. *Tetrahedron Lett.* **1989**, *30*, 997; Siegel, C.; Thornton, E.R. *J. Am. Chem. Soc.* **1989**, *111*, 5722; Faunce, J.A.; Grisso, B.A.; Mackenzie, P.B. *J. Am. Chem. Soc.* **1991**, *113*, 3418.

¹⁰⁷⁸ See Reetz, M.T.; Kessler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327.

¹⁰⁷⁹ See Short, R.P.; Masamune, S. *Tetrahedron Lett.* **1987**, *28*, 2841.

¹⁰⁸⁰ Notz, W.; Tanaka, F.; Barbas III, C.F. *Acc. Chem. Res.* **2004**, *37*, 580.

¹⁰⁸¹ See Northrup, A.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. See Suri, J.T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas III, C.F. *J. Org. Chem.* **2006**, *71*, 3822; Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron Asymmetry* **2006**, *17*, 2754. See Chimni, S.S.; Mahajan, D. *Tetrahedron* **2005**, *61*, 5019.

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¹⁰⁸³ See Mahrwald, R. *Org. Lett.* **2000**, *2*, 4011; Zhou, Y.; Shan, Z. *J. Org. Chem.* **2006**, *71*, 9510.

¹⁰⁸⁴ For a review, see Guillena, G.; Nájera, C.; Ramón, D.J. *Tetrahedron Asymmetry* **2007**, *18*, 2249. Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285; Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442; Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.P. *J. Am. Chem. Soc.* **2007**, *129*, 3074; Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654; Denmark, S.E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10393; Guillena, G.; Hita, M.d.C.; Nájera, C.; Vióquez, S.F. *J. Org. Chem.* **2008**, *73*, 5933; Wang, W.; Mei, Y.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 601; Krattiger, P.; Kovasy, R.; Revell, J.D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101; Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321; Revell, J.D.; Wennemers, H. *Tetrahedron* **2007**, *63*, 8420; Lombardo, M.; Easwar, S.; Pasi, F.; Trombini, C.; Dhavale, D.D. *Tetrahedron* **2008**, *64*, 9203; Guillena, G.; Hita, M.d.C.; Nájera, C. *Tetrahedron Asymmetry* **2006**, *17*, 1493; Tang, X.; Liégault, B.; Renaud, J.-L.; Bruneau, C. *Tetrahedron Asymmetry* **2006**, *17*, 2187; Rodríguez, B.; Bruckmann, A.; Bolm, C. *Chemistry: European J.* **2007**, *13*, 4710; Córdova, A.; Zou, W.; Ibrahim, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586; Sun, G.; Fan, J.; Wang, Z.; Li, Y. *Synlett* **2008**, 2491; Rambo, R.S.; Schneider, P.H. *Tetrahedron Asymm.* **2010**, *21*, 2254.

media.¹⁰⁸⁵ Chiral auxiliaries¹⁰⁸⁶ have been developed that can be used in conjunction with the aldol condensation, as well as chiral transition metal complexes¹⁰⁸⁷ and chiral ligands¹⁰⁸⁸ in catalytic reactions. The enantioselective condensation of methyl vinyl ketone and an aldehyde used a chiral Zn catalyst.¹⁰⁸⁹ Structural variations in the aldehyde or ketone are compatible with many enantioselective condensation reactions. An α -hydroxy ketone was condensed with an aldehyde using a chiral Zn catalyst to give the aldol (an α,β -dihydroxy ketone) with good syn selectivity and good enantioselectivity.¹⁰⁹⁰ Chiral vinylogous aldol reactions (Sec. 6.B) have been reported.¹⁰⁹¹ Formation of the magnesium enolate anion of a chiral amide, adds to aldehydes to give the alcohol enantioselectively.¹⁰⁹² Diamine protonic acids have been used for catalytic asymmetric aldol reactions.¹⁰⁹³

Silyl enol ethers react with aldehydes in the presence of chiral boranes¹⁰⁹⁴ or other additives¹⁰⁹⁵ to give aldols with good asymmetric induction (see the *Mukaiyama aldol Reaction* in **16-35**). Chiral boron enolates have been used.¹⁰⁹⁶ Since both new stereogenic centers are formed enantioselectively, this kind of process is called *double asymmetric synthesis*.¹⁰⁹⁷ Where both the enolate derivative and substrate were achiral, carrying out the reaction in the presence of an optically active boron compound¹⁰⁹⁸ or a diamine coordinated with a Sn compound¹⁰⁹⁹ gave the aldol product with excellent enantioselectivity for one stereoisomer. Boron triflate (R_2BOTf) derivatives have been used for the condensation of ketals and ketone to give β -alkoxy ketones.¹¹⁰⁰

¹⁰⁸⁵ See Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C.F. *J. Am. Chem. Soc.* **2006**, *128*, 734; Chi, Y.; Scroggins, S.T.; Boz, E.; Fréchet, J.M.J. *J. Am. Chem. Soc.* **2008**, *130*, 17287; Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247; Maya, V.; Raj, M.; Singh, V.K. *Org. Lett.* **2007**, *9*, 2593; Chimni, S.S.; Mahajan, D.; Suresh Babu, V.V. *Tetrahedron Lett.* **2005**, *46*, 5617; Akagawa, K.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2005**, *46*, 8185; Lei, L.; Shi, L.; Li, G.; Chen, S.; Weihai, W.; Ge, Z.; Cheng, T.; Li, R. *Tetrahedron* **2007**, *63*, 7892; Amedjkouh, M. *Tetrahedron Asymmetry* **2005**, *16*, 1411; Chimni, S.S.; Mahajan, D. *Tetrahedron Asymmetry* **2006**, *17*, 2108; Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 958; Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801.

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¹⁰⁸⁷ See Kantam, M.L.; Ramani, T.; Chakrapani, L.; Kumar, K.V. *Tetrahedron Lett.* **2008**, *49*, 1498; Inoue, H.; Kikuchi, M.; Ito, J.-i.; Nishiyama, H. *Tetrahedron* **2008**, *64*, 493.

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¹⁰⁹³ Trost, B.M.; Fettes, A.; Shireman, B.T. *J. Am. Chem. Soc.* **2004**, *126*, 2660.

¹⁰⁹⁴ Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483.

¹⁰⁹⁵ Corey, E.J.; Cywin, C.L.; Roper, T.D. *Tetrahedron Lett.* **1992**, *33*, 6907.

¹⁰⁹⁶ See Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 1901.

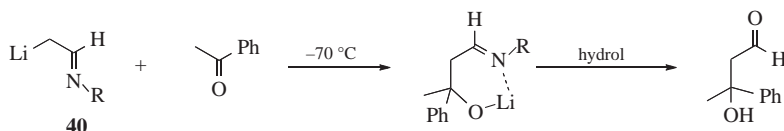
¹⁰⁹⁷ For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1.

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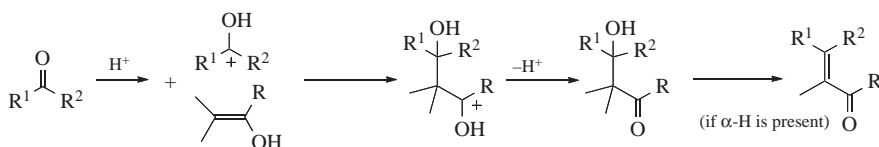
¹⁰⁹⁹ Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* **1990**, 1147.

¹¹⁰⁰ Li, L.-S.; Das, S.; Sinha, S.C. *Org. Lett.* **2004**, *6*, 127.

It is possible to make the α carbon of the aldehyde add to the carbonyl carbon of the ketone, by using an imine instead of an aldehyde, and $\text{LiN}(\text{iPr})_2$ as the base to form the α -lithio imine (**40**).¹¹⁰¹ This is known as a *directed aldol reaction*. Similar reactions have been performed with α -lithiated dimethylhydrazones of aldehydes or ketones¹¹⁰² and with α -lithiated aldoximes.¹¹⁰³



The aldol reaction can also be performed with acid catalysts, as mentioned above, in which case dehydration usually follows. Here there is initial protonation of the carbonyl group, which attacks the α carbon of the *enol* form of the other molecule¹¹⁰⁴:



With respect to the enol, this mechanism is similar to that of halogenation (Reaction 12-4). A side reaction that is sometimes troublesome is further condensation, since the product of an aldol reaction is still an aldehyde or ketone. The aldol condensation of aldehydes has also been done using a mixture of pyrrolidine and benzoic acid.¹¹⁰⁵

The intramolecular aldol condensation is well known, and aldol reactions are often used to close five- and six-membered rings. Because of the favorable entropy (Sec. 6.D), such ring closures generally take place with ease¹¹⁰⁶ when using hydroxide or alkoxide bases in protic solvents. In aprotic solvents with amide bases, formation of the enolate anion occurs by deprotonation of the more acidic site, followed by cyclization to the second carbonyl. The acid-catalyzed intramolecular aldol condensation is known, and the mechanism has been studied.¹¹⁰⁷ Stereoselective proline-catalyzed intramolecular aldol reactions give the cyclized product with good enantioselectivity.¹¹⁰⁸ Chiral ligands, in conjugation with transition metal compounds of Cu¹¹⁰⁹, lead to asymmetric intramolecular aldol condensation reactions. An asymmetric intramolecular aldol reaction was catalyzed by a chiral

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¹¹⁰² Corey, E.J.; Enders, D. *Tetrahedron Lett.* **1976**, 11. See also, Sugawara, T.; Toyoda, T.; Sasakura, K. *Synth. Commun.* **1979**, 9, 515; Depezay, J.; Le Merrer, Y. *Bull. Soc. Chim. Fr.* **1981**, II-306.

¹¹⁰³ Hassner, A.; Nümann, F. *Chem. Ber.* **1988**, 121, 1823.

¹¹⁰⁴ See Baigrie, L.M.; Cox, R.A.; Slebocka-Tilk, H.; Tencer, M.; Tidwell, T.T. *J. Am. Chem. Soc.* **1985**, 107, 3640.

¹¹⁰⁵ Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. *Synlett* **1999**, 450.

¹¹⁰⁶ See Guthrie, J.P.; Guo, J. *J. Am. Chem. Soc.* **1996**, 118, 11472; Eberle, M.K. *J. Org. Chem.* **1996**, 61, 3844.

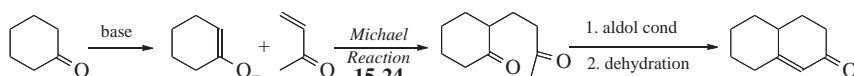
¹¹⁰⁷ Bouillon, J.-P.; Portella, C.; Bouquant, J.; Humbel, S. *J. Org. Chem.* **2000**, 65, 5823.

¹¹⁰⁸ Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2003**, 42, 2785.

¹¹⁰⁹ Lipshutz, B.H.; Amorelli, B.; Unger, J.B. *J. Am. Chem. Soc.* **2008**, 130, 14378.

amine.¹¹¹⁰ The regioselectivity of an intramolecular aldol condensation of unsaturated 1,5-diketones is strongly influenced by the presence or absence of a trialkylphosphine.¹¹¹¹

An important extension of the intramolecular aldol condensation is the *Robinson annulation* reaction,¹¹¹² which has often been used in the synthesis of steroids and terpenes. In original versions of this reaction, a cyclic ketone is converted to another cyclic ketone under equilibrium conditions using hydroxide or alkoxide bases in a protic solvent, forming one additional six-membered ring containing a double bond. The reaction can be done in a stepwise manner using amide bases in aprotic solvents. In the reaction with hydroxide or alkoxide bases in alcohol or water solvents, the substrate is treated with methyl vinyl ketone (or a simple derivative of methyl vinyl ketone) and a base.¹¹¹³ The enolate ion of the substrate adds to the methyl vinyl ketone in a *Michael reaction* (**15-24**) to give a diketone that undergoes or is made to undergo an internal aldol reaction and subsequent dehydration to give the product.¹¹¹⁴ The *Robinson annulation* can be combined with alkylation.¹¹¹⁵ Enantioselective *Robinson annulation* techniques have been developed, including a proline-catalyzed reaction.¹¹¹⁶ The *Robinson annulation* has been done in ionic liquids¹¹¹⁷ and a solvent-free version of the reaction is known.¹¹¹⁸



Because methyl vinyl ketone has a tendency to polymerize, surrogates are often used instead (i.e., compounds that will give methyl vinyl ketone when treated with a base). One common example, $\text{MeCOCH}_2\text{CH}_2\text{NEt}_2\text{Me}^+ \text{I}^-$ (see Reaction **17-9**), is easily prepared by quaternization of $\text{MeCOCH}_2\text{CH}_2\text{NEt}_2$, which itself is prepared by a *Mannich Reaction* (**16-19**) involving acetone, formaldehyde, and diethylamine. α -Silylated vinyl ketones $[\text{RCOC}(\text{SiMe}_3)=\text{CH}_2]$ have also been used successfully in annulation reactions¹¹¹⁹ because the SiMe_3 group is easily removed. When the ring closure of a 1,5-diketone is catalyzed by the amino acid (*S*)-proline, the product is optically active with high ee.¹¹²⁰ *Stryker's reagent*,¹¹²¹ $[(\text{Ph}_3\text{P})\text{CuH}]_6$, has been used for an intramolecular addition where a ketone enolate anion adds to a conjugated ketone, giving cyclic alcohol with a pendant ketone unit.¹¹²²

¹¹¹⁰ Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem. Int. Ed.* **2008**, 47, 7656.

¹¹¹¹ Thalji, R.K.; Roush, W.R. *J. Am. Chem. Soc.* **2005**, 127, 16778.

¹¹¹² Gawley, R.E. *Synthesis* **1976**, 777; Jung, M.E. *Tetrahedron* **1976**, 32, 1; Mundy, B.P. *J. Chem. Educ.* **1973**, 50, 110. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1356–1358.

¹¹¹³ See Heathcock, C.H.; Ellis, J.E.; McMurry, J.E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995.

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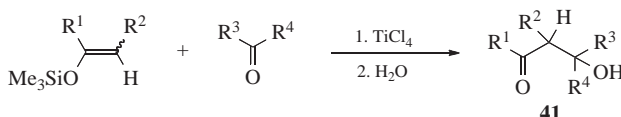
¹¹²² Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, 3, 1901.

OS I, 77, 78, 81, 199, 283, 341; II, 167, 214; III, 317, 353, 367, 747, 806, 829; V, 486, 869; VI, 496, 666, 692, 781, 901; VII, 185, 190, 332, 363, 368, 473; VIII, 87, 208, 241, 323, 339, 620; IX, 432, 610; X, 339.

16-35 Mukaiyama Aldol and Related Reactions¹¹²³

O-Hydro-C-(α -acylalkyl)-addition

An important variation of the aldol condensation involves treatment of an aldehyde or ketone with a silyl ketene acetal [$R_2C=C(OSiMe_3)OR'$]¹¹²⁴ or a silyl enol ether, in the presence of $TiCl_4$ ¹¹²⁵, to give **41**. This variation is known as the *Mukaiyama aldol reaction*, or simply the *Mukaiyama reaction*. The silyl ketene acetal can be considered a pre-formed enolate that gives aldol product with $TiCl_4$ in aqueous solution, or with no



catalyst at all.¹¹²⁶ A combination of $TiCl_4$ and *N*-tosyl imine has also been used to facilitate the Mukaiyama aldol reaction.¹¹²⁷ Reaction at the carbonyl of saturated carbonyl compounds is significantly faster than 1,2-addition to unsaturated carbonyl compounds.¹¹²⁸ The mechanism of this reaction has been explored.¹¹²⁹ Other catalysts have been used for this reaction, including $InCl_3$,¹¹³⁰ SmI_2 ,¹¹³¹ HgI_2 ,¹¹³² $Yb(OTf)_3$,¹¹³³ $Cu(OTf)_2$,¹¹³⁴ $LiClO_4$,¹¹³⁵ $VOCl_3$,¹¹³⁶ an Fe catalyst,¹¹³⁷ and $Bi(OTf)_3$.¹¹³⁸ Lithium perchlorate in acetonitrile (5 M) can be used for the reaction of an aldehyde and a silyl enol ether.¹¹³⁹

¹¹²³ See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 837–841.

¹¹²⁴ For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1745–1752. Also see Revis, A.; Hilty, T.K. *Tetrahedron Lett.* **1987**, 28, 4809, and references cited therein.

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¹¹²⁶ Miura, K.; Sato, H.; Tamaki, K.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1998**, 39, 2585. For a high pressure, uncatalyzed reaction, see Bellassoued, M.; Reboul, E.; Dumas, F. *Tetrahedron Lett.* **1997**, 38, 5631.

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¹¹³¹ Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1993**, 34, 3881.

¹¹³² Dicker, I.B. *J. Org. Chem.* **1993**, 58, 2324.

¹¹³³ This catalyst is tolerated in water. See Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, 59, 3590.

¹¹³⁴ Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1997**, 959.

¹¹³⁵ Reetz, M.T.; Fox, D.N.A. *Tetrahedron Lett.* **1993**, 34, 1119.

¹¹³⁶ Kurihara, M.; Hayashi, T.; Miyata, N. *Chem. Lett.* **2001**, 1324.

¹¹³⁷ Bach, T.; Fox, D.N.A.; Reetz, M.T. *J. Chem. Soc., Chem. Commun.* **1992**, 1634.

¹¹³⁸ Ollevier, T.; Desyroy, V.; Debailleul, B.; Vaur, S. *Eur. J. Org. Chem.* **2005**, 4971; **2006**, 1061; Ollevier, T.; Li, Z. *Eur. J. Org. Chem.* **2007**, 5665.

¹¹³⁹ Sudha, R.; Sankararaman, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 383.

The reaction can be done in water using a Sc catalyst¹¹⁴⁰ or on a Montmorillonite K-10 clay.¹¹⁴¹ Silyl enol ethers react with aq formaldehyde in the presence of TBAF to give the aldol product.¹¹⁴² A catalytic amount of Me₃SiCl facilitates the Ti mediated reaction.¹¹⁴³ Sulfonamides (e.g., HNTf₂) have been used as a catalyst¹¹⁴⁴ as has pyridine *N*-oxide¹¹⁴⁵ and *N*-methylimidazole.¹¹⁴⁶ An *ab initio* study of the uncatalyzed Mukaiyama aldol reaction showed that the nucleophilicity of silyl enol ether and the electrophilicity of the aldehyde are important in promoting the reactivity.¹¹⁴⁷ This reaction can also be run with the aldehyde or ketone in the form of its acetal [R³R⁴C(OR')₂], in which case the product is the ether R¹COCHR₂CR³R⁴OR' instead of **41**.¹¹⁴⁸ Vinylogous (Sec. 6.B) silyl ketene acetals with Ti,¹¹⁴⁹ Cu,¹¹⁵⁰ In,¹¹⁵¹ Fe,¹¹⁵² or Zn¹¹⁵³ catalysts or an organocatalyst,¹¹⁵⁴ give the product with good enantioselectivity.

Silyl enol ethers¹¹⁵⁵ derived from esters (silyl ketene acetals) react with aldehydes in the presence of various catalysts to give β-hydroxy esters. Water accelerates the reaction of an aldehyde and a ketene silyl acetal with no other additives.¹¹⁵⁶ The reaction is catalyzed by triphenylphosphine¹¹⁵⁷ and also by SiCl₄ with a chiral bis(phosphoramidate) catalyst.¹¹⁵⁸ The reaction was done without a catalyst in an ionic liquid.¹¹⁵⁹ A vinylogous reaction (Sec. 6.B) is known that gives δ-hydroxy-α,β-unsaturated esters.¹¹⁶⁰ An interesting variation in this reaction combined an intermolecular *Mukaiyama aldol* followed by an intramolecular reaction (a “domino” *Mukaiyama aldol*) that gave cyclic conjugated ketone products.¹¹⁶¹ Under different conditions, silyl ketene acetals of conjugated esters react with aldehydes to give conjugated lactones.¹¹⁶² Imines react with silyl ketene acetals in the presence of SmI₃

¹¹⁴⁰ Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **1999**, 40, 3773. See Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Bu, Y.-P.; Li, C.-J. *Tetrahedron Lett.* **2001**, 42, 1803; Komoto, I.; Kobayashi, S. *J. Org. Chem.* **2004**, 69, 680

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¹¹⁵⁵ See Carswell, E.L.; Hayes, D.; Henderson, K.W.; Kerr, W.J.; Russell, C.J. *Synlett* **2003**, 1017.

¹¹⁵⁶ Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* **2000**, 56, 7309.

¹¹⁵⁷ Matsukawa, S.; Okano, N.; Imamoto, T. *Tetrahedron Lett.* **2000**, 41, 103.

¹¹⁵⁸ Denmark, S.E.; Heemstra, Jr., J.R. *Org. Lett.* **2003**, 5, 2303; Denmark, S.E.; Wynn, T.; Beutner, G.L. *J. Am. Chem. Soc.* **2002**, 124, 13405.

¹¹⁵⁹ Chen, S.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron Lett.* **2004**, 45, 375.

¹¹⁶⁰ Bluet, G.; Campagne, J.-M. *J. Org. Chem.* **2001**, 66, 4293; Christmann, M.; Kalesse, M. *Tetrahedron Lett.* **2001**, 42, 1269.

¹¹⁶¹ Langer, P.; Köhler, V. *Org. Lett.* **2000**, 2, 1597.

¹¹⁶² Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. *Org. Lett.* **2001**, 3, 3807.

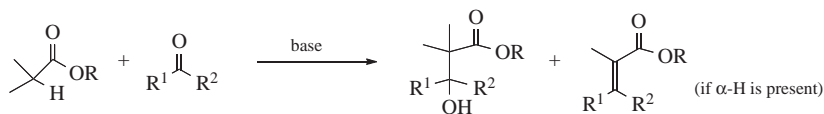
to give β -amino esters.¹¹⁶³ Imines react with silyl enol ethers in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give β -amino ketones.¹¹⁶⁴ Silyl ketene acetals also undergo conjugate addition in reactions with conjugated ketones.¹¹⁶⁵ Propargylic acetals react with silyl enol ethers and a Sc catalyst to give β -alkoxy ketones.¹¹⁶⁶ α -Silyl silyl enol ethers $[\text{RCH}=\text{CH}(\text{OTMS})\text{SiMe}_3]$ react with acetals in the presence of SnCl_4 to give β -alkoxy silyl ketones.¹¹⁶⁷ Borane derivatives [e.g., $\text{C}=\text{C}-\text{OB}(\text{NMe}_2)_2$] react with aldehydes to give β -amino ketones.¹¹⁶⁸

Asymmetric *Mukaiyama aldol reactions* and reactions of silyl ketene acetals have been reported,¹¹⁶⁹ usually using chiral additives¹¹⁷⁰ although chiral auxiliaries have also been used.¹¹⁷¹ Chiral catalysts, usually transition metal complexes using chiral ligands, are quite effective¹¹⁷² but chiral organocatalysts¹¹⁷³ are increasingly important.

Enol acetates and enol ethers also give this product when treated with acetals and TiCl_4 or a similar catalyst.¹¹⁷⁴ A variation of this condensation uses an enol acetate with an aldehyde in the presence of Et_2AlOEt to give the aldol product.¹¹⁷⁵

16-36 Aldol-Type Reactions between Carboxylic Acid Derivatives and Aldehydes or Ketones

O-Hydro-C-(α -alkoxycarbonylalkyl)-addition; α -Alkoxycarbonylalkylidene-de-oxo-bisubstitution



In the presence of a strong base, removal of a proton from the α carbon of a carboxylic ester or other acid derivative generates an enolate anion that can condense with the carbonyl carbon of an aldehyde or ketone to give a β -hydroxy ester,¹¹⁷⁶ amide, and so on. These products may or may not be dehydrated to the α,β -unsaturated derivative. This

¹¹⁶³ Hayakawa, R.; Shimizu, M. *Chem. Lett.* **1999**, 591.

¹¹⁶⁴ Akiyama, T.; Takaya, J.; Kagoshima, H. *Chem. Lett.* **1999**, 947.

¹¹⁶⁵ Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubu, M.; Oku, A. *Org. Lett.* **2001**, 3, 2101.

¹¹⁶⁶ Yoshimatsu, M.; Kuribayashi, M.; Koike, T. *Synlett* **2001**, 1799.

¹¹⁶⁷ Honda, M.; Oguchi, W.; Segi, M.; Nakajima, T. *Tetrahedron* **2002**, 58, 6815.

¹¹⁶⁸ Sugimoto, M.; Uehlin, L.; Yamamoto, A.; Murakami, M. *Org. Lett.* **2004**, 6, 1167.

¹¹⁶⁹ Bach, T. *Angew. Chem. Int. Ed.* **1994**, 33, 417. For a discussion of stereocontrol, see Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G.; Consolandi, E. *J. Org. Chem.* **1992**, 57, 456.

¹¹⁷⁰ See Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, 116, 4077; Kaneko, Y.; Matsuo, T.; Kiyooka, S. *Tetrahedron Lett.* **1994**, 35, 4107; Kiyooka, S.; Kido, Y.; Kaneko, Y. *Tetrahedron Lett.* **1994**, 35, 5243.

¹¹⁷¹ See Vasconcellos, M.L.; Desmaële, D.; Costa, P.R.R.; d'Angelo, J. *Tetrahedron Lett.* **1992**, 33, 4921.

¹¹⁷² **Ag**: Wadamoto, M.; Ozasa, N.; Yanigisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, 68, 5593. **Ce**: Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, 3, 165. **Cu**: Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, 55, 8739. **Pb**: Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, 122, 11531. **Sc**: Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, 126, 12236. **Ti**: Imashiro, R.; Kuroda, T. *J. Org. Chem.* **2003**, 68, 974. **Zr**: Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* **2001**, 57, 861.

¹¹⁷³ Denmark, S.E.; Beutner, G.L.; Wynn, T.; Eastgate, M.D. *J. Am. Chem. Soc.* **2005**, 127, 3774; Denmark, S.E.; Bui, T. *J. Org. Chem.* **2005**, 70, 10190; Adachi, S.; Harada, T. *Org. Lett.* **2008**, 10, 4999; Senapati, B.K.; Gao, L.; Lee, S.I.; Hwang, G.-S.; Ryu, D.H. *Org. Lett.* **2010**, 12, 5088.

¹¹⁷⁴ Kitazawa, E.; Imamura, T.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 569.

¹¹⁷⁵ Mukaiyama, T.; Shibata, J.; Shimamura, T.; Shiina, I. *Chem. Lett.* **1999**, 951.

¹¹⁷⁶ See Solladié, G. *Chimia* **1984**, 38, 233.

reaction is sometimes called the *Claisen reaction*,¹¹⁷⁷ an unfortunate usage since that name is more firmly connected to Reaction **16-85**. *Claisen condensation* is a better descriptor. Early reactions used hydroxide or an alkoxide base in water or alcohol solvents, where self-condensation was the major process. Under such conditions, the aldehyde or ketone was usually chosen for its lack of an α -proton. Much better control of the reaction was achieved when dialkylamide bases in aprotic solvents (e.g., ether or THF) were used. The reaction of *tert*-butyl acetate and LDA¹¹⁷⁸ in hexane or more commonly THF at $-78\text{ }^{\circ}\text{C}$ gives the enolate anion of *tert*-butyl acetate,¹¹⁷⁹ (Reaction **12-23**, e.g., although self-condensation is occasionally a problem even here). Additives play an important role in the LDA mediated enolization of esters¹¹⁸⁰. Subsequent reaction of a ketone provides a simple rapid alternative to the *Reformatsky Reaction* (**16-28**) as a means of preparing β -hydroxy *tert*-butyl esters. It is also possible for the α carbon of an aldehyde or ketone to add to the carbonyl carbon of a carboxylic ester, but this is a different reaction (**16-86**) involving nucleophilic substitution and not addition to a $\text{C}=\text{O}$ bond. It can, however, be a side reaction if the aldehyde or ketone has an α hydrogen.

Transition metal mediated condensation of esters with aldehydes is known. The reaction of a thioester and an aryl aldehyde with $\text{TiCl}_4\text{--NBU}_3$, for example, gave a β -hydroxy thioester with good syn selectivity.¹¹⁸¹ Selenoamides $[\text{RCH}_2\text{C}(=\text{Se})\text{NR}'_2]$ react with LDA and then an aldehyde to give β -hydroxy selenoamides.¹¹⁸² The reaction of an α,β -unsaturated ester and benzaldehyde with a chiral Rh catalyst gave a β -hydroxy ester with good diastereoselectivity and good enantioselectivity.¹¹⁸³

Besides ordinary esters (containing an α hydrogen), the reaction can also be carried out with lactones and, as in Reaction **16-34**, with the γ position of α,β -unsaturated esters (vinyloly; Sec. 6.B). The enolate anion of an amide can be condensed with an aldehyde.¹¹⁸⁴ Thioesters undergo aldol-type condensations.¹¹⁸⁵

For most esters, a much stronger base is needed than for aldol reactions; $(i\text{Pr})_2\text{NLi}$ (LDA, Sec. 8.F, category 7), Ph_3CNa and LiNH_2 are among those employed. However, esters of malonic and succinic acid react more easily, and such strong bases are not needed. For example, diethyl succinate and its derivatives condense with aldehydes and ketones in the presence of bases (e.g., NaOEt , NaH , or KOCMe_3). This reaction is called the *Stobbe condensation*.¹¹⁸⁶ One of the ester groups (sometimes both) is hydrolyzed in the course of the reaction. The following mechanism accounts for (1) the fact the succinic esters react so much better than others; (2) one ester group is always cleaved; and (3) the alcohol is not the product but the alkene. In addition, intermediate lactones (**42**) have been isolated from the mixture.¹¹⁸⁷ The *Stobbe condensation* has been extended to di-*tert*-butyl esters of glutaric acid.¹¹⁸⁸ The boron-mediated reaction is known.¹¹⁸⁹

¹¹⁷⁷ Because it was discovered by Claisen, L. *Ber.* **1890**, 23, 977.

¹¹⁷⁸ Huerta, F.F.; Bäckvall, J.-E. *Org. Lett.* **2001**, 3, 1209.

¹¹⁷⁹ Rathke, M.W.; Sullivan, D.F. *J. Am. Chem. Soc.* **1973**, 95, 3050.

¹¹⁸⁰ Ramirez, A.; Sun, X.; Collum, D.B. *J. Am. Chem. Soc.* **2006**, 128, 10326.

¹¹⁸¹ Tanabe, Y.; Matsumoto, N.; Funakoshi, S.; Manta, N. *Synlett* **2001**, 1959.

¹¹⁸² Murai, T.; Suzuki, A.; Kato, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2711.

¹¹⁸³ Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, 127, 6972.

¹¹⁸⁴ See Shang, X.; Liu, H.-J. *Synth. Commun.* **1994**, 24, 2485.

¹¹⁸⁵ Yost, J.M.; Zhou, G.; Coltart, D.M. *Org. Lett.* **2006**, 8, 1503.

¹¹⁸⁶ See Johnson, W.S.; Daub, G.H. *Org. React.* **1951**, 6, 1.

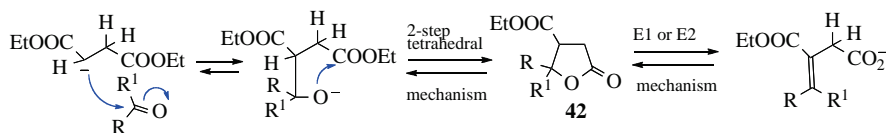
¹¹⁸⁷ Robinson, R.; Seijo, E. *J. Chem. Soc.* **1941**, 582.

¹¹⁸⁸ Puterbaugh, W.H. *J. Org. Chem.* **1962**, 27, 4010. See also, El-Newaihy, M.F.; Salem, M.R.; Enayat, E.I.; El-Bassiouny, F.A. *J. Prakt. Chem.* **1982**, 324, 379.

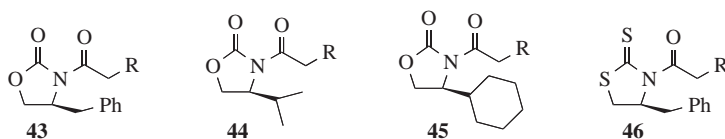
¹¹⁸⁹ See Abiko, A. *Acc. Chem. Res.* **2004**, 37, 387.

The intramolecular reaction of an aldehyde–carboxylic acid in the presence of triethylamine and a pyridinium salt led to the ring-forming condensation reaction, followed by formation of a β -lactone.¹¹⁹⁰

Amides participate in this condensation reaction, reacting with aldehydes in the presence of a Ba catalyst to give a β -hydroxy amide derivative.¹¹⁹¹ The reaction of an amide with LDA in the presence of an acyl silane, followed by reaction with an alkyl halide, leads to the β -hydroxy amide with the additional alkyl group at the β -carbon.¹¹⁹²



Chiral additives (e.g., diazaborolidines) can be added to an ester, and subsequent treatment with a base, and then an aldehyde leads to a chiral β -hydroxy ester.¹¹⁹³ A variety of chiral amide or oxazolidinone derivatives have been used to form amide linkages to carboxylic acid derivatives. These chiral auxiliaries lead to chirality transfer from the enolate anion of such derivatives, in both alkylation reactions and acyl substitution reactions with aldehydes and ketones. The so-called *Evans auxiliaries* (**43–45**) are commonly used and give good enantioselectivity.¹¹⁹⁴ A variation is the magnesium halide-catalyzed anti-aldol reaction of chiral *N*-acylthiazolidinethiones (see **46**).¹¹⁹⁵ The use of chiral *N*-acyloxazolidinethiones with TiCl_4 and sparteine also gave good selectivity in the acyl addition.¹¹⁹⁶ Chiral diazaboron derivatives have also been used to facilitate the condensation of a α -phenylthio ester with an aldehyde.¹¹⁹⁷



The condensation of an ester enolate and a ketone¹¹⁹⁸ can be used as part of a *Robinson annulation*-like sequence (see Reaction **16-34**).

OS I, 252; **III**, 132; **V**, 80, 564; **70**, 256; **X**, 437; **81**, 157. Also see, OS **IV**, 278, 478; **V**, 251.

¹¹⁹⁰ Oh, S.H.; Cortez, G.S.; Romo, D. *J. Org. Chem.* **2005**, 70, 2835.

¹¹⁹¹ Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, 128, 8704.

¹¹⁹² Lettan, II, R.B.; Reynolds, T.E.; Galliford, C.V.; Scheidt, K.A. *J. Am. Chem. Soc.* **2006**, 128, 15566.

¹¹⁹³ Corey, E.J.; Choi, S. *Tetrahedron Lett.* **2000**, 41, 2769.

¹¹⁹⁴ See Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* **1984**, 25, 4071.

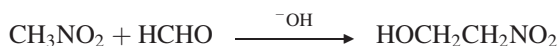
¹¹⁹⁵ Evans, D.A.; Downey, C.W.; Shaw, J.T.; Tedrow, J.S. *Org. Lett.* **2002**, 4, 1127.

¹¹⁹⁶ Crimmins, M.T.; McDougall, P.J. *Org. Lett.* **2003**, 5, 591.

¹¹⁹⁷ Corey, E.J.; Choi, S. *Tetrahedron Lett.* **2000**, 41, 2769.

¹¹⁹⁸ Posner, G.H.; Lu, S.; Asirvatham, E.; Silversmith, E.F.; Shulman, E.M. *J. Am. Chem. Soc.* **1986**, 108, 511;

Posner, G.H.; Webb, K.S.; Asirvatham, E.; Jew, S.; Degl'Innocenti, A. *J. Am. Chem. Soc.* **1988**, 110, 4754.

16-37 The Henry Reaction¹¹⁹⁹

The classical condensation of an aliphatic nitro compound with an aldehyde or ketone is usually called the *Henry reaction*¹²⁰⁰ or the *Kamlet reaction*, and is essentially a nitro aldol reaction. A variety of conditions have been reported, including the use of a recoverable polymer catalyst,¹²⁰¹ a silica catalyst,¹²⁰² a tetraalkylammonium hydroxide,¹²⁰³ proazaphosphatranes,¹²⁰⁴ and it has been done in an aqueous media¹²⁰⁵ or an ionic liquid.¹²⁰⁶ A solvent-free *Henry reaction* was reported in which a nitroalkane and an aldehyde were reacted on KOH powder.¹²⁰⁷ A solvent-free microwave assisted reaction was reported.¹²⁰⁸ Potassium phosphate has been used with nitromethane and aryl aldehydes.¹²⁰⁹ The *Henry reaction* has been done using ZnEt₂ and 20% ethanolamine.¹²¹⁰ A gel-entrapped base has been used to catalyze this reaction.¹²¹¹ Biocatalysts have been used.¹²¹²

Catalytic enantioselective *Henry reactions* are known,¹²¹³ including the use of a chiral Cu,¹²¹⁴ Zn,¹²¹⁵ Nd,¹²¹⁶ or Ti catalyst.¹²¹⁷ The *Henry reaction* of nitromethane and a chiral aldehyde under high pressure gives the β-nitro alcohol with excellent

¹¹⁹⁹ Baer, H.H.; Urbas, L. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Wiley, NY, **1970**, pp. 76–117. See also, Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* **1983**, 1014; Matsumoto, K. *Angew. Chem. Int. Ed.* **1984**, 23, 617; Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* **1985**, 107, 3601. For reviews of the nitroalkenes that are the products of this reaction, see Barrett, A.G.M.; Graboski, G.G. *Chem. Rev.* **1986**, 86, 751; Kabalka, G.W.; Varma, R.S. *Org. Prep. Proced. Int.* **1987**, 19, 283.

¹²⁰⁰ Henry, L. *Compt. Rend.* **1895**, 120, 1265; Kamlet, J. *U.S. Patent* 2,151,171 **1939** [*Chem. Abstr.*, 33: 5003⁹ **1939**]; Hass, H.B.; Riley, E.F. *Chem. Rev.* **1943**, 32, 373 (see p. 406); Lichtenthaler, F.W. *Angew. Chem. Int. Ed.* **1964**, 3, 211. For a review, see Luzzio, F.A. *Tetrahedron* **2001**, 57, 915.

¹²⁰¹ Yan, S.; Gao, Y.; Xing, R.; Shen, Y.; Liu, Y.; Wu, P.; Wu, H. *Tetrahedron* **2008**, 64, 6294.

¹²⁰² Demicheli, G.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G.; Bigi, F. *Tetrahedron Lett.* **2001**, 42, 2401; Hagiwara, H.; Sekifuji, M.; Tsubokawa, N.; Hoshi, T.; Suzuki, T. *Chem. Lett.* **2009**, 38, 790.

¹²⁰³ Bulbule, V.J.; Jnaneshwara, G.K.; Deshmukh, R.R.; Borate, H.B.; Deshpande, V.H. *Synth. Commun.* **2001**, 31, 3623.

¹²⁰⁴ Kisanga, P.B.; Verkade, J.G. *J. Org. Chem.* **1999**, 64, 4298.

¹²⁰⁵ Phukan, M.; Borah, K.J.; Borah, R. *Synth. Commun.* **2008**, 38, 3068.

¹²⁰⁶ Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G. *Tetrahedron Lett.* **2004**, 45, 2699.

¹²⁰⁷ Ballini, R.; Bosica, G.; Parrini, M. *Chem. Lett.* **1999**, 1105.

¹²⁰⁸ Gan, C.; Chen, X.; Lai, G.; Wang, Z. *Synlett* **2006**, 387.

¹²⁰⁹ Desai, U.V.; Pore, D.M.; Mane, R.B.; Solabannavar, S.B.; Wadgaonkar, P.P. *Synth. Commun.* **2004**, 34, 19.

¹²¹⁰ Klein, G.; Pandiaraju, S.; Reiser, O. *Tetrahedron Lett.* **2002**, 43, 7503.

¹²¹¹ Bandgar, B.P.; Uppalla, L.S. *Synth. Commun.* **2000**, 30, 2071.

¹²¹² Purkarthofer, T.; Gruber, K.; Gruber-Khadjawi, M.; Waich, K.; Skranc, W.; Mink, D.; Griengl, H. *Angew. Chem. Int. Ed.* **2006**, 45, 3454.

¹²¹³ Christensen, C.; Juhl, K.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* **2002**, 67, 4875. For reviews, see Boruwa, J.; Gogoi, N.; Saikia, P.P.; Barua, N.C. *Tetrahedron Asymmetry* **2006**, 17, 3315; Palomo, C.; Oiárbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561.

¹²¹⁴ Jammi, S.; Saha, P.; Sanyashi, S.; Sakthivel, S.; Punniyamurthy, T. *Tetrahedron* **2008**, 64, 11724.

¹²¹⁵ Bulut, A.; Aslan, A.; Dogan, Ö. *J. Org. Chem.* **2008**, 73, 7373.

¹²¹⁶ Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, 49, 272.

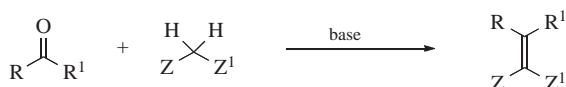
¹²¹⁷ Tur, F.; Saá, J.M. *Org. Lett.* **2007**, 9, 5079.

enantioselectivity.¹²¹⁸ Enantioselective nitro–aldol reactions are catalyzed by organo-catalysts (e.g., Cinchona alkaloids¹²¹⁹ or other organocatalysts).¹²²⁰

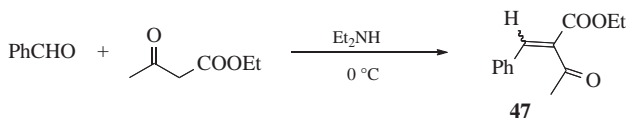
A variation of this reaction converts nitro compounds to nitronates [$\text{RCH}=\text{N}^+(\text{OTMS})-\text{O}^-$], which subsequently react with aldehydes in the presence of a Cu catalyst to give the β -nitro alcohol.¹²²¹ *Aza-Henry reactions* condense nitroalkanes with imine derivatives, and the resulting amino nitro compounds are formed with good enantioselectivity in the presence of organocatalysts¹²²² or Brønsted acid catalysts.¹²²³ *Aza-Henry products* are also formed by the reaction of amines with activated unsaturated compounds.¹²²⁴

16-38 The Knoevenagel Reaction

Bis(ethoxycarbonyl)methylene-de-oxo-bisubstitution, and so on



The condensation of aldehydes or ketones, usually not containing an α hydrogen, with compounds of the form $\text{Z}-\text{CH}_2-\text{Z}'$ or $\text{Z}-\text{CHR}-\text{Z}'$ is called the *Knoevenagel reaction*.¹²²⁵ Both Z and Z' may be CHO, COR, CO₂H, CO₂R, CN, NO₂, SOR, SO₂R, SO₂OR, or similar groups. The presence of two electron-withdrawing groups makes the α -proton much more acidic (Table 8.1 in Sec. 8.A.i), and such compounds have a significantly higher enol content.¹²²⁶ When Z = CO₂H, decarboxylation of the product often takes place *in situ*.¹²²⁷ As shown in the example, the reaction of β -keto esters and aldehydes to give **47** is promoted by diethylamine at 0 °C. Nitroalkanes,¹¹⁹⁹ as well as β -keto sulfoxides,¹²²⁸ undergo the reaction.



As with Reaction **16-34**, these reactions have sometimes been mediated by an acid catalyst.¹²²⁹ Ionic liquid solvents have been used,¹²³⁰ and heating on quaternary

¹²¹⁸ Misumi, Y.; Matsumoto, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 1031.

¹²¹⁹ Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732.

¹²²⁰ Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392; Mandal, T.; Samanta, S.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 943; Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595; Liu, S.; Wolf, C. *Org. Lett.* **2008**, *10*, 1831; Marcelli, T.; van der Haas, R.N.S.; van Maarseveen, J.H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 929; Toussaint, A.; Pfaltz, A. *Eur. J. Org. Chem.* **2008**, 4591.

¹²²¹ Risgaard, T.; Gothelf, K.V.; Jørgensen, K.A. *Org. Biomol. Chem.* **2003**, *1*, 153.

¹²²² Robak, M.T.; Trincado, M.; Ellman, J.A. *J. Am. Chem. Soc.* **2007**, *129*, 15110; Singh, A.; Johnston, J.N. *J. Am. Chem. Soc.* **2008**, *130*, 5866.

¹²²³ Rueping, M.; Antonchick, A.P. *Org. Lett.* **2008**, *10*, 1731.

¹²²⁴ Ziyaei-Halimehjani, A.; Saidi, M.R. *Tetrahedron Lett.* **2008**, *49*, 1244.

¹²²⁵ For reviews, see Jones, G. *Org. React.* **1967**, *15*, 204; Wilk, B.K. *Tetrahedron* **1997**, *53*, 7097.

¹²²⁶ Rochlin, E.; Rappoport, Z. *J. Org. Chem.* **2003**, *68*, 1715.

¹²²⁷ See Tanaka, M.; Oota, O.; Hiramatsu, H.; Fujiwara, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2473.

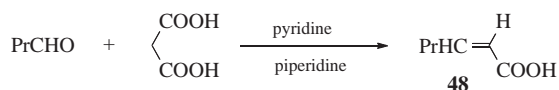
¹²²⁸ Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* **1974**, 107. See also, Huckin, S.N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 2157.

¹²²⁹ See Bartoli, G.; Beleggia, R.; Giuli, S.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Paoletti, M. *Tetrahedron Lett.* **2006**, *47*, 6501.

¹²³⁰ Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* **2002**, *43*, 1127. See Su, C.; Chen, Z.-C.; Zheng, Q.G. *Synthesis* **2003**, 555.

ammonium salts without solvent leads to a *Knoevenagel reaction*.¹²³¹ Other solvent-free reactions are known.¹²³² Ultrasound has been used to promote the reaction,¹²³³ and it has also been done using microwave irradiation¹²³⁴ or on silica,¹²³⁵ with microwave irradiation. Another solid-state variation is done on moist LiBr,¹²³⁶ heating with sodium carbonate and molecular sieves 4 Å promotes the reaction,¹²³⁷ as do zeolites.¹²³⁸ High-pressure conditions have been used.¹²³⁹ Transition metal compounds of Pd,¹²⁴⁰ Sm¹²⁴¹ Ce,¹²⁴² Ti,¹²⁴³ or Bi¹²⁴⁴ have been used to promote the *Knoevenagel reaction*.

With most of these reagents the alcohol is not isolated (only the alkene) if the alcohol has a hydrogen in the proper position,¹²⁴⁵ but with a careful workup the alcohol may be the major product. With suitable reactants, the *Knoevenagel reaction*, like the aldol condensation (**16-34**), has been carried out diastereoselectively¹²⁴⁶ and enantioselectively.¹²⁴⁷ When the reactant is of the form ZCH₂Z', aldehydes react much better than ketones and few successful reactions with ketones have been reported. However, it is possible to get good yields of the alkene from the condensation of diethyl malonate [CH₂(CO₂Et)₂] with ketones, as well as with aldehydes, if the reaction is run with TiCl₄ and pyridine in THF.¹²⁴⁸ In reactions with ZCH₂Z', the catalyst is most often a secondary amine (piperidine is the most common, but see formation of **47**), but many other catalysts have been used. Alkoxides are also common catalysts. When the catalyst is pyridine (to which piperidine may or may not be added) the reaction is known as the *Doebner modification* of the *Knoevenagel reaction* and the product is usually the conjugated acid (**48**). Microwave-induced *Doebner condensation* reactions are known.¹²⁴⁹



¹²³¹ Bose, D.S.; Narsaiah, A.V. *J. Chem. Res. (S)* **2001**, 36.

¹²³² See Pillai, M.K.; Singh, S.; Jonnalagadda, S.B. *Synth. Commun.* **2010**, 40, 3710.

¹²³³ Li, J.-T.; Zang, H.-J.; Feng, Y.-Y.; Li, L.-J.; Li, T.-S. *Synth. Commun.* **2001**, 31, 653.

¹²³⁴ Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Visali, B.; Narsaiah, A.V.; Nagaiah, K. *Eur. J. Org. Chem.* **2004**, 546.

¹²³⁵ Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Srinivas, D.; Yadav, J.S. *Org. Prep. Proceed. Int.* **2000**, 32, 81;

Peng, Y.; Song, G.; Qian, X. *J. Chem. Res. (S)* **2001**, 188.

¹²³⁶ Prajapati, D.; Lakhok, K.C.; Sandhu, J.S.; Ghosh, A.C. *J. Chem. Soc. Perkin Trans. 1* **1996**, 959.

¹²³⁷ Siebenhaar, B.; Casagrande, B.; Studer, M.; Blaser, H.-U. *Can. J. Chem.* **2001**, 79, 566.

¹²³⁸ Reddy, T.I.; Varma, R.S. *Tetrahedron Lett.* **1997**, 38, 1721.

¹²³⁹ Jenner, G. *Tetrahedron Lett.* **2001**, 42, 243.

¹²⁴⁰ You, J.; Verkade, J.G. *J. Org. Chem.* **2003**, 68, 8003.

¹²⁴¹ Chandrasekhar, S.; Yu, J.; Falck, J.R.; Mioskowski, C. *Tetrahedron Lett.* **1994**, 35, 5441.

¹²⁴² Bartoli, G.; Beleggia, R.; Giuli, S.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Paoletti, M. *Tetrahedron Lett.* **2006**, 47, 6501.

¹²⁴³ Yamashita, K.; Tanaka, T.; Haya, M. *Tetrahedron* **2005**, 61, 7981.

¹²⁴⁴ A solvent free reaction. See Prajapati, D.; Sandhu, J.S. *Chem. Lett.* **1992**, 1945.

¹²⁴⁵ For lists of reagents (with references) see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 317–325, 341–350. For those that give the alcohol product, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1178–1179, 1540–1541, 1717–1724, 1727, 1732–1736, 1778–1780, 1801–1805.

¹²⁴⁶ See Barrett, A.G.M.; Robyr, C.; Spilling, C.D. *J. Org. Chem.* **1989**, 54, 1233; Pyne, S.G.; Boche, G. *J. Org. Chem.* **1989**, 54, 2663.

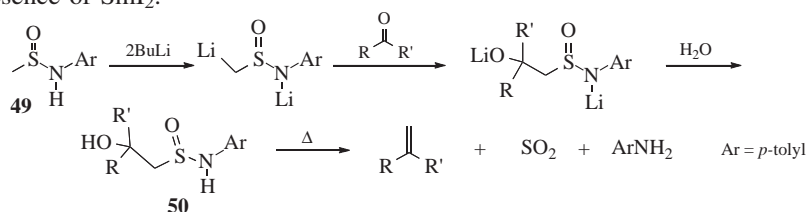
¹²⁴⁷ See Togni, A.; Pastor, S.D. *J. Org. Chem.* **1990**, 55, 1649; Sakuraba, H.; Ushiki, S. *Tetrahedron Lett.* **1990**, 31, 5349; Niwa, S.; Soai, K. *J. Chem. Soc. Perkin Trans. 1* **1990**, 937.

¹²⁴⁸ Lehnert, W. *Tetrahedron* **1973**, 29, 635; *Synthesis* **1974**, 667 and references cited therein.

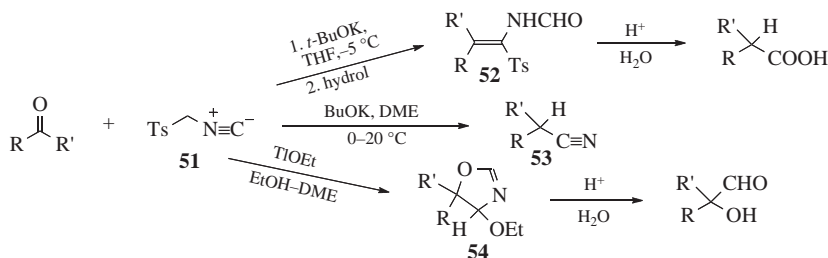
¹²⁴⁹ Pellón, R.F.; Mamposo, T.; González, E.; Calderón, O. *Synth. Commun.* **2000**, 30, 3769.

A number of special applications of the *Knoevenagel reaction* follow:

1. The dilithio derivative of *N*-methanesulfinyl-*p*-toluidine¹²⁵⁰ (**49**) adds to aldehydes and ketones to give, after hydrolysis, the hydroxysulfinamides (**50**). Subsequent heating leads to a stereospecific syn eliminations to give an alkene.¹²⁵¹ The reaction is thus a method for achieving the conversion $RR'CO \rightarrow RR'C=CH_2$ and represents an alternative to the *Wittig reaction*.¹²⁵² Note that sulfones with an amide group at the α -position, $[ArSO_2CH(R)N(R)C=O]$ react with ketones via acyl addition in the presence of SmI_2 .¹²⁵³



2. The reaction of ketones with tosylmethylisocyanide (**51**) gives different products,¹²⁵⁴ depending on the reaction conditions. When the reaction is run with potassium *tert*-butoxide in THF at -5°C , one obtains (after hydrolysis) the normal *Knoevenagel* product (**52**), except that the isocyano group has been hydrated (Reaction 16-97).¹²⁵⁵ With the same base but with 1,2-dimethoxyethane (DME) as solvent the product is the nitrile (**53**).¹²⁵⁶ When the ketone is treated with **51** and thallium(I) ethoxide in a 4: 1 mixture of absolute ethanol and DME at room temperature, the product is a 4-ethoxy-2-oxazoline (**54**).¹²⁵⁷ Since **53** can be hydrolyzed to a carboxylic acid¹¹⁹⁸ and **54** to an α -hydroxy aldehyde,¹²⁵⁷ this versatile reaction provides a means for achieving the conversion of $RCOR'$ to $RCHR'CO_2H$, $RCHR'CN$, or $RCR'(OH)CHO$. The conversions to $RCHR'COOH$ and to $RCHR'CN$ ¹²⁵⁸ have also been carried out with certain aldehydes ($R' = H$).



¹²⁵⁰ For a method of preparing **49**, see Bowlus, S.B.; Katzenellenbogen, J.A. *Synth. Commun.* **1974**, *4*, 137.

¹²⁵¹ Corey, E.J.; Durst, T. *J. Am. Chem. Soc.* **1968**, *90*, 5548, 5553.

¹²⁵² See Yamamoto, K.; Tomo, Y.; Suzuki, S. *Tetrahedron Lett.* **1980**, *21*, 2861; Martin, S.F.; Phillips, G.W.; Puckette, T.A.; Colapret, J.A. *J. Am. Chem. Soc.* **1980**, *102*, 5866; Arenz, T.; Vostell, M.; Frauenrath, H. *Synlett* **1991**, 23.

¹²⁵³ Yoda, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 9225.

¹²⁵⁴ See Schöllkopf, U. *Pure Appl. Chem.* **1979**, *51*, 1347; *Angew. Chem. Int. Ed.* **1977**, *16*, 339; Hoppe, D. *Angew. Chem. Int. Ed.* **1974**, *13*, 789.

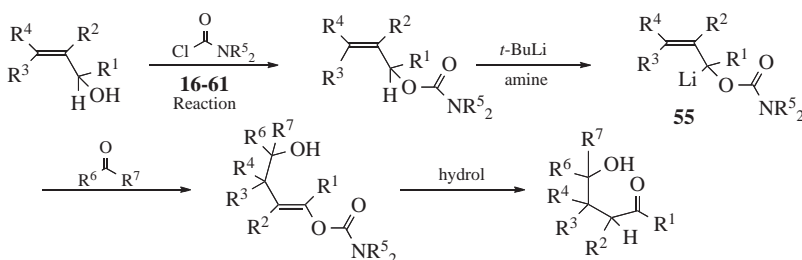
¹²⁵⁵ Schöllkopf, U.; Schröder, U.; Blume, E. *Liebigs Ann. Chem.* **1972**, 766, 130; Schöllkopf, U.; Schröder, U. *Angew. Chem. Int. Ed.* **1972**, *11*, 311.

¹²⁵⁶ Oldenzil, O.H.; van Leusen, D.; van Leusen, A.M. *J. Org. Chem.* **1977**, *42*, 3114.

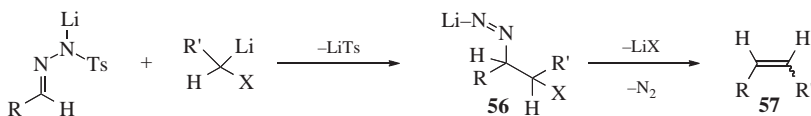
¹²⁵⁷ Oldenzil, O.H.; van Leusen, A.M. *Tetrahedron Lett.* **1974**, 163, 167. See, Moskal, J.; van Leusen, A.M. *Tetrahedron Lett.* **1984**, *25*, 2585; van Leusen, A.M.; Oosterwijk, R.; van Echten, E.; van Leusen, D. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 50.

¹²⁵⁸ van Leusen, A.M.; Oomkes, P.G. *Synth. Commun.* **1980**, *10*, 399.

3. Aldehydes and ketones (RCOR') react with α -methoxyvinyl lithium $[\text{CH}_2=\text{C}(\text{Li})\text{OMe}]$ to give hydroxy enol ethers $[\text{RR}'\text{C}(\text{OH})\text{C}(\text{OMe})=\text{CH}_2]$, which are easily hydrolyzed to acyloins $[\text{RR}'\text{C}(\text{OH})\text{COMe}]$.¹²⁵⁹ In this reaction, the $\text{CH}_2=\text{C}(\text{Li})\text{OMe}$ is a synthon for the unavailable $\text{H}_3\text{C}-\text{C}=\text{O}$,¹²⁶⁰ and is termed an *acyl anion equivalent*. The reagent also reacts with esters (RCOOR') to give $\text{RC}(\text{OH})(\text{COMe}=\text{CH}_2)_2$. A synthon for the $\text{Ph}-\text{C}=\text{O}$ ion is $\text{PhC}(\text{CN})\text{OSiMe}_3$, which adds to aldehydes and ketones (RCOR') to give, after hydrolysis, the α -hydroxy ketones $[\text{RR}'\text{C}(\text{OH})\text{COPh}]$.¹²⁶¹
4. Lithiated allylic carbamates (**55**) (prepared as shown) react with aldehydes or ketones (R^6COR^7), in a reaction accompanied by an allylic rearrangement, to give (after hydrolysis) γ -hydroxy aldehydes or ketones.¹²⁶² The reaction is called *the homoaldol reaction*, since the product is a homologue of the product of Reaction 16-34. The reaction has been performed enantioselectively.¹²⁶³



5. The lithium salt of an active hydrogen compound adds to the lithium salt of the tosylhydrazone of an aldehyde to give product **56**. If $\text{X} = \text{CN}$, SPh , or SO_2R , **56** spontaneously loses N_2 and LiX to give the alkene **57**. The entire process is done in one reaction vessel: The active hydrogen compound is mixed with the tosylhydrazone and the mixture is treated with $(i\text{Pr})_2\text{NLi}$ to form both salts at once.¹²⁶⁴ This process is another alternative to the *Wittig reaction* for forming double bonds.



OS **I**, 181, 290, 413; **II**, 202; **III**, 39, 165, 317, 320, 377, 385, 399, 416, 425, 456, 479, 513, 586, 591, 597, 715, 783; **IV**, 93, 210, 221, 234, 293, 327, 387, 392, 408, 441, 463, 471, 549, 573, 730, 731, 777; **V**, 130, 381, 572, 585, 627, 833, 1088, 1128; **VI**, 41, 95, 442, 598, 683; **VII**, 50, 108, 142, 276, 381, 386, 456; **VIII**, 258, 265, 309, 353, 391, 420; **X**, 271. Also see, OS **III**, 395; **V**, 450.

¹²⁵⁹ Baldwin, J.E.; Höfle, G.A.; Lever, Jr., O.W. *J. Am. Chem. Soc.* **1974**, 96, 7125. For a similar reaction, see Tanaka, K.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1978**, 4809.

¹²⁶⁰ Also see Reetz, M.T.; Heimbach, H.; Schwellnus, K. *Tetrahedron Lett.* **1984**, 25, 511.

¹²⁶¹ Hünig, S.; Wehner, G. *Synthesis* **1975**, 391.

¹²⁶² For a review, see Hoppe, D. *Angew. Chem. Int. Ed.* **1984**, 23, 932.

¹²⁶³ Krämer, T.; Hoppe, D. *Tetrahedron Lett.* **1987**, 28, 5149.

¹²⁶⁴ Vedejs, E.; Dolphin, J.M.; Stolle, W.T. *J. Am. Chem. Soc.* **1979**, 101, 249.

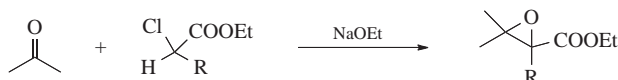
16-39 The Perkin Reaction

 α -Carboxyalkylidene-de-oxo-bisubstitution

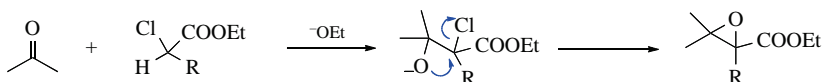
The condensation of aromatic aldehydes with anhydrides is called the *Perkin reaction*.¹²⁶⁵ When the anhydride has two α hydrogen atoms (as shown), dehydration almost always occurs; the β -hydroxy acid salt is rarely isolated. In some cases, anhydrides of the form $(\text{R}_2\text{CHCO})_2\text{O}$ have been used, and then the hydroxy compound is the product since dehydration cannot take place. The base in the *Perkin reaction* is nearly always the salt of the acid corresponding to the anhydride. Although the Na and K salts have been most frequently used, higher yields and shorter reaction times have been reported for the Cs salt.¹²⁶⁶ Besides aromatic aldehydes, their vinylogs ($\text{ArCH}=\text{CHCHO}$) also give the reaction (see Sec. 6.B). Otherwise, the reaction is not suitable for aliphatic aldehydes.¹²⁶⁷

OS I, 398; II, 61, 229; III, 426.

16-40 Darzens Glycidic Ester Condensation

(2+1) OC,CC-cyclo- α -Alkoxycarbonylmethylene-addition

Aldehydes and ketones condense with α -halo esters in the presence of bases to give α,β -epoxy esters, called *glycidic esters*. This is called the *Darzens condensation*.¹²⁶⁸ The reaction consists of an initial *Knoevenagel-type* Reaction (16-38), followed by an internal S_N^2 Reaction (10-9)¹²⁶⁹:



Although the intermediate halo alkoxide is generally not isolated,¹²⁷⁰ it has been done, not only with α -fluoro esters (since fluorine is such a poor leaving group in nucleophilic substitutions), but also with α -chloro esters.¹²⁷¹ This is only one of several types of evidence that rule out a carbene intermediate.¹²⁷² Sodium ethoxide is often used as the base, but other bases, including sodium amide, are sometimes used. Aromatic aldehydes and ketones give good yields. The reaction can be made to give good yields ($\sim 80\%$) with simple aliphatic aldehydes, as well as with aromatic aldehydes and ketones, by treatment of the α -halo ester with the base lithium bis(trimethylsilyl)amide $[\text{LiN}(\text{SiMe}_3)_2]$ in THF at

¹²⁶⁵ See Johnson, J.R. *Org. React.* **1942**, 1, 210.

¹²⁶⁶ Koeppe, E.; Vögtle, F. *Synthesis* **1987**, 177.

¹²⁶⁷ Crawford, M.; Little, W.T. *J. Chem. Soc.* **1959**, 722.

¹²⁶⁸ See Berti, G. *Top. Stereochem.* **1973**, 7, 93, pp. 210–218. Also see, Bakó, P.; Szöllösy, Á; Bombicz, P.; Töke, L. *Synlett* **1997**, 291.

¹²⁶⁹ See Bansal, R.K.; Sethi, K. *Bull. Chem. Soc. Jpn.* **1980**, 53, 1197.

¹²⁷⁰ See Yliniemelä, A.; Brunow, G.; Flügge, J.; Teleman, O. *J. Org. Chem.* **1996**, 61, 6723.

¹²⁷¹ Ballester, M.; Pérez-Blanco, D. *J. Org. Chem.* **1958**, 23, 652; Elkik, E.; Francesch, C. *Bull. Soc. Chim. Fr.* **1973**, 1277, 1281.

¹²⁷² See also, Zimmerman, H.E.; Ahramjian, L. *J. Am. Chem. Soc.* **1960**, 82, 5459.

–78 °C (to form the conjugate base of the ester) and addition of the aldehyde or ketone to this solution.¹²⁷³ If a preformed dianion of an α -halo carboxylic acid ($\text{Cl}^-\text{CRCO}_2^-$) is used instead, α,β -epoxy acids are produced directly.¹²⁷⁴ The *Darzens reaction* has also been carried out on α -halo ketones, α -halo nitriles,¹²⁷⁵ α -halo sulfoxides¹²⁷⁶ and sulfones,¹²⁷⁷ α -halo N,N-disubstituted amides,¹²⁷⁸ α -halo ketimines,¹²⁷⁹ and even on allylic¹²⁸⁰ and benzylic halides. Phase-transfer catalysis has been used.¹²⁸¹ Note that the reaction of a β -bromo- α -oxo ester and a *Grignard reagent* leads to the glycidic ester.¹²⁸² Acid-catalyzed *Darzens reactions* have also been reported.¹²⁸³ (see also, Reaction 16-46).

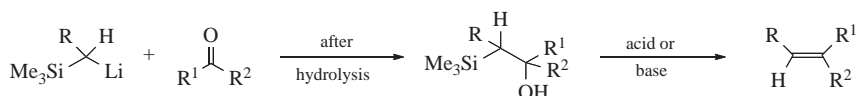
Diastereoselective *Darzens condensations* are possible.¹²⁸⁴ The *Darzens reaction* has been performed with good enantioselectivity,¹²⁸⁵ and chiral additives have proven to be effective.¹²⁸⁶ Chiral phase-transfer agents have been used to give epoxy ketones with modest enantioselectivity.¹²⁸⁷

Glycidic esters can easily be converted to aldehydes (Reaction 12-40). The reaction has been extended to the formation of analogous aziridines by treatment of an imine with an α -halo ester or an α -halo N,N-disubstituted amide and *t*-BuOK in the solvent 1,2-dimethoxyethane.¹²⁸⁸ However, yields were not high.

OS III, 727; IV, 459, 649.

16-41 The Peterson Alkenylation Reaction

Alkylidene-de-oxo-bisubstitution



In the *Peterson alkenylation reaction*¹²⁸⁹, the lithio (or sometimes magnesio) derivative of a trialkylsilane adds to an aldehyde or ketone to give a β -hydroxysilane, which spontaneously eliminates water, or can be made to do so by treatment with acid or base, to produce an alkene. This reaction is still another alternative to the *Wittig reaction* (16-44), and is sometimes

¹²⁷³ Borch, R.F. *Tetrahedron Lett.* **1972**, 3761.

¹²⁷⁴ Johnson, C.R.; Bade, T.R. *J. Org. Chem.* **1982**, 47, 1205.

¹²⁷⁵ See White, D.R.; Wu, D.K. *J. Chem. Soc., Chem. Commun.* **1974**, 988.

¹²⁷⁶ Satoh, T.; Sugimoto, A.; Itoh, M.; Yamakawa, K. *Tetrahedron Lett.* **1989**, 30, 1083.

¹²⁷⁷ Arai, S.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1998**, 39, 8299.

¹²⁷⁸ Tung, C.C.; Speziale, A.J.; Frazier, H.W. *J. Org. Chem.* **1963**, 28, 1514.

¹²⁷⁹ Mauzé, B. *J. Organomet. Chem.* **1979**, 170, 265.

¹²⁸⁰ Sulmon, P.; De Kimpe, N.; Schamp, N.; Declercq, J.; Tinant, B. *J. Org. Chem.* **1988**, 53, 4457.

¹²⁸¹ See Arai, S.; Suzuki, Y.; Tokumaru, K.; Shioiri, T. *Tetrahedron Lett.* **2002**, 43, 833. See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis* Academic Press, NY, **1978**, pp. 197–198.

¹²⁸² Jung, M.E.; Mengel, W.; Newton, T.W. *Synth. Commun.* **1999**, 29, 3659.

¹²⁸³ Sipos, G.; Schöbel, G.; Sirokmán, F. *J. Chem. Soc. Perkin Trans. 2* **1975**, 805.

¹²⁸⁴ Achard, T.J.R.; Belokon', Y.N.; Hunt, J.; North, M.; Pizzato, F. *Tetrahedron Lett.* **2007**, 48, 2961.

¹²⁸⁵ Achard, T.J.R.; Belokon', Y.N.; Ilyin, M.; Moskalenko, M.; North, M.; Pizzato, F. *Tetrahedron Lett.* **2007**, 48, 2965. For a review, see Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *Chem. Commun.* **1996**, 2411.

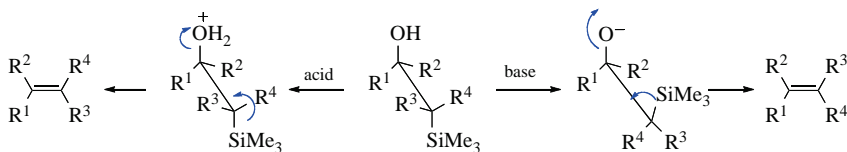
¹²⁸⁶ Aggarwal, V.K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* **2002**, 124, 9964.

¹²⁸⁷ Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, 55, 6375.

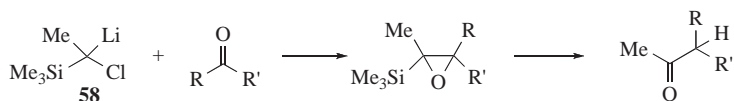
¹²⁸⁸ Deyrup, J.A. *J. Org. Chem.* **1969**, 34, 2724.

¹²⁸⁹ Peterson, D.J. *J. Org. Chem.* **1968**, 33, 780. See Ager, D.J. *Org. React.* **1990**, 38, 1; *Synthesis* **1984**, 384; Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, **1988**, pp. 63–75; Weber, W.P. *Silicon Reagents for Organic Synthesis*, Springer, NY, **1983**, pp. 58–78; Magnus, P. *Aldrichimica Acta* **1980**, 13, 43; Chan, T. *Acc. Chem. Res.* **1977**, 10, 442. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 337–341.

called the *silyl-Wittig reaction*.¹²⁹⁰ The R group can also be a COOR group, in which case the product is an α,β -unsaturated ester,¹²⁹¹ or an SO₂Ph group, in which case the product is a vinylic sulfone.¹²⁹² The stereochemistry of the product can often be controlled by whether an acid or a base is used to achieve elimination. The role of Si—O interactions has also been examined.¹²⁹³ Use of a base generally gives syn elimination (Ei mechanism, see Sec. 17.C.i), while an acid usually results in anti elimination (E2 mechanism, see Sec. 17.A.i).¹²⁹⁴ Samarium(II) iodide in HMPA has also been used for elimination of the hydroxy sulfone.¹²⁹⁵



When aldehydes or ketones are treated with reagents of the form **58**, the product is an epoxy silane (Reaction **16-46**), which can be hydrolyzed to a methyl ketone.¹²⁹⁶ For aldehydes, this is a method for converting RCHO to a methyl ketone (RCH₂COMe).



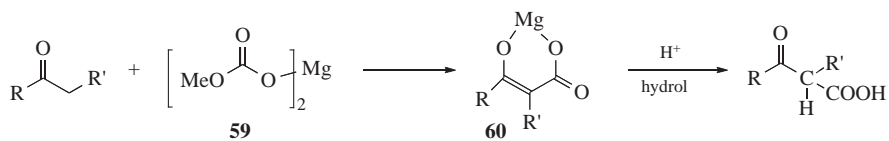
The reagents Me₃SiCHRM (M = Li or Mg) are often prepared from Me₃SiCHRCI¹²⁹⁷ (by Reaction **12-38** or **12-39**), but they have also been made by Reaction **12-22** and other procedures.¹²⁹⁸ Lithio alkenylsilanes have been used for this reaction.¹²⁹⁹

A new version of the reaction has been developed, reacting Me₃SiCH₂CO₂Et with an aldehyde and a catalytic amount of CsF in DMSO.¹³⁰⁰ A seleno-amide derivative has been used in a similar manner.¹³⁰¹

There are no references in *Organic Syntheses*, but see OS **VIII**, 602, for a related reaction.

16-42 The Addition of Active Hydrogen Compounds to CO₂ and CS₂

α -Acylalkyl-de-methoxy-substitution (Overall reaction)



¹²⁹⁰ See Hudrlik, P.F.; Agwaramgbo, E.L.O.; Hudrlik, A.M. *J. Org. Chem.* **1989**, *54*, 5613.

¹²⁹¹ See Streckowski, L.; Visnick, M.; Battiste, M.A. *Tetrahedron Lett.* **1984**, *25*, 5603.

¹²⁹² Craig, D.; Ley, S.V.; Simpkins, N.S.; Whitham, G.H.; Prior, M.J. *J. Chem. Soc. Perkin Trans. 1* **1985**, 1949.

¹²⁹³ Bassindale, A.R.; Ellis, R.J.; Taylor, P.G. *J. Chem. Res. (S)* **1996**, 34.

¹²⁹⁴ See Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, **1988**, pp. 65–69.

¹²⁹⁵ Markò, I.E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* **2001**, *57*, 2609.

¹²⁹⁶ Cooke, F.; Roy, G.; Magnus, P. *Organometallics* **1982**, *1*, 893.

¹²⁹⁷ For a review of these reagents, see Anderson, R. *Synthesis* **1985**, 717.

¹²⁹⁸ See Barrett, A.G.M.; Flygare, J.A. *J. Org. Chem.* **1991**, *56*, 638.

¹²⁹⁹ Tsubouchi, A.; Kira, T.; Takeda, T. *Synlett* **2006**, 2577.

¹³⁰⁰ Bellassoued, M.; Ozanne, N. *J. Org. Chem.* **1995**, *60*, 6582.

¹³⁰¹ Murai, T.; Fujishima, A.; Iwamoto, C.; Kato, S. *J. Org. Chem.* **2003**, *68*, 7979.

Ketones of the form RCOCH_3 and $\text{RCOCH}_2\text{R}'$ can be carboxylated indirectly by treatment with magnesium methyl carbonate (**59**).¹³⁰² Because formation of the chelate (**60**) provides the driving force of the reaction, carboxylation cannot be achieved at a disubstituted α position. The reaction has also been performed on CH_3NO_2 , on compounds of the form RCH_2NO_2 ¹³⁰³ and on certain lactones.¹³⁰⁴ Direct carboxylation has been reported in a number of instances. Ketones have been carboxylated in the α position to give β -keto acids.¹³⁰⁵ The base here was lithium 4-methyl-2,6-di-*tert*-butylphenoxide.

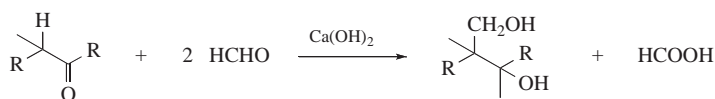
Ketones ($\text{RCOCH}_2\text{R}'$), as well as other active hydrogen compounds, undergo base-catalyzed addition to CS_2 ¹³⁰⁶ to give a dianion intermediate ($\text{RCOC}^-\text{R}'\text{CSS}^{2-}$), which can be dialkylated with a halide (R^2X) to produce α -dithiomethylene ketones $[\text{RCOCR}'=\text{C}(\text{SR}^2)_2]$.¹³⁰⁷ Compounds of the form $\text{ZCH}_2\text{Z}'$ also react with bases and CS_2 to give analogous dianions.¹³⁰⁸

Although reactions with $\text{N}=\text{O}$ derivatives do not formally fall into this category of reactions, it is somewhat related. Nitroso compounds react with activated nitriles in the presence of LiBr and microwave irradiation to give a cyano imine $[\text{ArN}=\text{C}(\text{CN})\text{Ar}]$.¹³⁰⁹ This transformation has been called the *Ehrlich–Sachs reaction*.¹³¹⁰

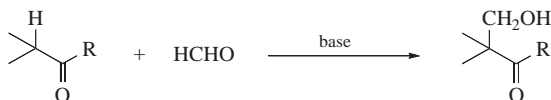
OS VII, 476. See also, OS VIII, 578.

16-43 Tollens' Reaction

O-Hydro-C (β -hydroxyalkyl)-addition



In the *Tollens' reaction*, an aldehyde or ketone containing an α hydrogen is treated with formaldehyde in the presence of Ca(OH)_2 or a similar base. The first step is a mixed-aldol reaction (**16-34**).



The reaction can be stopped at this point, but more often a second equivalent of formaldehyde is permitted to reduce the newly formed aldol to a 1,3-diol, in a *crossed-Cannizzaro Reaction* (**19-81**). If the aldehyde or ketone has several α hydrogen atoms, they can all be replaced. An

¹³⁰² Stiles, M. *J. Am. Chem. Soc.* **1959**, 81, 2598; *Ann. N.Y. Acad. Sci.* **1960**, 88, 332; Crombie, L.; Hemesley, P.; Pattenden, G. *Tetrahedron Lett.* **1968**, 3021.

¹³⁰³ Finkbeiner, H.L.; Stiles, M. *J. Am. Chem. Soc.* **1963**, 85, 616; Finkbeiner, H.L.; Wagner, G.W. *J. Org. Chem.* **1963**, 28, 215.

¹³⁰⁴ Martin, J.; Watts, P.C.; Johnson, F. *Chem. Commun.* **1970**, 27.

¹³⁰⁵ Tirpak, R.E.; Olsen, R.S.; Rathke, M.W. *J. Org. Chem.* **1985**, 50, 4877. For an enantioselective version, see Hogeveen, H.; Menge, W.M.P.B. *Tetrahedron Lett.* **1986**, 27, 2767.

¹³⁰⁶ See Dunn, A.D.; Rudolf, W. *Carbon Disulphide in Organic Chemistry*, Ellis Horwood, Chichester, **1989**, pp. 120–225; Yokoyama, M.; Imamoto, T. *Synthesis* **1984**, 797, pp. 797–804.

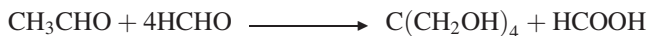
¹³⁰⁷ See Corey, E.J.; Chen, R.H.K. *Tetrahedron Lett.* **1973**, 3817.

¹³⁰⁸ See Konen, D.A.; Pfeffer, P.E.; Silbert, L.S. *Tetrahedron* **1976**, 32, 2507, and references cited therein.

¹³⁰⁹ Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* **2001**, 31, 1427.

¹³¹⁰ Ehrlich, P.; Sachs, F. *Chem. Ber.* **1899**, 32, 2341

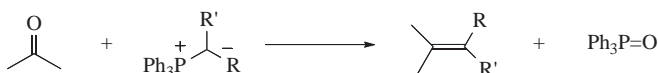
important use of the reaction is to prepare pentaerythritol from acetaldehyde:



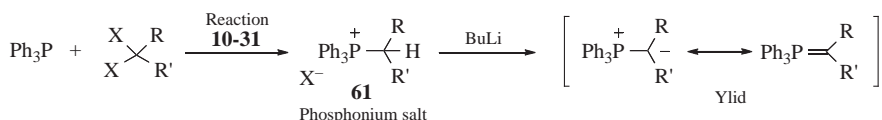
OS I, 425; IV, 907; V, 833.

16-44 The Wittig Reaction

Alkylidene-de-oxo-bisubstitution



In the *Wittig reaction*, an aldehyde or ketone is treated with a *phosphorus ylid* (a *phosphorane*; also spelled *ylide*) to give an alkene.¹³¹¹ The conversion of a carbonyl compound to an alkene with a phosphorus ylid is called the *Wittig reaction*. Phosphorus ylids are usually prepared by treatment of a phosphonium salt with a base,¹³¹² and phosphonium salts (**61**) are usually prepared from a triaryl phosphine and an alkyl halide (Reaction **10-31**):



The reaction of triphenylphosphine and an alkyl halides is facilitated by the use of microwave irradiation.¹³¹³ Indeed, the *Wittig reaction* itself is assisted by microwave irradiation.¹³¹⁴ Phosphonium salts are also prepared by addition of phosphines to *Michael alkenes* (like Reaction **15-8**) and in other ways.

The phosphonium salts are most often converted to the ylids by treatment with a strong base (e.g., butyllithium, sodium amide,¹³¹⁵ sodium hydride, or a sodium alkoxide, though weaker bases can be used if the salt is acidic enough. In some cases, and excess of fluoride ion is sufficient.¹³¹⁶ For $(\text{Ph}_3\text{P}^+)_2\text{CH}_2$, sodium carbonate is a strong enough base.¹³¹⁷ When the base used does not contain lithium, the ylid is said to be prepared under “salt-free” conditions¹³¹⁸ because the lithium halide (where the halide counterion comes from

¹³¹¹ See Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, **1979**; Johnson, A.W. *Ylid Chemistry*, Academic Press, NY, **1966**. For reviews, see Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, 89, 863; Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, 109, 85; Pommer, H.; Thieme, P.C. *Top. Curr. Chem.* **1983**, 109, 165; Pommer, H. *Angew. Chem. Int. Ed.* **1977**, 16, 423; Maercker, A. *Org. React.* **1965**, 14, 270; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 682–709. For related reviews, see Zbiral, E. *Synthesis* **1974**, 775; Bestmann, H.J. *Angew. Chem. Int. Ed.* **1965**, 4, 583, 645–660, 830–838; *Newer Methods Prep. Org. Chem.* **1968**, 5, 1; Horner, L. *Fortschr. Chem. Forsch.*, **1966**, 7, 1. For a historical background, see Wittig, G. *Pure Appl. Chem.* **1964**, 9, 245. For a list of reagents and references for the Wittig and related reactions, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 327–337.

¹³¹² When phosphonium *fluorides* are used, no base is necessary, as these react directly with the substrate to give the alkene: Schiemenz, G.P.; Becker, J.; Stöckigt, J. *Chem. Ber.* **1970**, 103, 2077.

¹³¹³ Kiddle, J.J. *Tetrahedron Lett.* **2000**, 41, 1339.

¹³¹⁴ Wu, J.; Wu, H.; Wei, S.; Dai, W.-M. *Tetrahedron Lett.* **2004**, 45, 4401.

¹³¹⁵ See Schlosser, M.; Schaub, B. *Chimia* **1982**, 36, 396.

¹³¹⁶ Kobayashi, T.; Eda, T.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2002**, 67, 3156.

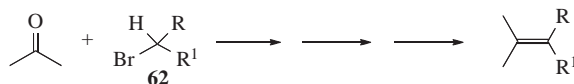
¹³¹⁷ Ramirez, F.; Pilot, J.F.; Desai, N.B.; Smith, C.P.; Hansen, B.; McKelvie, N. *J. Am. Chem. Soc.* **1967**, 89, 6273.

¹³¹⁸ Bestmann, H.J. *Angew. Chem. Int. Ed.* **1965**, 4, 586.

the phosphonium salt) is absent. *Wittig reactions* can be done in aqueous media in the presence of surfactants.¹³¹⁹

When the phosphorus ylid reacts with the aldehyde or ketone to form an alkene, a phosphine oxide is also formed. When triphenylphosphine is used to give $\text{Ph}_3\text{P}=\text{CRR}'$, for example, the byproduct is triphenylphosphine oxide (Ph_3PO), which is sometimes difficult to separate from the other reaction products. Other triarylphosphines¹³²⁰ and trialkylphosphines¹³²¹ have been used. Phosphines that have an α -hydrogen should be avoided, so that reaction with the chosen alkyl halide will lead to a phosphonium salt (**61**) with the α -proton at the desired position. This limitation is essential if a specific ylid is to be formed from the alkyl halide precursor. The *Wittig reaction* has been carried out with polymer-supported ylids.¹³²² It has also been done on silica gel.¹³²³ Polymer-bound aryldiphenylphosphino compounds¹³²⁴ have been used in reactions with alkyl halides to complete a *Wittig reaction*.

If an alkyl halide is viewed as the starting material (alkyl halide phosphonium salt \rightarrow phosphorus ylid \rightarrow alkene), the halogen-bearing carbon of an alkyl halide must contain at least one hydrogen, as in **62** (for deprotonation at the phosphonium salt stage).



The reaction is very general.¹³²⁵ The aldehyde or ketone may be aliphatic, alicyclic, or aromatic (including diaryl ketones). *Wittig reactions* are known in which the ylid and/or the carbonyl substrate contain double or triple bonds; various functional groups may be present (e.g., OH, OR, NR_2 , aromatic nitro or halo, acetal, amide,¹³²⁶ or even ester groups).¹³²⁷ Note, however, that a *Wittig reaction* has been reported in which the carbonyl group of an ester was converted to a vinyl ether.¹³²⁸ An important advantage of the *Wittig reaction* is that the *position* of the new double bond is always certain, in contrast to the result in most of the base-catalyzed condensations (Reactions **16-34–16-43**). Ylids have been shown to react with lactones, however, to form ω -alkenyl alcohols.¹³²⁹ β -Lactams have also been converted to alkenyl-azetidine derivatives using phosphorus ylids.¹³³⁰ Double or triple bonds *conjugated* with the carbonyl also do not interfere, the attack being at the $\text{C}=\text{O}$ carbon. The carbonyl partner can be generated *in situ*, in the presence of an ylid; the reaction of an alcohol with a mixture of an oxidizing agent and an ylid generates an alkene. Oxidizing agents used in this manner include BaMnO_4 ,¹³³¹ MnO_2 ,¹³³² and $\text{PhI}(\text{OAc})_2$.¹³³³

¹³¹⁹ Orsini, F.; Sello, G.; Fumagalli, T. *Synlett* **2006**, 1717.

¹³²⁰ Schiemenz, G.P.; Thobe, J. *Chem. Ber.* **1966**, 99, 2663.

¹³²¹ See Bestmann, H.J.; Kratzer, O. *Chem. Ber.* **1962**, 95, 1894.

¹³²² Bernard, M.; Ford, W.T.; Nelson, E.C. *J. Org. Chem.* **1983**, 48, 3164.

¹³²³ Patil, V.J.; Mävers, U. *Tetrahedron Lett.* **1996**, 37, 1281.

¹³²⁴ Betancort, J.M.; Barbas, III, C.F. *Org. Lett.* **2001**, 3, 3737.

¹³²⁵ See Dunne, E.C.; Coyne, É.J.; Crowley, P.B.; Gilheany, D.G. *Tetrahedron Lett.* **2002**, 43, 2449.

¹³²⁶ Smith, M.B.; Kwon, T.W. *Synth. Commun.* **1992**, 22, 2865. Also see Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, 126, 7559.

¹³²⁷ See Harcken, C.; Martin, S.F. *Org. Lett.* **2001**, 3, 3591; Yu, X.; Huang, X. *Synlett* **2002**, 1895. Also see Greenwald, R.; Chaykovsky, M.; Corey, E.J. *J. Org. Chem.* **1963**, 28, 1128.

¹³²⁸ Tsunoda, T.; Takagi, H.; Takaba, D.; Kaku, H.; Itô, S. *Tetrahedron Lett.* **2000**, 41, 235.

¹³²⁹ Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* **1996**, 37, 3853.

¹³³⁰ Baldwin, J.E.; Edwards, A.J.; Farthing, C.N.; Russell, A.T. *Synlett* **1993**, 49.

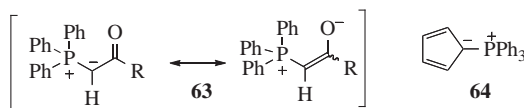
¹³³¹ Shuto, S.; Niizuma, S.; Matsuda, A. *J. Org. Chem.* **1998**, 63, 4489.

¹³³² Reid, M.; Roman, E.; Taylor, R.J.K. *Synlett* **2004**, 819.

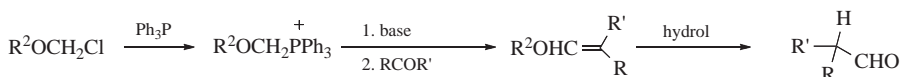
¹³³³ Zhang, P.-F.; Chen, Z.-C. *Synth. Commun.* **2001**, 31, 1619.

Weinreb amides (Reaction 16-82) can be converted to the corresponding aldehyde via the *Wittig reaction*.¹³³⁴

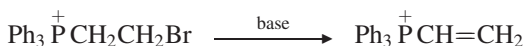
As noted above, the phosphorus ylid may also contain double or triple bonds and certain functional groups. Simple ylids ($R, R' = \text{hydrogen or alkyl}$) are highly reactive, reacting with oxygen, water, hydrohalic acids, and alcohols, as well as carbonyl compounds and carboxylic esters, so the reaction must be run under conditions where these materials are absent. When an electron-withdrawing group (e.g., COR, CN, CO₂R, CHO) is present in the α position, the ylids are much more stable, because the charge on the carbon is delocalized by



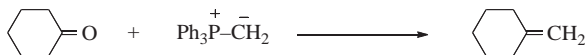
resonance as in **63**. Such ylids react readily with aldehydes, but slowly or not at all with ketones.¹³³⁵ In extreme cases (e.g., **64** where the carbanion unit is part of the aromatic cyclopentadienyl anion), the ylid does not react with ketones *or* aldehydes. Besides these groups, the ylid may contain one or two α halogens¹³³⁶ or



an α OR or OAr group. In the latter case, the product is an enol ether, which can be hydrolyzed (Reaction 10-6) to an aldehyde,¹³³⁷ so that this reaction is a means of achieving the conversion $\text{RCOR}' \rightarrow \text{RR}'\text{CHCHO}$.¹³³⁸ However, the ylid may not contain an α nitro group. If the phosphonium salt contains a potential leaving group (e.g., Br or OMe) in the β position, treatment with a base gives elimination, instead of the ylid:



However, a β COO⁻ group may be present, and the product is a β,γ -unsaturated acid:¹³³⁹ This is the only convenient way to make these compounds, since elimination by any other route gives the thermodynamically more stable α,β -unsaturated isomers. This is an illustration of the utility of the *Wittig* method for the specific location of a double bond. Another illustration is the conversion of cyclohexanones to alkenes containing exocyclic double bonds, for example:¹³⁴⁰



¹³³⁴ Hisler, K.; Tripoli, R.; Murphy, J.A. *Tetrahedron Lett.* **2006**, 47, 6293.

¹³³⁵ See Isaacs, N.S.; El-Din, G.N. *Tetrahedron Lett.* **1987**, 28, 2191. See also, Dauben, W.G.; Takasugi, J.J. *Tetrahedron Lett.* **1987**, 28, 4377.

¹³³⁶ Smithers, R.H. *J. Org. Chem.* **1978**, 43, 2833; Miyano, S.; Izumi, Y.; Fujii, K.; Ohno, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1979**, 52, 1197; Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, 30, 2173.

¹³³⁷ See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1441–1444, 1457–1458.

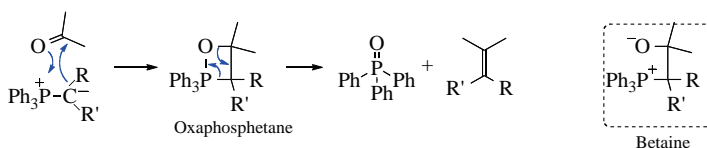
¹³³⁸ See Ceruti, M.; Degani, I.; Fochi, R. *Synthesis* **1987**, 79; Moskal, J.; van Leusen, A.M. *Recl. Trav. Chim. Pays-Bas* **1987**, 106, 137; Doad, G.J.S. *J. Chem. Res. (S)* **1987**, 370.

¹³³⁹ Corey, E.J.; McCormick, J.R.D.; Swensen, W.E. *J. Am. Chem. Soc.* **1964**, 86, 1884.

¹³⁴⁰ Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, 87, 1318.

Still another example is the formation of *anti-Bredt* bicycloalkenones¹³⁴¹ (see Sec. 4.Q.iii). As indicated above, α,α' -dihalophosphoranes can be used to prepare 1,1-dihaloalkenes. Another way to prepare haloalkenes¹³⁴² is to treat the carbonyl compound with a mixture of CX_4 ($X = Cl, Br, \text{ or } I$) and triphenylphosphine, either with or without the addition of zinc dust, which allows less Ph_3P to be used.¹³⁴³ Aryl aldehydes react with these dihalophosphoranes to give aryl alkynes after treatment of the initially formed vinyl halide with potassium *tert*-butoxide.¹³⁴⁴

The mechanism¹³⁴⁵ of the key step of the *Wittig reaction* is as follows:¹³⁴⁶



The energetics of ylid formation and their reaction in solution has been studied.¹³⁴⁷ For many years it was assumed that a diionic compound, called a *betaine*, is an intermediate on the pathway from the starting compounds to the oxaphosphetane, but it has been argued that there is little evidence for it.¹³⁴⁸ However, “betaine” precipitates have been isolated in certain *Wittig reactions*,¹³⁴⁹ although these are betaine–lithium halide adducts, and might just as well have been formed from the oxaphosphetane as from a true betaine.¹³⁵⁰ There is one report of an observed betaine lithium salt during the course of a *Wittig reaction*.¹³⁵¹ An X-ray structure was determined for a *gauche* betaine from a thio-*Wittig reaction*.¹³⁵² In contrast, there is much evidence for the presence of the oxaphosphetane intermediates, at least with unstable ylids. For example, ^{31}P NMR spectra taken of the reaction mixtures at low temperatures¹³⁵³ are compatible with an oxaphosphetane structure that persists for some time but not with a tetra-coordinated phosphorus species. Since a betaine, an ylid, and a phosphine oxide all have tetracoordinated phosphorus, these species could not be causing the spectra, leading to the conclusion that an oxaphosphetane intermediate is present in the solution. In certain cases, oxaphosphetanes have been isolated.¹³⁵⁴ It has even been

¹³⁴¹ Bestmann, H.J.; Schade, G. *Tetrahedron Lett.* **1982**, 23, 3543.

¹³⁴² For a list of references to the preparation of haloalkenes by Wittig reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 725–727.

¹³⁴³ See Li, P.; Alper, H. *J. Org. Chem.* **1986**, 51, 4354.

¹³⁴⁴ Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* **1999**, 40, 8575. See Michael, P.; Rassat, A. *Tetrahedron Lett.* **1999**, 40, 8579.

¹³⁴⁵ See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups: Supplement A*, pt. 1, Wiley, NY, **1977**, pp. 232–240; Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* **1988**, 110, 3948.

¹³⁴⁶ It has been contended that another mechanism, involving single electron transfer, may be taking place in some cases: Olah, G.A.; Krishnamurthy, V.V. *J. Am. Chem. Soc.* **1982**, 104, 3987; Yamataka, H.; Nagareda, K.; Hanafusa, T.; Nagase, S. *Tetrahedron Lett.* **1989**, 30, 7187. A diradical mechanism has also been proposed for certain cases: Ward, Jr., W.J.; McEwen, W.E. *J. Org. Chem.* **1990**, 55, 493.

¹³⁴⁷ Arnett, E.M.; Wernett, P.C. *J. Org. Chem.* **1993**, 58, 301.

¹³⁴⁸ See Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* **1990**, 112, 3905.

¹³⁴⁹ See Schlosser, M.; Christmann, K.F. *Liebigs Ann. Chem.* **1967**, 708, 1.

¹³⁵⁰ Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, 89, 863, see p. 865.

¹³⁵¹ Neumann, R.A.; Berger, S. *Eur. J. Org. Chem.* **1998**, 1085.

¹³⁵² Puke, C.; Erker, G.; Wibbeling, B.; Fröhlich, R. *Eur. J. Org. Chem.* **1999**, 1831.

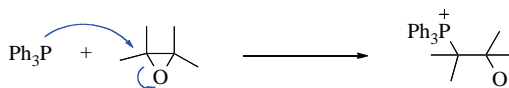
¹³⁵³ Vedejs, E.; Meier, G.P.; Snoble, K.A.J. *J. Am. Chem. Soc.* **1981**, 103, 2823. See also, Nesmayanov, N.A.;

Binshtok, E.V.; Reutov, O.A. *Doklad. Chem.* **1973**, 210, 499.

¹³⁵⁴ Mazhar-Ul-Haque; Caughlan, C.N.; Ramirez, F.; Pilot, J.F.; Smith, C.P. *J. Am. Chem. Soc.* **1971**, 93, 5229.

possible to detect *cis* and *trans* isomers of the intermediate oxaphosphetanes by NMR spectroscopy.¹³⁵⁵ According to this mechanism, an optically active phosphonium salt ($\text{RR}^1\text{R}^2\text{P}^+\text{CHR}^2$) should retain its configuration all the way through the reaction, and it should be preserved in the phosphine oxide ($\text{RR}^1\text{R}^2\text{PO}$). This has been shown to be the case.¹³⁵⁶

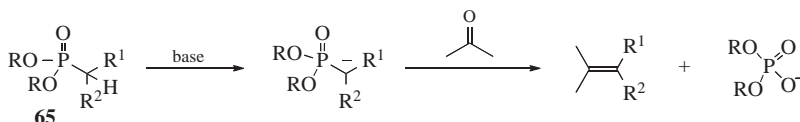
Note that the proposed betaine intermediates can be formed, in a completely different manner, by nucleophilic substitution by a phosphine on an epoxide (**10-35**):



Betaines formed in this way can then be converted to the alkene. This is one reason why betaine intermediates were long accepted in the *Wittig reaction*. It is also noteworthy that stable phosphonium enolate zwitterions have been formed by the reaction of an aryl aldehyde, a phosphine, and a propargylic ester.¹³⁵⁷

Phosphorus is not the only key element used to produce useful ylids. Triphenylarsine¹³⁵⁸ has been used. Tellurium ylids have been prepared *in situ* from α -halo esters and $\text{BrTeBu}_2\text{OTeBu}_2\text{Br}$ and react with aldehydes to give conjugated esters.¹³⁵⁹

The *Wittig reaction* has been carried out with phosphorus ylids other than phosphoranes, the most important being prepared from phosphonate esters (e.g., **65**).¹³⁶⁰



This method, sometimes called the *Horner-Emmons*, *Wadsworth-Emmons*, *Wittig-Horner*, or *Horner-Wadsworth-Emmons reaction*,¹³⁶¹ has several advantages over the use of phosphoranes, including selectivity.¹³⁶² These ylids are more reactive than the corresponding phosphoranes, and when R^1 or R^2 is an electron-withdrawing group, these compounds often react with ketones that are inert to phosphoranes. High pressure has been used to facilitate this reaction.¹³⁶³ In addition, the phosphorus product is a phosphate ester, and hence soluble in water, unlike Ph_3PO , which makes it easy to separate it from the

¹³⁵⁵ Maryanoff, B.E.; Reitz, A.B.; Mutter, M.S.; Inners, R.R.; Almond Jr., H.R.; Whittle, R.R.; Olofson, R.A. *J. Am. Chem. Soc.* **1986**, *108*, 7664. See also, Piskala, A.; Rehan, A.H.; Schlosser, M. *Coll. Czech. Chem. Commun.* **1983**, *48*, 3539.

¹³⁵⁶ McEwen, W.E.; Kumli, K.F.; Bladé-Font, A.; Zanger, M.; VanderWerf, C.A. *J. Am. Chem. Soc.* **1964**, *86*, 2378.

¹³⁵⁷ Zhu, X.-F.; Henry, C.E.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 6722.

¹³⁵⁸ For a catalytic version, see Shi, L.; Wang, W.; Wang, Y.; Huang, Y. *J. Org. Chem.* **1989**, *54*, 2027; Huang, Z.-Z.; Huang, X.; Huang, Y.-Z. *Tetrahedron Lett.* **1995**, *36*, 425.

¹³⁵⁹ Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2002**, *67*, 5320.

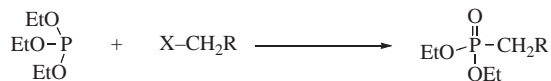
¹³⁶⁰ Horner, L.; Hoffmann, H.; Wippel, H.G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499; Wadsworth, Jr., W.S.; Emmons, W.D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

¹³⁶¹ Wadsworth, Jr., W.S. *Org. React.* **1977**, *25*, 73; Stec, W.J. *Acc. Chem. Res.* **1983**, *16*, 411; Walker, B.J. in Cadogan, J.I.G. *Organophosphorous Reagents in Organic Synthesis*, Academic Press, NY, **1979**, pp. 156–205; Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87; Segueineau, P.; Villieras, J. *Tetrahedron Lett.* **1988**, *29*, 477, and other papers in this series.

¹³⁶² Motoyoshiya, J.; Kasaura, T.; Kokin, K.; Yokoya, S.-i.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* **2001**, *57*, 1715.

¹³⁶³ Has-Becker, S.; Bodmann, K.; Kreuder, R.; Santoni, G.; Rein, T.; Reiser, O. *Synlett* **2001**, 1395.

alkene product. Phosphonates are also cheaper than phosphonium salts and can easily be prepared by the *Arbuzov reaction*.¹³⁶⁴



Phosphonates have also been prepared from alcohols and $(\text{ArO})_2\text{P}(=\text{O})\text{Cl}$, NEt_3 , and a TiCl_4 catalyst.¹³⁶⁵ The reaction of $(\text{RO})_2\text{P}(=\text{O})\text{H}$ and aryl iodides with a CuI catalyst leads to aryl phosphonates.¹³⁶⁶ Polymer-bound phosphonate esters have been used for olefination.¹³⁶⁷ Dienes are produced when allylic phosphonate esters react with aldehydes.¹³⁶⁸ Nucleophilicity parameters have been determined for phosphoryl-stabilized carbanions.¹³⁶⁹ A Zn promoted reaction is known using diprotic phosphonates.¹³⁷⁰ *Wittig reactions* of stabilized phosphorus ylids have also been done in water.¹³⁷¹

Stereoselective alkenylation reactions have been achieved using chiral additives¹³⁷² or auxiliaries.¹³⁷³ Ylids formed from phosphine oxides $[\text{Ar}_2\text{P}(=\text{O})\text{CHRR}']$, phosphonic acid bis(amides), $(\text{R}_2^2\text{N})_2\text{POCHRR}^1]$,¹³⁷⁴ and alkyl phosphonothionates $[(\text{MeO})_2\text{PSCHRR}^1]$,¹³⁷⁵ share some of these advantages. Reagents (e.g., $\text{Ph}_2\text{POCH}_2\text{NR}_2'$) react with aldehydes or ketones (R^2COR^3) to give good yields of enamines ($\text{R}^2\text{R}^3\text{C}=\text{CHNR}$).¹³⁷⁶ (*Z*)-Selective reagents are also known,¹³⁷⁷ including the use of a di(2,2,2-trifluoroethoxy)phosphonate with KHMDs and 18-crown-6.¹³⁷⁸ An interesting intramolecular version of the *Horner–Emmons reaction* leads to alkynes.¹³⁷⁹ The reaction of a functionalized aldehyde ($\text{R}-\text{CHO}$) with $(\text{MeO})_2\text{POCHN}_2$, leads to an alkyne ($\text{R}-\text{C}\equiv\text{CH}$).¹³⁸⁰

¹³⁶⁴ Also known as the *Michaelis–Arbuzov rearrangement*. For reviews, see Petrov, A.A.; Dogadina, A.V.; Ionin, B.I.; Garibina, V.A.; Leonov, A.A. *Russ. Chem. Rev.* **1983**, 52, 1030; Bhattacharya, A.K.; Thyagarajan, G. *Chem. Rev.* **1981**, 81, 415. See also Shokol, V.A.; Kozhushko, B.N. *Russ. Chem. Rev.* **1985**, 53, 98; Brill, T.B.; Landon, S.J. *Chem. Rev.* **1984**, 84, 577; Lherbet, C.; Castonguay, R.; Keillor, J.W. *Tetrahedron Lett.* **2005**, 46, 3565; Huang, C.; Tang, X.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2006**, 71, 5020.

¹³⁶⁵ Jones, S.; Selitsianos, D. *Org. Lett.* **2002**, 4, 3671.

¹³⁶⁶ Gelman, D.; Jiang, L.; Buchwald, S.L. *Org. Lett.* **2003**, 5, 2315.

¹³⁶⁷ Barrett, A.G.M.; Cramp, S.M.; Roberts, R.S.; Zecri, F.J. *Org. Lett.* **1999**, 1, 579.

¹³⁶⁸ Wang, Y.; West, F.G. *Synthesis* **2002**, 99.

¹³⁶⁹ Appel, R.; Loos, R.; Mayr, H. *J. Am. Chem. Soc.* **2009**, 131, 704.

¹³⁷⁰ Schauer, D.J.; Helquist, P. *Synthesis* **2006**, 3654.

¹³⁷¹ Wu, J.; Zhang, D.; Wei, S. *Synth. Commun.* **2005**, 35, 1213; Wu, J.; Li, D.; Zhang, D. *Synth. Commun.* **2005**, 35, 2543. See also McNulty, J.; Das, P. *Tetrahedron Lett.* **2009**, 50, 5737; McNulty, J.; Das, P.; McLeod, D. *Chemistry: Eur. J.* **2010**, 16, 6756.

¹³⁷² Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem. Int. Ed.* **1998**, 37, 515. Also see, Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, 39, 2997. For a review of asymmetric Wittig-type reactions see Rein, T.; Pedersen, T.M. *Synthesis* **2002**, 579.

¹³⁷³ Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, 37, 1077.

¹³⁷⁴ Corey, E.J.; Cane, D.E. *J. Org. Chem.* **1969**, 34, 3053. For a chiral derivative, see Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, 33, 7655, 7659.

¹³⁷⁵ Corey, E.J.; Kwiatkowski, G.T. *J. Am. Chem. Soc.* **1966**, 88, 5654.

¹³⁷⁶ Broekhof, N.L.J.M.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1984**, 103, 305; Broekhof, N.L.J.M.; van Elburg, P.; Hoff, D.J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1984**, 103, 317.

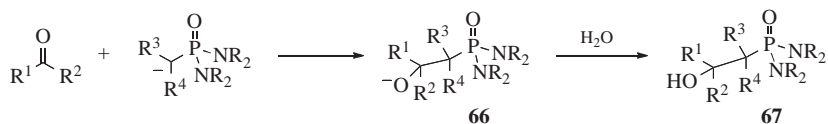
¹³⁷⁷ Ando, K. *Tetrahedron Lett.* **1995**, 36, 4105.

¹³⁷⁸ Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* **1999**, 40, 6725.

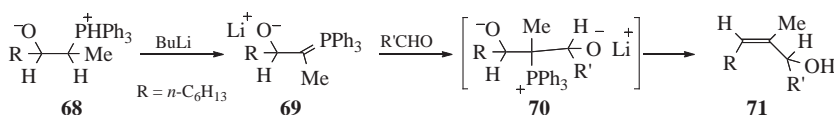
¹³⁷⁹ Nangia, A.; Prasuna, G.; Rao, P.B. *Tetrahedron Lett.* **1994**, 35, 3755; Couture, A.; Deniau, E.; Gimbert, Y.; Grandclaude, P. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2463.

¹³⁸⁰ Hauske, J.R.; Dorff, P.; Julin, S.; Martinelli, G.; Bussolari, J. *Tetrahedron Lett.* **1992**, 33, 3715.

Some *Wittig reactions* give the (*Z*)-alkene; some the (*E*), and others give mixtures. The question of which factors determine the stereoselectivity has been much studied.¹³⁸¹ It is generally found that ylids containing stabilizing groups or formed from trialkylphosphines give (*E*)-alkenes. The origin of the (*E*) selectivity in salt-free stabilized ylids may be related to dipole–dipole interactions.¹³⁸² The energy of the elimination transition state must also be taken into account.¹³⁸³ It has been shown that ylids formed from triarylphosphines and not containing stabilizing groups often give (*Z*) or a mixture of (*Z*)- and (*E*)-alkenes.¹³⁸⁴ One explanation for this¹³⁵⁶ is that the reaction of the ylid with the carbonyl compound is a [2+2]-cycloaddition, which in order to be concerted must adopt the $[\pi 2_s + \pi 2_a]$ -pathway. As discussed in Reaction **15-63**, this pathway leads to the formation of the more sterically crowded product, in this case the (*Z*)-alkene. If this explanation is correct, it is not easy to explain the predominant formation of (*E*) products from stable ylids, but (*E*) compounds are of course generally thermodynamically more stable than the (*Z*) isomers, and the stereochemistry seems to depend on many factors.



The (*E/Z*) ratio of the product can often be changed by a change in solvent or by the addition of salts.¹³⁸⁵ Another way of controlling the stereochemistry of the product is by use of the aforementioned phosphonic acid bis(amides). In this case, the betaine (**66**) does form and when treated with water gives the β -hydroxyphosphonic acid bis(amides) (**67**), which can be crystallized and then cleaved to $\text{R}^1\text{R}^2\text{C}=\text{CR}^3\text{R}^4$ by refluxing in benzene or toluene in the presence of silica gel.¹³⁷⁴ β -Hydroxy products (**67**) are generally formed as mixtures of diastereomers, and these mixtures can be separated by recrystallization. Each diastereomer will give one of the two isomeric alkenes. Optically active phosphonic acid bis(amides) have been used to give optically active alkenes.¹³⁸⁶ Another method of controlling the stereochemistry of the alkene [to obtain either the (*Z*)- or (*E*)-isomer] starting with a phosphine oxide ($\text{Ph}_2\text{POCH}_2\text{R}$) has been reported.¹³⁸⁷



¹³⁸¹ See Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, 89, 863; Gosney, I.; Rowley, A.G. in Cadogan, J.I.G. *Organophosphorous Reagents in Organic Synthesis*, Academic Press, NY, **1979**, pp. 17–153; Reucroft, J.; Sammes, P.G. *Q. Rev. Chem. Soc.* **1971**, 25, 135, see pp. 137–148, 169; Schlosser, M. *Top. Stereochem.* **1970**, 5, 1. Also see, Takeuchi, K.; Paschal, J.W.; Loncharich, R.J. *J. Org. Chem.* **1995**, 60, 156.

¹³⁸² Robiette, R.; Richardson, J.; Aggarwal, V.K.; Harvey, J.N. *J. Am. Chem. Soc.* **2005**, 127, 13468.

¹³⁸³ Robiette, R.; Richardson, J.; Aggarwal, V.K.; Harvey, J.N. *J. Am. Chem. Soc.* **2006**, 128, 2394.

¹³⁸⁴ See Maryanoff, B.E.; Reitz, A.B.; Duhl-Emswiler, B.A. *J. Am. Chem. Soc.* **1985**, 107, 217; Le Bigot, Y.; El Gharbi, R.; Delmas, M.; Gaset, A. *Tetrahedron* **1986**, 42, 3813. Also see Schlosser, M.; Schaub, B.; de Oliveira-Neto, J.; Jeganathan, S. *Chimia* **1986**, 40, 244.

¹³⁸⁵ See Reitz, A.B.; Nortey, S.O.; Jordan, Jr., A.D.; Mutter, M.S.; Maryanoff, B.E. *J. Org. Chem.* **1986**, 51, 3302.

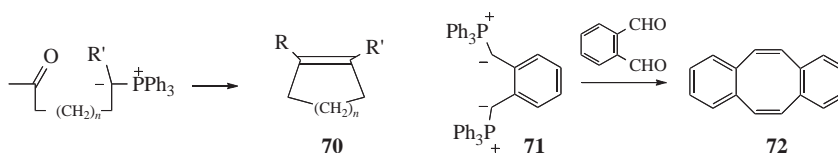
¹³⁸⁶ See Rein, T.; Reiser, O. *Acta Chem. Scand. B*, **1996**, 50, 369. For a review of asymmetric ylid reactions, see Li, A.-H.; Dai, L.-X.; Aggarwal, V.K. *Chem. Rev.* **1997**, 97, 2341.

¹³⁸⁷ Ayrey, P.M.; Warren, S. *Tetrahedron Lett.* **1989**, 30, 4581.

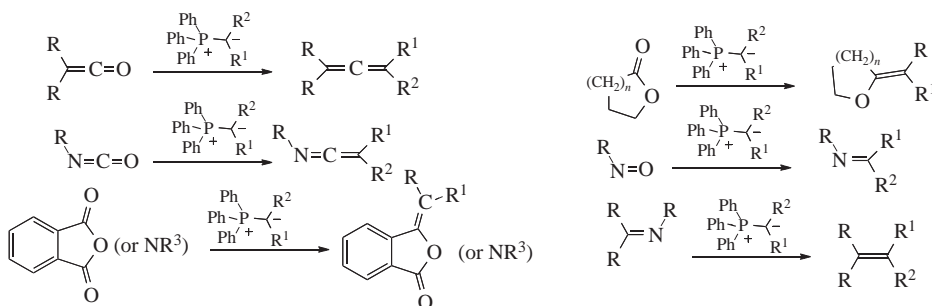
In reactions where the betaine–lithium halide intermediate is present, it is possible to extend the chain further if a hydrogen is present α to the phosphorus. For example, reaction of ethylenetriphenylphosphorane with heptanal at $-78\text{ }^{\circ}\text{C}$ gave **68**, and subsequent treatment with butyllithium gave the ylid, (**69**). Treatment of **69** with an aldehyde ($\text{R}'\text{CHO}$) gave the intermediate (**70**) that gave, after workup, **71**¹³⁸⁸ stereoselectively. Alkoxide **69** also reacts with other electrophiles. For example, treatment of **69** with NCS or PhICl_2 gave the vinylic chloride ($\text{RCH}=\text{CMeCl}$) stereoselectively: NCS gave the cis and PhICl_2 the trans-isomer.¹³⁸⁹ The use of Br_2 and FCIO_3 (several explosions¹³⁹⁰ have been observed with this reagent) gives the corresponding bromide or fluoride, respectively.¹³⁹¹ Reactions of **69** with electrophiles have been called *scoopy reactions* (α substitution plus carbonyl alkenylation via β -oxido phosphorus ylids).¹³⁹²

The reaction of a phosphonate ester, DBU, NaI, and HMPA with an aldehyde leads to a conjugated ester with excellent (*Z*)-selectivity.¹³⁹³ A (*Z*)-selective reaction was reported using a trifluoroethyl phosphonate in a reaction with an aldehyde and potassium *tert*-butoxide.¹³⁹⁴

The Wittig reaction has been carried out intramolecularly, to prepare rings containing from 5 to 16 carbons,¹³⁹⁵ both by single-ring closure to give alkenes (e.g., **70**), or by double-ring closure, as in the conversion of **71** to **72**).¹³⁹⁶



The Wittig reaction has proved very useful in the synthesis of natural products, some of which are quite difficult to prepare in other ways.¹³⁹⁷



¹³⁸⁸ See Schlosser, M.; Tuong, H.B.; Respondek, J.; Schaub, B. *Chimia* **1983**, 37, 10.

¹³⁸⁹ See Corey, E.J.; Shulman, J.I.; Yamamoto, H. *Tetrahedron Lett.* **1970**, 447.

¹³⁹⁰ Peet, J.H.J.; Rockett, B.W. *J. Organomet. Chem.* **1974**, 82, C57; Adcock, W.; Khor, T. *J. Organomet. Chem.* **1975**, 91, C20.

¹³⁹¹ Schlosser, M.; Christmann, K.-F. *Synthesis* **1969**, 38.

¹³⁹² Schlosser, M. *Top. Stereochem.* **1970**, 5, 1, p. 22.

¹³⁹³ Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, 65, 4745.

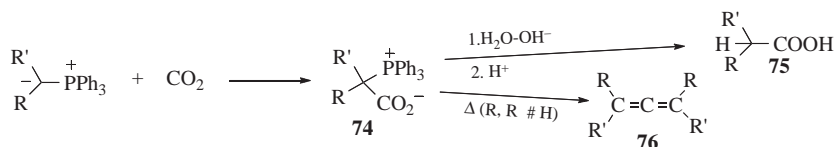
¹³⁹⁴ Touchard, F.P. *Tetrahedron Lett.* **2004**, 45, 5519.

¹³⁹⁵ For a review, see Becker, K.B. *Tetrahedron* **1980**, 36, 1717.

¹³⁹⁶ For a review of these double ring closures, see Vollhardt, K.P.C. *Synthesis* **1975**, 765.

¹³⁹⁷ See Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, 109, 85.

Phosphorus ylids also react in a similar manner with the C=O bonds of ketenes,¹³⁹⁸ isocyanates,¹³⁹⁹ certain anhydrides¹⁴⁰⁰ lactones,¹⁴⁰¹ and imides,¹⁴⁰² the N=O of nitroso groups, and the C=N of imines,¹⁴⁰³ as shown in the composite reaction. Phosphorus ylids react with carbon dioxide to give the isolable salts (**74**),¹⁴⁰⁴ which can be hydrolyzed to the carboxylic acids (**75**) (thus achieving the conversion $RR'CHX \rightarrow RR'CHCOOH$) or (if neither R nor R' is hydrogen) dimerized to allenes (**76**).



Although phosphorus ylids are most commonly used for alkenylation reactions, nitrogen ylids can occasionally be used. However, nitrogen ylids are often difficult to form, are unstable and highly reactive. The reaction of *N*-benzyl-*N*-phenylpiperidinium bromide with base to give an N-ylid is one example, and it reacted with benzaldehyde to form styrene.¹⁴⁰⁵ The structure has been determined for an intermediate in an *aza*-Wittig reaction.¹⁴⁰⁶ An *aza*-Wittig reaction¹⁴⁰⁷ has been used to prepare pyrrolines and tetrahydropyridines.¹⁴⁰⁸

OS V, 361, 390, 499, 509, 547, 751, 949, 985; VI, 358; VII, 164, 232; VIII, 265, 451; 75, 139, OS IX, 39, 230.

16-45 Tebbe, Petasis, and Alternative Alkenylations

Methylene-de-oxo-bisubstitution



A useful alternative to phosphorus ylids are Ti reagents (e.g., **77**) prepared from dicyclopentadienyltitanium dichloride and trimethylaluminum.¹⁴⁰⁹ Treatment of a carbonyl compound with **77** (*Tebbe reagent*) in toluene–THF containing a small amount of

¹³⁹⁸ See Aksnes, G.; Frøyen, P. *Acta Chem. Scand.* **1968**, 22, 2347.

¹³⁹⁹ See Frøyen, P. *Acta Chem. Scand. Ser. B* **1974**, 28, 586.

¹⁴⁰⁰ See Kayser, M.M.; Breau, L. *Can. J. Chem.* **1989**, 67, 1401. For a study of the mechanism, see Abell, A.D.; Clark, B.M.; Robinson, W.T. *Aust. J. Chem.* **1988**, 41, 1243.

¹⁴⁰¹ With microwave irradiation, see Sabitha, G.; Reddy, M.M.; Srinivas, D.; Yadov, J.S. *Tetrahedron Lett.* **1999**, 40, 165.

¹⁴⁰² Murphy, P.J.; Brennan, J. *Chem. Soc. Rev.* **1988**, 17, 1; Flitsch, W.; Schindler, S.R. *Synthesis* **1975**, 685.

¹⁴⁰³ Bestmann, H.J.; Seng, F. *Tetrahedron* **1965**, 21, 1373.

¹⁴⁰⁴ Bestmann, H.J.; Denzel, T.; Salbaum, H. *Tetrahedron Lett.* **1974**, 1275.

¹⁴⁰⁵ Lawrence, N.J.; Beynek, H. *Synlett* **1998**, 497.

¹⁴⁰⁶ Kano, N.; Hua, X.J.; Kawa, S.; Kawashima, T. *Tetrahedron Lett.* **2000**, 41, 5237.

¹⁴⁰⁷ For a review, see Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J.M. *Tetrahedron* **2007**, 63, 523.

¹⁴⁰⁸ Singh, P.N.D.; Klima, R.F.; Muthukrishnan, S.; Murthy, R.S.; Sankaranarayanan, J.; Stahlecker, H.M.; Patel, B.; Gudmundsdóttir, A.D. *Tetrahedron Lett.* **2005**, 46, 4213.

¹⁴⁰⁹ For *in situ* generation of this reagent, see Cannizzo, L.F.; Grubbs, R.H. *J. Org. Chem.* **1985**, 50, 2386.

pyridine¹⁴¹⁰ leads to the alkene. Dimethyltitanocene (Me_2TiCp_2), called the *Petasis reagent*, is a convenient and highly useful alternative to **77**.¹⁴¹¹ The mechanism of *Petasis olefination* has been examined.¹⁴¹² Both the *Tebbe* and the *Petasis reagent* give good results with ketones.¹⁴¹³ An important feature of these new reagents is that carboxylic esters and lactones¹⁴¹⁴ can be converted to the corresponding enol ethers in good yields. The enol ether can be hydrolyzed to a ketone (Reaction **10-6**), so this is also an indirect method for making the conversion $\text{RCO}_2\text{R}' \rightarrow \text{RCOCH}_3$ (see also, Reaction **16-82**). Conjugated esters are converted to alkoxy-dienes with this reagent.¹⁴¹⁵ Lactams, including β -lactams, are converted with alkylidene cycloamines (alkylidene azetidines from β -lactams, which are easily hydrolyzed to β -amino ketones).¹⁴¹⁶

Besides stability and ease of preparation, another advantage of the *Petasis reagent* is that structural analogues can be prepared, including $\text{Cp}_2\text{Ti}(\text{C}_3\text{H}_5)_2$ ¹⁴¹⁷ (C_3H_5 = cyclopropyl), $\text{CpTi}(\text{CH}_2\text{SiMe}_3)_3$,¹⁴¹⁸ and $\text{Cp}_2\text{TiMe}(\text{CH}=\text{CH}_2)$.¹⁴¹⁹ In another variation, 2 molar equivalents of $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$ reacted with a ketone in the presence of 1,1-diphenylthiocyclobutane to give the alkenylcyclobutane derivative.¹⁴²⁰ An alternative Ti reagent was prepared using TiCl_4 , Mg metal and dichloromethane, reacting with both ketones¹⁴²¹ and esters¹⁴²² to give alkenes or vinyl ethers, respectively. Alkenes are generated from ketones and alkyl iodides in the presence of a catalytic amount of $\text{Cp}_2\text{Ti}[\text{POEt}]_3$.¹⁴²³

Carboxylic esters undergo the conversion $\text{C}=\text{O} \rightarrow \text{C}=\text{CHR}$ (R = primary or secondary alkyl) when treated with RCHBr_2 , Zn ,¹⁴²⁴ and TiCl_4 in the presence of N,N,N',N' -tetramethylethylenediamine.¹⁴²⁵ Metal carbene complexes¹⁴²⁶ $\text{R}_2\text{C}=\text{ML}_n$ (L = ligand), where M is a transition metal (e.g., Zr , W , or Ta) have also been used to convert the $\text{C}=\text{O}$ of carboxylic esters and lactones to CR_2 .¹⁴²⁷ It is likely that the complex $\text{Cp}_2\text{Ti}=\text{CH}_2$ is an

¹⁴¹⁰ Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* **1978**, *100*, 3611; Pine, S.H.; Pettit, R.J.; Geib, G. D.; Cruz, S.G.; Gallego, C.H.; Tijerina, T.; Pine, R.D. *J. Org. Chem.* **1985**, *50*, 1212. See also, Clawson, L.; Buchwald, S.L.; Grubbs, R.H. *Tetrahedron Lett.* **1984**, *25*, 5733; Clift, S.M.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 8300.

¹⁴¹¹ Petasis, N.A.; Bzowej, E.I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

¹⁴¹² Meurer, E.C.; Santos, L.S.; Pilli, R.A.; Eberlin, M.N. *Org. Lett.* **2003**, *5*, 1391.

¹⁴¹³ Pine, S.H.; Shen, G.S.; Hoang, H. *Synthesis* **1991**, 165.

¹⁴¹⁴ Martínez, I.; Andrews, A.E.; Emch, J.D.; Ndakala, A.J.; Wang, J.; Howell, A.R. *Org. Lett.* **2003**, *5*, 399.

¹⁴¹⁵ Petasis, N.A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393.

¹⁴¹⁶ Tehrani, K.A.; De Kimpe, N. *Tetrahedron Lett.* **2000**, *41*, 1975. See Martínez, I.; Howell, A.R. *Tetrahedron Lett.* **2000**, *41*, 5607.

¹⁴¹⁷ Petasis, N.A.; Browej, E.I. *Tetrahedron Lett.* **1993**, *34*, 943.

¹⁴¹⁸ Petasis, N.A.; Akritopoulou, I. *Synlett* **1992**, 665.

¹⁴¹⁹ Petasis, N.A.; Hu, Y.-H. *J. Org. Chem.*, **1997**, *62*, 782. Also see, Petasis, N.A.; Browej, E.I. *J. Org. Chem.* **1992**, *57*, 1327.

¹⁴²⁰ Fujiwara, T.; Iwasaki, N.; Takeda, T. *Chem. Lett.* **1998**, 741. For an example using a *gem*-dichloride, see Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* **1998**, *63*, 7286.

¹⁴²¹ Yan, T.H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett.* **2004**, *6*, 4961.

¹⁴²² Yan, T.-H.; Chien, C.-T.; Tsai, C.-C.; Lin, K.-W.; Wu, Y.-H. *Org. Lett.* **2004**, *6*, 4965.

¹⁴²³ Takeda, T.; Shimane, K.; Ito, K.; Saeki, N.; Tsubouchi, A. *Chem. Commun.* **2002**, 1974.

¹⁴²⁴ Ishino, Y.; Mihara, M.; Nishihama, S.; Nishiguchi, I. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2669.

¹⁴²⁵ Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410; Matsubara, S.; Ukai, K.; Mizuno, T.; Utimoto, K. *Chem. Lett.* **1999**, 825; Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1065.

¹⁴²⁶ For a review, see Agüero, A.; Osborn, J.A. *New J. Chem.* **1988**, *12*, 111.

¹⁴²⁷ See Hartner Jr., F.W.; Schwartz, J.; Clift, S.M. *J. Am. Chem. Soc.* **1990**, *105*, 640.

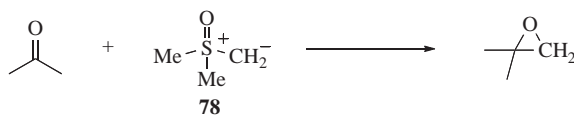
intermediate in the reaction with the *Tebbe reagent*. Indeed, Ti carbenoids have been used to convert carbonyl groups to the corresponding alkene.¹⁴²⁸

There are a few other methods for converting ketones or aldehydes to alkenes.¹⁴²⁹ Carbonyl compounds react with bis(iodozincio)methane to give alkenes.¹⁴³⁰ When a ketone is treated with $\text{CH}_3\text{CHBr}_2/\text{Sm}/\text{SmI}_2$, with a catalytic amount of CrCl_3 , the alkene is formed.¹⁴³¹ α -Halo esters also react with CrCl_2 in the presence of a ketone to give vinyl halides.¹⁴³² Organozinc reagents have been used to convert carbonyl compounds to alkenes in the presence of Lewis acids.¹⁴³³ α -Diazo esters react with ketones in the presence of an iron catalyst to give the corresponding alkene.¹⁴³⁴ α -Diazo silylalkanes react similarly in the presence of a Rh catalyst.¹⁴³⁵ Ketone olefination has been accomplished using methyltrioxorhenium.¹⁴³⁶ α -Halosulfones react with aldehydes in the presence of LiHMDS and $\text{MgBr}_2 \cdot \text{OEt}_2$ to give a vinyl chloride.¹⁴³⁷

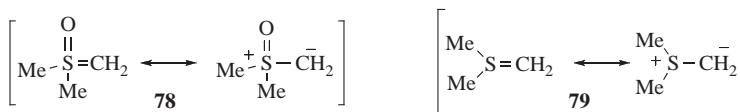
OS VIII, 512, IX, 404; X, 355.

16-46 The Formation of Epoxides from Aldehydes and Ketones

(1+2)OC,CC-cyclo-Methylene-addition



Aldehydes and ketones can be converted to epoxides¹⁴³⁸ in good yields with the sulfur ylids¹⁴³⁹ dimethyloxosulfonium methylid (**78**)¹⁴⁴⁰ and dimethylsulfonium methylid (**79**).¹⁴⁴¹ Ylid **79** is much less stable



¹⁴²⁸ Hartley, R.C.; Li, J.; Main, C.A.; McKiernan, G.J. *Tetrahedron* **2007**, 63, 4825.

¹⁴²⁹ See List, B.; Doehring, A.; Fonseca, M.T.H.; Job, A.; Torres, R.R. *Tetrahedron* **2006**, 62, 476.

¹⁴³⁰ Sada, M.; Komagawa, S.; Uchiyama, M.; Kobata, M.; Mizuno, T.; Utimoto, K.; Oshima, K.; Matsubara, S. *J. Am. Chem. Soc.* **2010**, 132, 17452.

¹⁴³¹ Matsubara, S.; Horiuchi, M.; Takai, K.; Utimoto, K. *Chem. Lett.* **1995**, 259. See also, Concellón, J.M.; Concellón, C. *J. Org. Chem.* **2006**, 71, 1728.

¹⁴³² Barma, D.K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J.R. *J. Am. Chem. Soc.* **2003**, 125, 3218.

¹⁴³³ Peng, Z.-Y.; Ma, F.-F.; Zhu, L.-F.; Xie, X.-M.; Zhang, Z. *J. Org. Chem.* **2009**, 74, 6855.

¹⁴³⁴ Chen, Y.; Huang, L.; Zhang, X.P. *Org. Lett.* **2003**, 5, 2493; Aggarwal, V.K.; Fulton, J.R.; Sheldon, C.G.; de Vicente, J. *J. Am. Chem. Soc.* **2003**, 125, 6034.

¹⁴³⁵ Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* **2004**, 6, 3047. For a synthesis of dienes from conjugated aldehydes, see Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, 126, 320.

¹⁴³⁶ Pedro, F.M.; Hirner, S.; Kühn, F.E. *Tetrahedron Lett.* **2005**, 46, 7777.

¹⁴³⁷ Lebrun, M.-E.; Le Marquand, P.; Berthelette, C. *J. Org. Chem.* **2006**, 71, 2009.

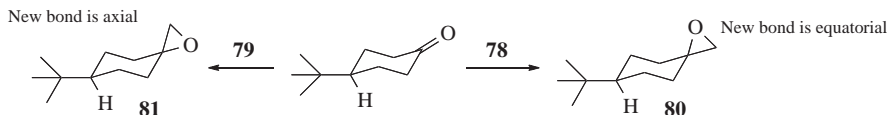
¹⁴³⁸ See Block, E. *Reactions of Organosulfur Compounds* Academic Press, NY, **1978**, pp. 101–105; Berti, G. *Top. Stereochem.* **1973**, 7, 93, pp. 218–232. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 944–951.

¹⁴³⁹ The bond enthalpies for S and Se ylids has been determined. See Stoffregen, S.A.; McCulla, R.D.; Wilson, R.; Cercone, S.; Miller, J.; Jenks, W.S. *J. Org. Chem.* **2007**, 72, 8235.

¹⁴⁴⁰ See Paxton, R.J.; Taylor, R.J.K. *Synlett* **2007**, 633.

¹⁴⁴¹ See Kavanagh, S.A.; Piccinini, A.; Fleming, E.M.; Connon, S.J. *Org. Biomol. Chem.* **2008**, 6, 1339. For reviews, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 709–733; Durst, T. *Adv. Org. Chem.* **1969**, 6, 285, see pp. 321–330. For a monograph on sulfur ylids, see Trost, B.M.; Melvin, Jr., L.S. *Sulfur Ylids*, Academic Press, NY, **1975**.

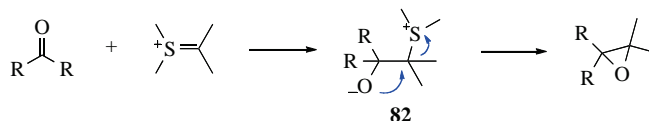
and ordinarily must be used as soon as it is formed, while **78** can be stored several days at room temperature. When diastereomeric epoxides can be formed, **79** usually attacks from the more hindered and **78** from the less-hindered side. Thus, 4-*tert*-butylcyclohexanone, treated with **78** gave exclusively **80** while **79** gave mostly **81**.¹⁴⁴² Another difference in behavior between the two reagents is that with α,β -unsaturated ketones, **78** gives



only cyclopropanes (Reaction **15-64**), while **79** gives oxirane formation. Other sulfur ylids have been used in an analogous manner, to transfer CHR or CR₂.¹⁴⁴³ Other sulfur ylids convert aldehydes to epoxides.¹⁴⁴⁴ High yields have been achieved by the use of sulfonium ylids anchored to insoluble polymers under phase-transfer conditions.¹⁴⁴⁵ A solvent-free version of this reaction has been developed using powdered K *tert*-butoxide and Me₃S⁺T⁻.¹⁴⁴⁶ Note that treatment of epoxides with 2 equiv of Me₂S=CH₂ leads to allylic alcohols.¹⁴⁴⁷

Chiral sulfur ylids¹⁴⁴⁸ have been prepared, giving the epoxide with good asymmetric induction,¹⁴⁴⁹ and chiral additives have also been used.¹⁴⁵⁰ Chiral Se ylids have been used in a similar manner.¹⁴⁵¹

The generally accepted mechanism for the reaction between sulfur ylids and aldehydes or ketone is formation of **82**, with displacement of the Me₂S leaving group by the alkoxide.¹⁴⁵² This mechanism is similar to that of the reaction of sulfur ylids with C=C double bonds (Reaction **15-64**).¹⁴⁵³ The stereochemical difference in the behavior of **78** and **79** has been attributed to formation of the betaine (**82**) being reversible for **78**, but not for the less stable **79**, so that the more-hindered product is the result of kinetic control and the less hindered of thermodynamic control.¹⁴⁵⁴



¹⁴⁴² Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

¹⁴⁴³ Adams, J.; Hoffman, Jr., L.; Trost, B.M. *J. Org. Chem.* **1970**, *35*, 1600; Braun, H.; Huber, G.; Kresze, G. *Tetrahedron Lett.* **1973**, 4033; Corey, E.J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, 2325.

¹⁴⁴⁴ See Forbes, D.C.; Amin, S.R.; Bean, C.J.; Standen, M.C. *J. Org. Chem.* **2006**, *71*, 8287.

¹⁴⁴⁵ Farrall, M.J.; Durst, T.; Fréchet, J.M.J. *Tetrahedron Lett.* **1979**, 203.

¹⁴⁴⁶ Toda, F.; Kanemoto, K. *Heterocycles* **1997**, *46*, 185.

¹⁴⁴⁷ Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* **1994**, *35*, 5449. Also see, Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* **1994**, *35*, 5453.

¹⁴⁴⁸ See Aggarwal, V.K.; Anglaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonguerna, S.J.; Ford, G.D.; Hynd, G.; Jones, E.; Jones, R.V.H.; Jubault, P.; Palmer, M.J.; Ratcliffe, P.D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2604.

¹⁴⁴⁹ See Sone, T.; Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 10078.

¹⁴⁵⁰ Hansch, M.; Illa, O.; McGarrigle, E.M.; Aggarwal, V.K. *Chemistry: Asian J.* **2008**, *3*, 1657.

¹⁴⁵¹ See Takada, H.; Metzner, P.; Philouze, C. *Chem. Commun.* **2001**, 2350.

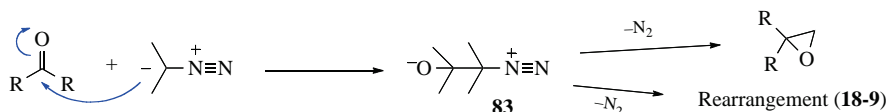
¹⁴⁵² See Aggarwal, V.K.; Harvey, J.N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747.

¹⁴⁵³ See Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* **1973**, *95*, 7424.

¹⁴⁵⁴ Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* **1973**, *95*, 7424.

Phosphorus ylids do not give this reaction, but give **16-44** instead.

Aldehydes and ketones can also be converted to epoxides by treatment with a diazoalkane.¹⁴⁵⁵ Most commonly it is diazomethane, but an important side reaction is the formation of an aldehyde or ketone with one more carbon than the starting compound (Reaction **18-9**). The reaction can be carried out with many aldehydes, ketones, and quinones, usually with a Rh catalyst.¹⁴⁵⁶ A mechanism that accounts for both products follows:



Compound **83** or nitrogen-containing derivatives of it have sometimes been isolated.

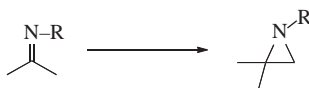
An alternative route to epoxides from ketones uses α -chloro sulfones and potassium *tert*-butoxide to give α,β -epoxy sulfones.¹⁴⁵⁷ A similar reaction was reported using KOH and 10% of a chiral phase-transfer agent, giving moderate enantioselectivity in the epoxy sulfone product.¹⁴⁵⁸

Dihalocarbenes and carbenoids, which readily add to C=C bonds (Reaction **15-64**), do not generally add to the C=O bonds of ordinary aldehydes and ketones.¹⁴⁵⁹ See also, Reaction **16-91**.

There is a report of a strained azetidinium ylid that has been used for epoxidation.¹⁴⁶⁰ OS V, 358, 755.

16-47 The Formation of Aziridines from Imines

(1+2)NC,CC-cyclo-Methylene-addition



Just as sulfur ylids (e.g., **78**) react with the carbonyl of an aldehyde or ketone to give an epoxide, Te ylids react with imines to give an aziridine. The reaction of an allylic Te salt ($\text{RCH=CHCH}_2\text{Te}^+\text{Bu}_2\text{Br}^-$), with lithium hexamethyldisilazide in HMPA/toluene leads to the tellurium ylid via deprotonation. In the presence of an imine, the ylid add to the imine and subsequent displacement of Bu_2Te generates an aziridine with a pendant vinyl group.¹⁴⁶¹ Catalytic aziridination of tosylimines was reported and mediated by arsonium ylids.¹⁴⁶²

¹⁴⁵⁵ See Gutsche, C.D. *Org. React.* **1954**, 8, 364.

¹⁴⁵⁶ See Davies, H.M.L.; De Meese, J. *Tetrahedron Lett.* **2001**, 42, 6803.

¹⁴⁵⁷ Mąkosza, M.; Urbańska, N.; Chesnokov, A.A. *Tetrahedron Lett.* **2003**, 44, 1473.

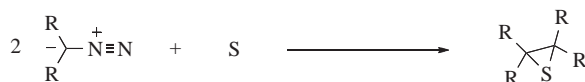
¹⁴⁵⁸ Arai, S.; Shioiri, T. *Tetrahedron* **2002**, 58, 1407.

¹⁴⁵⁹ For exceptions, see Sadhu, K.M.; Matteson, D.S. *Tetrahedron Lett.* **1986**, 27, 795; Araki, S.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1286.

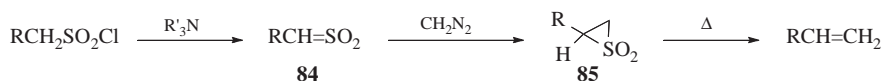
¹⁴⁶⁰ Alex, A.; Larmanjat, B.; Marrot, J.; Couty, F.; David, O. *Chem. Commun.* **2007**, 2500.

¹⁴⁶¹ Liao, W.-W.; Deng, X.-M.; Tang, Y. *Chem. Commun.* **2004**, 1516.

¹⁴⁶² Zhu, S.; Liao, Y.; Zhu, S. *Synlett* **2005**, 1429.

16-48 The Formation of Episulfides and Episulfones¹⁴⁶³

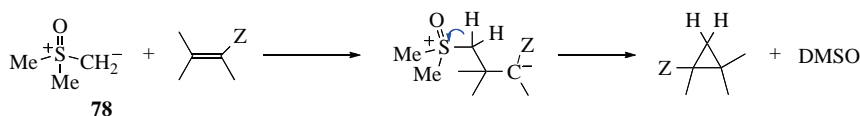
Epoxides can be converted directly to episulfides by treatment with NH_4SCN and ceric ammonium nitrate.¹⁴⁶⁴ Diazoalkanes, treated with sulfur, give episulfides.¹⁴⁶⁵ It is likely that $\text{R}_2\text{C}=\text{S}$ is an intermediate, which is attacked by another molecule of diazoalkane, in a process similar to that shown in Reaction 16-46. Thioketones *do* react with diazoalkanes to give episulfides,¹⁴⁶⁶ and have also been converted to episulfides with sulfur ylids.¹⁴⁴² Carbenes (e.g., the dichlorocarbene from CHCl_3) and base react with thioketones to give an α,α -dichloro episulfide.¹⁴⁶⁷



Alkanesulfonyl chlorides, when treated with diazomethane in the presence of a base (usually a tertiary amine), give episulfones (85).¹⁴⁶⁸ The base removes HCl from the sulfonyl halide to produce the highly reactive sulfene (84) (see Reaction 17-14), which then adds CH_2 . The episulfone can then be heated to give off SO_2 (see Reaction 17-20), making the entire process a method for achieving the conversion $\text{RCH}_2\text{SO}_2\text{Cl} \rightarrow \text{RCH}=\text{CH}_2$.¹⁴⁶⁹ OS V, 231, 877.

16-49 Cyclopropanation of Conjugated Carbonyl Compounds

Double-bond compounds that undergo the *Michael reaction* (15-24) can be converted to cyclopropane derivatives with sulfur ylids.¹⁴⁷⁰ Among the most common of these is dimethyloxosulfonium methylid (78),¹⁴⁷¹



which is widely used to transfer CH_2 to activated double bonds, but other sulfur ylids have also been used. A combination of DMSO and KOH in an ionic liquid converts conjugated

¹⁴⁶³ For a review, see Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, **1967**, pp. 57–86.

¹⁴⁶⁴ Iranpoor, N.; Kazemi, F. *Synthesis* **1996**, 821.

¹⁴⁶⁵ Schönberg, A.; Frese, E. *Chem. Ber.* **1962**, 95, 2810.

¹⁴⁶⁶ For example, see Beiner, J.M.; Lecadet, D.; Paquer, D.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1973**, 1983.

¹⁴⁶⁷ Mlostóń, G.; Romański, J.; Swiatek, A.; Heimgartner, H. *Helv. Chim. Acta* **1999**, 82, 946.

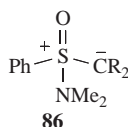
¹⁴⁶⁸ Opitz, G.; Fischer, K. *Angew. Chem. Int. Ed.* **1965**, 4, 70.

¹⁴⁶⁹ For a review of this process, see Fischer, N.S. *Synthesis* **1970**, 393.

¹⁴⁷⁰ Trost, B.M.; Melvin, Jr., L.S. *Sulfur Ylids*, Academic Press, NY, **1975**. For reviews, see Fava, A. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, **1985**, pp. 299–354; Belkin, Yu.V.; Polezhaeva, N.A. *Russ. Chem. Rev.* **1981**, 50, 481; Block, E. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, part 2, Wiley, NY, **1981**, pp. 680–702; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**, pp. 91–127.

¹⁴⁷¹ See Gololobov, Yu.G.; Nesmeyanov, A.N.; Lysenko, V.P.; Boldeskul, I.E. *Tetrahedron* **1987**, 43, 2609.

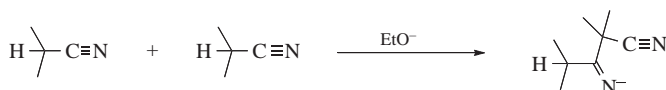
ketones to α,β -cyclopropyl ketones.¹⁴⁷² Both CHR and CR₂ can be added in a similar manner with certain nitrogen-containing compounds. For example, ylids¹⁴⁷³ (e.g., **86**), add various groups to activated double bonds.¹⁴⁷⁴ Sulfur ylids react with allylic alcohols in the presence of MnO₂ and molecular sieve 4 Å to give the cyclopropyl aldehyde.¹⁴⁷⁵ Similar reactions have been performed with phosphorus ylids,¹⁴⁷⁶ with pyridinium ylids,¹⁴⁷⁷ and with the compounds (PhS)₃CLi and Me₃Si(PhS)₂CLi.¹⁴⁷⁸ The reactions with ylids such as these of course involve nucleophilic acyl addition. Enantioselective cyclopropanation occurs in the presence of certain organocatalysts¹⁴⁷⁹ or chiral metal catalysts.¹⁴⁸⁰



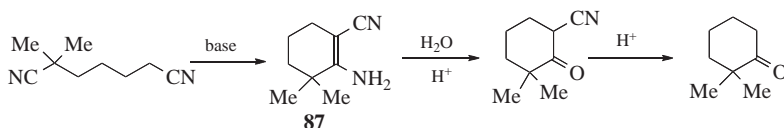
Other reagents can be used to convert an aldehyde or ketone to a cyclopropane derivative. Tellurium ylids react with conjugated imines to the cyclopropyl aldehyde after hydrolysis of the imine.¹⁴⁸¹ Conjugated ketones react with Cp₂Zr(CH₂=CH₂) and PMe₃ to give a vinyl cyclopropane derivative after treatment with aq H₂SO₄.¹⁴⁸²

16-50 The Thorpe Reaction

N-Hydro-C-(α -cyanoalkyl)-addition



In the *Thorpe reaction*, the α carbon of one nitrile molecule is added to the CN carbon of another, so this reaction has analogies with the aldol reaction (**16-34**). The C=NH bond is, of course, hydrolyzable (Reaction **16-2**), so β -keto nitriles can be prepared in this manner. The *Thorpe reaction* can be done intramolecularly, in which case it



is called the *Thorpe–Ziegler reaction*.¹⁴⁸³ As with other cyclization methods, yields are high for 5–8-membered rings, fall off to about zero for rings of 9–13 members, but are high

¹⁴⁷² Chandrasekhar, S.; Jagadeshwar, N.V.; Reddy, K.V. *Tetrahedron Lett.* **2003**, 44, 3629.

¹⁴⁷³ See Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* **1980**, 9, 477.

¹⁴⁷⁴ Johnson, C.R. *Aldrichimica Acta* **1985**, 18, 1; *Acc. Chem. Res.* **1973**, 6, 341; Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* **1975**, 4, 189; Trost, B.M. *Acc. Chem. Res.* **1974**, 7, 85.

¹⁴⁷⁵ Oswald, M.F.; Raw, S.A.; Taylor, R.J.K. *Org. Lett.* **2004**, 6, 3997.

¹⁴⁷⁶ Bestmann, H.J.; Seng, F. *Angew. Chem. Int. Ed.* **1962**, 1, 116; Grieco, P.A.; Finkelhor, R.S. *Tetrahedron Lett.* **1972**, 3781.

¹⁴⁷⁷ Shestopalov, A.M.; Sharanin, Yu.A.; Litvinov, V.P.; Nefedov, O.M. *J. Org. Chem. USSR* **1989**, 25, 1000.

¹⁴⁷⁸ Cohen, T.; Myers, M. *J. Org. Chem.* **1988**, 53, 457.

¹⁴⁷⁹ Kunz, R.K.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2005**, 127, 3240.

¹⁴⁸⁰ Kakei, H.; Sone, T.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, 129, 13410.

¹⁴⁸¹ Zheng, J.-C.; Liao, W.-W.; Tang, Y.; Sun, X.-L.; Daim L.-X. *J. Am. Chem. Soc.* **2005**, 127, 12222.

¹⁴⁸² Bertus, P.; Gandon, V.; Szymoniak, J. *Chem. Commun.* **2000**, 171.

¹⁴⁸³ Taylor, E.C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and ortho-Amino Nitriles*, Wiley, NY, **1970**; Schaefer, J.P.; Bloomfield, J.J. *Org. React.* **1967**, 15, 1.

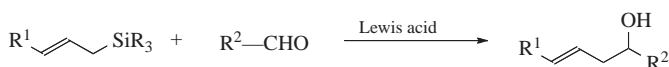
again for 14-membered and larger rings, if high-dilution techniques are employed. The product in the *Thorpe–Ziegler reaction* is not the imine, but the tautomeric enamine (e.g., **87**); if desired this can be hydrolyzed to an α -cyano ketone (Reaction **16-2**), which can in turn be hydrolyzed and decarboxylated (Reactions **16-4** and **12-40**). Other active-hydrogen compounds can also be added to nitriles.¹⁴⁸⁴

OS VI, 932.

H. Other Carbon or Silicon Nucleophiles

16-51 Addition of Silanes

O-Hydro-*C*-alkyl-addition

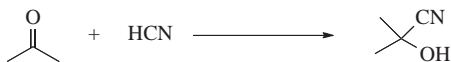


Allylic silanes react with aldehydes, in the presence of Lewis acids, to give a homoallylic alcohol.¹⁴⁸⁵ In the case of benzylic silanes, this addition reaction has been induced with Mg (ClO₄)₂ under photochemical conditions.¹⁴⁸⁶ Cyclopropylcarbinyl silanes add to acetals in the presence of TMSOTf to give a homoallylic alcohol.¹⁴⁸⁷ Allyltrichlorosilane adds an allyl group to an aldehyde in the presence of a cyclic urea and AgOTf.¹⁴⁸⁸ In a related reaction, allylic silanes react with acyl halides to produce the corresponding carbonyl derivative. The reaction of phenyl chloroformate, allyltrimethylsilane, and AlCl₃, for example, gave phenyl but-3-enoate.¹⁴⁸⁹ The use of chiral additives leads to the alcohol with good asymmetric induction.¹⁴⁹⁰

Allylic silanes also add to imines, in the presence of TiCl₄, to give amines.¹⁴⁹¹ Silanes also add to iminium salts, mediated by alkyltin compounds.¹⁴⁹²

16-52 The Formation of Cyanohydrins

O-Hydro-*C*-cyano-addition



The addition of HCN to aldehydes or ketones produces cyanohydrins.¹⁴⁹³ This is an equilibrium reaction, and for aldehydes and aliphatic ketones the equilibrium lies to the right; therefore the reaction is quite feasible, except with sterically hindered ketones (e.g., diisopropyl ketone). However, ketones (ArCOR) give poor yields, and the reaction cannot be carried out with ArCOAr since the equilibrium lies too far to the left. With aromatic

¹⁴⁸⁴ See Page, P.C.B.; van Niel, M.B.; Westwood, D. *J. Chem. Soc. Perkin Trans. 1* **1988**, 269.

¹⁴⁸⁵ Panek, J.S.; Liu, P. *Tetrahedron Lett.* **1997**, 38, 5127.

¹⁴⁸⁶ Fukuzumi, S.; Okamoto, T.; Otera, J. *J. Am. Chem. Soc.* **1994**, 116, 5503.

¹⁴⁸⁷ Braddock, D.C.; Badine, D.M.; Gottschalk, T. *Synlett* **2001**, 1909.

¹⁴⁸⁸ Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, 40, 3633.

¹⁴⁸⁹ Mayr, H.; Gabriel, A.O.; Schumacher, R. *Liebigs Ann. Chem.* **1995**, 1583.

¹⁴⁹⁰ Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, 115, 11490. See Malkov, A.V.; Liddon, A.J.P.S.; Ramírez-López, P.; Bendová, L.; Haigh, D.; Kočovský, P. *Angew. Chem. Int. Ed.* **2006**, 45, 1432.

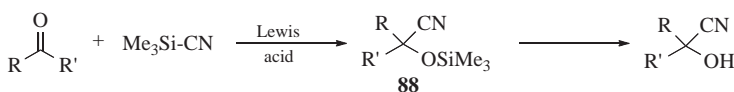
¹⁴⁹¹ Kercher, T.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, 118, 4200.

¹⁴⁹² Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, 129, 1902.

¹⁴⁹³ Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, **1983**, pp. 1345–1390; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 72–77.

aldehydes the *benzoin condensation* (Reaction **16-55**) competes. With α,β -unsaturated aldehydes and ketones, 1,4-addition competes (Reaction **15-38**).

Ketones of low reactivity (e.g., ArCOR) can be converted to cyanohydrins by treatment with diethylaluminum cyanide (Et_2AlCN) (see OS **VI**, 307) or, indirectly, with cyano-trimethylsilane (Me_3SiCN)¹⁴⁹⁴ in the presence of a Lewis acid or base,¹⁴⁹⁵ followed by hydrolysis of the resulting *O*-trimethylsilyl cyanohydrin (**88**). Both direct formation of the cyanohydrin (hydrocyanation) and formation of the cyano-*O*-silyl ether have been carried out enantioselectively using chiral catalysts,¹⁴⁹⁶ including chiral organocatalysts,¹⁴⁹⁷ or chiral additives.¹⁴⁹⁸ Biocatalysts have been used.¹⁴⁹⁹ Hydrogen cyanide adds to aldehydes in the presence of a lyase to give the cyanohydrin with good enantioselectivity.¹⁵⁰⁰ Cyanohydrins have been formed using a lyase in an ionic liquid.¹⁵⁰¹



Solvent-free conditions have been reported using TMSCN , an aldehyde, and potassium carbonate.¹⁵⁰² Amine *N*-oxides catalyze the reaction,¹⁵⁰³ as does tetrabutylammonium cyanide.¹⁵⁰⁴ Lithium perchlorate in ether facilitates this reaction,¹⁵⁰⁵ and LiCl catalyzes the reaction with Me_3SiCN .¹⁵⁰⁶ *N*-Heterocyclic carbenes catalyze the reaction,¹⁵⁰⁷ as do certain ionic liquids.¹⁵⁰⁸ With MgBr_2 as a catalyst, the reaction proceeds with good syn selectivity.¹⁵⁰⁹ Other useful catalysts include Pt ,¹⁵¹⁰ Au ,¹⁵¹¹ or Ti ¹⁵¹² compounds, and InBr_3 .¹⁵¹³ The use of chiral additives leads to cyanohydrins with good asymmetric

¹⁴⁹⁴ Rasmussen, J.K.; Heilmann, S.M.; Krepski, L. *Adv. Silicon Chem.* **1991**, *1*, 65; Yoneda, R.; Santo, K.; Harusawa, S.; Kurihara, T. *Synthesis* **1986**, 1054; Sukata, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3820.

¹⁴⁹⁵ See Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 2405. The reaction works in some cases without a Lewis acid, see Manju, K.; Trehan, S. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2383.

¹⁴⁹⁶ See Gröger, H.; Capan, E.; Barthuber, A.; Vorlop, K.-D. *Org. Lett.* **2001**, *3*, 1969, and references cited therein; Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592; Kim, S.S.; Kwak, J.M. *Tetrahedron* **2006**, *62*, 48; Shen, K.; Liu, X.; Li, Q.; Feng, X. *Tetrahedron* **2008**, *64*, 147; Kim, S.S.; Song, D. H. *Eur. J. Org. Chem.* **2005**, 1777. See also, North, M.; Omedes-Pujol, M.; Williamson, C. *Chemistry: Eur. J.* **2010**, *16*, 11367. See Bruneh, J.-M.; Holmes, I.P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2752.

¹⁴⁹⁷ Ryu, D.H.; Corey, E.J. *J. Am. Chem. Soc.* **2005**, *127*, 5384; Douglas E.; Fuerst, D.E.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2005**, *127*, 8964; Liu, X.; Qin, B.; Zhou, X.; He, B.; Feng, X. *J. Am. Chem. Soc.* **2005**, *127*, 12224; Wen, Y.; Huang, X.; Huang, J.; Xiong, Y.; Qin, B.; Feng, X. *Synlett* **2005**, 2445.

¹⁴⁹⁸ Lv, C.; Wu, M.; Wang, S.; Xia, C.; Sun, W. *Tetrahedron Asymmetry* **2010**, *21*, 1869.

¹⁴⁹⁹ van Langen, L.M.; Selassa, R.P.; van Rantwijk, F.; Sheldon, R.A. *Org. Lett.* **2005**, *7*, 327.

¹⁵⁰⁰ Gerrits, P.J.; Marcus, J.; Birikaki, L.; van der Gen, A. *Tetrahedron Asymmetry* **2001**, *12*, 971.

¹⁵⁰¹ Gaisberger, R.P.; Fechter, M.H.; Griengl, H. *Tetrahedron Asymmetry* **2004**, *15*, 2959.

¹⁵⁰² He, B.; Li, Y.; Feng, X.; Zhang, G. *Synlett* **2004**, 1776.

¹⁵⁰³ Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Tetrahedron* **2003**, *59*, 5667. See Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* **2004**, 129.

¹⁵⁰⁴ Amurrio, I.; Córdoba, R.; Csáky, A.G.; Plumet, J. *Tetrahedron* **2004**, *60*, 10521.

¹⁵⁰⁵ Jenner, G. *Tetrahedron Lett.* **1999**, *40*, 491.

¹⁵⁰⁶ Kurono, N.; Yamaguchi, M.; Suzuki, K.; Ohkuma, T. *J. Org. Chem.* **2005**, *70*, 6530.

¹⁵⁰⁷ Song, J.J.; Gallou, F.; Reeves, J.T.; Tan, Z.; Yee, N.K.; Senanayake, C.H. *J. Org. Chem.* **2006**, *71*, 1273; Suzuki, Y.; Abu Bakar M.D.; Muramatsu, K.; Sato, M. *Tetrahedron* **2006**, *62*, 4227.

¹⁵⁰⁸ Shen, Z.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 3137.

¹⁵⁰⁹ Ward, D.E.; Hrapchak, M.J.; Sales, M. *Org. Lett.* **2000**, *2*, 57.

¹⁵¹⁰ Fossey, J.S.; Richards, C.J. *Tetrahedron Lett.* **2003**, *44*, 8773.

¹⁵¹¹ Cho, W.K.; Kang, S.M.; Medda, A.K.; Lee, J.K.; Choi, I.S.; Lee, H.-S. *Synthesis* **2008**, 50.

¹⁵¹² Huang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett.* **2004**, *45*, 4763; He, B.; Chen, F.-X.; Li, Y.; Feng, X.; Zhang, G. *Tetrahedron Lett.* **2004**, *45*, 5465.

¹⁵¹³ Bandini, M.; Cozzi, P.G.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett.* **2001**, *42*, 3041.

induction.¹⁵¹⁴ Chiral transition metal catalysts have been used to give *O*-trialkylsilyl cyanohydrins with good enantioselectivity.¹⁵¹⁵ A vanadium catalyst has been used in an ionic liquid.¹⁵¹⁶ Note that the reaction of an aldehyde and TMSCN in the presence of aniline and a BiCl₃ catalyst leads to an α -cyano amine.¹⁵¹⁷ Potassium cyanide and acetic anhydride react with an aldehyde in the presence of a chiral Ti catalyst to give an α -acetoxy nitrile.¹⁵¹⁸

Rather than direct reaction with an aldehyde or ketone, the bisulfite addition product is often treated with cyanide. The addition is nucleophilic and the actual nucleophile is ⁻CN, so the reaction rate is increased by the addition of base.¹⁵¹⁹ This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.¹⁵²⁰ This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin *in situ* to the corresponding α -hydroxy acid. This reaction is important in the *Kiliani–Fischer* method of extending the carbon chain of a sugar.

A particularly useful variation of this reaction uses cyanide rather than HCN. α -Amino nitriles¹⁵²¹ can be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH₄Cl. This is called the *Strecker synthesis*;¹⁵²² and it is a special case of the *Mannich reaction* (16-19). Since the CN group is easily hydrolyzed to the acid, this is a convenient method for the preparation of α -amino acids. The reaction has also been carried out with NH₃ + HCN and with NH₄CN. Salts of primary and secondary amines can be used instead of NH₄⁺ to obtain *N*-substituted and *N,N*-disubstituted α -amino nitriles. Brønsted acids can also be used.¹⁵²³ Unlike Reaction 16-52, the *Strecker synthesis* is useful for aromatic as well as aliphatic ketones. As in Reaction 16-52, the Me₃SiCN method has been used; **76** is converted to the product with ammonia or an amine.¹⁵²⁴ The effect of pressure on the *Strecker synthesis* has been studied.¹⁵²⁵ A catalyst-free multi-component *Strecker reaction* is known.¹⁵²⁶ There is also an In mediated *Strecker reaction* in aq media.¹⁵²⁷ Enantioselective *Strecker syntheses* are possible using chiral ammonium salts¹⁵²⁸ and

¹⁵¹⁴ See Ryu, D.H.; Corey, E.J. *J. Am. Chem. Soc.* **2004**, *126*, 8106.

¹⁵¹⁵ See He, B.; Qin, B.; Feng, X.; Zhang, G. *J. Org. Chem.* **2004**, *69*, 7910; Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. *Tetrahedron* **2004**, *60*, 10449; Uang, B.-J.; Fu, I.-P.; Hwang, C.-D.; Chang, C.-W.; Yang, C.-T.; Hwang, D.-R. *Tetrahedron* **2004**, *60*, 10479. Also see Aspinall, H.C.; Greeves, N.; Smith, P.M. *Tetrahedron Lett.* **1999**, *40*, 1763; Deng, H.; Isler, M.P.; Snapper, M.L.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* **2002**, *41*, 1009; Karimi, B.; Ma'Mani, L. *Org. Lett.* **2004**, *6*, 4813.

¹⁵¹⁶ Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron Lett.* **2003**, *44*, 6813.

¹⁵¹⁷ De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* **2004**, *45*, 7407.

¹⁵¹⁸ Belokon, Y.N.; Gutnov, A.V.; Moskalenko, M.A.; Yashkina, L.V.; Lesovoy, D.E.; Ikonnikov, N.S.; Larichev, V.S.; North, M. *Chem. Commun.* **2002**, 244; Kawasaki, Y.; Fujii, A.; Nakano, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1999**, *64*, 4214.

¹⁵¹⁹ Ogata, Y.; Kawasaki, A. in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, **1970**, pp. 21–32. See also, Ching, W.; Kallen, R.G. *J. Am. Chem. Soc.* **1978**, *100*, 6119.

¹⁵²⁰ Lapworth, A. *J. Chem. Soc.* **1903**, 83, 998.

¹⁵²¹ See Shafran, Yu.M.; Bakulev, V.A.; Mokrushin, V.S. *Russ. Chem. Rev.* **1989**, *58*, 148.

¹⁵²² See Williams, R.M. *Synthesis of Optically Active α -Amino Acids* Pergamon, Elmsford, NY, **1989**, pp. 208–229; Yet, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 875; Gröger, H. *Chem. Rev.* **2003**, *103*, 2795.

¹⁵²³ See Zhang, G.-W.; Zheng, D.-H.; Nie, J.; Wang, T.; Ma, J.-A. *Org. Biomol. Chem.* **2010**, *8*, 1399. See also, Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 5522.

¹⁵²⁴ See Mai, K.; Patil, G. *Tetrahedron Lett.* **1984**, *25*, 4583; *Synth. Commun.* **1985**, *15*, 157.

¹⁵²⁵ Jenner, G.; Salem, R.B.; Kim, J.C.; Matsumoto, K. *Tetrahedron Lett.* **2003**, *44*, 447.

¹⁵²⁶ Martínez, R.; Ramón, D.J.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 8471.

¹⁵²⁷ Shen, Z.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron* **2008**, *64*, 8159.

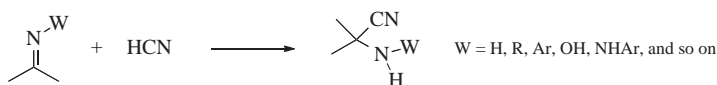
¹⁵²⁸ Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548.

other organocatalysts,¹⁵²⁹ chiral acids,¹⁵³⁰ or chiral metal complexes.¹⁵³¹ There is a radical version of the *Strecker synthesis*.¹⁵³²

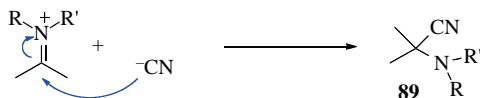
OS I, 336; II, 7, 29, 387; III, 436; IV, 58, 506; VI, 307; VII, 20, 381, 517, 521. For the reverse reaction, see OS III, 101. For the Strecker synthesis, see OS I, 21, 355; III, 66, 84, 88, 275; IV, 274; V, 437; VI, 334.

16-53 The Addition of HCN to C=N and C≡N Bonds

N-Hydro-C-cyano-addition

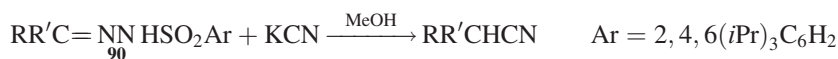


Hydrogen cyanide adds to imines, *Schiff bases*, hydrazones, oximes, and similar compounds. Cyanide can be added to iminium ions to give α -cyano amines (**89**). As in Reaction 16-50, the addition to imines has been carried out enantioselectively.¹⁵³³ Chiral ammonium salts have been used with HCN.¹⁵³⁴ Trimethylsilyl cyanide (TMSCN) reacts with *N*-tosyl



imines in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give the α -cyano *N*-tosyl amine.¹⁵³⁵ In the presence of a chiral Zr^{1536} or Al^{1537} catalyst, Bu_3SnCN reacts with imines to give α -cyanoamines enantioselectively. The imine can be formed *in situ* by reaction of an aldehyde or ketone with an amine, in the presence of TMSCN and a suitable promoter.¹⁵³⁸ The reaction of an imine and TMSCN gives the cyano amine with good enantioselectivity using a chiral Sc catalyst.¹⁵³⁹ Titanium catalysts have been used in the presence of a chiral *Schiff base*.¹⁵⁴⁰

The addition of KCN to triisopropylbenzenesulfonyl hydrazones (**90**) provides an indirect method for achieving the conversion $\text{RR}'\text{CO} \rightarrow \text{RR}'\text{CHCN}$.¹⁵⁴¹ The reaction is successful for hydrazones of aliphatic aldehydes and ketones.



¹⁵²⁹ Hou, Z.; Wang, J.; Liu, X.; Feng, X. *Chemistry: European J.* **2008**, *14*, 4484.

¹⁵³⁰ Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 2617.

¹⁵³¹ Blacker, J.; Clutterbuck, L.A.; Crampton, M.R.; Grosjean, C.; North, M. *Tetrahedron Asymmetry* **2006**, *17*, 1449.

¹⁵³² Cannella, R.; Clerici, A.; Panzeri, W.; Pastori, N.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* **2006**, *128*, 5358.

¹⁵³³ Saito, K.; Harada, K. *Tetrahedron Lett.* **1989**, *30*, 4535.

¹⁵³⁴ Huang, J.; Corey, E.J. *Org. Lett.* **2004**, *6*, 5027.

¹⁵³⁵ Prasad, B.A.B.; Bisai, A.; Singh, V.K. *Tetrahedron Lett.* **2004**, *45*, 9565.

¹⁵³⁶ Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762.

¹⁵³⁷ Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron Asymmetry* **2004**, *15*, 1513.

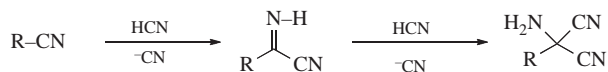
¹⁵³⁸ Royer, L.; De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* **2005**, *46*, 4595.

¹⁵³⁹ Chavarot, M.; Byrne, J.J.; Chavant, P.Y.; Vallée, Y. *Tetrahedron Asymmetry* **2001**, *12*, 1147.

¹⁵⁴⁰ Krueger, C.A.; Kuntz, K.W.; Dzierba, C.D.; Wirschun, W.G.; Gleason, J.D.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1999**, *121*, 4284.

¹⁵⁴¹ Jiricny, J.; Orere, D.M.; Reese, C.B. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1487. Also see Okimoto, M.; Chiba, T. *J. Org. Chem.* **1990**, *55*, 1070.

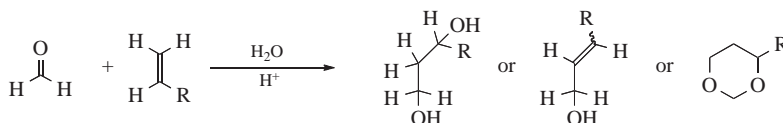
Hydrogen cyanide can also be added to the $C\equiv N$ bond to give iminonitriles or α -amino-malononitriles.¹⁵⁴²



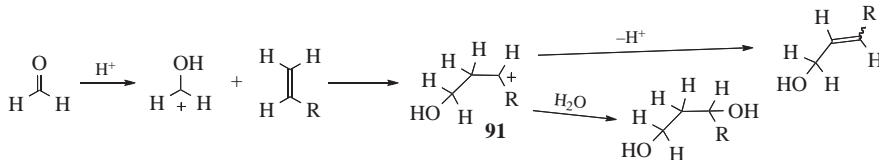
The acylcyanation of imines is known, and enantioselectivity is achieved with a suitable catalyst.¹⁵⁴³

OS V, 344. See also, OS V, 269.

16-54 The Prins Reaction



The addition of an alkene to formaldehyde in the presence of an acid¹⁵⁴⁴ catalyst is called the *Prins reaction*.¹⁵⁴⁵ Three main products are possible; which one predominates depends on the alkene and the conditions. When the product is the 1,3-diol or the dioxane,¹⁵⁴⁶ the reaction involves addition to the $C=C$ as well as to the $C=O$. The mechanism is one of electrophilic attack on both double bonds. The acid first protonates the $C=O$, and the resulting carbocation is attacked by the $C=C$ to give **91**. The cation product **91** can



undergo loss of H^+ to give the alkene or add water to give the diol.¹⁵⁴⁷ It has been proposed that **91** is stabilized by neighboring-group attraction, with either the oxygen¹⁵⁴⁸ or a carbon¹⁵⁴⁹ stabilizing the charge (**92** and **94**, respectively). This stabilization is postulated to explain the fact that with 2-butenes¹⁵⁵⁰ and with cyclohexenes the addition is anti. A backside attack of H_2O on the three- or four-membered ring would account for it. Other products are obtained too, which can be explained on the basis of **92** or **93**.^{1548,1549}

¹⁵⁴² See Ferris, J.P.; Sanchez, R.A. *Org. Synth.* **V**, 344.

¹⁵⁴³ Pan, S.C.; Zhou, J.; List, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 612.

¹⁵⁴⁴ With basic catalysts: Griengl, H.; Sieber, W. *Monatsh. Chem.* **1973**, *104*, 1008, 1027.

¹⁵⁴⁵ See Adams, D.R.; Bhatnagar, S.P. *Synthesis* **1977**, 661; Isagulyants, V.I.; Khaimova, T.G.; Melikyan, V.R.; Pokrovskaya, S.V. *Russ. Chem. Rev.* **1968**, *37*, 17. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, p. 248.

¹⁵⁴⁶ See Safarov, M.G.; Nigmatullin, N.G.; Ibatullin, U.G.; Rafikov, S.R. *Doklad. Chem.* **1977**, *236*, 507.

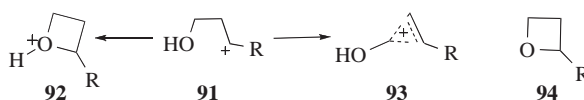
¹⁵⁴⁷ Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* **1966**, 1890, 3217.

¹⁵⁴⁸ Blomquist, A.T.; Wolinsky, J. *J. Am. Chem. Soc.* **1957**, *79*, 6025; Schowen, K.B.; Smissman, E.E.; Schowen, R.L. *J. Org. Chem.* **1968**, *33*, 1873.

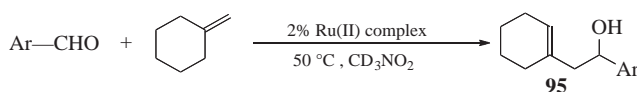
¹⁵⁴⁹ See Safarov, M.G.; Isagulyants, V.I.; Nigmatullin, N.G. *J. Org. Chem. USSR* **1974**, *10*, 1378.

¹⁵⁵⁰ Fremaux, B.; Davidson, M.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* **1967**, 4250.

Additional evidence for the intermediacy of **92** is the finding that oxetanes (**94**) subjected to the reaction conditions, which would protonate **94** to give **92**, give essentially the same product ratios as the corresponding alkenes.¹⁵⁵¹ An argument against the intermediacy of **92** and **93** is that not all alkenes show the anti-stereoselectivity mentioned above. Indeed, the stereochemical results are often quite complex, with syn, anti, and nonstereoselective addition reported, depending on the nature of the reactants and the reaction conditions.¹⁵⁵² Since addition to the C=C bond is electrophilic, the reactivity of the alkene increases with alkyl substitution and *Markovnikov's rule* is followed. The dioxane product may arise from a reaction between the 1,3-diol and formaldehyde¹⁵⁵³ (**16-5**) or between **92** and formaldehyde. Racemization may occur in the *Prins cyclization* reaction by 2-oxonia-Cope rearrangements (see **18-32**) by way of a (Z)-oxocarbenium ion intermediate.¹⁵⁵⁴



Iodine can promote the *Prins reaction*.¹⁵⁵⁵ Lewis acids (e.g., SnCl₄) also catalyze the reaction, in which case the species that adds to the alkenes is H₂C⁺-O-SnCl₄.¹⁵⁵⁶ The reaction can also be catalyzed by peroxides, in which case the mechanism is probably a free radical one. Other transition metal complexes can be used to form homoallylic alcohols. A typical example is the reaction of methylenecyclohexane with an aryl aldehyde to give **95**.¹⁵⁵⁷



Samarium iodide promotes this addition reaction.¹⁵⁵⁸ In a related reaction, simple alkene units add to esters in the presence of sodium and liquid ammonia to give an alcohol.¹⁵⁵⁹ Dienes react with alcohols in the presence of a transition metal compound, to give alkenyl alcohols.¹⁵⁶⁰ Allenes also add to aldehydes.¹⁵⁶¹ Enynes undergo *Prins cyclization* with Au catalysts.¹⁵⁶²

¹⁵⁵¹ Meresz, O.; Leung, K.P.; Denes, A.S. *Tetrahedron Lett.* **1972**, 2797.

¹⁵⁵² See Wilkins, C.L.; Marianelli, R.S. *Tetrahedron* **1970**, 26, 4131; Karpaty, M.; Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* **1971**, 1736; Coryn, M.; Anteunis, M. *Bull. Soc. Chim. Belg.* **1974**, 83, 83.

¹⁵⁵³ See Isagulyants, V.I.; Isagulyants, G.V.; Khairudinov, I.R.; Rakhmankulov, D.L. *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, **1973**, 22, 1810; Sharf, V.Z.; Kheifets, V.I.; Freidlin, V.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **1974**, 23, 1681.

¹⁵⁵⁴ Jasti, R.; Rychnovsky, S.D. *J. Am. Chem. Soc.* **2006**, 128, 13640.

¹⁵⁵⁵ Yadav, J.S.; Subba Reddy, B.V.; Hara Gopal, A.V.; Narayana Kumar, G.G.K.S.; Madavi, C.; Kunwar, A.C. *Tetrahedron Lett.* **2008**, 49, 4420; Reddy, S.; Krishna, V.H.; Swamy, T.; Narayana Kumar, G.G.K.S. *Can. J. Chem.* **2007**, 85, 412.

¹⁵⁵⁶ Yang, D.H.; Yang, N.C.; Ross, C.B. *J. Am. Chem. Soc.* **1959**, 81, 133.

¹⁵⁵⁷ Ellis, W.W.; Odenkirk, W.; Bosnich, B. *Chem. Commun.* **1998**, 1311.

¹⁵⁵⁸ Sarkar, T.K.; Nandy, S.K. *Tetrahedron Lett.* **1996**, 37, 5195.

¹⁵⁵⁹ Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.* **1998**, 63, 3141.

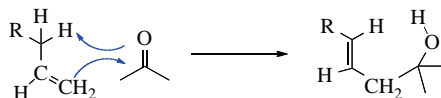
¹⁵⁶⁰ Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, 128, 8559; Cho, H.Y.; Morken, J.P. *J. Am. Chem. Soc.* **2008**, 130, 16140. See Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, 129, 2248.

¹⁵⁶¹ Song, M.; Montgomery, J. *Tetrahedron* **2005**, 61, 11440.

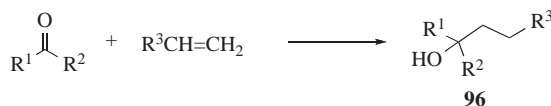
¹⁵⁶² Jiménez-Núñez, E.; Claverie, C.K.; Nieto-Oberhuber, C.; Echavarren, A.M. *Angew. Chem. Int. Ed.* **2006**, 45, 5452.

Structural variations in the alkene lead to different products. Homoallylic alcohols react with aldehydes in the presence of Montmorillonite-KSF clay to give 4-hydroxytetrahydropyrans.¹⁵⁶³ A variation of this reaction converts an aryl aldehyde and a homoallylic alcohol to a 4-chlorotetrahydropyran in the presence of InCl_3 .¹⁵⁶⁴ Homoallylic alcohols, protected as $-\text{O}(\text{CHMeOAc})$ react with $\text{BF}_3 \cdot \text{OEt}_2$ and acetic acid to give 4-acetoxytetrahydropyrans or with SnBr_4 to give 4-bromotetrahydropyrans.¹⁵⁶⁵ Homoallylic alcohols with a vinyl silane moiety react with InCl_3 and an aldehyde to give a dihydropyran.¹⁵⁶⁶

A closely related reaction has been performed with activated aldehydes or ketones; without a catalyst (e.g., chloral and acetoacetic ester), but with heat.¹⁵⁶⁷ The product in these cases is a β -hydroxy alkene, and the mechanism is pericyclic:¹⁵⁶⁸



This reaction is reversible and suitable β -hydroxy alkenes can be cleaved by heat (**17-32**). There is evidence that the cleavage reaction occurs by a cyclic mechanism (see **17-32**), and, by the principle of microscopic reversibility, the addition mechanism should be cyclic too.¹⁵⁶⁹ Note that this reaction is an oxygen analogue of the ene synthesis (**15-23**). This reaction can also be done with unactivated aldehydes¹⁵⁷⁰ and ketones¹⁵⁷¹ if Lewis acid catalysts [e.g., dimethylaluminum chloride (Me_2AlCl) or ethylaluminum dichloride (EtAlCl_2)] are used.¹⁵⁷² Lewis acid catalysts also increase rates with activated aldehydes.¹⁵⁷³ The use of optically active catalysts has given optically active products with a high % ee.¹⁵⁷⁴



In a related reaction, alkenes can be added to aldehydes and ketones to give reduced alcohols (**96**). This has been accomplished by several methods,¹⁵⁷⁵ including treatment

¹⁵⁶³ Yadav, J.S.; Reddy, B.V.S.; Kumar, G.M.; Murthy, Ch.V.S.R. *Tetrahedron Lett.* **2001**, 42, 89.

¹⁵⁶⁴ Yang, J.; Viswanathan, G.S.; Li, C.-J. *Tetrahedron Lett.* **1999**, 40, 1627.

¹⁵⁶⁵ Jaber, J.J.; Mitsui, K.; Rychnovsky, S.D. *J. Org. Chem.* **2001**, 66, 4679.

¹⁵⁶⁶ Dobbs, A.P.; Martinović, S. *Tetrahedron Lett.* **2002**, 43, 7055.

¹⁵⁶⁷ Arnold, R.T.; Veeravagu, P. *J. Am. Chem. Soc.* **1960**, 82, 5411; Klimova, E.I.; Abramov, A.I.; Antonova, N.D.; Arbuzov, Yu.A. *J. Org. Chem. USSR* **1969**, 5, 1308; Klimova, E.I.; Antonova, N.D.; Arbuzov, Yu.A. *J. Org. Chem. USSR* **1969**, 5, 1312, 1315.

¹⁵⁶⁸ See Ben Salem, R.; Jenner, G. *Tetrahedron Lett.* **1986**, 27, 1575. There is evidence that the mechanism is somewhat more complicated than shown here: Kwart, H.; Brechbiel, M. *J. Org. Chem.* **1982**, 47, 3353.

¹⁵⁶⁹ Also see Achmatowicz, Jr., O.; Szymoniak, J. *J. Org. Chem.* **1980**, 45, 1228; Ben Salem, R.; Jenner, G. *Tetrahedron Lett.* **1986**, 27, 1575; Papadopoulos, M.; Jenner, G. *Tetrahedron Lett.* **1981**, 22, 2773.

¹⁵⁷⁰ See Cartaya-Marin, C.P.; Jackson, A.C.; Snider, B.B. *J. Org. Chem.* **1984**, 49, 2443.

¹⁵⁷¹ Jackson, A.C.; Goldman, B.E.; Snider, B.B. *J. Org. Chem.* **1984**, 49, 3988.

¹⁵⁷² See Song, Z.; Beak, P. *J. Org. Chem.* **1990**, 112, 8126.

¹⁵⁷³ Benner, J.P.; Gill, G.B.; Parrott, S.J.; Wallace, B. *J. Chem. Soc. Perkin Trans. 1* **1984**, 291, 315, 331.

¹⁵⁷⁴ Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, 112, 3949.

¹⁵⁷⁵ See Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, 30, 2837; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1178–1179.

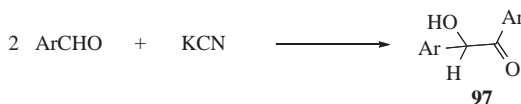
with SmI_2 ¹⁵⁷⁶ or Zn and Me_3SiCl ,¹⁵⁷⁷ and by electrochemical¹⁵⁷⁸ and photochemical¹⁵⁷⁹ methods. Most of these methods have been used for intramolecular addition and most or all involve free radical intermediates.

There is an *aza-Prins reaction*, promoted by TiI_4 and I_2 .¹⁵⁸⁰

OS IV, 786. See also, OS VII, 102.

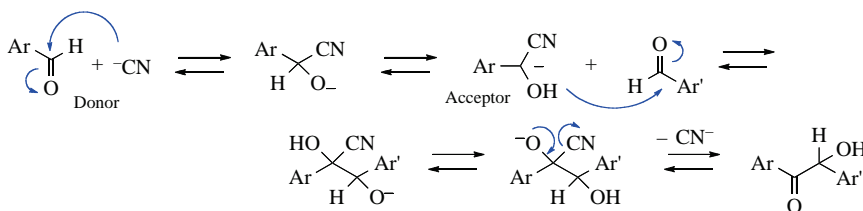
16-55 The Benzoin Condensation

Benzoin aldehyde condensation



When certain aldehydes are treated with cyanide ion, *benzoins* (**97**) are produced in a reaction called the *benzoin condensation*. The condensation can be regarded as involving the addition of one molecule of aldehyde to the $\text{C}=\text{O}$ group of another. The reaction only occurs with aromatic aldehydes, but not all of them,¹⁵⁸¹ and for glyoxals (RCOCHO). The two molecules of aldehyde obviously perform different functions. The one that no longer has a $\text{C}-\text{H}$ bond in the product is called the *donor*, because it has “donated” its hydrogen to the oxygen of the other molecule, the *acceptor*. Some aldehydes can perform only one of these functions, and hence cannot be self-condensed, though they can often be condensed with a different aldehyde. For example, *p*-dimethylaminobenzaldehyde is not an acceptor, but only a donor. Thus it cannot condense with itself. It can condense with benzaldehyde, which can perform both functions, but is a better acceptor than it is a donor. *N*-alkyl-3-methylimidazolium salts catalyze the reaction,¹⁵⁸² as does an imidazole-based solid supported catalyst.¹⁵⁸³

The following is the accepted mechanism¹⁵⁸⁴ for this reversible reaction, which was originally proposed by Lapworth in 1903.¹⁵⁸⁵



¹⁵⁷⁶ Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, 30, 2837.

¹⁵⁷⁷ Corey, E.J.; Pyne, S.G. *Tetrahedron Lett.* **1983**, 24, 2821.

¹⁵⁷⁸ See Shono, T.; Kashimura, S.; Mori, Y.; Hayashi, T.; Soejima, T.; Yamaguchi, Y. *J. Org. Chem.* **1989**, 54, 6001.

¹⁵⁷⁹ See Belotti, D.; Cossy, J.; Pete, J.P.; Portella, C. *J. Org. Chem.* **1986**, 51, 4196.

¹⁵⁸⁰ Shimizu, M.; Baba, T.; Toudou, S.; Hachiya, I. *Chem. Lett.* **2007**, 36, 12.

¹⁵⁸¹ For a review, see Ide, W.S.; Buck, J.S. *Org. React.* **1948**, 4, 269.

¹⁵⁸² Xu, L.-W.; Gao, Y.; Yin, J.-J.; Li, L.; Xia, C.-G. *Tetrahedron Lett.* **2005**, 46, 5317. See also, Iwamoto, K.; Kimura, H.; Oike, M.; Sato, M. *Org. Biomol. Chem.* **2008**, 6, 912; Iwamoto, K.; Hamaya, M.; Hashimoto, N.; Kimura, H.; Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **2006**, 47, 7175;

¹⁵⁸³ Storey, J.M.D.; Williamson, C. *Tetrahedron Lett.* **2005**, 46, 7337.

¹⁵⁸⁴ See Kuebrich, J.P.; Schowen, R.L.; Wang, M.; Lupes, M.E. *J. Am. Chem. Soc.* **1971**, 93, 1214.

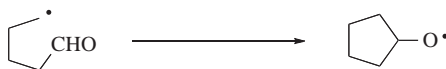
¹⁵⁸⁵ Lapworth, A. *J. Chem. Soc.* **1903**, 83, 995; **1904**, 85, 1206.

The key step, the loss of the aldehyde proton, can take place because the acidity of this C—H bond is increased by the electron-withdrawing power of the CN group. Thus, cyanide is a highly specific catalyst for this reaction, because, almost uniquely, it can perform three functions: (1) It acts as a nucleophile; (2) its electron-withdrawing ability permits loss of the aldehyde proton; and (3) having done this, it then acts as a leaving group. Certain thiazolium salts can also catalyze the reaction.¹⁵⁸⁶ In this case, aliphatic aldehydes can also be used¹⁵⁸⁷ (the products are called *acyloins*), and mixtures of aliphatic and aromatic aldehydes give mixed α -hydroxy ketones.¹⁵⁸⁸ The reaction has also been carried out without cyanide, by using the benzoylated cyanohydrin as one of the components in a phase-transfer catalyzed process. By this means, products can be obtained from aldehydes that normally fail to self-condense.¹⁵⁸⁹ The condensation has also been done with excellent enantioselectivity using benzoyl formate decarboxylase.¹⁵⁹⁰ Enantiopure triazolium salts have been evaluated as catalysts in the enantioselective benzoin condensation.¹⁵⁹¹ *N*-Heterocyclic carbene catalysts have been used for asymmetric induction.¹⁵⁹²

A “mixed”-benzoin condensation has been accomplished by using aryl silyl ketones [ArC(=O)SiMe₂Ph] and aldehydes with a La catalyst.¹⁵⁹³ The reaction of acylsilanes and aldehydes, catalyzed by metal cyanides, is known as the silyl-benzoin reaction.¹⁵⁹⁴

OS I, 94; VII, 95.

16-56 Addition of Radicals to C=O, C=S, C=N Compounds



Radical cyclization is not limited to reaction with a C=C unit (see **15-29** and **15-30**), and reactions with both C=N and C=O moieties are known. Reaction of MeON=CH(CH₂)₃CHO with Bu₃SnH and AIBN, for example, led to *trans*-2-(methoxyamino)cyclopentanol in good yield.¹⁵⁹⁵ Conjugated ketones add to aldehyde via the β carbon under radical conditions (2 molar equivalents of Bu₃SnH and 0.1 equiv of CuCl) to give a β -hydroxy ketone.¹⁵⁹⁶

In a related reaction, diazo compounds add to ketenes to give allenes.¹⁵⁹⁷

Addition of radical to the C=N unit of R—C=N—SPh¹⁵⁹⁸ or R—C=N—OBz¹⁵⁹⁹ led to cyclic imines. Radical addition to simple imines leads to aminocycloalkenes.¹⁶⁰⁰ Radicals

¹⁵⁸⁶ See Diederich, F.; Lutter, H. *J. Am. Chem. Soc.* **1989**, *111*, 8438. Also see Lappert, M.F.; Maskell, R.K. *J. Chem. Soc., Chem. Commun.* **1982**, 580.

¹⁵⁸⁷ Kuhlmann, H. *Org. Synth.* **VII**, 95; Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* **1985**, *50*, 603.

¹⁵⁸⁸ Stetter, H.; Dämbkes, G. *Synthesis* **1977**, 403.

¹⁵⁸⁹ Rozwadowska, M.D. *Tetrahedron* **1985**, *41*, 3135.

¹⁵⁹⁰ Demir, A.S.; Dünnwald, T.; Iding, H.; Pohl, M.; Müller, M. *Tetrahedron Asymmetry* **1999**, *10*, 4769.

¹⁵⁹¹ Enders, D.; Han, J. *Tetrahedron Asymmetry* **2008**, *19*, 1367; O'Toole, S.E.; Connon, S.J. *Org. Biomol. Chem.* **2009**, *7*, 3584; Baragwanath, L.; Rose, C.A.; Zeitler, K.; Connon, S.J. *J. Org. Chem.* **2009**, *74*, 9214.

¹⁵⁹² Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 1463. See also, Mavis, M.E.; Yolacan, C.; Aydogu, F. *Tetrahedron Lett.* **2010**, *51*, 4509.

¹⁵⁹³ Bausch, C.C.; Johnson, J.S. *J. Org. Chem.* **2004**, *69*, 4283.

¹⁵⁹⁴ Linghu, X.; Bausch, C.C.; Jeffrey S.; Johnson, J.S. *J. Am. Chem. Soc.* **2005**, *127*, 1833.

¹⁵⁹⁵ Tormo, J.; Hays, D.S.; Fu, G.C. *J. Org. Chem.* **1998**, *63*, 201.

¹⁵⁹⁶ Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2133.

¹⁵⁹⁷ Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc.* **2007**, *129*, 1494.

¹⁵⁹⁸ Boivin, J.; Fouquet, E.; Zard, S.Z. *Tetrahedron* **1994**, *50*, 1745.

¹⁵⁹⁹ Boivin, J.; Schiano, A.-M.; Zard, S.Z. *Tetrahedron Lett.* **1994**, *35*, 249.

¹⁶⁰⁰ Bowman, W.R.; Stephenson, P.T.; Terrett, N.K.; Young, A.R. *Tetrahedron Lett.* **1994**, *35*, 6369.

also add to the carbonyl unit of phenylthio esters to give cyclic ketones.¹⁶⁰¹ Carbon-centered radicals add to imines.¹⁶⁰² The reaction of an alkyl halide with BEt_3 in aq methanol, for example, gives the imine addition product, an alkylated amine.¹⁶⁰³

Secondary alkyl iodides add to *O*-alkyl oximes in the presence of BEt_3 and AIBN. This methodology was used to convert $\text{MeO}_2\text{C}-\text{CH}=\text{NOBn}$ to $\text{MeO}_2\text{C}-\text{CH}(\text{R})\text{NOBn}$.¹⁶⁰⁴ Benzylic halides add to imines under photochemical conditions, and in the presence of 1-benzyl-1,4-dihydronicotinamide¹⁶⁰⁵ or with BEt_3 in aq methanol.¹⁶⁰⁶ Tertiary alkyl iodides add to oxime ethers using $\text{BF}_3 \cdot \text{OEt}_2$ in the presence of BEt_3/O_2 .¹⁶⁰⁷ *O*-Trityl oximes of 5- and 6-iodoaldehydes undergo radical cyclization to give oximes¹⁶⁰⁸ (also see Reaction 15-30). Enantioselective radical addition reactions to *N*-benzoyl hydrazones used chiral ammonium salts.¹⁶⁰⁹ The Mn mediated reaction of allyl iodides with chiral *N*-acylhydrazones leads to chiral hydrazine derivatives.¹⁶¹⁰

N,N-Dimethylaniline reacts with aldehydes under photochemical conditions to give acyl addition via the carbon atom of one of the methyl groups.¹⁶¹¹ The reaction of PhNMe_2 and benzaldehyde, for example, gave $\text{PhN}(\text{Me})\text{CH}_2\text{CH}(\text{OH})\text{Ph}$ upon photolysis.

16.B.ii. Acyl Substitution Reactions

A. O,N, and S Nucleophiles

16-57 Hydrolysis of Acyl Halides

Hydroxy-de-halogenation



Acyl halides are so reactive that hydrolysis is easily carried out.¹⁶¹² In fact, most simple acyl halides must be stored under anhydrous conditions or they may react with water in the air. Consequently, water is usually a strong enough nucleophile for the reaction, but in unreactive systems hydroxide ion may be required. The reaction is seldom synthetically useful, because acyl halides are normally prepared from acids. The reactivity order is $\text{F} < \text{Cl} < \text{Br} < \text{I}$.¹⁶¹³ If a carboxylic acid is used as the nucleophile, an exchange may take place (see Reaction 16-79). The mechanism¹⁶¹³ of hydrolysis can be either $\text{S}_{\text{N}}1$ or tetrahedral, the former occurring in highly polar solvents and in the absence of strong nucleophiles.¹⁶¹⁴ There is also evidence for the $\text{S}_{\text{N}}2$ mechanism in some cases.¹⁶¹⁵

¹⁶⁰¹ Kim, S.; Jon, S.Y. *Chem. Commun.* **1996**, 1335.

¹⁶⁰² For a review, see Friestad, G.K. *Tetrahedron* **2001**, 57, 5461.

¹⁶⁰³ Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, 65, 5043.

¹⁶⁰⁴ Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* **2000**, 56, 2413.

¹⁶⁰⁵ Jin, M.; Zhang, D.; Yang, L.; Liu, Y.; Liu, Z. *Tetrahedron Lett.* **2000**, 41, 7357.

¹⁶⁰⁶ McNabb, S.B.; Ueda, M.; Naito, T. *Org. Lett.* **2004**, 6, 1911.

¹⁶⁰⁷ Halland, N.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290.

¹⁶⁰⁸ Clive, D.L.J.; Pham, M.P.; Subedi, R. *J. Am. Chem. Soc.* **2007**, 129, 2713.

¹⁶⁰⁹ Jang, D.O.; Kim, S.Y. *J. Am. Chem. Soc.* **2008**, 130, 16152.

¹⁶¹⁰ Friestad, G.K.; Marié, J.-C.; Suh, Y.S.; Qin, J. *J. Org. Chem.* **2006**, 71, 7016.

¹⁶¹¹ Kim, S.S.; Mah, Y.J.; Kim, A.R. *Tetrahedron Lett.* **2001**, 42, 8315.

¹⁶¹² See Bentley, T.W.; Shim, C.S. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1659.

¹⁶¹³ Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10; Elsevier, NY, **1972**, pp. 226–257. See Kivinen, A. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, **1972**, pp. 177–230.

¹⁶¹⁴ Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* **1963**, 85, 30. See also, Song, B.D.; Jencks, W.P. *J. Am. Chem. Soc.* **1989**, 111, 8470; Bentley, T.W.; Koo, I.S.; Norman, S.J. *J. Org. Chem.* **1991**, 56, 1604.

¹⁶¹⁵ Guthrie, J.P.; Pike, D.C. *Can. J. Chem.* **1987**, 65, 1951. See also, Lee, I.; Sung, D.D.; Uhm, T.S.; Ryu, Z.H. *J. Chem. Soc. Perkin Trans. 2* **1989**, 1697.

Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of F.¹⁶¹⁶ There are several methods available for the hydrolysis of acyl fluorides.¹⁶¹⁷

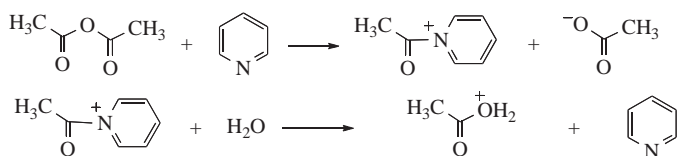
OS II, 74.

16-58 Hydrolysis of Anhydrides

Hydroxy-de-acyloxy-substitution



Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral.¹⁶¹⁸ The S_N1 mechanism only occurs with acid catalysis and seldom even then.¹⁶¹⁹ Anhydride hydrolysis can also be catalyzed by bases. Of course, hydroxide ion attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (Sec. 16.A.i, category 4), is actually the result of two successive tetrahedral mechanisms. For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner.¹⁶²⁰

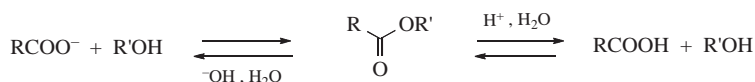


Many other nucleophiles similarly catalyze the reaction.

OS I, 408; II, 140, 368, 382; IV, 766; V, 8, 813.

16-59 Hydrolysis of Carboxylic Esters

Hydroxy-de-alkoxylation



Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When bases catalyze the reaction, the attacking species is the more powerful nucleophile [−]OH. This reaction is called *saponification* and gives the salt of the acid. Acids catalyze the reaction by making the carbonyl carbon more positive, and therefore more susceptible to attack by the nucleophile. Both reactions are equilibrium reactions, so there must be a way to shift the equilibrium to the right for this to be useful. Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution,

¹⁶¹⁶ Bevan, C.W.L.; Hudson, R.F. *J. Chem. Soc.* **1953**, 2187; Satchell, D.P.N. *J. Chem. Soc.* **1963**, 555.

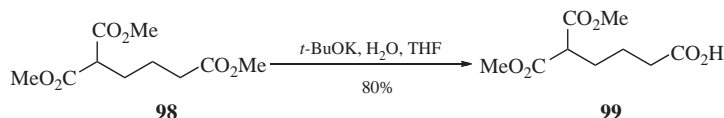
¹⁶¹⁷ Motie, R.E.; Satchell, D.P.N.; Wassef, W.N. *J. Chem. Soc. Perkin Trans. 2* **1992**, 859; **1993**, 1087.

¹⁶¹⁸ See Satchell, D.P.N.; Wassef, W.N.; Bhatti, Z.A. *J. Chem. Soc. Perkin Trans. 2* **1993**, 2373.

¹⁶¹⁹ Satchell, D.P.N. *Q. Rev. Chem. Soc.* **1963**, 17, 160, see pp. 172–173. See Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, **1972**, pp. 280–287.

¹⁶²⁰ See Deady, L.W.; Finlayson, W.L. *Aust. J. Chem.* **1983**, 36, 1951.

unless the compound is base sensitive. Even in the case of **98**, however, selective base hydrolysis of the ethyl ester gave an 80% yield of the acid–dimethyl ester (**99**).¹⁶²¹



Ester hydrolysis can also be catalyzed¹⁶²² by metal ions, by cyclodextrins,¹⁶²³ by enzymes,¹⁶²⁴ and by nucleophiles.¹⁶²¹ Other reagents used to cleave carboxylic esters include Dowex-50,¹⁶²⁵ Me_3SiI ,¹⁶²⁶ and InCl_3 on moist silica gel using microwave irradiation.¹⁶²⁷ Cleavage of phenolic esters is usually faster than carboxylic esters derived from aliphatic acids. The reagent Sm/I_2 at -78°C has been used,¹⁶²⁸ ammonium acetate in aq methanol,¹⁶²⁹ Amberlyst 15 in methanol,¹⁶³⁰ and phenolic esters have been selectively hydrolyzed in the presence of alkyl esters on alumina with microwave irradiation.¹⁶³¹ Allylic esters were cleaved with $\text{DMSO}-\text{I}_2$.¹⁶³² Thiophenol with K_2CO_3 in NMP quantitatively converted methyl benzoate to benzoic acid.¹⁶³³ Allylic esters were cleaved with 2% Me_3SiOTf in dichloromethane,¹⁶³⁴ with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}-\text{NaI}$,¹⁶³⁵ and with NaHSO_4 –silica gel.¹⁶³⁶ Lactones also undergo the reaction¹⁶³⁷ (but if the lactone is five- or six-membered, the hydroxy acid often spontaneously re-forms the lactone) and thiol esters (RCOSR') give thiols $\text{R}'\text{SH}$. Typical reagents for this latter transformation include NaSMe in methanol,¹⁶³⁸ borohydride exchange resin– $\text{Pd}(\text{OAc})_2$ for reductive cleavage of thiol esters to thiols,¹⁶³⁹ and TiCl_4/Zn for the conversion of phenylthioacetates to thiophenols.¹⁶⁴⁰ Sterically hindered esters are hydrolyzed with difficulty (Sec. 10.G.i), but reaction of 2 equiv of $t\text{-BuOK}$ with 1 equiv of water is effective.¹⁶⁴¹ Hindered esters can also be cleaved by sequential treatment with zinc bromide and then water,¹⁶⁴² with

¹⁶²¹ Wilk, B.K. *Synth. Commun.* **1996**, 26, 3859.

¹⁶²² For a list of catalysts and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1959–1968.

¹⁶²³ See Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer, NY, **1978**, pp. 34–41. The mechanism is shown in Saenger, W. *Angew. Chem. Int. Ed.* **1980**, 19, 344.

¹⁶²⁴ For reviews of ester hydrolysis catalyzed by pig liver esterase, see Zhu, L.; Tedford, M.C. *Tetrahedron* **1990**, 46, 6587; Ohno, M.; Otsuka, M. *Org. React.* **1989**, 37, 1. See Wong, C. *Science* **1989**, 244, 1145; Whitesides, G.M.; Wong, C. *Angew. Chem. Int. Ed.* **1985**, 24, 617; Barbayanni, E.; Fotakopoulou, I.; Schmidt, M.; Constantinou-Kokotou, V.; Bornscheuer, U.T.; Kokotos, G. *J. Org. Chem.* **2005**, 70, 8730; Fotakopoulou, I.; Barbayanni, E.; Constantinou-Kokotou, V.; Bornscheuer, U.T.; Kokotos, G. *J. Org. Chem.* **2007**, 72, 782.

¹⁶²⁵ Basu, M.K.; Sarkar, D.C.; Ranu, B.C. *Synth. Commun.* **1989**, 19, 627.

¹⁶²⁶ See Olah, G.A.; Husain, A.; Singh, B.P.; Mehrotra, A.K. *J. Org. Chem.* **1983**, 48, 3667.

¹⁶²⁷ Ranu, B.C.; Dutta, P.; Sarkar, A. *Synth. Commun.* **2000**, 30, 4167.

¹⁶²⁸ Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett* **1995**, 1261.

¹⁶²⁹ Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron* **2003**, 59, 1049.

¹⁶³⁰ Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* **2003**, 44, 5465.

¹⁶³¹ Varma, R.S.; Varma, M.; Chatterjee, A.K. *J. Chem. Soc. Perkin Trans. 1* **1993**, 999.

¹⁶³² Taksande, K.N.; Sakate, S.S.; Lokhande, P.D. *Tetrahedron Lett.* **2006**, 47, 643.

¹⁶³³ Sharma, L.; Nayak, M.K.; Chakraborti, A.K. *Tetrahedron* **1999**, 55, 9595.

¹⁶³⁴ Nishizawa, M.; Yamamoto, H.; Seo, K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2002**, 4, 1947.

¹⁶³⁵ Yadav, J.S.; Reddy, B.V.S.; Rao, C.V.; Chand, P.K.; Prasad, A.R. *Synlett* **2002**, 137.

¹⁶³⁶ Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron Lett.* **2003**, 44, 1465.

¹⁶³⁷ See Kaiser, E.T.; Kézdy, F.J. *Prog. Bioorg. Chem.* **1976**, 4, 239, pp. 254–265.

¹⁶³⁸ Wallace, O.B.; Springer, D.M. *Tetrahedron Lett.* **1998**, 39, 2693.

¹⁶³⁹ Choi, J.; Yoon, N.M. *Synth. Commun.* **1995**, 25, 2655.

¹⁶⁴⁰ Jin, C.K.; Jeong, H.J.; Kim, M.K.; Kim, J.Y.; Yoon, Y.-J.; Lee, S.-G. *Synlett* **2001**, 1956.

¹⁶⁴¹ Gassman, P.G.; Schenk, W.N. *J. Org. Chem.* **1977**, 42, 918.

¹⁶⁴² Wu, Y.-g.; Limburg, D.C.; Wilkinson, D.E.; Vaal, M.J.; Hamilton, G.S. *Tetrahedron Lett.* **2000**, 41, 2847.

silica gel in refluxing toluene,¹⁶⁴³ and on alumina when irradiated with microwaves.¹⁶⁴⁴ For esters insoluble in water the rate of two-phase ester saponification can be greatly increased by the application of ultrasound,¹⁶⁴⁵ and phase-transfer techniques have been applied.¹⁶⁴⁶

Enzymatic hydrolysis of diesters with esterase has been shown to give the hydroxy-ester,¹⁶⁴⁷ and selective hydrolysis of dimethyl succinate to monomethyl succinic acid was accomplished with aq NaOH in THF.¹⁶⁴⁸ Hydrolysis of vinyl esters leads to ketones, and the reaction of *C*-substituted vinyl acetates with an esterase derived from *Marchantia polymorpha* gave substituted ketones with high enantioselectivity.¹⁶⁴⁹ Scandium triflate was shown to hydrolyze α -acetoxy ketones to α -hydroxy ketones.¹⁶⁵⁰

Ingold¹⁶⁵¹ has classified the acid- and base-catalyzed hydrolyses of esters (and the formation of esters, since these are reversible reactions and thus have the same mechanisms) into eight possible mechanisms (Table 16.3),^{1651,1652} depending on the following criteria: (1) acid- or base catalyzed, (2) unimolecular or bimolecular, and (3) acyl cleavage or alkyl cleavage.¹⁶⁵³ All eight of these are S_N1 , S_N2 , or tetrahedral mechanisms. The acid-catalyzed mechanisms are shown with reversible arrows. They are not only reversible, but also symmetrical; that is, the mechanisms for ester formation are exactly the same as for hydrolysis, except that H replaces R. Internal proton transfers, such as shown for **B** and **C**, may not actually be direct but may take place through the solvent. There is much physical evidence to show that esters are initially protonated on the carbonyl and not on the alkyl oxygen (Chap 8, Ref. 17). Nevertheless the $A_{AC}1$ mechanism is shown as proceeding through the ether-protonated intermediate **A**, since it is difficult to envision OR' as a leaving group here. It is of course possible for a reaction to proceed through an intermediate even if only a tiny concentration is present. The designations $A_{AC}1$, and so on, are those of Ingold. The $A_{AC}2$ and $A_{AC}1$ mechanisms are also called $A2$ and $A1$, respectively. Note that the $A_{AC}1$ mechanism is actually the same as the S_N1cA mechanism for this type of substrate and that $A_{AL}2$ is analogous to S_N2cA . Some authors use $A1$ and $A2$ to refer to all types of nucleophilic substitution in which the leaving group first acquires a proton. The base-catalyzed reactions are not shown with reversible arrows, since they are reversible only in theory and not in practice. Hydrolyses taking place under neutral conditions are classified as B mechanisms. Molecular dynamics has shown that “the rate of hydrolysis of methyl formate in pure water is consistent with mechanisms involving cooperative catalysis by autoionization-generated hydroxide and hydronium, a process known to have an activation free energy of $23.8 \text{ kcal mol}^{-1}$ (99.6 kJ mol^{-1}).”¹⁶⁵⁴

¹⁶⁴³ Jackson, R.W. *Tetrahedron Lett.* **2001**, 42, 5163.

¹⁶⁴⁴ Ley, S.V.; Mynett, D.M. *Synlett* **1993**, 793.

¹⁶⁴⁵ Moon, S.; Duchin, L.; Cooney, J.V. *Tetrahedron Lett.* **1979**, 3917.

¹⁶⁴⁶ Loupy, A.; Pedoussaut, M.; Sansoulet, J. *J. Org. Chem.* **1986**, 51, 740.

¹⁶⁴⁷ See Nair, R.V.; Shukla, M.R.; Patil, P.N.; Salunkhe, M.M. *Synth. Commun.* **1999**, 29, 1671.

¹⁶⁴⁸ Niwayama, S. *J. Org. Chem.* **2000**, 65, 5834.

¹⁶⁴⁹ Hirata, T.; Shimoda, K.; Kawano, T. *Tetrahedron Asymmetry* **2000**, 11, 1063.

¹⁶⁵⁰ Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, 72, 1553.

¹⁶⁵¹ Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2d ed., Cornell University Press, Ithaca, NY, **1969**, pp. 1129–1131.

¹⁶⁵² As given here, the IUPAC designations for $B_{AC}1$ and $B_{AL}1$ are the same, but Rule A.2 adds further symbols so that they can be distinguished: $Su-AL$ for $B_{AL}1$ and $Su-AC$ for $B_{AC}1$. See the IUPAC rules: Guthrie, R.D. *Pure Appl. Chem.* **1989**, 61, 23, see p. 49.

¹⁶⁵³ Kirby, A.J. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, **1972**, pp. 57–207; Euranto, E.K. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, **1969**, pp. 505–588.

¹⁶⁵⁴ Gunaydin, H.; Houk, K.N. *J. Am. Chem. Soc.* **2008**, 130, 15232.

TABLE 16.3 Classification of the Eight Mechanisms for Ester Hydrolysis and Formation

Name		IUPAC ^a	Type
Ingold			
$A_{AC}1$	$ \begin{array}{c} \text{R}-\text{C}(=\text{O})-\text{OR}' \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(=\text{O}^+-\text{H})-\text{OR}' \xrightleftharpoons[\text{R}'\text{OH}]{\text{slow}} \text{R}-\text{C}(=\text{O})-\text{H} + \text{R}'\text{OH} \xrightleftharpoons[\text{slow}]{\text{H}_2\text{O}} \text{R}-\text{C}(=\text{O}^+-\text{H})-\text{H} \rightleftharpoons \text{R}-\text{C}(\text{OH})^+-\text{H} \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(=\text{O})-\text{OH} \end{array} $ <p style="text-align: center;">A</p>	$A_h + D_N + A_N + D_h$	S_N1
$A_{AC}2$	$ \begin{array}{c} \text{R}-\text{C}(=\text{O})-\text{OR}' \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(\text{OH})^+-\text{OR}' \xrightleftharpoons[\text{slow}]{\text{H}_2\text{O}} \text{R}-\text{C}(\text{OH})(\text{OR}')(=\text{OH}_2^+) \rightleftharpoons \text{R}-\text{C}(\text{OH})(\text{OH})(\text{OR}') \xrightleftharpoons[\text{R}'\text{OH}]{\text{slow}} \text{R}-\text{C}(\text{OH})^+-\text{H} \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(=\text{O})-\text{OH} \end{array} $ <p style="text-align: center;">B C</p>	$A_h + A_N + A_h D_h + D_h$	Tetrahedral
$A_{AL}1$	$ \begin{array}{c} \text{R}-\text{C}(=\text{O})-\text{OR}' \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(\text{OH})^+-\text{OR}' \rightleftharpoons \text{R}-\text{C}(=\text{O})-\text{OH} + \text{R}'^+ \xrightleftharpoons[\text{slow}]{\text{H}_2\text{O}} \text{RO}_2 \xrightleftharpoons{\text{H}^+} \text{R}'\text{OH} \end{array} $	$A_h + D_N + A_N + D_h$	S_N1
$A_{AL}2$	$ \begin{array}{c} \text{R}-\text{C}(=\text{O})-\text{OR}' \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(=\text{O}^+-\text{H})-\text{OR}' \xrightleftharpoons{\text{H}_2\text{O}} \text{R}-\text{C}(=\text{O})-\text{OH} + \text{R}'\text{OH}_2^+ \xrightleftharpoons[\text{H}^+]{\text{H}^+} \text{R}'\text{OH} \end{array} $	$A_h + A_N D_N + D_h$	S_N2
$B_{AC}1$	$ \text{R}-\text{C}(=\text{O})-\text{OR}' \xrightarrow[\text{slow}]{} \text{R}-\text{C}(=\text{O}) + \text{OR}'^- \xrightarrow{} \text{R}-\text{C}(=\text{O})-\text{OH} + \text{OR}'^- \xrightarrow{} \text{R}-\text{C}(=\text{O})-\text{O}^- + \text{HOR}' $	$D_N + A_N + A_{xh} D_h$	S_N1

(continued)

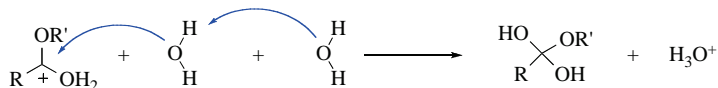
TABLE 16.3 (Continued)

Name			IUPAC ^a	Type
Ingold				
B _{AC} 2	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}' \xrightarrow[\text{slow}]{^-\text{OH}} \text{R}-\overset{\text{OH}}{\underset{\text{O}^-}{\text{C}}}-\text{OR}' \longrightarrow \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH} + ^-\text{OR}' \longrightarrow \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}^- + \text{HOR}'$		A _N +D _N +A _{AB} D _B	Tetrahedral
B _{AL} 1	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}' \xrightarrow{\text{slow}} \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}^- + \text{R}' \xrightarrow{\text{H}_2\text{O}} \text{R}'\text{OH}_2^+ \xrightarrow{^-\text{OH}} \text{R}'\text{OH}$		D _N +A _N +A _{AB} D _B	S _N 1
B _{AL} 2	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}' \xrightarrow{^-\text{OH}} \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}^- + \text{R}'\text{OH}$		A _N D _N	S _N 2

Adapted material from *Structure and Mechanism in Organic Chemistry*, 2d ed., Cornell University Press, Ithaca, NY, **1969**, pp. 1129–1131, edited by Ingold, C.K. Copyright © 1969 by Cornell University. Used by permission of the publisher, Cornell University Press.

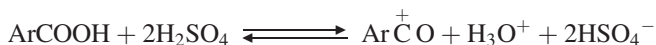
^aSee Ref. 1652

Of the eight mechanisms, seven have actually been observed in the hydrolysis of carboxylic esters. The one that has not been observed is the $B_{AC}1$ mechanism.¹⁶⁵⁵ The most common mechanisms are the $B_{AC}2$ for basic catalysis and the $A_{AC}2$ ¹⁶⁵⁶ for acid catalysis, that is, the two tetrahedral mechanisms. Both involve acyl–oxygen cleavage. The evidence is (1) hydrolysis with $H_2^{18}O$ results in the ^{18}O appearing in the acid and not in the alcohol;¹⁶⁵⁷ (2) esters with chiral R' groups give alcohols with *retention* of configuration;¹⁶⁵⁸ (3) allylic R' gives no allylic rearrangement;¹⁶⁵⁹ (4) neopentyl R' gives no rearrangement¹⁶⁶⁰; all these facts indicate that the $O-R'$ bond is not broken. It has been concluded that two molecules of water are required in the $A_{AC}2$ mechanism, as shown:



If this were so, the protonated derivatives **B** and **C** would not appear at all. This conclusion stems from a value of w (see Sec. 8.C) of ~ 5 , indicating that water acts as a proton donor here as well as a nucleophile.¹⁶⁶¹ Termolecular processes are rare, but in this case the two water molecules are already connected by a hydrogen bond. (A similar mechanism, called $B_{AC}3$, also involving two molecules of water, has been found for esters that hydrolyze without a catalyst.¹⁶⁶² Such esters are mostly those containing halogen atoms in the R group.)

The other mechanism involving acyl cleavage is the $A_{AC}1$ mechanism. This is rare, being found only where R is very bulky, so that bimolecular attack is sterically hindered, and only in ionizing solvents. The mechanism has been demonstrated for esters of 2,4,6-trimethylbenzoic acid (mesitoic acid). This acid depresses the freezing point of sulfuric acid four times as much as would be predicted from its molecular weight, which is evidence for the equilibrium



In a comparable solution of benzoic acid, the freezing point is depressed only twice the predicted amount, indicating only a normal acid–base reaction. Further, a sulfuric acid solution of methyl mesitoate when poured into water gave mesitoic acid, while a similar solution of methyl benzoate similarly treated did not.¹⁶⁶³ The $A_{AC}1$ mechanism is also found when acetates of phenols or of primary alcohols are hydrolyzed in concentrated ($>90\%$) H_2SO_4 (the mechanism under the more usual dilute acid conditions is the normal $A_{AC}2$).¹⁶⁶⁴

The mechanisms involving alkyl–oxygen cleavage are ordinary S_N1 and S_N2 mechanisms in which $OCOR$ (an acyloxy group) or its conjugate acid is the leaving group. Two of the three mechanisms, the $B_{AL}1$ and $A_{AL}1$ mechanisms, occur most readily when R' comes off as a stable carbocation (i.e., when R' is tertiary alkyl, allylic, benzylic, etc.). For acid

¹⁶⁵⁵ This is an S_N1 mechanism with OR' as leaving group, which does not happen.

¹⁶⁵⁶ See Zimmermann, H.; Rudolph, J. *Angew. Chem. Int. Ed.* **1965**, 4, 40.

¹⁶⁵⁷ See Polanyi, M.; Szabo, A.L. *Trans. Faraday Soc.* **1934**, 30, 508.

¹⁶⁵⁸ Holmberg, B. *Ber.* **1912**, 45, 2997.

¹⁶⁵⁹ Ingold, C.K.; Ingold, E.H. *J. Chem. Soc.* **1932**, 758.

¹⁶⁶⁰ Norton, H.M.; Quayle, O.R. *J. Am. Chem. Soc.* **1940**, 62, 1170.

¹⁶⁶¹ Martin, R.B. *J. Am. Chem. Soc.* **1962**, 84, 4130. See also Yates, K. *Acc. Chem. Res.* **1971**, 6, 136; Huskey, W. P.; Warren, C.T.; Hogg, J.L. *J. Org. Chem.* **1981**, 46, 59.

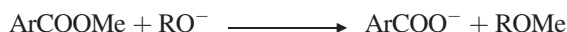
¹⁶⁶² See Euranto, E.K.; Kanerva, L.T. *Acta Chem. Scand. Ser. B* **1988**, 42, 717.

¹⁶⁶³ Treffers, H.P.; Hammett, L.P. *J. Am. Chem. Soc.* **1937**, 59, 1708. For other evidence for this mechanism, see Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* **1963**, 85, 37.

¹⁶⁶⁴ Yates, K. *Acc. Chem. Res.* **1971**, 6, 136; Al-Shalchi, W.; Selwood, T.; Tillett J.G. *J. Chem. Res. (S)* **1985**, 10.

catalysis, most esters with this type of alkyl group (especially tertiary alkyl) cleave by this mechanism, but even for these substrates, the B_{AL}1 mechanism occurs only in neutral or weakly basic solution, where the rate of attack by hydroxide is so slowed that the normally slow (by comparison) unimolecular cleavage takes over. These two mechanisms have been established by kinetic studies, ¹⁸O labeling, and isomerization of R'.¹⁶⁶⁵ Secondary and benzylic acetates hydrolyze by the A_{AC}2 mechanism in dilute H₂SO₄, but in concentrated acid the mechanism changes to A_{AL}1.¹⁶⁶⁵ Despite its designation, the B_{AL}1 mechanism is actually uncatalyzed (as is the unknown B_{AC}1 mechanism).

The two remaining mechanisms, B_{AL}2 and A_{AL}2, are very rare. The B_{AL}2 mechanism because it requires hydroxide ion to attack an alkyl carbon when an acyl carbon is also available,¹⁶⁶⁶ and the A_{AL}2 because it requires water to be a nucleophile in an S_N2 process. Both have been observed, however. The B_{AL}2 has been seen in the hydrolysis of β-lactones under neutral conditions¹⁶⁶⁷ (because cleavage of the C—O bond in the transition state opens the four-membered ring and relieves strain), the alkaline hydrolysis of methyl 2,4,6-tri-*tert*-butyl benzoate,¹⁶⁶⁸ and in the unusual reaction:¹⁶⁶⁹



When it does occur, the B_{AL}2 mechanism is easy to detect, since it is the only one of the base-catalyzed mechanisms that requires inversion at R'. However, in the last example given, the mechanism is evident from the nature of the product, since the ether could have been formed in no other way. The A_{AL}2 mechanism has been reported in the acid cleavage of γ-lactones.¹⁶⁷⁰

To sum up the acid-catalysis mechanisms, A_{AC}2 and A_{AL}1 are the common mechanisms, the latter for R' that give stable carbocations, the former for practically all the rest. The A_{AC}1 mechanism is rare, being found mostly with strong acids and sterically hindered R. The A_{AL}2 mechanism is even rarer. For basic catalysis, B_{AC}2 is almost universal; B_{AL}1 occurs only with R' that give stable carbocations and then only in weakly basic or neutral solutions; B_{AL}2 is very rare; and B_{AC}1 has never been observed.

The above results pertain to reactions in solution. In the gas phase,¹⁶⁷¹ reactions can take a different course, as illustrated by the reaction of carboxylic esters with MeO[−], which in the gas phase was shown to take place only by the B_{AL}2 mechanism,¹⁶⁷² even with aryl esters,¹⁶⁷³ where this means that an S_N2 mechanism takes place at an aryl substrate. However, when the gas-phase reaction of aryl esters was carried out with MeO[−] ions, each of which was solvated with a single molecule of MeOH or H₂O, the B_{AC}2 mechanism was observed.¹⁶⁷²

In the special case of alkaline hydrolysis of *N*-substituted aryl carbamates, there is another mechanism¹⁶⁷⁴ involving elimination–addition:¹⁶⁷⁵

¹⁶⁶⁵ For discussions, see Kirby, A.J. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, pp. 86–101; Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithica, NY, **1969**, pp. 1137–1142, 1157–1163.

¹⁶⁶⁶ Douglas, J.E.; Campbell, G.; Wigfield, D.C. *Can. J. Chem.* **1993**, *71*, 1841.

¹⁶⁶⁷ Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *J. Chem. Soc.* **1937**, 1264; Long, F. A.; Purchase, M. *J. Am. Chem. Soc.* **1950**, *73*, 3267.

¹⁶⁶⁸ Barclay, L.R.C.; Hall, N.D.; Cooke, G.A. *Can. J. Chem.* **1962**, *40*, 1981.

¹⁶⁶⁹ Snee, R.A.; Rosenberg, A.M. *J. Org. Chem.* **1961**, *26*, 2099. See also, Müller, P.; Siegfried, B. *Helv. Chim. Acta* **1974**, *57*, 987.

¹⁶⁷⁰ Moore, J.A.; Schwab, J.W. *Tetrahedron Lett.* **1991**, *32*, 2331.

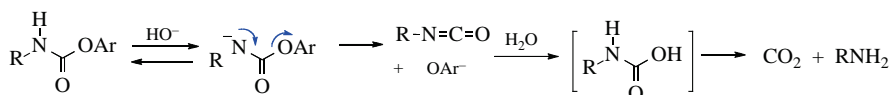
¹⁶⁷¹ Takashima, K.; José, S.M.; do Amaral, A.T.; Riveros, J.M. *J. Chem. Soc., Chem. Commun.* **1983**, 1255.

¹⁶⁷² Comisarow, M. *Can. J. Chem.* **1977**, *55*, 171.

¹⁶⁷³ Fukuda, E.K.; McIver, Jr., R.T. *J. Am. Chem. Soc.* **1979**, *101*, 2498.

¹⁶⁷⁴ See Williams, A.; Douglas, K.T. *Chem. Rev.* **1975**, *75*, 627.

¹⁶⁷⁵ See Broxton, T.J.; Chung, R.P. *J. Org. Chem.* **1986**, *51*, 3112.



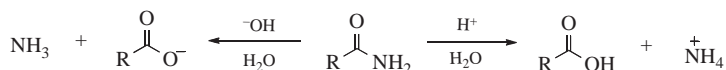
This mechanism does not apply to unsubstituted or *N,N*-disubstituted aryl carbamates, which hydrolyze by the normal mechanisms. Carboxylic esters substituted in the α position by an electron-withdrawing group (e.g., CN or CO₂Et) can also hydrolyze by a similar mechanism involving a ketene intermediate.¹⁶⁷⁶ These elimination–addition mechanisms usually are referred to as E1cB mechanisms, because that is the name given to the elimination portion of the mechanism (Sec. 17.A.iii).

The acid-catalyzed hydrolysis of enol esters (RCOOCR' = CR) can take place either by the normal A_{AC}2 mechanism or by a mechanism involving initial protonation on the double-bond carbon, similar to the mechanism for the hydrolysis of enol ethers given in Reaction 10-6,¹⁶⁷⁷ depending on reaction conditions.¹⁶⁷⁸ In either case, the products are the carboxylic acid (RCO₂H) and the aldehyde or ketone (R—CHCOR').

OS I, 351, 360, 366, 379, 391, 418, 523; II, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; III, 3, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809 (but see OS V, 1050), 833, 835; IV, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; V, 8, 445, 509, 687, 762, 887, 985, 1031; VI, 75, 121, 560, 690, 824, 913, 1024; VII, 4, 190, 210, 297, 319, 323, 356, 411; VIII, 43, 141, 219, 247, 258, 263, 298, 486, 516, 527. Ester hydrolyses with concomitant decarboxylation are listed at Reaction 12-40.

16-60 Hydrolysis of Amides

Hydroxy-de-amination



Unsubstituted amides (RCONH₂) can be hydrolyzed with either acidic or basic catalysis, and the products are, respectively, the free acid and the ammonium ion or the salt of the acid and ammonia. *N*-Substituted (RCONHR') and *N,N*-disubstituted (RCONR'₂) amides can be hydrolyzed analogously, and the product is the primary or secondary amine, respectively (or their salts), rather than ammonia. Twisting of the amide bond leads to an acceleration of water-promoted hydrolysis reactions.¹⁶⁷⁹ Lactams, imides, cyclic imides, hydrazides, and so on, also undergo the reaction.

Water alone is not sufficient to hydrolyze most amides,¹⁶⁸⁰ since NH₂ is even a poorer leaving group than OR.¹⁶⁸¹ Prolonged heating is often required, even with acidic or basic catalysts.¹⁶⁸² Treatment of primary amides with phthalic anhydride at 250 °C and 4 atm

¹⁶⁷⁶ Inoue, T.C.; Bruice, T.C. *J. Org. Chem.* **1986**, 51, 959; Isaacs, N.S.; Najem, T.S. *Can. J. Chem.* **1986**, 64, 1140; *J. Chem. Soc. Perkin Trans. 2* **1988**, 557.

¹⁶⁷⁷ Allen, A.D.; Kitamura, T.; Roberts, K.A.; Stang, P.J.; Tidwell, T.T. *J. Am. Chem. Soc.* **1988**, 110, 622.

¹⁶⁷⁸ See Euranto, E.K. *Pure Appl. Chem.* **1977**, 49, 1009.

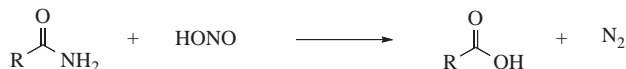
¹⁶⁷⁹ Mujika, J.I.; Mercero, J.M.; Lopez, X. *J. Am. Chem. Soc.* **2005**, 127, 4445.

¹⁶⁸⁰ See Zahn, D. *Eur. J. Org. Chem.* **2004**, 4020.

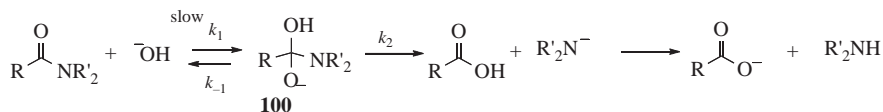
¹⁶⁸¹ See Kahne, D.; Still, W.C. *J. Am. Chem. Soc.* **1988**, 110, 7529.

¹⁶⁸² For a list of catalysts and, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1976–1977. Also see, Bagno, A.; Lovato, G.; Scorrano, G. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1091.

gives the carboxylic acid and phthalimide.¹⁶⁸³ Hydrolysis of carbamates (RNHCO₂R) to the corresponding amine can be categorized in this section. Although the product is an amine and the carboxyl unit fragments, this reaction is simply a variation of amide hydrolysis. Strong acids [e.g., trifluoroacetic acid (in dichloromethane)] are usually employed.¹⁶⁸⁴ Treatment of *N*-Boc derivatives (RNHCO₂*t*-Bu) with AlCl₃¹⁶⁸⁵ or with aq sodium *tert*-butoxide¹⁶⁸⁶ gave the amine. The byproducts of this reaction are typically carbon dioxide and isobutylene.



In difficult cases, nitrous acid, NOCl, N₂O₄,¹⁶⁸⁷ or a similar compound can be used (unsubstituted amides only¹⁶⁸⁸). These reactions involve a diazonium ion (see Reaction **13-19**) and are much faster than ordinary hydrolysis. The benzamide–nitrous acid reaction took place 2.5×10^7 times faster than ordinary hydrolysis, for example.¹⁶⁸⁹ Another procedure for difficult cases involves treatment with aq sodium peroxide.¹⁶⁹⁰ In still another method, the amide is treated with water and *t*-BuOK at room temperature.¹⁶⁹¹ A kinetic study has been done on the alkaline hydrolyses of *N*-trifluoroacetyl aniline derivatives.¹⁶⁹² Amide hydrolysis can also be catalyzed by nucleophiles (see Sec. 16.A.i, category 4).



The same framework of eight possible mechanisms discussed for ester hydrolysis in Reaction **16-59** can also be applied to amide hydrolysis.¹⁶⁹³ Both the acid- and base-catalyzed hydrolyses are essentially irreversible, since salts are formed in both cases. For basic catalysis¹⁶⁹⁴ the mechanism is B_{AC}2. There is much evidence for this mechanism, similar to that discussed for ester hydrolysis. Molecular orbital studies on the mechanism of amide hydrolysis suggest a highly tetrahedral transition state.¹⁶⁹⁵ In certain cases, kinetic studies have shown that the reaction is second order in OH[−] indicating that **100** can lose a proton to give **101**.¹⁶⁹⁶ Depending on the nature of R', **101** can cleave directly to give the two negative ions (path *a*) or become N-protonated prior to or during the act of cleavage

¹⁶⁸³ Chemat, F. *Tetrahedron Lett.* **2000**, 41, 3855.

¹⁶⁸⁴ Schwyzer, R.; Costopanagiotis, A.; Sieber, P. *Helv. Chim. Acta* **1963**, 46, 870.

¹⁶⁸⁵ Bose, D.S.; Lakshminarayana, V. *Synthesis* **1999**, 66.

¹⁶⁸⁶ Tom, N.J.; Simon, W.M.; Frost, H.N.; Ewing, M. *Tetrahedron Lett.* **2004**, 45, 905.

¹⁶⁸⁷ Kim, Y.H.; Kim, K.; Park, Y.J. *Tetrahedron Lett.* **1990**, 31, 3893.

¹⁶⁸⁸ See Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* **1983**, 48, 2424.

¹⁶⁸⁹ Ladenheim, H.; Bender, M.L. *J. Am. Chem. Soc.* **1960**, 82, 1895.

¹⁶⁹⁰ Vaughan, H.L.; Robbins, M.D. *J. Org. Chem.* **1975**, 40, 1187.

¹⁶⁹¹ Gassman, P.G.; Hodgson, P.K.G.; Balchunis, R.J. *J. Am. Chem. Soc.* **1976**, 98, 1275.

¹⁶⁹² Hibbert, F.; Malana, M.A. *J. Chem. Soc. Perkin Trans. 2* **1992**, 755.

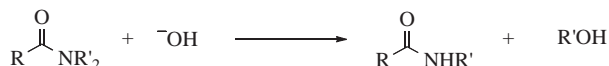
¹⁶⁹³ O'Connor, C. *Q. Rev. Chem. Soc.* **1970**, 24, 553; Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, pp. 257–280; Challis, B.C.; Challis, J.C. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 731–857.

¹⁶⁹⁴ See DeWolfe, R.H.; Newcomb, R.C. *J. Org. Chem.* **1971**, 36, 3870.

¹⁶⁹⁵ Hori, K.; Kamimura, A.; Ando, K.; Mizumura, M.; Ihara, Y. *Tetrahedron* **1997**, 53, 4317. See Marlier, J.F.; Campbell, E.; Lai, C.; Weber, M.; Reinhardt, L.A.; Cleland, W.W. *J. Org. Chem.* **2006**, 71, 3829.

¹⁶⁹⁶ Khan, M.N.; Olagbemiro, T.O. *J. Org. Chem.* **1982**, 47, 3695.

The four mechanisms involving alkyl–N cleavage (the AL mechanisms) do not apply to this reaction. They are not possible for unsubstituted amides, since the only N–C bond is the acyl bond. They are possible for *N*-substituted and *N,N*-disubstituted amides, but in these cases they give entirely different products and are not amide hydrolyses at all.



The reaction shown involves attack by the base on an *N*-alkyl group to give an alcohol. While rare, it has been observed for various *N-tert*-butylamides in 98% sulfuric acid, where the mechanism was A_{AL}1,¹⁷⁰³ and for certain amides containing an azo group, where a B_{AL}1 mechanism was postulated.¹⁷⁰⁴ Of the two first-order acyl cleavage mechanisms, only the A_{AC}1 has been observed, in concentrated sulfuric acid solutions.¹⁷⁰⁵ Of course, the diazotization of unsubstituted amides might be expected to follow this mechanism, and there is evidence that this is true.¹⁶⁸⁹

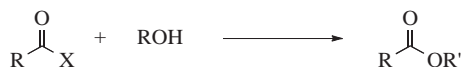
OS **I**, 14, 111, 194, 201, 286; **II**, 19, 25, 28, 49, 76, 208, 330, 374, 384, 457, 462, 491, 503, 519, 612; **III**, 66, 88, 154, 256, 410, 456, 586, 591, 661, 735, 768, 813; **IV**, 39, 42, 55, 58, 420, 441, 496, 664; **V**, 27, 96, 341, 471, 612, 627; **VI**, 56, 252, 507, 951, 967; **VII**, 4, 287; **VIII**, 26, 204, 241, 339, 451.

The oxidation of aldehydes to carboxylic acids can proceed by a nucleophilic mechanism, but more often it does not. The reaction is considered in Reaction **19-23**. Basic cleavage of β-keto esters and the haloform reaction could be considered at this point, but they are also electrophilic substitutions and are treated in Reactions **12-43** and **12-44**.

B. Attack by OR at an Acyl Carbon

16-61 Alcoholysis of Acyl Halides

Alkoxy-de-halogenation



The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. It is believed to proceed by a S_N2 mechanism.¹⁷⁰⁶ As with Reaction **16-57**, however, the mechanism can be S_N1 or tetrahedral.¹⁶¹³ Lewis acids (e.g., lithium perchlorate) can be used.¹⁷⁰⁷ The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aq alkali is used, this is called the *Schotten–Baumann procedure*, but pyridine is also frequently used. Indeed, pyridine catalyzes the reaction by the nucleophilic catalysis route (see Reaction **16-58**). Both R and R' may be primary, secondary, or tertiary alkyl or aryl. Enol esters can also be prepared by this method, though C-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R', the alkoxide can be used instead of the alcohol.¹⁷⁰⁸ Activated alumina has also been used as a catalyst,

¹⁷⁰³ Lacey, R.N. *J. Chem. Soc.* **1960**, 1633; Druet, L.M.; Yates, K. *Can. J. Chem.* **1984**, 62, 2401.

¹⁷⁰⁴ Stodola, F.H. *J. Org. Chem.* **1972**, 37, 178.

¹⁷⁰⁵ See Barnett, J.W.; O'Connor, C.J. *J. Chem. Soc., Chem. Commun.* **1972**, 525; *J. Chem. Soc. Perkin Trans. 2* **1972**, 2378.

¹⁷⁰⁶ Bentley, T.W.; Llewellyn, G.; McAlister, J.A. *J. Org. Chem.* **1996**, 61, 7927.

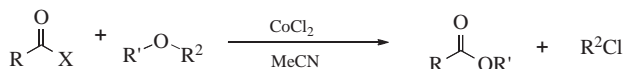
¹⁷⁰⁷ Bandgar, B.P.; Kamble, V.T.; Sadavarte, V.S.; Uppalla, L.S. *Synlett* **2002**, 735.

¹⁷⁰⁸ See Kaiser, E.M.; Woodruff, R.A. *J. Org. Chem.* **1970**, 35, 1198.

for tertiary R'.¹⁷⁰⁹ Thallium salts of phenols give very high yields of phenolic esters,¹⁷¹⁰ and BiOCl is very effective for the preparation of phenolic acetates.¹⁷¹¹ Phase-transfer catalysis has been used for hindered phenols.¹⁷¹² Zinc has been used to couple alcohols and acyl chlorides,¹⁷¹³ Zr compounds were used,¹⁷¹⁴ and catalytic Cu(acac)₂ and benzoyl chloride was used to prepare the monobenzoate of ethylene glycol.¹⁷¹⁵ Selective acylation is possible in some cases.¹⁷¹⁶

Acyl halides react with thiols, in the presence of Zn, to give the corresponding thio-ester.¹⁷¹⁷ The reaction of acid chlorides or anhydrides (see **16-62**) with diphenyldiselenide, in the presence of Sm/CoCl₂¹⁷¹⁸ or Sm/CrCl₃¹⁷¹⁹ gave the corresponding seleno ester (PhSeCOMe).

Acyl halides can also be converted to carboxylic acids by using ethers instead of alcohols, as shown, in MeCN in the presence of certain catalysts [e.g., cobalt(II) chloride].¹⁷²⁰ A variation of this reaction has been reported that uses acetic anhydride (also see **16-62**).¹⁷²¹

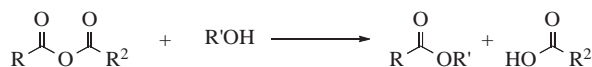


This is a method for the cleavage of ethers (see also, Reaction **10-49**).

OS **I**, 12; **III**, 142, 144, 167, 187, 623, 714; **IV**, 84, 263, 478, 479, 608, 616, 788; **V**, 1, 166, 168, 171; **VI**, 199, 259, 312, 824; **VII**, 190; **VIII**, 257, 516.

16-62 Alcoholysis of Anhydrides

Alkoxy-de-acyloxy-substitution



The scope of this reaction is similar to that of **16-61**. Anhydrides are somewhat less reactive than acyl halides, but they are often used to prepare carboxylic esters. Acids,¹⁷²² Lewis acids,¹⁷²³ and bases (e.g., pyridine) are often used as catalysts.¹⁷²⁴ Acetic anhydride

¹⁷⁰⁹ Nagasawa, K.; Yoshitake, S.; Amiya, T.; Ito, K. *Synth. Commun.* **1990**, 20, 2033.

¹⁷¹⁰ Taylor, E.C.; McLay, G.W.; McKillop, A. *J. Am. Chem. Soc.* **1968**, 90, 2422.

¹⁷¹¹ Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* **2004**, 45, 6775.

¹⁷¹² Illi, V.O. *Tetrahedron Lett.* **1979**, 2431. For another method, see Nekhoroshev, M.V.; Ivakhnenko, E.P.; Okhlobystin, O.Yu. *J. Org. Chem. USSR* **1977**, 13, 608.

¹⁷¹³ Yadav, J.S.; Reddy, G.S.; Svinivas, D.; Himabindu, K. *Synth. Commun.* **1998**, 28, 2337.

¹⁷¹⁴ Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* **2005**, 46, 147.

¹⁷¹⁵ Sirkecioglu, O.; Karlaga, B.; Talinli, N. *Tetrahedron Lett.* **2003**, 44, 8483.

¹⁷¹⁶ Srivastava, V.; Tandon, A.; Ray, S. *Synth. Commun.* **1992**, 22, 2703.

¹⁷¹⁷ Meshram, H.M.; Reddy, G.S.; Bindu, K.H.; Yadav, J.S. *Synlett* **1998**, 877.

¹⁷¹⁸ Chen, R.; Zhang, Y. *Synth. Commun.* **2000**, 30, 1331.

¹⁷¹⁹ Liu, Y.; Zhang, Y. *Synth. Commun.* **1999**, 29, 4043.

¹⁷²⁰ See Ahmad, S.; Iqbal, J. *Chem. Lett.* **1987**, 953, and references cited therein.

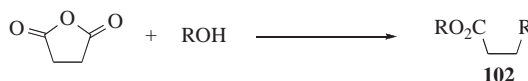
¹⁷²¹ Lakouraj, M.; Movassagh, B.; Fasihi, J. *J. Chem. Res. (S)* **2001**, 378.

¹⁷²² Nafion-H has been used: Kumareswaran, R.; Pachamuthu, K.; Vankar, Y.D. *Synlett* **2000**, 1652.

¹⁷²³ **Ce**: Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett.* **2003**, 44, 5621. **Cu**: Saravanan, P.; Singh, V.K. *Tetrahedron Lett.* **1999**, 40, 2611. **In**: Chakraborti, A.K.; Gulhane, R. *Tetrahedron Lett.* **2003**, 44, 6749. **Li**: Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* **2001**, 1584. **Mg**: Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* **2003**, 4611. **Ru**: De, S.K. *Tetrahedron Lett.* **2004**, 45, 2919. **Ti**: Chandrasekhar, S.; Ramachandar, T.; Reddy, M.V.; Takhi, M. *J. Org. Chem.* **2000**, 65, 4729. **Yb**: Dumeunier, R.; Markó, I.E. *Tetrahedron Lett.* **2004**, 45, 825.

¹⁷²⁴ For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1955–1957.

and NiCl_2 with microwave irradiation converts benzylic alcohols to the corresponding acetate.¹⁷²⁵ The monoacetates of 1,2-diols have been prepared using CeCl_3 as a catalyst.¹⁷²⁶ Pyridine is a nucleophilic-type catalyst (see Reaction **16-58**), but DMAP is superior and can be used in cases where pyridine fails.¹⁷²⁷ Nonaromatic amidine derivatives have been used to catalyze the reaction with acetic anhydride.¹⁷²⁸ Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols¹⁷²⁹ or phenols¹⁷³⁰ with acetic-formic anhydride. Cyclic anhydrides give monoesterified dicarboxylic acids (e.g., **102**).¹⁷³¹ The asymmetric alcoholysis of cyclic anhydrides has been reviewed.¹⁷³²

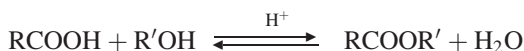


Alcohols can also be acylated by mixed organic–inorganic anhydrides [e.g., acetic-phosphoric anhydride, $\text{MeCOOPO}(\text{OH})_2$,¹⁷³³ see Reaction **16-68**]. Thioesters of the type $\text{ArS}(\text{C}=\text{O})\text{Me}$ have been prepared by simple reaction of thiols and anhydrides in the presence of potassium carbonate,¹⁷³⁴ and from diphenyl disulfide and PBU_3 , followed by treatment with acetic anhydride.¹⁷³⁵

OS **I**, 285, 418; **II**, 69, 124; **III**, 11, 127, 141, 169, 237, 281, 428, 432, 690, 833; **IV**, 15, 242, 304; **V**, 8, 459, 591, 887; **VI**, 121, 245, 560, 692; 486; **VIII**, 141, 258.

16-63 Esterification of Carboxylic Acids

Alkoxy-de-hydroxylation



The acid-catalyzed esterification of carboxylic acids with alcohols¹⁷³⁶ is the reverse of Reaction **16-60** and can be accomplished only if a means is available to drive the equilibrium to the right.¹⁷³⁷ There are many ways of doing this, among which are (1) addition of an excess of one of the reactants, usually the alcohol; (2) removal of the ester or the water by distillation; (3) removal of water by azeotropic distillation; and (4) removal of water by use of a dehydrating agent, silica gel,¹⁷³⁸ or a molecular sieve. When R' is methyl, the most common way of driving the equilibrium is by adding excess MeOH ; when R' is

¹⁷²⁵ Constantinou-Kokotou, V.; Peristeraki, A. *Synth. Commun.* **2004**, 34, 4227. Also see Bandgar, B.P.; Kasture, S.P.; Kamble, V.T. *Synth. Commun.* **2001**, 31, 2255.

¹⁷²⁶ Clarke, P.A.; Kayaleh, N.E.; Smith, M.A.; Baker, J.R.; Bird, S.J.; Chan, C. *J. Org. Chem.* **2002**, 67, 5226; Clarke, P.A. *Tetrahedron Lett.* **2002**, 43, 4761.

¹⁷²⁷ Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc.* **2007**, 129, 14775. See Scriven, E.F.V. *Chem. Soc. Rev.* **1983**, 12, 129; Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed.* **1978**, 17, 569.

¹⁷²⁸ Birman, V.B.; Li, X.; Han, Z. *Org. Lett.* **2007**, 9, 37.

¹⁷²⁹ See van Es, A.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* **1965**, 84, 704.

¹⁷³⁰ See Sofuku, S.; Muramatsu, I.; Hagitani, A. *Bull. Chem. Soc. Jpn.* **1967**, 40, 2942.

¹⁷³¹ See Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, 122, 9542.

¹⁷³² Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, 103, 2965.

¹⁷³³ Fatiadi, A.J. *Carbohydr. Res.* **1968**, 6, 237.

¹⁷³⁴ Temperini, A.; Annesi, D.; Testaferri, L.; Tiecco, M. *Tetrahedron Lett.* **2010**, 51, 5368.

¹⁷³⁵ Ayers, J.T.; Anderson, S.R. *Synth. Commun* **1999**, 29, 351. See Movassagh, B.; Lakouraj, M.M.; Fadaei, Z. *J. Chem. Res. (S)* **2001**, 22.

¹⁷³⁶ For a review of some methods, see Haslam, E. *Tetrahedron* **1980**, 36, 2409.

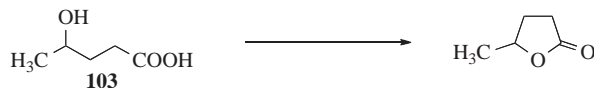
¹⁷³⁷ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1932–1941.

¹⁷³⁸ Nascimento, M.de G.; Zanutto, S.P.; Scremin, M.; Rezende, M.C. *Synth. Commun.* **1996**, 26, 2715.

ethyl or larger, it is preferable to remove water by azeotropic distillation.¹⁷³⁹ The most common catalysts are H_2SO_4 and TsOH , but some reactive carboxylic acids (e.g., formic,¹⁷⁴⁰ trifluoroacetic¹⁷⁴¹) do not require a catalyst. Ammonium salts have been used to initiate esterification,¹⁷⁴² and boric acid has been used to esterify α -hydroxy acids.¹⁷⁴³ The R' group may be primary or secondary alkyl groups other than methyl or ethyl, but tertiary alcohols usually give carbocations and elimination. Phenols can sometimes be used to prepare phenolic esters, but yields are generally very low. Selective esterification of an aliphatic carboxylic acid in the presence of an aromatic acid was accomplished with $\text{NaHSO}_4 \cdot \text{SiO}_2$ and methanol.¹⁷⁴⁴ Diphenylammonium triflate was useful for direct esterification of carboxylic acids with longer chain aliphatic alcohols.¹⁷⁴⁵ Photoirradiation of carboxylic acid with CBr_4 ¹⁷⁴⁶ or CCl_4 ¹⁷⁴⁷ in methanol was shown to give the methyl ester, with high selectivity for nonconjugated acids in the case of CBr_4 . Esterification has been accomplished in ionic liquids.¹⁷⁴⁸ A solid-state esterification was reported on $\text{P}_2\text{O}_5/\text{SiO}_2$.¹⁷⁴⁹ Diols are converted to the monoacetate by heating with acetic acid on a zeolite.¹⁷⁵⁰ Vinyl acetate and iodine has been used for the acetylation of alcohols.¹⁷⁵¹

O-Alkylisoureas react with conjugated carboxylic acids to give the corresponding ester with microwave irradiation,¹⁷⁵² and a polymer-bound *O*-alkylurea has been used as well.¹⁷⁵³ Transition metal compounds of Ti,¹⁷⁵⁴ or Co¹⁷⁵⁵ catalyze esterification. Allylic sulfonium salts react with carboxylic acids to give allylic esters in the presence of CuBr .¹⁷⁵⁶ Triphenylphosphine dibromide is a useful esterification reagent.¹⁷⁵⁷ Phenols can be esterified using amide acetals.¹⁷⁵⁸

The reaction of a carboxylic acid with an alcohol, in the presence of triphenylphosphine and DEAD gives the corresponding ester. This reaction is known as the *Mitsunobu reaction* (see 10-17). A variation of this esterification reaction used azopyridines to mediate formation of the ester.¹⁷⁵⁹



¹⁷³⁹ Newman, M.S. *An Advanced Organic Laboratory Course*, Macmillan, NY, **1972**, pp. 8–10.

¹⁷⁴⁰ See Werner, W. *J. Chem. Res. (S)* **1980**, 196; Hill, D.R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S.J. *Org. Lett.* **2002**, 4, 111.

¹⁷⁴¹ Johnston, B.H.; Knipe, A.C.; Watts, W.E. *Tetrahedron Lett.* **1979**, 4225.

¹⁷⁴² See Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, 127, 4168.

¹⁷⁴³ Houston, T.A.; Wilkinson, B.L.; Blanchfield, J.T. *Org. Lett.* **2004**, 6, 679.

¹⁷⁴⁴ Das, B.; Venkataiah, B.; Madhusudan, P. *Synlett* **2000**, 59.

¹⁷⁴⁵ Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, 41, 5249.

¹⁷⁴⁶ Lee, A.S.-Y.; Yang, H.-C.; Su, F.-Y. *Tetrahedron Lett.* **2001**, 42, 301.

¹⁷⁴⁷ Hwu, J.R.; Hsu, C.-Y.; Jain, M.L. *Tetrahedron Lett.* **2004**, 45, 5151.

¹⁷⁴⁸ McNulty, J.; Cheekoori, S.; Nair, J.J.; Larichev, V.; Capretta, A.; Robertson, A.J. *Tetrahedron Lett.* **2005**, 46, 3641; Yoshino, T.; Imori, S.; Togo, H. *Tetrahedron* **2006**, 62, 1309.

¹⁷⁴⁹ Eshghi, H.; Rafei, M.; Karimi, M.H. *Synth. Commun.* **2001**, 31, 771.

¹⁷⁵⁰ Srinivas, K.V.N.S.; Mahender, I.; Das, B. *Synlett* **2003**, 2419.

¹⁷⁵¹ Bosco, J.W.J.; Agrahari, A.; Saikia, A.K. *Tetrahedron Lett.* **2006**, 47, 4065.

¹⁷⁵² Crosignani, S.; White, P.D.; Linclau, B. *Org. Lett.* **2002**, 4, 2961.

¹⁷⁵³ See Crosignani, S.; White, P.D.; Linclau, B. *J. Org. Chem.* **2004**, 69, 5897.

¹⁷⁵⁴ Chen, C.-T.; Munot, Y.S. *J. Org. Chem.* **2005**, 70, 8625.

¹⁷⁵⁵ Velusamy, S.; Borpuzari, S.; Punniyamurthy, T. *Tetrahedron* **2005**, 61, 2011.

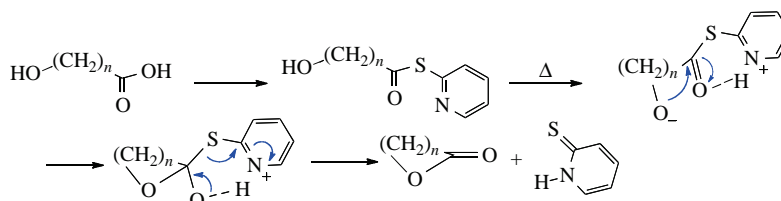
¹⁷⁵⁶ Sedighi, M.; Çalimsiz, S.; Lipton, M.A. *J. Org. Chem.* **2006**, 71, 9517.

¹⁷⁵⁷ Salomé, C.; Kohn, H. *Tetrahedron* **2009**, 65, 456.

¹⁷⁵⁸ Vorbrüggen, H. *Synlett* **2008**, 1603.

¹⁷⁵⁹ Iranpoor, N.; Firouzabadi, H.; Khalili, D.; Motevalli, S. *J. Org. Chem.* **2008**, 73, 4882.

Both γ - and δ -hydroxy acids (e.g., **103**) are easily converted to a lactone by treatment with acids, or often simply on standing, but larger and smaller lactone rings cannot be made in this manner, because polyester formation occurs more readily.¹⁷⁶⁰ Often the conversion of one group to a hydroxyl group, gives the lactone directly, since the hydroxy acid cyclizes too rapidly for isolation. Such groups include keto or halogen that are γ or δ to a carbonyl group. β -Substituted β -hydroxy acids can be converted to β -lactones by treatment with benzenesulfonyl chloride in pyridine at 0–5 °C.¹⁷⁶¹ ϵ -Lactones (seven-membered rings) have been made by cyclization of ϵ -hydroxy acids at high dilution.¹⁷⁶² Macrocyclic lactones¹⁷⁶³ can be prepared indirectly in very good yields by conversion of the hydroxy acids to 2-pyridinethiol esters and adding these to refluxing xylene.¹⁷⁶⁴



A closely related method, which often gives higher yields of a macrocyclic lactone, involves treatment of the hydroxy acids with 1-methyl- or 1-phenyl-2-halopyridinium salts, especially 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).¹⁷⁶⁵ A macrocyclization technique has been developed based on formation of a mixed anhydride. The *Yamaguchi protocol*¹⁷⁶⁶ reacts a seco acid (the hydroxy acid precursor of a macrocyclic lactone) with 2,4,6-trichlorobenzoyl chloride. The resulting mixed anhydride is heated with DMAP in toluene.

Esterification is catalyzed by acids (not bases) in ways that were presented in Table 16.3 in Reaction **16-59**.¹⁶⁵³ The mechanisms are usually $A_{AC}2$, but $A_{AC}1$ and $A_{AL}1$ have also been observed.¹⁷⁶⁷ Certain acids (e.g., 2,6-di-ortho-substituted benzoic acids), cannot be esterified by the $A_{AC}2$ mechanism because of steric hindrance (Sec. 10.G.i, category 1). In such cases, esterification can be accomplished by dissolving the acid in 100% H_2SO_4 (forming the ion RCO^+) and pouring the solution into the alcohol ($A_{AC}1$ mechanism). The

¹⁷⁶⁰ Wolfe, J.F.; Ogliaruso, M.A. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 2, Wiley, NY, **1979**, pp. 1062–1330. For a list of methods for converting hydroxy acids to lactones, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1989**, pp. 1861–1867.

¹⁷⁶¹ Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* **1972**, *94*, 2000. Also see Merger, F. *Chem. Ber.* **1968**, *101*, 2413; Blume, R.C. *Tetrahedron Lett.* **1969**, 1047.

¹⁷⁶² Lardelli, G.; Lamberti, V.; Weller, W.T.; de Jonge, A.P. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 481.

¹⁷⁶³ See Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911.

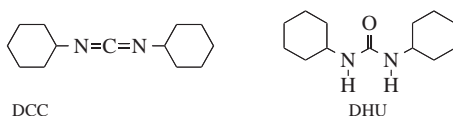
¹⁷⁶⁴ Wollenberg, R.H.; Nimitz, J.S.; Gokcek, D.Y. *Tetrahedron Lett.* **1980**, *21*, 2791; Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* **VII**, 470. See also, Schmidt, U.; Heermann, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 308; Trost, B.M.; Chisholm, J.D. *Org. Lett.* **2002**, *4*, 3743.

¹⁷⁶⁵ See Mukaiyama, T. *Angew. Chem. Int. Ed.* **1979**, *18*, 707; Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 3401. For a microwave-assisted reaction, see Donati, D.; Morelli, C.; Taddei, M. *Tetrahedron Lett.* **2005**, *46*, 2817.

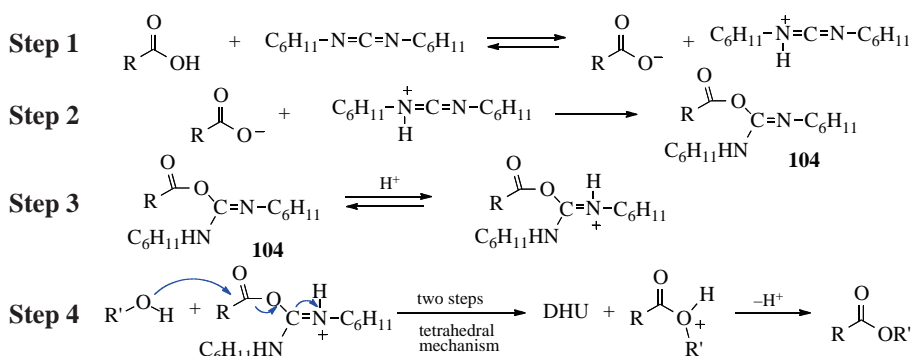
¹⁷⁶⁶ Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; Mundy, B.P.; Ellerd, M.G.; Favaloro, Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley–Interscience, New Jersey, **2005**, pp. 710–711. For a discussion of the mechanism, see Dhimitruka, I.; SantaLucia, Jr., J. *Org. Lett.* **2006**, *8*, 47.

¹⁷⁶⁷ See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, pp. 466–481.

reluctance of hindered acids to undergo the normal $A_{AC}2$ mechanism can sometimes be put to advantage when, in a molecule containing two CO_2H groups, only the less hindered one is esterified. The $A_{AC}1$ pathway cannot be applied to unhindered carboxylic acids.



Another way to esterify a carboxylic acid is to treat it with an alcohol in the presence of a dehydrating agent.¹⁷³⁸ One of these is dicyclohexylcarbodiimide (DCC), which is converted in the process to dicyclohexylurea (DHU). The mechanism¹⁷⁶⁸ has much in common with the nucleophilic catalysis mechanism; the acid is converted to a compound with a better leaving group, but the conversion is not by a tetrahedral mechanism (as it is in nucleophilic catalysis), since the C—O bond remains intact during this step:



Evidence for this mechanism was the preparation of *O*-acylureas similar to **104** and the finding that when catalyzed by acids they react with alcohols to give esters.¹⁷⁶⁹ Hindered tertiary alcohols can be coupled via DCC to give the hindered ester.¹⁷⁷⁰ A polymer-bound carbodiimide has been used to prepare macrocyclic lactones.¹⁷⁷¹ In at least one case, the reaction of $HOOCCH_2CN$ with DCC and *tert*-butanol gave the *tert*-butyl ester via a ketene intermediate.¹⁷⁷²

There are limitations to the use of DCC; yields are variable and *N*-acylureas are side products. Many other dehydrating agents¹⁷⁷³ have been used, including DCC and an aminopyridine,¹⁷⁷⁴ chlorosilanes,¹⁷⁷⁵ and *N,N'*-carbonyldiimidazole (**105**).¹⁷⁷⁶ In the latter case, imidazolides (**106**) are intermediates that react with alcohols.

¹⁷⁶⁸ Balcom, B.J.; Petersen, N.O. *J. Org. Chem.* **1989**, *54*, 1922.

¹⁷⁶⁹ Doleschall, G.; Lempert, K. *Tetrahedron Lett.* **1963**, 1195.

¹⁷⁷⁰ Shimizu, T.; Hiramoto, K.; Nakata, T. *Synthesis* **2001**, 1027.

¹⁷⁷¹ Keck, G.E.; Sanchez, C.; Wager, C.A. *Tetrahedron Lett.* **2000**, *41*, 8673.

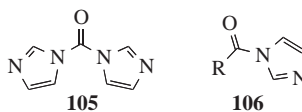
¹⁷⁷² Nahmany, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733.

¹⁷⁷³ See Arrieta, A.; García, T.; Lago, J.M.; Palomo, C. *Synth. Commun.* **1983**, *13*, 471.

¹⁷⁷⁴ Boden, E.P.; Keck, G.E. *J. Org. Chem.* **1985**, *50*, 2394.

¹⁷⁷⁵ Brook, M.A.; Chan, T.H. *Synthesis* **1983**, 201.

¹⁷⁷⁶ See Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* **1968**, *5*, 61. See also, Morton, R.C.; Mangroo, D.; Gerber, G.E. *Can. J. Chem.* **1988**, *66*, 1701.



It is known that the Lewis acid BF_3 promotes the esterification by converting the acid to $\text{RCO}^+\text{BF}_3^-\text{OH}$, so the reaction proceeds by an $\text{A}_{\text{AC}}1$ type of mechanism. The use of BF_3 -etherate is simple and gives high yields.¹⁷⁷⁷ Other Lewis acids can be used.¹⁷⁷⁸

Carboxylic esters can also be prepared by treating carboxylic acids with *tert*-butyl ethers and acid catalysts:¹⁷⁷⁹



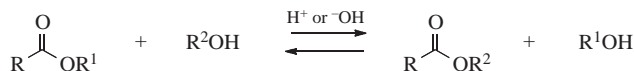
Carboxylic esters can be formed from the carboxylate anion and a suitable alkylating agent (Reaction **10-26**).

Thioesters of the type $\text{RSC}(=\text{S})\text{R}'$ (a dithiocarboxylic ester) and $\text{RSC}(\text{C}=\text{O})\text{R}'$ (a thio-carboxylic ester) can be generated by reaction of carboxylic acids with thiols. In one example, phosphorous pentasulfide was used in conjunction with a thiol to make dithiocarboxylic esters¹⁷⁸⁰ or thiocarboxylic esters.¹⁷⁸¹ Thiocarboxylic esters were prepared from thiols and triflic acid.¹⁷⁸²

OS **I**, 42, 138, 237, 241, 246, 254, 261, 451; **II**, 260, 264, 276, 292, 365, 414, 526; **III**, 46, 203, 237, 381, 413, 526, 531, 610; **IV**, 169, 178, 302, 329, 390, 398, 427, 506, 532, 635, 677; **V**, 80, 762, 946; **VI**, 471, 797; **VII**, 93, 99, 210, 319, 356, 386, 470; **VIII**, 141, 251, 597; **IX**, 24, 58; **75**, 116; **75**, 129. Also see, OS **III**, 536, 742.

16-64 Transesterification

Alkoxy-de-alkoxylation



Transesterification¹⁷⁸³ is catalyzed¹⁷⁸⁴ by acids¹⁷⁸⁵ or bases,¹⁷⁸⁶ or done under neutral conditions.¹⁷⁸⁷ It is an equilibrium reaction that must be shifted in the desired direction.¹⁷⁸⁸

In many cases, low-boiling esters can be converted to higher-boiling ones by the distillation of the lower-boiling alcohol as fast as it is formed. Reagents used to catalyze¹⁷⁸⁹

¹⁷⁷⁷ See Kadaba, P.K. *Synth. Commun.* **1974**, 4, 167.

¹⁷⁷⁸ **Bi**: Carrigan, D.; Freiberg, D.A.; Smith, R.C.; Zerth, H.M.; Mohan, R.S. *Synthesis* **2001**, 2091; Mohammadpoor-Baltork, I.; Khosropour, A.R.; Aliyan, H. *J. Chem. Res.* **2001**, 280. **Ce**: Pan, W.-B.; Chang, F.-R.; Wei, L.-M.; Wu, M.J.; Wu, Y.-C. *Tetrahedron Lett.* **2003**, 44, 331. **Fe**: Sharma, G.V.M.; Mahalingam, A.K.; Nagarajan, M.; Ilangovan, P.; Radhakrishna, P. *Synlett* **1999**, 1200; Zhang, G.-S. *Synth. Commun.* **1999**, 29, 607. **Hf**: Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, 58, 8179.

¹⁷⁷⁹ Derevitskaya, V.A.; Klimov, E.M.; Kochetkov, N.K. *Tetrahedron Lett.* **1970**, 4269. See also, Mohacsi, E. *Synth. Commun.* **1982**, 12, 453.

¹⁷⁸⁰ Sudalai, A.; Kanagasabapathy, S.; Benicewicz, B.C. *Org. Lett.* **2000**, 2, 3213.

¹⁷⁸¹ Curphey, T.J. *Tetrahedron Lett.* **2002**, 43, 371.

¹⁷⁸² Iimura, S.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2002**, 94.

¹⁷⁸³ Otera, J. *Chem. Rev.* **1993**, 93, 1449.

¹⁷⁸⁴ For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1969–1973.

¹⁷⁸⁵ See Chavan, S.P.; Subbarao, Y.T.; Dantale, S.W.; Sivappa, R. *Synth. Commun.* **2001**, 31, 289.

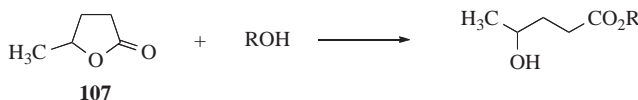
¹⁷⁸⁶ Stanton, M.G.; Gagné, M.R. *J. Org. Chem.* **1997**, 62, 8240; Vasin, V.A.; Razin, V.V. *Synlett* **2001**, 658.

¹⁷⁸⁷ See Imwinkelried, R.; Schiess, M.; Seebach, D. *Org. Synth.*, 65, 230; Bandgar, B.P.; Uppalla, L.S.; Sadavarte, V.S. *Synlett* **2001**, 1715.

¹⁷⁸⁸ See Bose, D.S.; Satyender, A.; Rudra Das, A.P.; Mereyala, H.B. *Synthesis* **2006**, 2392.

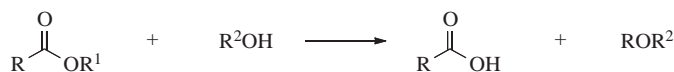
¹⁷⁸⁹ For a review see Grasa, G.A.; Singh, R.; Nolan, S.P. *Synthesis* **2004**, 971.

transesterification include various Lewis acids.¹⁷⁹⁰ Zwitterionic salts have been used as organocatalysts for this reaction.¹⁷⁹¹ A polymer-bound siloxane has been used to induce transesterification.¹⁷⁹² Vinyl acetate has been used for transesterification, usually with a coreagent or metal mediator.¹⁷⁹³ This reaction has been used as a method for the acylation of a primary OH in the presence of a secondary OH.¹⁷⁹⁴ Regioselectivity has also been accomplished by using enzymes (lipases) as catalysts.¹⁷⁹⁵ Lactones, (e.g., **107**) are easily opened by treatment with alcohols¹⁷⁹⁶ to give open-chain hydroxy esters.

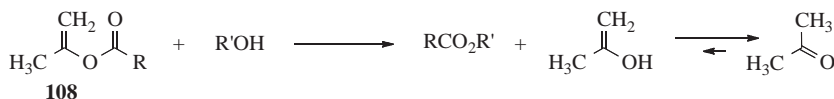


Transesterification has been carried out with phase-transfer catalysts, without an added solvent.¹⁷⁹⁷ Nonionic superbases (see Sec. 8.A.i) of the type $\text{P}(\text{RNCH}_2\text{CH}_2)_3\text{N}$ catalyze the transesterification of carboxylic acid esters at 25 °C.¹⁷⁹⁸ Silyl esters ($\text{R}'\text{CO}_2\text{SiR}_3$) have been converted to alkyl esters ($\text{R}'\text{CO}_2\text{R}$) via reaction with alkyl halides and tetrabutylammonium fluoride.¹⁷⁹⁹ Thioesters are converted to phenolic esters by treatment with triphosgene–pyridine and then phenol.¹⁸⁰⁰

Transesterification occurs by mechanisms¹⁸⁰¹ that are identical with those of ester hydrolysis, except that ROH replaces HOH (by the acyl–oxygen fission mechanisms). When alkyl fission takes place, the products are the *acid* and the *ether*:



Therefore, transesterification reactions frequently fail when R' is tertiary, since this type of substrate most often reacts by alkyl–oxygen cleavage. In such cases, the reaction is of the Williamson type with OCOR as the leaving group (see Reaction 10-10).



¹⁷⁹⁰ Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Synlett* **2001**, 1338; Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Synth. Commun.* **2001**, 31, 2063; Štefane, B.; Kočevár, M.; Polanc, S. *Synth. Commun.* **2002**, 32, 1703.

¹⁷⁹¹ Ishihara, K.; Niwa, M.; Kosugi, Y. *Org. Lett.* **2008**, 10, 2187.

¹⁷⁹² Hagiwara, H.; Koseki, A.; Isobe, K.; Shimizu, K.-i.; Hoshi, T.; Suzuki, T. *Synlett* **2004**, 2188.

¹⁷⁹³ See Shirae, Y.; Mino, T.; Hasegawa, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2005**, 46, 5877.

¹⁷⁹⁴ Yamada, S. *Tetrahedron Lett.* **1992**, 33, 2171. See also, Costa, A.; Riego, J.M. *Can. J. Chem.* **1987**, 65, 2327.

¹⁷⁹⁵ Wong, C.H.; Whitesides, G. M. in Baldwin, J.E. *Enzymes in Synthetic Organic Chemistry, Tetrahedron Organic Chemistry Series* Vol. 12, Pergamon Press, NY, **1994**; Faber, K. *Biotransformations in Organic Chemistry. A Textbook*, 2nd ed, Springer-Verlag, NY, **1995**; Córdova, A.; Janda, K.D. *J. Org. Chem.* **2001**, 66, 1906; Ciuffreda, P.; Casati, S.; Santaniello, E. *Tetrahedron Lett.* **2003**, 44, 3663.

¹⁷⁹⁶ Anand, R.C.; Sevlapalam, N. *Synth. Commun.* **1994**, 24, 2743.

¹⁷⁹⁷ Barry, J.; Bram, G.; Petit, A. *Tetrahedron Lett.* **1988**, 29, 4567. See also, Nishiguchi, T.; Taya, H. *J. Chem. Soc. Perkin Trans. 1* **1990**, 172.

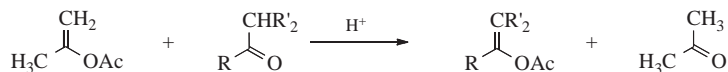
¹⁷⁹⁸ Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* **1999**, 64, 3086.

¹⁷⁹⁹ Ooi, T.; Sugimoto, H.; Maruoka, K. *Heterocycles* **2001**, 54, 593.

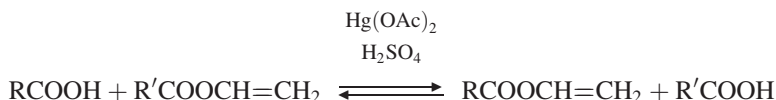
¹⁸⁰⁰ Joshi, U.M.; Patkar, L.N.; Rajappa, S. *Synth. Commun.* **2004**, 34, 33.

¹⁸⁰¹ See Koskikallio, E.A. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, **1969**, pp. 103–136.

With enol esters (e.g., **108**), reaction with an alcohol gives an ester and the enol of a ketone, which readily tautomerizes to the ketone as shown. Hence, enol esters are good acylating agents for alcohols.¹⁸⁰² This transformation has been accomplished in ionic liquid media,¹⁸⁰³ and there is a PdCl₂/CuCl₂ mediated version.¹⁸⁰⁴ Isopropenyl acetate can also be used to convert other ketones to the corresponding enol acetates in an exchange reaction:¹⁸⁰⁵



Enol esters can also be prepared in the opposite type of exchange reaction, catalyzed by mercuric acetate¹⁸⁰⁶ or Pd(II) chloride,¹⁸⁰⁷ for example,

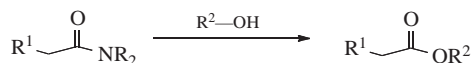


A closely related reaction is equilibration of a dicarboxylic acid and its diester to produce monoesters: The reaction of a carboxylic acid with ethyl acetate, in the presence of NaHSO₄·SiO₂, was shown to give the corresponding ethyl ester.¹⁸⁰⁸ Iodine catalyzes the transesterification of β-keto esters.¹⁸⁰⁹

OS II, 5, 122, 360; **III**, 123, 146, 165, 231, 281, 581, 605; **IV**, 10, 549, 630, 977; **V**, 155, 545, 863; **VI**, 278; **VII**, 4, 164, 411; **VIII**, 155, 201, 235, 263, 350, 444, 528. See also, OS **VII**, 87; **VIII**, 71.

16-65 Alcoholysis of Amides

Alkoxy-deamidation



Alcoholysis of amides is possible,¹⁸¹⁰ although it is usually difficult. It has been most common with the imidazolidine type of amides (e.g., **100**). For other amides, an activating agent is usually necessary before the alcohol will replace the NR₂ unit. *N,N*-Dimethylformamide, however, reacted with primary alcohols in the presence of 2,4,6-trichloro-1,3,5-pyrazine (cyanuric acid) to give the corresponding formate ester.¹⁸¹¹ Treatment of an amide with triflic anhydride (CF₃SO₂OSO₂CF₃) in the presence of pyridine, and then with an excess of alcohol, leads to the ester,¹⁸¹² as does treatment with Me₂NCH(OMe)₂ followed by

¹⁸⁰² Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* **1999**, *64*, 9063.

¹⁸⁰³ Grasa, G.A.; Kissling, R.M.; Nolan, S.P. *Org. Lett.* **2002**, *4*, 3583.

¹⁸⁰⁴ Bosco, J.W.J.; Saikia, A.K. *Chem. Commun.* **2004**, 1116.

¹⁸⁰⁵ See House, H.O.; Trost, B.M. *J. Org. Chem.* **1965**, *30*, 2502.

¹⁸⁰⁶ See Mondal, M.A.S.; van der Meer, R.; German, A.L.; Heikens, D. *Tetrahedron* **1974**, *30*, 4205.

¹⁸⁰⁷ Henry, P.M. *J. Am. Chem. Soc.* **1971**, *93*, 3853; *Acc. Chem. Res.* **1973**, *6*, 16.

¹⁸⁰⁸ Das, B.; Venkataiah, B. *Synthesis* **2000**, 1671.

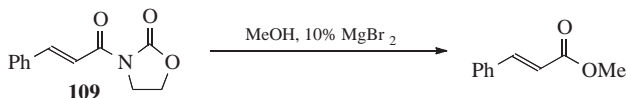
¹⁸⁰⁹ Chavan, S.P.; Kale, R.R.; Shivasankar, K.; Chandake, S.I.; Benjamin, S.B. *Synthesis* **2003**, 2695.

¹⁸¹⁰ For example, see Czarnik, A.W. *Tetrahedron Lett.* **1984**, *25*, 4875. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 197–1978.

¹⁸¹¹ DeLuca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, 5152.

¹⁸¹² Charette, A.B.; Chua, P. *Synlett* **1998**, 163.

the alcohol.¹⁸¹³ Trimethyloxonium tetrafluoroborate converted primary amides to methyl esters.¹⁸¹⁴ The reaction of acetanilide derivatives with sodium nitrite in the presence of acetic anhydride–acetic acid leads to phenolic acetates.¹⁸¹⁵ Acyl hydrazides (RCONHNH₂) were converted to esters by reaction with alcohols and various reagents,¹⁸¹⁶ and methoxyamides (RCONHOMe) were converted to esters with TiCl₄/ROH.¹⁸¹⁷ The reaction of an oxazolidinone amide (**109**) with methanol and 10% MgBr₂ gave the corresponding methyl ester.¹⁸¹⁸



C. Attack by OCOR at an Acyl Carbon

16-66 Acylation of Carboxylic Acids with Acyl Halides

Acyloxy-de-halogenation

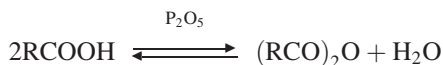


Unsymmetrical, as well as symmetrical, anhydrides are often prepared by the treatment of an acyl halide with a carboxylic acid salt. If a metallic salt is used, Na⁺, K⁺, or Ag⁺ are the most common cations, but more often pyridine or another tertiary amine is added to the free acid. The resulting salt is subsequently treated with the acyl halide. Zinc–DMF has been used to mediate the synthesis of symmetrical anhydrides from acid chlorides.¹⁸¹⁹ Cobalt(II) chloride (CoCl₂) has been used as a catalyst.¹⁸²⁰ Mixed formic anhydrides are prepared from sodium formate and an aryl halide, by use of a solid-phase copolymer of pyridine-1-oxide.¹⁸²¹ Symmetrical anhydrides can be prepared by reaction of the acyl halide with aq NaOH or NaHCO₃ under phase-transfer conditions,¹⁸²² or with sodium bicarbonate with ultrasound.¹⁸²³

OS **III**, 28, 422, 488; **IV**, 285; **VI**, 8, 910; **VIII**, 132. See also, OS **VI**, 418.

16-67 Acylation of Carboxylic Acids with Carboxylic Acids

Acyloxy-de-hydroxylation



¹⁸¹³ Anelli, P.L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* **1997**, 38, 2367.

¹⁸¹⁴ Kiessling, A.J.; McClure, C.K. *Synth. Commun.* **1997**, 27, 923.

¹⁸¹⁵ Glatzhofer, D.T.; Roy, R.R.; Cossey, K.N. *Org. Lett.* **2002**, 4, 2349. See Naik, R.; Pasha, M.A. *Synth. Commun.* **2005**, 35, 2823.

¹⁸¹⁶ See Yamaguchi, J.-i.; Aoyagi, T.; Fujikura, R.; Suyama, T. *Chem. Lett.* **2001**, 466.

¹⁸¹⁷ Fisher, L.E.; Caroon, J.M.; Stabler, S.R.; Lundberg, S.; Zaidi, S.; Sorensen, C.M.; Sparacino, M.L.; Muchowski, J.M. *Can. J. Chem.* **1994**, 72, 142.

¹⁸¹⁸ Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* **2001**, 637.

¹⁸¹⁹ Serieys, A.; Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A. *Tetrahedron Lett.* **2008**, 49, 5322.

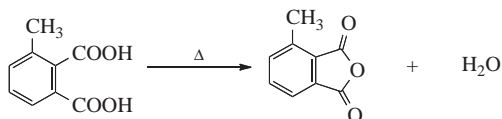
¹⁸²⁰ Srivastava, R.R.; Kabalka, G.W. *Tetrahedron Lett.* **1992**, 33, 593.

¹⁸²¹ Fife, W.K.; Zhang, Z. *J. Org. Chem.* **1986**, 51, 3744. For a review of acetic formic anhydride see Strazzolini, P.; Giumanini, A.G.; Cauci, S. *Tetrahedron* **1990**, 46, 1081.

¹⁸²² Plusquellec, D.; Roulleau, F.; Lefevre, M.; Brown, E. *Tetrahedron* **1988**, 44, 2471; Wang, J.; Hu, Y.; Cui, W. *J. Chem. Res. (S)* **1990**, 84.

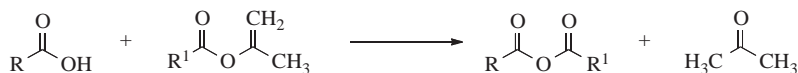
¹⁸²³ Hu, Y.; Wang, J.-X.; Li, S. *Synth. Commun.* **1997**, 27, 243.

Anhydrides can be formed from two molecules of an ordinary carboxylic acid only if a dehydrating agent is present so that the equilibrium can be driven to the right. Common dehydrating agents¹⁸²⁴ are acetic anhydride, trifluoroacetic anhydride, dicyclohexylcarbodiimide,¹⁸²⁵ and P_2O_5 . Triphenylphosphine/ CCl_3CN with triethylamine has also been used with benzoic acid derivatives.¹⁸²⁶ The method is very poor for the formation of mixed anhydrides, which in any case generally undergo disproportionation to the two simple anhydrides when they are heated. However, simple heating of dicarboxylic acids does give cyclic anhydrides, provided that the ring formed contains five, six, or seven members, for example:



Malonic acid and its derivatives, which would give four-membered cyclic anhydrides, do not give this reaction when heated, but undergo decarboxylation (**12-40**) instead.

Carboxylic acids exchange with amides and esters; these methods are sometimes used to prepare anhydrides if the equilibrium can be shifted. Enolic esters are especially good for this purpose, because the equilibrium is shifted by formation of the ketone.



The combination of KF with 2-acetoxypropene under microwave conditions was effective.¹⁸²⁷ Carboxylic acids also exchange with anhydrides; indeed, this is how acetic anhydride acts as a dehydrating agent in this reaction.

Anhydrides can be formed from certain carboxylic acid salts (e.g., by treatment of trimethylammonium carboxylates with phosgene):¹⁸²⁸



or of thallium(I) carboxylates with thionyl chloride,¹⁷¹⁰ or of sodium carboxylates with CCl_4 and a catalyst (e.g., CuCl or FeCl_2).¹⁸²⁹

OS **I**, 91, 410; **II**, 194, 368, 560; **III**, 164, 449; **IV**, 242, 630, 790; **V**, 8, 822; **IX**, 151. Also see, OS **VI**, 757; **VII**, 506.

¹⁸²⁴ For lists of other dehydrating agents with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1930–1932; Ogliaruso, M.A.; Wolfe, J.F. in Patai, S. *The Chemistry of Acid Derivatives*, pt.1, Wiley, NY, **1979**, pp. 437–438.

¹⁸²⁵ See Rammler, D.H.; Khorana, H.G. *J. Am. Chem. Soc.* **1963**, 85, 1997. See also, Hata, T.; Tajima, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1968**, 41, 2746.

¹⁸²⁶ Kim, J.; Jang, D.O. *Synth. Commun.* **2001**, 31, 395.

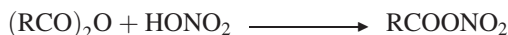
¹⁸²⁷ Villemin, D.; Labiad, B.; Loupy, A. *Synth. Commun.* **1993**, 23, 419.

¹⁸²⁸ Rinderknecht, H.; Ma, V. *Helv. Chim. Acta* **1964**, 47, 152. See also, Nangia, A.; Chandrasekaran, S. *J. Chem. Res. (S)* **1984**, 100.

¹⁸²⁹ Weiss, J.; Havelka, F.; Nefedov, B.K. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1978**, 27, 193.

16-68 Preparation of Mixed Organic–Inorganic Anhydrides

Nitrooxy-de-acyloxy-substitution

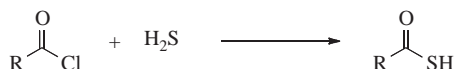


Mixed organic–inorganic anhydrides are seldom isolated, although they are often intermediates when acylation is carried out with acid derivatives catalyzed by inorganic acids. Sulfuric, perchloric, phosphoric, and other acids form similar anhydrides, most of which are unstable or not easily obtained because the equilibrium lies in the wrong direction. These intermediates are formed from amides, carboxylic acids, and esters, as well as anhydrides. Organic anhydrides of phosphoric acid are more stable than most others and, for example, $\text{RCOOPO}(\text{OH})_2$ can be prepared in the form of its salts.¹⁸³⁰ Mixed anhydrides of carboxylic and sulfonic acids ($\text{RCOOSO}_2\text{R}'$) are obtained in high yields by treatment of sulfonic acids with acyl halides or (less preferred) anhydrides.¹⁸³¹

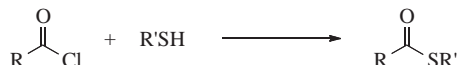
OS I, 495; VI, 207; VII, 81.

16-69 Attack by SH or SR at an Acyl Carbon¹⁸³²

Mercapto-de-halogenation



Alkylthio-de-halogenation



Thiol acids and thiol esters¹⁸³³ can be prepared in this manner, which is analogous to Reaction 16-57 and 16-64. Anhydrides¹⁸³⁴ and aryl esters (RCOOAr)¹⁸³⁵ are also used as substrates, but the reagents in these cases are usually HS^- and RS^- . Thiol esters can also be prepared by treatment of carboxylic acids with P_4S_{10} – Ph_3SbO ,¹⁸³⁶ or with a thiol (RSH) and either polyphosphate ester or phenyl dichlorophosphate (PhOPOCl_2).¹⁸³⁷ Carboxylic acids are converted to thioacids with *Lawesson's reagent* (structure 18 in Reaction 16-11).¹⁸³⁸ Esters RCOOR' can be converted to thiol esters (RCOSR') by treatment with trimethylsilyl sulfides ($\text{Me}_3\text{SiSR}'$) and AlCl_3 .¹⁸³⁹

Alcohols, when treated with a thiol acid and zinc iodide, give thiol esters ($\text{R}'\text{COSR}$)¹⁸⁴⁰
OS III, 116, 599; IV, 924, 928; VII, 81; VIII, 71.

¹⁸³⁰ Avison, A.W.D. *J. Chem. Soc.* **1955**, 732.

¹⁸³¹ Karger, M.H.; Mazur, Y. *J. Org. Chem.* **1971**, 36, 528.

¹⁸³² See Satchell, D.P.N. *Q. Rev. Chem. Soc.* **1963**, 17, 160, pp. 182–184.

¹⁸³³ See Scheithauer, S.; Mayer, R. *Top. Sulfur Chem.* **1979**, 4, 1.

¹⁸³⁴ Ahmad, S.; Iqbal, J. *Tetrahedron Lett.* **1986**, 27, 3791.

¹⁸³⁵ Hirabayashi, Y.; Mizuta, M.; Mazume, T. *Bull. Chem. Soc. Jpn.* **1965**, 38, 320.

¹⁸³⁶ Nomura, R.; Miyazaki, S.; Nakano, T.; Matsuda, H. *Chem. Ber.* **1990**, 123, 2081.

¹⁸³⁷ Imamoto, T.; Koder, M.; Yokoyama, M. *Synthesis* **1982**, 134. See also, Dellaria, Jr., F.F.; Nordeen, C.; Swett, L.R. *Synth. Commun.* **1986**, 16, 1043.

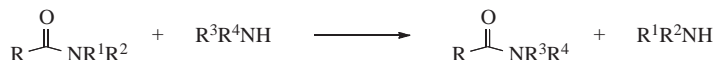
¹⁸³⁸ Rao, Y.; Li, X.; Nagorny, P.; Hayashida, J.; Danishefsky, S.J. *Tetrahedron Lett.* **2009**, 50, 6684.

¹⁸³⁹ Mukaiyama, T.; Takeda, T.; Atsumi, K. *Chem. Lett.* **1974**, 187. See also, Hatch, R.P.; Weinreb, S.M. *J. Org. Chem.* **1977**, 42, 3960; Cohen, T.; Gapinski, R.E. *Tetrahedron Lett.* **1978**, 4319.

¹⁸⁴⁰ Gauthier, J.Y.; Bourdon, F.; Young, R.N. *Tetrahedron Lett.* **1986**, 27, 15.


16-70 Transamidation

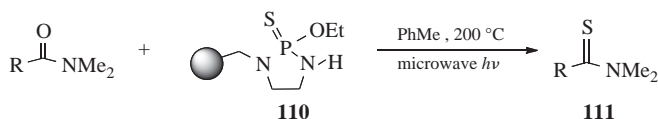
Alkylamino-de-amidation



It is sometimes necessary to replace one amide group with another, particularly when the group attached to nitrogen functions as a protecting group.¹⁸⁴¹ *N*-Benzyl amides can be converted to the corresponding *N*-allyl amide with allylamine and Ti catalysts.¹⁸⁴² Reaction of *N*-Boc 2-phenylethylamine with Ti(OiPr)₄ and benzyl alcohol, for example, gives the *N*-Cbz derivative.¹⁸⁴³ *N*-Carbamoyl amines were converted to *N*-acetyl amines with acetic anhydride, Bu₃SnH, and a Pd catalyst.¹⁸⁴⁴ Triethylaluminum converts methyl carbamates (ArNHCO₂Me) to the corresponding propanamide.¹⁸⁴⁵

A related process reacts acetamide with amines and aluminum chloride to give the *N*-acetyl amine.¹⁸⁴⁶ Another related process converted imides to *O*-benzyloxy amides by the Sm catalyzed reaction with *O*-benzylhydroxylamine.¹⁸⁴⁷

Thioamides can be prepared from amide by reaction with an appropriate sulfur reagent. The reaction of *N,N*-dimethylacetamide under microwave irradiation, with the polymer-bound reagent **110** (where  = polymeric backbone) gave **111**.¹⁸⁴⁸ Reaction of the thioamide with Bi(NO₃)₃·5 H₂O regenerates the amide.¹⁸⁴⁹ Other methods are known to convert a thioamide to an amide.¹⁸⁵⁰ Selenoamides [RC(=Se)NR'₂] have also been prepared from amides.¹⁸⁵¹



D. Attack by Halogen

16-71 The Conversion of Carboxylic Acids to Halides

Halo-de-oxido,oxo-tersubstitution



In certain cases, carboxyl groups can be replaced by halide. Acrylic acid derivatives (ArCH=CHCOOH), for example, react with 3 molar equivalents of Oxone in the presence of NaBr to give a vinyl bromide (ArCH=CHBr).¹⁸⁵² Diphosphorus tetraiodide/tetraethylammonium bromide (TEAB) readily converts conjugated acids to vinyl

¹⁸⁴¹ See Knipe, A.C. *J. Chem. Soc. Perkin Trans. 2* **1973**, 589.

¹⁸⁴² Eldred, S.E.; Stone, D.A.; Gellman, S.H.; Stahl, S.S. *J. Am. Chem. Soc.* **2003**, *125*, 3422.

¹⁸⁴³ Shapiro, G.; Marzi, M. *J. Org. Chem.* **1997**, *62*, 7096.

¹⁸⁴⁴ Roos, E.C.; Bernabé, P.; Hiemstra, H.; Speckamp, W.N.; Kaptein, B.; Boesten, W.H.J. *J. Org. Chem.* **1995**, *60*, 1733.

¹⁸⁴⁵ El Kaim, L.; Grimaud, L.; Lee, A.; Perroux, Y.; Tiria, C. *Org. Lett.* **2004**, *6*, 381.

¹⁸⁴⁶ Bon, E.; Bigg, D.C.H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 4035.

¹⁸⁴⁷ Sibi, M.P.; Hasegawa, H.; Ghorpade, S.R. *Org. Lett.* **2002**, *4*, 3343.

¹⁸⁴⁸ Ley, S.V.; Leach, A.G.; Storer, R.I. *J. Chem. Soc. Perkin Trans. 1* **2001**, 358.

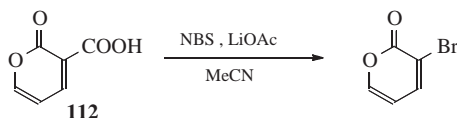
¹⁸⁴⁹ Mohammadpoor-Baltork, I.; Khodaei, M.M.; Nikoofar, K. *Tetrahedron Lett.* **2003**, *44*, 591.

¹⁸⁵⁰ Inamoto, K.; Shiraishi, M.; Hiroya, K.; Doi, T. *Synthesis* **2010**, 3087.

¹⁸⁵¹ Saravanan, V.; Mukherjee, C.; Das, S.; Chandrasekaran, S. *Tetrahedron Lett.* **2004**, *45*, 681.

¹⁸⁵² You, H.-W.; Lee, K.-J. *Synlett* **2001**, 105.

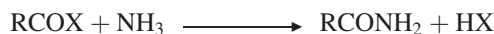
bromides.¹⁸⁵³ In other cases, conjugated acids, (e.g., **112**), have been converted to the bromide by reaction with (NBS, Reaction **14-3**) and LiOAc.¹⁸⁵⁴



E. Attack by Nitrogen at an Acyl Carbon¹⁸⁵⁵

16-72 Acylation of Amines by Acyl Halides

Amino-de-halogenation



The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.¹⁸⁵⁶ The reaction is exothermic and must be carefully controlled, usually by cooling or dilution. Ammonia gives unsubstituted amides, primary amines give *N*-substituted amides,¹⁸⁵⁷ and secondary amines give *N,N*-disubstituted amides. Arylamines can be similarly acylated. Hydroxamic acids have been prepared by this route.¹⁸⁵⁸ In some cases, aq alkali is added to combine with the liberated HCl. This is called the *Schotten–Baumann procedure*, as in Reaction **16-61**. Activated Zn can be used to increase the rate of amide formation when hindered amines and/or acid chlorides are used.¹⁸⁵⁹ A solvent-free reaction was reported using DABCO and methanol.¹⁸⁶⁰ Metal-mediated reactions using In,¹⁸⁶¹ Sm,¹⁸⁶² or a BiOCl mediated reaction¹⁸⁶³ have been reported. A variation of this basic reaction uses DMF with acyl halides to give *N,N*-dimethylamides.¹⁸⁶⁴ Formic acid and iodine react with amines to give the formamide.¹⁸⁶⁵

Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides (RCONHNH_2)¹⁸⁶⁶ and hydroxamic acids (RCONHOH).¹⁸⁶⁷ When phosgene is the acyl halide, both aliphatic and aromatic primary amines give chloroformamides

¹⁸⁵³ Telvekar, V.N.; Chettiar, S.N. *Tetrahedron Lett.* **2007**, 48, 4529.

¹⁸⁵⁴ Cho, C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* **2001**, 42, 1065.

¹⁸⁵⁵ See Challis, M.S.; Butler, A.R. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, **1968**, pp. 279–290.

¹⁸⁵⁶ See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 73–185; Jedrzejczak, M.; Motie, R.E.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* **1993**, 599.

¹⁸⁵⁷ See Bhattacharyya, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* **2003**, 44, 6099.

¹⁸⁵⁸ Reddy, A.S.; Kumar, M.S.; Reddy, G.R. *Tetrahedron Lett.* **2000**, 41, 6285.

¹⁸⁵⁹ Meshram, H.M.; Reddy, G.S.; Reddy, M.M.; Yadav, J.S. *Tetrahedron Lett.* **1998**, 39, 4103.

¹⁸⁶⁰ Hajipour, A.R.; Mazloumi, Gh. *Synth. Commun.* **2002**, 32, 23.

¹⁸⁶¹ Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* **2004**, 45, 2285.

¹⁸⁶² Shi, F.; Li, J.; Li, C.; Jia, X. *Tetrahedron Lett.* **2010**, 51, 6049.

¹⁸⁶³ Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* **2004**, 45, 6775.

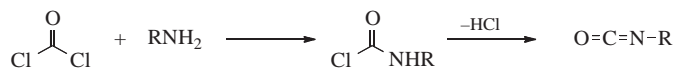
¹⁸⁶⁴ Lee, W.S.; Park, K.H.; Yoon, Y.-J. *Synth. Commun.* **2000**, 30, 4241.

¹⁸⁶⁵ Kim, J.-G.; Jang, D.O. *Synlett* **2010**, 2093. For other formylation reactions, see Shekhar, A.C.; Kumar, A.R.; Sathaiyah, G.; Paul, V.L.; Sridhar, M.; Rao, P.S. *Tetrahedron Lett.* **2009**, 50, 7099; Brahmachari, G.; Laskar, S. *Tetrahedron Lett.* **2010**, 51, 2319; Rahman, M.; Kundu, D.; Hajra, A.; Majee, A. *Tetrahedron Lett.* **2010**, 51, 2896; Deutsch, J.; Eckelt, R.; Köckritz, A.; Martin, A. *Tetrahedron* **2009**, 65, 10365.

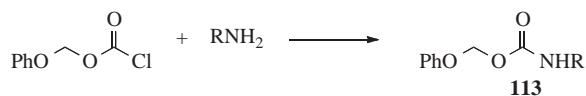
¹⁸⁶⁶ See Paulsen, H.; Stoye, D. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 515–600.

¹⁸⁶⁷ For an improved method, see Ando, W.; Tsumaki, H. *Synth. Commun.* **1983**, 13, 1053.

(ClCONHR) that lose HCl to give isocyanates (RNCO).¹⁸⁶⁸ This is one of the most common methods for the preparation of isocyanates.¹⁸⁶⁹ Similar



treatment with thiophosgene¹⁸⁷⁰ gives isothiocyanates. A safer substitute for phosgene in this reaction is trichloromethyl chloroformate (CCl₃OCOC(=O)Cl).¹⁸⁷¹ When chloroformates (ROCOCl) are treated with primary amines, carbamates (ROCONHR') are obtained.¹⁸⁷² An example of this reaction is the use of benzyl chloroformate to protect the amino group of amino acids and peptides.



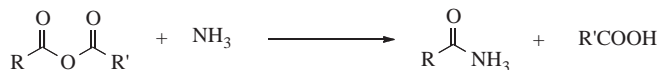
The PhCH₂OCO group in **113** has been called the carbobenzoxy group,¹⁸⁷³ and is often abbreviated Cbz or Z, but it is really a benzyl carbamate. Another important group similarly used is Boc, which is a *tert*-butyl carbamate. In this case, the chloride (Me₃COC(=O)Cl) is unstable, so the anhydride [(Me₃COC(=O))₂O] is used instead, in an example of Reaction **16-73**. Amino groups in general are often protected by conversion to amides.¹⁸⁷⁴ The reactions proceed by the tetrahedral mechanism.¹⁸⁷⁵

An interesting variation of this transformation reacts carbamoyl chlorides with organocuprates to give the corresponding amide.¹⁸⁷⁶

OS **I**, 99, 165; **II**, 76, 208, 278, 328, 453; **III**, 167, 375, 415, 488, 490, 613; **IV**, 339, 411, 521, 620, 780; **V**, 201, 336; **VI**, 382, 715; **VII**, 56, 287, 307; **VIII**, 16, 339; **IX**, 559; **81**, 254. See also, OS **VII**, 302.

16-73 Acylation of Amines by Anhydrides

Amino-de-acyloxy-substitution



¹⁸⁶⁸ Richter, R.; Ulrich, H. pp. 619–818, and Drobnica, L.; Kristián, P.; Augustín, J. pp. 1003–1221, in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2, Wiley, NY, **1977**.

¹⁸⁶⁹ See Ozaki, S. *Chem. Rev.* **1972**, 72, 457, see pp. 457–460. For a review of the industrial preparation of isocyanates by this reaction, see Twitchett, H.J. *Chem. Soc. Rev.* **1974**, 3, 209.

¹⁸⁷⁰ For a review of thiophosgene, see Sharma, S. *Sulfur Rep.* **1986**, 5, 1.

¹⁸⁷¹ Kurita, K.; Iwakura, Y. *Org. Synth.* **VI**, 715.

¹⁸⁷² Heydari, A.; Shiroodi, R.K.; Hamadi, H.; Esfandyari, M.; Pourayoubi, M. *Tetrahedron Lett.* **2007**, 48, 5865; Upadhyaya, D.J.; Barge, A.; Stefania, R.; Cravotto, G. *Tetrahedron Lett.* **2007**, 48, 8318; Shrikhande, J.J.; Gawande, M.B.; Jayaram, R.V. *Tetrahedron Lett.* **2008**, 49, 4799. See Vilaivan, T. *Tetrahedron Lett.* **2006**, 47, 6739.

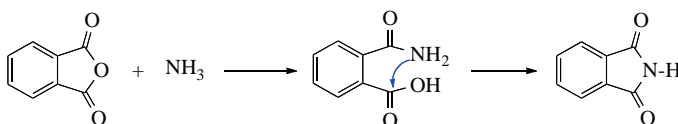
¹⁸⁷³ See Yasuhara, T.; Nagaoka, Y.; Tomioka, K. *J. Chem. Soc. Perkin Trans. 1* **1999**, 2233.

¹⁸⁷⁴ Greene, T.W. *Protective Groups in Organic Synthesis* Wiley, NY, **1980**, pp 222–248, 324–326; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, NY, **1991**, pp 327–330; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, NY, **1999**, pp 518–525; 737–739.

¹⁸⁷⁵ Kivinen, A. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, **1972**; Bender, M.L.; Jones, M.J. *J. Org. Chem.* **1962**, 27, 3771. See also, Song, B.D.; Jencks, W.P. *J. Am. Chem. Soc.* **1989**, 111, 8479.

¹⁸⁷⁶ Lemoucheux, L.; Seitz, T.; Rouden, J.; Lasne, M.-C. *Org. Lett.* **2004**, 6, 3703.

This reaction, similar in scope and mechanism¹⁸⁷⁷ to Reaction **16-72**, can be carried out with ammonia or primary or secondary amines.¹⁸⁷⁸ Note that there is a report where a tertiary amine (an *N*-alkylpyrrolidine) reacted with acetic anhydride at 120 °C, in the presence of a BF₃·etherate catalyst, to give *N*-acetylpyrrolidine (an acylative dealkylation).¹⁸⁷⁹ Amino acids can be *N*-acylated using acetic anhydride and ultrasound.¹⁸⁸⁰ However, ammonia and primary amines can also give imides, in which two acyl groups are attached to the nitrogen. The conversion of cyclic anhydrides to cyclic imides is generally facile,¹⁸⁸¹ although elevated temperatures are occasionally required to generate the imide.¹⁸⁸² Microwave irradiation of formamide and a cyclic anhydride generates the cyclic imide.¹⁸⁸³ Cyclic imides have also been formed in ionic liquids.¹⁸⁸⁴ Cyclic imides were also formed by microwave irradiation of a polymer-bound phthalate after initial reaction with an amine.¹⁸⁸⁵



The second step for imide formation, which is much slower than the first, is the attack of the amide nitrogen on the carboxylic carbon. Unsubstituted and *N*-substituted amides have been used instead of ammonia. Since the other product of this reaction is RCOOH, this is a way of “hydrolyzing” such amides in the absence of water.¹⁸⁸⁶

Even though formic anhydride is not a stable compound (see Reaction **11-17**), amines can be formylated with the mixed anhydride of acetic and formic acids (HCOOCOME)¹⁸⁸⁷ or with a mixture of formic acid and acetic anhydride. Acetamides are not formed with these reagents. Secondary amines can be acylated in the presence of a primary amine by conversion to their salts and addition of 18-crown-6.¹⁸⁸⁸ The crown ether complexes the primary ammonium salt, preventing its acylation, while the secondary ammonium salts, which do not fit easily into the cavity, are free to be acylated. Dimethyl carbonate can be used to prepare methyl carbamates in a related procedure.¹⁸⁸⁹ *N*-Acetylsulfonamides were prepared from acetic anhydride and a primary sulfonamide, catalyzed by Montmorillonite K10-FeO¹⁸⁹⁰ or sulfuric acid.¹⁸⁹¹

¹⁸⁷⁷ For a discussion of the mechanism, see Kluger, R.; Hunt, J.C. *J. Am. Chem. Soc.* **1989**, *111*, 3325.

¹⁸⁷⁸ See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 86–96. See also, Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B.K. *Eur. J. Org. Chem.* **2004**, 1254.

¹⁸⁷⁹ Dave, P.R.; Kumar, K.A.; Duddu, R.; Axenrod, T.; Dai, R.; Das, K.K.; Guan, X.-P.; Sun, J.; Trivedi, N.J.; Gilardi, R.D. *J. Org. Chem.* **2000**, *65*, 1207.

¹⁸⁸⁰ Anuradha, M.V.; Ravindranath, B. *Tetrahedron* **1997**, *53*, 1123.

¹⁸⁸¹ See Wheeler, O.H.; Rosado, O. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 335–381; Hargreaves, M.K.; Pritchard, J.G.; Dave, H.R. *Chem. Rev.* **1970**, *70*, 439 (cyclic imides).

¹⁸⁸² Tsubouchi, H.; Tsuji, K.; Ishikawa, H. *Synlett* **1994**, 63.

¹⁸⁸³ Kacprzak, K. *Synth. Commun.* **2003**, *33*, 1499.

¹⁸⁸⁴ Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* **2004**, 995.

¹⁸⁸⁵ Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* **2003**, *5*, 1851.

¹⁸⁸⁶ Eaton, J.T.; Rounds, W.D.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* **1988**, *29*, 6553.

¹⁸⁸⁷ Vlietstra, E.J.; Zwikker, J.W.; Nolte, R.J.M.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 460.

¹⁸⁸⁸ Barrett, A.G.M.; Lana, J.C.A. *J. Chem. Soc., Chem. Commun.* **1978**, 471.

¹⁸⁸⁹ Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* **2000**, *41*, 6347.

¹⁸⁹⁰ Singh, D.U.; Singh, P.R.; Samant, S.D. *Tetrahedron Lett.* **2004**, *45*, 4805.

¹⁸⁹¹ Martin, M.T.; Roschangar, F.; Eaddy, J.F. *Tetrahedron Lett.* **2003**, *44*, 5461.

There are acylating reagents other than anhydrides of course. The reaction with acyl halides is discussed in Reaction **16-72**. There are a few specialized reagents. Kinetic resolution of racemic amines was accomplished using (1*S*,2*S*)-*N*-acetyl-1,2- bis(trifluoromethanesulfonamido)cyclohexane.¹⁸⁹²

OS **I**, 457; **II**, 11; **III**, 151, 456, 661, 813; **IV**, 5, 42, 106, 657; **V**, 27, 373, 650, 944, 973; **VI**, 1; **VII**, 4, 70; **VIII**, 132; **76**, 123.

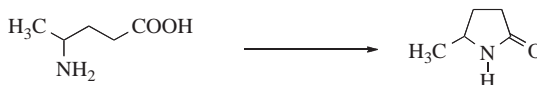
16-74 Acylation of Amines by Carboxylic Acids

Amino-de-hydroxylation



When carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia or primary or secondary amines can be pyrolyzed to give amides,¹⁸⁹³ but the method is less convenient than Reaction **16-72**, **16-73**, and **16-75** and is seldom of preparative value.¹⁸⁹⁴ Heating in the presence of a base (e.g., hexamethyldisilazide) makes the amide-forming process more efficient.¹⁸⁹⁵ Boronic acids catalyze the direct conversion of carboxylic acid and amine to amides.¹⁸⁹⁶ Polymer-bound reagents have also been used.¹⁸⁹⁷ Triphenylphosphine/-trichloroisocyanuric acid converts acids and amides to the amide.¹⁸⁹⁸ The *Burgess reagent* ($\text{Et}_3\text{N}^+\text{SO}_2\text{N}^-\text{CO}_2\text{Me}$; see Reaction **17-29**) activates carboxylic acids for amide formation.¹⁸⁹⁹ The reaction of a carboxylic acid and imidazole under microwave irradiation gives the amide.¹⁹⁰⁰ Microwave irradiation of a secondary amine, formic acid, 2-chloro-4,6-dimethoxy [1,3,5]triazine, and a catalytic amount of DMAP leads to the formamide.¹⁹⁰¹ Ammonium bicarbonate and formamide converts acids to amides with microwave irradiation.¹⁹⁰² Formamides are produced from formic acid and anion nitriles in the presence of ZnO .¹⁹⁰³

Lactams are readily produced from γ - or δ -amino acids,¹⁹⁰⁴ for example,



¹⁸⁹² Arseniyadis, S.; Subhash, P.V.; Valleix, A.; Mathew, S.P.; Blackmond, D.G.; Wagner, A.; Mioskowski, C. *J. Am. Chem. Soc.* **2005**, 127, 6138.

¹⁸⁹³ See Gooßen, L.J.; Ohlmann, D.M.; Lange, P.P. *Synthesis* **2009**, 160.

¹⁸⁹⁴ See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 105–109.

¹⁸⁹⁵ Chou, W.-C.; Chou, M.-C.; Lu, Y.-Y.; Chen, S.-F. *Tetrahedron Lett.* **1999**, 40, 3419. Also see White, J.M.; Tunoori, A.R.; Turunen, B.J.; Georg, G.I. *J. Org. Chem.* **2004**, 69, 2573.

¹⁸⁹⁶ Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* **2001**, 1371.

¹⁸⁹⁷ Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* **2004**, 6, 4579; Chichilla, R.; Dodsworth, D.J.; Nájera, C.; Soriano, J.M. *Tetrahedron Lett.* **2003**, 44, 463.

¹⁸⁹⁸ da C. Rodrigues, R.; Barros, I.M.A.; Lima, E.L.S. *Tetrahedron Lett.* **2005**, 46, 5945.

¹⁸⁹⁹ Wodka, D.; Robbins, M.; Lan, P.; Martinez, R.L.; Athanasopoulos, J.; Makara, G.M. *Tetrahedron Lett.* **2006**, 47, 1825.

¹⁹⁰⁰ Khalafi-Nezhad, A.; Mokhtari, B.; Rad, M.N.S. *Tetrahedron Lett.* **2003**, 44, 7325; Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, 58, 2155. See also, Bose, A.K.; Ganguly, S.N.; Manhas, M.S.; Guha, A.; Pombo-Villars, E. *Tetrahedron Lett.* **2006**, 47, 4605.

¹⁹⁰¹ De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* **2004**, 2570.

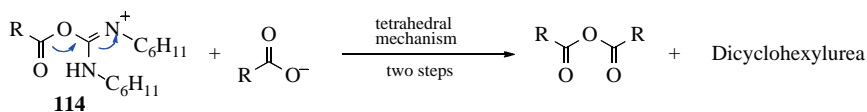
¹⁹⁰² Peng, Y.; Song, G. *Org. Prep. Proceed. Int.* **2002**, 34, 95.

¹⁹⁰³ Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, 71, 6652.

¹⁹⁰⁴ See Bladé-Font, A. *Tetrahedron Lett.* **1980**, 21, 2443. Also see Wei, Z.-Y.; Knaus, E.E. *Tetrahedron Lett.* **1993**, 34, 4439 for a variation of this reaction.

This lactonization process can be promoted by enzymes (e.g., pancreatic porcine lipase).¹⁹⁰⁵ Reduction of ω -azide carboxylic acids leads to macrocyclic lactams.¹⁹⁰⁶

Although treatment of carboxylic acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above by the use of coupling agents,¹⁹⁰⁷ the most important of which is dicyclohexylcarbodiimide. This reagent is very convenient and is used¹⁹⁰⁸ a great deal in peptide synthesis.¹⁹⁰⁹ A polymer-supported carbodiimide has been used.¹⁹¹⁰ The mechanism is probably the same as in Reaction 16-63 up to the formation of **114**. This intermediate is then attacked by another molecule of RCOO^- to give the anhydride $(\text{RCO})_2\text{O}$, which is the actual species that reacts with the amine:



The anhydride has been isolated from the reaction mixture and then used to acylate an amine.¹⁹¹¹

The synthetically important *Weinreb amides* $[\text{RCON}(\text{Me})\text{OMe}]$, see Reaction 16-82] can be prepared from the carboxylic acid and $\text{MeO}(\text{Me})\text{NH}\cdot\text{HCl}$ in the presence of tributylphosphine and 2-pyridine-*N*-oxide disulfide.¹⁹¹² Di(2-pyridyl)carbonate has been used in a related reaction that generates amides directly.¹⁹¹³ Other promoting agents¹⁹¹⁴ are $\text{ArB}(\text{OH})_2$ reagents,¹⁹¹⁵ N,N' -carbonyldiimidazole (**115**, in Reaction 16-63),¹⁹¹⁶ POCl_3 ,¹⁹¹⁷ TiCl_4 ,¹⁹¹⁸ molecular sieves,¹⁹¹⁹ *Lawesson's reagent* (Reaction 16-11),¹⁹²⁰ and $(\text{MeO})_2\text{POCl}$.¹⁹²¹ Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases, the cyclic anhydride is an intermediate and is the species actually attacked by the amine.¹⁹²² Carboxylic acids can also be

¹⁹⁰⁵ Gutman, A.L.; Meyer, E.; Yue, X.; Abell, C. *Tetrahedron Lett.* **1992**, 33, 3943.

¹⁹⁰⁶ Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, 34, 4671. See Bai, D.; Shi, Y. *Tetrahedron Lett.* **1992**, 33, 943 for the preparation of lactam units in *p*-cyclophanes.

¹⁹⁰⁷ See Klausner, Y.S.; Bodansky, M. *Synthesis* **1972**, 453.

¹⁹⁰⁸ It was first used this way by Sheehan, J.C.; Hess, G.P. *J. Am. Chem. Soc.* **1955**, 77, 1067.

¹⁹⁰⁹ See Gross, E.; Meienhofer, J. *The Peptides*, 3 Vols., Academic Press, NY, **1979–1981**. See Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, Springer, NY, **1984**.

¹⁹¹⁰ Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, 42, 6667.

¹⁹¹¹ See Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* **1974**, 96, 1606. Also see Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* **1973**, 95, 4052.

¹⁹¹² Banwell, M.; Smith, J. *Synth. Commun.* **2001**, 31, 2011. For another procedure, see Kim, M.; Lee, H.; Han, K.-J.; Kay, K.-Y. *Synth. Commun.* **2003**, 33, 4013.

¹⁹¹³ Shiina, I.; Suenaga, Y.; Nakano, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, 73, 2811.

¹⁹¹⁴ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1941–1949.

¹⁹¹⁵ Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, 61, 4196.

¹⁹¹⁶ See Vaidyanathan, R.; Kalthod, V.G.; Ngo, D.; Manley, J.M.; Lapekas, S.P. *J. Org. Chem.* **2004**, 69, 2565. Also see Grzyb, J.A.; Batey, R.A. *Tetrahedron Lett.* **2003**, 44, 7485.

¹⁹¹⁷ Klosa, J. *J. Prakt. Chem.* **1963**, [4] 19, 45.

¹⁹¹⁸ Wilson, J.D.; Weingarten, H. *Can. J. Chem.* **1970**, 48, 983.

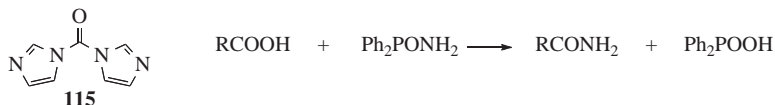
¹⁹¹⁹ Cossy, J.; Pale-Grosdemange, C. *Tetrahedron Lett.* **1989**, 30, 2771.

¹⁹²⁰ Thorsen, M.; Andersen, T.P.; Pedersen, U.; Yde, B.; Lawesson, S. *Tetrahedron* **1985**, 41, 5633.

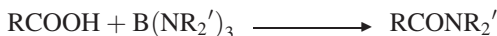
¹⁹²¹ Jászay, Z.M.; Petneházy, I.; Töke, L. *Synth. Commun.* **1998**, 28, 2761.

¹⁹²² Higuchi, T.; Miki, T.; Shah, A.C.; Herd, A.K. *J. Am. Chem. Soc.* **1963**, 85, 3655.

converted to amides by heating with amides of carboxylic acids (exchange),¹⁹²³ sulfonic acids, or phosphoric acids, for example,¹⁹²⁴



or by treatment with trisalkylaminoboranes $[\text{B}(\text{NHR}')_3]$, with trisdialkylaminoboranes $[\text{B}(\text{NR}_2')_3]$,¹⁹²⁵



or with bis(diorganoamino)magnesium reagents $[(\text{R}_2\text{N})_2\text{Mg}]$.¹⁹²⁶ The reaction of thio-carboxylic acids and azides, in the presence of triphenylphosphine, gives the corresponding amide.¹⁹²⁷

An important technique, discovered by R.B. Merrifield¹⁹²⁸ and since used for the synthesis of many peptides,¹⁹²⁹ is called *solid-phase synthesis* or *polymer-supported synthesis*.¹⁹³⁰ The reactions used are the same as in ordinary synthesis, but one of the reactants is anchored onto a solid polymer. For example, if it is desired to couple two amino acids (to form a dipeptide), the polymer selected might be polystyrene with CH_2Cl side chains. One of the amino acids, protected by (Boc), would then be coupled to the side chains. It is not necessary that all the side chains be converted, but a random selection will be converted. The Boc group is then removed by hydrolysis with trifluoroacetic acid in CH_2Cl_2 and the second amino acid is coupled to the first, using DCC or some other coupling agent. The second Boc group is removed, resulting in a dipeptide that is still anchored to the polymer. If this dipeptide is the desired product, it can be cleaved from the

¹⁹²³ For example, see Schindbauer, H. *Monatsh. Chem.* **1968**, 99, 1799.

¹⁹²⁴ Zhmurova, I.N.; Voitsekhovskaya, I.Yu.; Kirsanov, A.V. *J. Gen. Chem. USSR* **1959**, 29, 2052. See also, Liu, H.; Chan, W.H.; Lee, S.P. *Synth. Commun.* **1979**, 9, 31.

¹⁹²⁵ Pelter, A.; Levitt, T.E.; Nelson, P. *Tetrahedron* **1970**, 26, 1539; Pelter, A.; Levitt, T.E. *Tetrahedron* **1970**, 26, 1545, 1899.

¹⁹²⁶ Sanchez, R.; Vest, G.; Despres, L. *Synth. Commun.* **1989**, 19, 2909.

¹⁹²⁷ Park, S.-D.; Oh, J.-H.; Lim, D. *Tetrahedron Lett.* **2002**, 43, 6309.

¹⁹²⁸ Merrifield, R.B. *J. Am. Chem. Soc.* **1963**, 85, 2149.

¹⁹²⁹ Birr, C. *Aspects of the Merrifield Peptide Synthesis*, Springer, NY, **1978**. For reviews, see Bayer, E. *Angew. Chem. Int. Ed.* **1991**, 30, 113; Kaiser, E.T. *Acc. Chem. Res.* **1989**, 22, 47; Jacquier, R. *Bull. Soc. Chim. Fr.* **1989**, 220; Barany, G.; Kneib-Cordonier, N.; Mullen, D.G. *Int. J. Pept. Protein Res.* **1987**, 30, 705; Andreev, S.M.; Samoilova, N.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* **1987**, 56, 366; Gross, E.; Meienhofer, J. *The Peptides*, Vol. 2, Academic Press, NY, **1980**, the articles by Barany, G.; Merrifield, R.B. pp. 1–184; Fridkin, M. pp. 333–363; Erickson, B.W.; Merrifield, R.B. in Neurath, H.; Hill, R.L.; Boeder, C.-L. *The Proteins*, 3rd ed., Vol. 2, Academic Press, NY, **1976**, pp. 255–527. For R. B. Merrifield's Nobel Prize lecture, see Merrifield, R.B. *Angew. Chem. Int. Ed.* **1985**, 24, 799.

¹⁹³⁰ Laszlo, P. *Preparative Organic Chemistry Using Supported Reagents*, Academic Press, NY, **1987**; Mathur, N.K.; Narang, C.K.; Williams, R.E. *Polymers as Aids in Organic Chemistry*, Academic Press, NY **1980**; Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis*, Wiley, NY, **1980**. For reviews, see Pillai, V.N.R.; Mutter, M. *Top. Curr. Chem.* **1982**, 106, 119; Akelah, A.; Sherrington, D.C. *Chem. Rev.* **1981**, 81, 557; Akelah, A. *Synthesis* **1981**, 413; Rebek, J. *Tetrahedron* **1979**, 35, 723; McKillop, A.; Young, D.W. *Synthesis* **1979**, 401, 481; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* **1976**, 9, 135; Patchornik, A.; Kraus, M.A. *Pure Appl. Chem.* **1975**, 43, 503.

polymer by various methods,¹⁹³¹ one of which is treatment with HF. If a longer peptide is wanted, additional amino acids can be added by repeating the requisite steps.

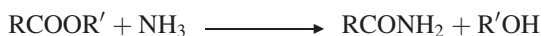
The basic advantage of the polymer support techniques is that the polymer (including all chains attached to it) is easily separated from all other reagents, because it is insoluble in the solvents used. Excess reagents, other reaction products (e.g., dicyclohexylurea), side products, and the solvents themselves are quickly washed away. Purification of the polymeric species is rapid and complete. The process can even be automated,¹⁹³² to the extent that six or more amino acids can be added to a peptide chain in one day. Commercial automated peptide synthesizers are now available.¹⁹³³

Although the solid-phase technique was first developed for the synthesis of peptide chains and has seen considerable use for this purpose, it has also been used to synthesize chains of polysaccharides and polynucleotides; in the latter case, solid-phase synthesis has almost completely replaced synthesis in solution.¹⁹³⁴ The technique has been applied less often to reactions in which only two molecules are brought together (nonrepetitive syntheses), but many examples have been reported.¹⁹³⁵ Combinatorial chemistry in some ways can be viewed as an extension of the *Merrifield synthesis*, particularly when applied to peptide synthesis, and continues as an important part of modern organic chemistry.¹⁹³⁶

OS I, 3, 82, 111, 172, 327; II, 65, 562; III, 95, 328, 475, 590, 646, 656, 768; IV, 6, 62, 513; V, 670, 1070; VIII, 241; 81, 262. Also see, OS III, 360; VI, 263; VIII, 68.

16-75 Acylation of Amines by Carboxylic Esters

Amino-de-alkoxylation



The conversion of carboxylic esters to amides is a useful reaction, and unsubstituted, *N*-substituted, and *N,N*-disubstituted amides can be prepared this way from the appropriate amine¹⁹³⁷ or ammonia.¹⁹³⁸ Both R and R' can be alkyl or aryl, but *an especially good leaving group is p-nitrophenyl*. Ethyl trifluoroacetate was found to react selectively with primary amines to form the corresponding trifluoroacetyl amide.¹⁹³⁹ Many simple esters

¹⁹³¹ See Whitney, D.B.; Tam, J.P.; Merrifield, R.B. *Tetrahedron* **1984**, 40, 4237.

¹⁹³² Merrifield, R.B.; Stewart, J.M.; Jernberg, N. *Anal. Chem.* **1966**, 38, 1905.

¹⁹³³ See Schnorrenberg, G.; Gerhardt, H. *Tetrahedron* **1989**, 45, 7759.

¹⁹³⁴ For a review, see Bannwarth, W. *Chimia* **1987**, 41, 302.

¹⁹³⁵ Fréchet, J.M.J. *Tetrahedron* **1981**, 37, 663; Fréchet, J.M.J. in Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis*, Wiley, NY, **1980**, pp. 293–342, Leznoff, C.C. *Acc. Chem. Res.* **1978**, 11, 327; *Chem. Soc. Rev.* **1974**, 3, 64.

¹⁹³⁶ Czarnik, A.W.; DeWitt, S.H. *A Practical Guide to Combinatorial Chemistry*, American Chemical Society, Washington, D.C., **1997**; Chaiken, I.N.; Janda, K.D. *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*, American Chemical Society, Washington, D.C.; **1996**; Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed.* **1996**, 35, 2289; Thompson, L.A.; Ellman, J.A. *Chem. Rev.* **1996**, 96, 555; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* **1976**, 9, 135; Leznoff, C.C. *Acc. Chem. Res.* **1978**, 11, 327.

¹⁹³⁷ Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 96–105. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1973–1976. See Sabot, C.; Kumar, K.A.; Meunier, S.; Mioskowski, C. *Tetrahedron Lett.* **2007**, 48, 3863.

¹⁹³⁸ See Mizuhara, T.; Hioki, K.; Yamada, M.; Sasaki, H.; Morisaki, D.; Kunishima, M. *Chem. Lett.* **2008**, 37, 1190. Magnesium nitride is a useful source of ammonia in this reaction. See Veitch, G.E.; Bridgwood, K.L.; Ley, S.V. *Org. Lett.* **2008**, 10, 3623.

¹⁹³⁹ Xu, D.; Prasad, K.; Repic, O.; Blacklock, T.J. *Tetrahedron Lett.* **1995**, 36, 7357.

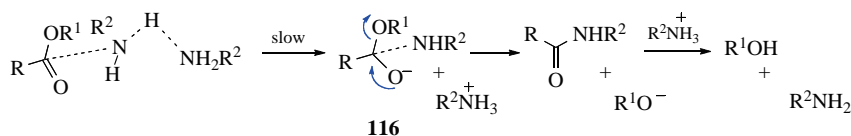
(R = Me, Et, etc.) are not very reactive, and strongly basic catalysis has been used in such cases,¹⁹⁴⁰ but catalysis by cyanide ion¹⁹⁴¹ MgBr₂,¹⁹⁴² InI₃,¹⁹⁴³ and acceleration by high pressure¹⁹⁴⁴ have been reported. Methyl esters¹⁹⁴⁵ and ethyl esters¹⁹⁴⁶ have been converted to the corresponding amide under microwave irradiation. Lithium amides have been used to convert esters to amides as well.¹⁹⁴⁷ β-Keto esters undergo the reaction especially easily.¹⁹⁴⁸ Aniline was treated with *n*-butyllithium to form the lithium amide, which reacted with an ester to give the amide.¹⁹⁴⁹ An enzyme-mediated amidation is known using amino cyclase I.¹⁹⁵⁰ The reaction of dimethyl carbonate and an amine is an effective way to prepare methyl carbamates.¹⁹⁵¹

Lactones give lactams when treated with ammonia or primary amines. Lactams are also produced from γ- and δ-amino esters in an internal example of this reaction. Lactonization has been accomplished in ionic liquids.¹⁹⁵²

As in Reaction 16-72, hydrazides and hydroxamic acids can be prepared from carboxylic esters, with hydrazine and hydroxylamine,¹⁹⁵³ respectively. Both hydrazine and hydroxylamine react more rapidly than ammonia or primary amines (the alpha effect, Sec. 10.G.ii). Imidates [RC(=NH)OR'] give amidines [RC(=NH)NH₂]. Isopropenyl formate is a useful compound for the formylation of primary and secondary amines.¹⁹⁵⁴



Although more studies have been devoted to the mechanism of the acylation of amines with carboxylic esters than with other reagents, the mechanistic details are not yet entirely clear.¹⁹⁵⁵ In its broad outlines, the mechanism appears to be essentially B_{AC}2.¹⁹⁵⁶ Under normal basic conditions, the reaction is general base catalyzed,¹⁹⁵⁷ indicating that a proton is being transferred in the rate-determining step and that two molecules



¹⁹⁴⁰ See Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* **1989**, 122, 1357.

¹⁹⁴¹ Högberg, T.; Ström, P.; Ebner, M.; Råmsby, S. *J. Org. Chem.* **1987**, 52, 2033.

¹⁹⁴² Guo, Z.; Dowdy, E.D.; Li, W.-S.; Polniaszek, R.; Delaney, E. *Tetrahedron Lett.* **2001**, 42, 1843.

¹⁹⁴³ Ranu, B.C.; Dutta, P. *Synth. Commun.* **2003**, 33, 297.

¹⁹⁴⁴ Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* **1989**, 122, 1357.

¹⁹⁴⁵ Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* **1999**, 40, 6177.

¹⁹⁴⁶ Zradni, F.-Z.; Hamelin, J.; Derdour, A. *Synth. Commun.* **2002**, 32, 3525.

¹⁹⁴⁷ See Wang, J.; Rosigana, M.; Discordia, R.P.; Soundararajan, N.; Polniaszek, R. *Synlett* **2001**, 1485.

¹⁹⁴⁸ Labelle, M.; Gravel, D. *J. Chem. Soc., Chem. Commun.* **1985**, 105.

¹⁹⁴⁹ Ooi, T.; Tayama, E.; Yamada, M.; Maruoka, K. *Synlett.* **1999**, 729.

¹⁹⁵⁰ Youshko, M.I.; van Rantwijk, F.; Sheldon, R.A. *Tetrahedron Asymmetry* **2001**, 12, 3267.

¹⁹⁵¹ Distaso, M.; Quaranta, E. *Tetrahedron* **2004**, 60, 1531.

¹⁹⁵² Orrling, K.M.; Wu, X.; Russo, F.; Larhed, M. *J. Org. Chem.* **2008**, 73, 8627.

¹⁹⁵³ Ho, C.Y.; Strobel, E.; Ralbovsky, J.; Galemme, Jr., R.A. *J. Org. Chem.* **2005**, 70, 4873.

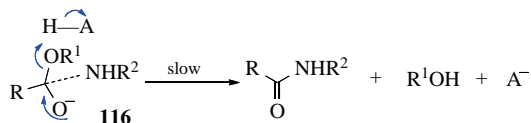
¹⁹⁵⁴ van Melick, J.E.W.; Wolters, E.T.M. *Synth. Commun.* **1972**, 2, 83.

¹⁹⁵⁵ Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, **1969**, pp. 410–431; Ilieva, S.; Galabov, B.; Musaev, D.G.; Morokuma, K.; Schaefer, III, H.F. *J. Org. Chem.* **2003**, 68, 1496.

¹⁹⁵⁶ Bruice, T.C.; Donzel, A.; Huffman, R.W.; Butler, A.R. *J. Am. Chem. Soc.* **1967**, 89, 2106.

¹⁹⁵⁷ Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* **1960**, 82, 665; Jencks, W.P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, 82, 675; Bruice, T.C.; Mayahi, M.F. *J. Am. Chem. Soc.* **1960**, 82, 3067.

of amine are involved.¹⁹⁵⁸ Alternatively, another base (e.g., H₂O or OH[−]) can substitute for the second molecule of amine. With some substrates and under some conditions, especially at low pH, the breakdown of **116** can become rate determining.¹⁹⁵⁹ The reaction also takes place under acidic conditions and is general acid catalyzed, so that breakdown of **116** is rate determining and proceeds as follows:¹⁹⁶⁰



Here HA may be R²NH₃⁺ or another acid. Intermediate **116** may or may not be further protonated on the nitrogen. Even under basic conditions, a proton donor may be necessary to assist leaving-group removal. Evidence for this is that the rate is lower with NR₂[−] in liquid ammonia than with NHR₂ in water, apparently owing to the lack of acids to protonate the leaving oxygen.¹⁹⁶¹

In the special case of β-lactones, where small-angle strain is an important factor, alkyl-oxygen cleavage is observed (B_{AL}2 mechanism, as in the similar case of hydrolysis of β-lactones, Reaction **16-59**), and the product is not an amide but a β-amino acid (β-alanine).

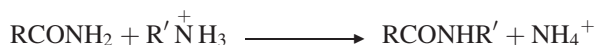


A similar result has been found for certain sterically hindered esters.¹⁹⁶² This reaction is similar to **10-31**, with OCOR as the leaving group. Other lactones have been opened to ω-hydroxy amides with Dibal-H:BnNH₂.¹⁹⁶³

OS **I**, 153, 179; **II**, 67, 85; **III**, 10, 96, 108, 404, 440, 516, 536, 751, 765; **IV**, 80, 357, 441, 486, 532, 566, 819; **V**, 168, 301, 645; **VI**, 203, 492, 620, 936; **VII**, 4, 30, 41, 411; **VIII**, 26, 204, 528. Also see, OS **I**, 5; **V**, 582; **VII**, 75.

16-76 Acylation of Amines by Amides

Alkylamino-de-amination



¹⁹⁵⁸ Bruice, T.C.; Felton, S.M. *J. Am. Chem. Soc.* **1969**, 91, 2799; Felton, S.M.; Bruice, T.C. *J. Am. Chem. Soc.* **1969**, 91, 6721; Nagy, O.B.; Reuliaux, V.; Bertrand, N.; Van Der Mensbrugghe, A.; Leseul, J.; Nagy, J.B. *Bull. Soc. Chim. Belg.* **1985**, 94, 1055.

¹⁹⁵⁹ Gresser, M.J.; Jencks, W.P. *J. Am. Chem. Soc.* **1977**, 99, 6963, 6970. See also, Um, I.-H.; Lee, J.-Y.; Lee, H.W.; Nagano, Y.; Fujio, M.; Tsuno, Y. *J. Org. Chem.* **2005**, 70, 4980.

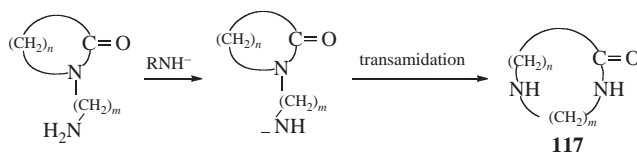
¹⁹⁶⁰ Blackburn, G.M.; Jencks, W.P. *J. Am. Chem. Soc.* **1968**, 90, 2638.

¹⁹⁶¹ Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* **1960**, 82, 665.

¹⁹⁶² Zaugg, H.E.; Helgren, P.F.; Schaefer, A.D. *J. Org. Chem.* **1963**, 28, 2617. See also, Weintraub, L.; Terrell, R. *J. Org. Chem.* **1965**, 30, 2470; Harada, R.; Kinoshita, Y. *Bull. Chem. Soc. Jpn.* **1967**, 40, 2706.

¹⁹⁶³ Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* **2001**, 42, 9039. See also, Taylor, S.K.; Ide, N.D.; Silver, M.E.; Stephan, M. *Synth. Commun.* **2001**, 31, 2391.

This is an exchange reaction and is usually carried out with the salt of the amine.¹⁹⁶⁴ The leaving group is usually NH_2 rather than NHR or NR_2 and primary amines (in the form of their salts) are the most common reagents. Boron trifluoride can be added to complex with the leaving ammonia. Neutral amines also react in some cases to give the new amide.¹⁹⁶⁵ The reaction is catalyzed by Al(III) .¹⁹⁶⁶ The reaction is often used to convert urea to substituted ureas: $\text{NH}_2\text{CONH}_2 + \text{RNH}_3^+ \rightarrow \text{NH}_2\text{CONHR} + \text{NH}_4^+$.¹⁹⁶⁷ An *N*-aryl group of a urea can be converted to a *N,N*-dialkyl group by heating the urea with the amine in an autoclave.¹⁹⁶⁸ *N*-alkyl substituted amides (alkyl = R) are converted to *N*-R'-substituted amides, where alkyl = R', by treatment with N_2O_4 to give an *N*-nitroso compound, followed by treatment of this with a primary amine ($\text{R}'\text{NH}_2$).¹⁹⁶⁹ Lactams can be converted to ring-expanded lactams (e.g., **117**) if a side chain containing an amino group is present on the nitrogen. A strong base is used to convert the NH_2 to NH^- , which then acts as a nucleophile, expanding the ring by means of a transamidation.¹⁹⁷⁰ The discoverers call it the *Zip reaction*, by analogy with the action of zippers.¹⁹⁷¹



Lactams can be opened to ω -amino amides by reaction with amines at 10 kbar.¹⁹⁷²

OS I, 302 (but see V, 589), 450, 453; II, 461; III, 151, 404; IV, 52, 361. See also, OS VIII, 573.

16-77 Acylation of Amines by Other Acid Derivatives

Acylamino-de-halogenation or dealkoxylation



Acid derivatives that can be converted to amides include thiol acids (RCOSH), thiol esters (RCOSR),¹⁹⁷³ acyloxyboranes [RCOB(OR')_2],¹⁹⁷⁴ α -keto nitriles, acyl azides, and nonenolizable ketones (see the *Haller–Bauer Reaction 12-34*). *N*-Acylsulfonamides react with primary amines to the amide (AcNHR).¹⁹⁷⁵ Carbonylation reactions can be used to

¹⁹⁶⁴ For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1978–1982.

¹⁹⁶⁵ Murakami, Y.; Kondo, K.; Miki, K.; Akiyama, Y.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1997**, 38, 3751.

¹⁹⁶⁶ Hoerter, J.M.; Otte, K.M.; Gellman, S.H.; Stahl, S.S. *J. Am. Chem. Soc.* **2006**, 128, 5177.

¹⁹⁶⁷ See Chimishkyan, A.L.; Snagovskii, Yu.S.; Gulyaev, N.D.; Leonova, T.V.; Kusakin, M.S. *J. Org. Chem. USSR* **1985**, 21, 1955.

¹⁹⁶⁸ Yang, Y.; Lu, S. *Org. Prep. Proceed. Int.* **1999**, 31, 559.

¹⁹⁶⁹ Garcia, J.; Vilarasa, J. *Tetrahedron Lett.* **1982**, 23, 1127.

¹⁹⁷⁰ Askitoglu, E.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **1985**, 68, 750 and references cited therein. For a carbon analog, see Süssle, M.; Hájíček, J.; Hesse, M. *Helv. Chim. Acta* **1985**, 68, 1986.

¹⁹⁷¹ See Stach, H.; Hesse, M. *Tetrahedron* **1988**, 44, 1573.

¹⁹⁷² Kotsuki, H.; Iwasaki, M.; Nishizawa, H. *Tetrahedron Lett.* **1992**, 33, 4945.

¹⁹⁷³ See Douglas, K.T. *Acc. Chem. Res.* **1986**, 19, 186.

¹⁹⁷⁴ See Collum, D.B.; Chen, S.; Ganem, B. *J. Org. Chem.* **1978**, 43, 4393.

¹⁹⁷⁵ Coniglio, S.; Aramini, A.; Cesta, M.C.; Colagioia, S.; Curti, R.; D'Alessandro, F.; D'anniballe, G.; D'Elia, V.; Nano, G.; Orlando, V.; Allegretti, M. *Tetrahedron Lett.* **2004**, 45, 5375.

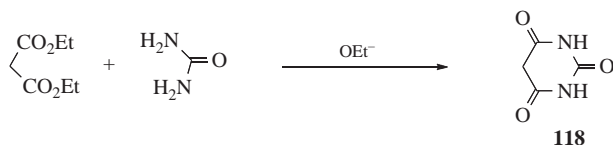
prepare amides and related compounds. The reaction of a primary amine, an alkyl halide with CO_2 , in the presence of $\text{Cs}_2\text{CO}_3/\text{Bu}_4\text{NI}$, gave the corresponding carbamate.¹⁹⁷⁶

OS **III**, 394; **IV**, 6, 569; **V**, 160, 166; **VI**, 1004.

Imides can be prepared by the attack of amides or their salts on acyl halides, anhydrides, and carboxylic acids or esters.¹⁹⁷⁷ A good synthetic method for the preparation of acyclic imides is the reaction between an amide and an anhydride at 100°C catalyzed by H_2SO_4 .¹⁹⁷⁸

When acyl chlorides are treated with amides in a 2: 1 molar ratio at low temperatures in the presence of pyridine, the products are *N,N*-diacylamides $[(\text{RCO})_3\text{N}]$.¹⁹⁷⁹

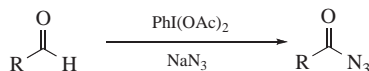
This reaction is often used to prepare urea derivatives, an important example being the preparation of barbituric acid (**118**).¹⁹⁸⁰



When the substrate is oxalyl chloride (ClCOCOCl) and the reagent an unsubstituted amide, an acyl isocyanate (RCONCO) is formed. The “normal” product (RCONHCOCOCl) does not form, or if it does, it rapidly loses CO and HCl .¹⁹⁸¹

OS **II**, 60, 79, 422; **III**, 763; **IV**, 245, 247, 496, 566, 638, 662, 744; **V**, 204, 944.

16-78 Acylation of Azides



The reaction of an aldehyde with sodium azide and $\text{Et}_4^+\text{I}(\text{OAc})_2$ or polymer-bound $\text{PhI}(\text{OAc})_2$ leads to an acyl azide.¹⁹⁸² Acyl azides are also prepared directly from aldehydes using *tert*-butyl hypochlorite.¹⁹⁸³

F. Attack by Halogen at an Acyl Carbon

16-79 Formation of Acyl Halides from Carboxylic Acids

Halo-de-hydroxylation



¹⁹⁷⁶ Salvatore, R.N.; Shin, S.I.; Nagle, A.S.; Jung, K.W. *J. Org. Chem.* **2001**, 66, 1035.

¹⁹⁷⁷ For a review, see Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 759–773.

¹⁹⁷⁸ Baburao, K.; Costello, A.M.; Petterson, R.C.; Sander, G.E. *J. Chem. Soc. C* **1968**, 2779; Davidson, D.; Skovronek, H. *J. Am. Chem. Soc.* **1958**, 80, 376.

¹⁹⁷⁹ See LaLonde, R.T.; Davis, C.B. *J. Org. Chem.* **1970**, 35, 771.

¹⁹⁸⁰ See Bojarski, J.T.; Mokrosz, J.L.; Barton, H.J.; Paluchowska, M.H. *Adv. Heterocycl. Chem.* **1985**, 38, 229.

¹⁹⁸¹ Speziale, A.J.; Smith, L.R.; Fedder, J.E. *J. Org. Chem.* **1965**, 30, 4306.

¹⁹⁸² Marinescu, L.G.; Pedersen, C.M.; Bols, M. *Tetrahedron* **2005**, 61, 123. See Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* **2003**, 68, 9453; Hüinig, S.; Schaller, R. *Angew. Chem. Int. Ed.* **1982**, 21, 36.

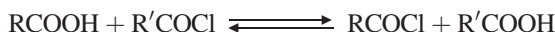
¹⁹⁸³ Arote, N.D.; Akamanchi, K.G. *Tetrahedron Lett.* **2007**, 48, 5661.

The same inorganic acid halides that convert alcohols to alkyl halides (Reaction **10-48**) also convert carboxylic acids to acyl halides.¹⁹⁸⁴ The reaction is the best and the most common method for the preparation of acyl chlorides. Bromides and iodides¹⁹⁸⁵ are also made in this manner, but much less often. Acyl bromides can be prepared with BBr₃ on alumina,¹⁹⁸⁶ or with ethyl tribromoacetate/PPh₃.¹⁹⁸⁷ Thionyl chloride¹⁹⁸⁸ is a good reagent, since the byproducts are gases and the acyl halide is easily isolated, but PX₃ and PX₅ (X = Cl or Br) are also commonly used.¹⁹⁸⁹ Hydrogen halides do not give the reaction. A particularly mild procedure, similar to one mentioned in Reaction **10-48**, involves reaction of the acid with Ph₃P in CCl₄, whereupon acyl chlorides are produced without obtaining any acidic compound as a byproduct.¹⁹⁹⁰

Oxalyl chloride (**113**) and oxalyl bromide are mild and often superior reagents, since the oxalic acid byproduct decomposes to CO and CO₂, and the equilibrium is thus driven to the side of the other acyl halide.¹⁹⁹¹ These reagents are commonly the reagent of choice, particularly when sensitive functionality is present elsewhere in the molecule.



Acyl fluorides can be prepared by treatment of carboxylic acids with cyanuric fluoride.¹⁹⁹² *N*-Chelated di-*n*-butyltin(IV) fluoride has been used to prepare acyl fluorides.¹⁹⁹³ Acid salts are also sometimes used as substrates and acyl halides are used as reagents in an exchange reaction:



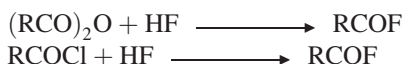
which probably involves an anhydride intermediate. This is an equilibrium reaction that must be driven to the desired side.

OS **I**, 12, 147, 394; **II**, 74, 156, 169, 569; **III**, 169, 490, 547, 555, 613, 623, 712, 714; **IV**, 34, 88, 154, 263, 339, 348, 554, 608, 616, 620, 715, 739, 900; **V**, 171, 258, 887; **VI**, 95, 190, 549, 715; **VII**, 467; **VIII**, 441, 486, 498.

16-80 Formation of Acyl Halides from Acid Derivatives

Halo-de-acyloxy-substitution

Halo-de-halogenation



¹⁹⁸⁴ See Ansell, M.F. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, **1972**, pp. 35–68.

¹⁹⁸⁵ See Keinan, E.; Sahai, M. *J. Org. Chem.* **1990**, *55*, 3922.

¹⁹⁸⁶ Bains, S.; Green, J.; Tan, L.C.; Pagni, R.M.; Kabalka, G.W. *Tetrahedron Lett.* **1992**, *33*, 7475.

¹⁹⁸⁷ Kang, D.H.; Joo, T.Y.; Lee, E.H.; Chaysripongkul, S.; Chavasiri, W.; Jang, D.O. *Tetrahedron Lett.* **2006**, *47*, 5693.

¹⁹⁸⁸ See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, **1974**, pp. 321–357. See Mohanazadeh, F.; Momeni, A. *R. Org. Prep. Proceed. Int.* **1996**, *28*, 492.

¹⁹⁸⁹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1929–1930.

¹⁹⁹⁰ Lee, J.B. *J. Am. Chem. Soc.* **1966**, *88*, 3440. See Venkataraman, K.; Wagle, D.R. *Tetrahedron Lett.* **1979**, 3037; Devos, A.; Remion, J.; Frisque-Hesbain, A.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180.

¹⁹⁹¹ Adams, R.; Ulich, L.H. *J. Am. Chem. Soc.* **1920**, *42*, 599; Wood, T.R.; Jackson, F.L.; Baldwin, A.R.; Longenecker, H.E. *J. Am. Chem. Soc.* **1944**, *66*, 287; Zhang, A.; Nie, J. *J. Agric. Food Chem.* **2005**, *53*, 2451.

¹⁹⁹² Olah, G.A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 487. For other methods of preparing acyl fluorides, see Mukaiyama, T.; Tanaka, T. *Chem. Lett.* **1976**, 303; Ishikawa, N.; Sasaki, S. *Chem. Lett.* **1976**, 1407.

¹⁹⁹³ Švec, P.; Eisner, A.; Kolářová, L.; Weidlich, T.; Pejchal, V.; Růžička, A. *Tetrahedron Lett.* **2008**, *49*, 6320.

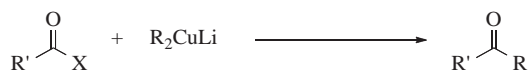
These reactions are most important for the preparation of acyl fluorides.¹⁹⁹⁴ Acyl chlorides and anhydrides can be converted to acyl fluorides by treatment with polyhydrogen fluoride–pyridine solution¹⁹⁹⁵ or with liquid HF at $-10\text{ }^{\circ}\text{C}$.¹⁹⁹⁶ Formyl fluoride, which is a stable compound, was prepared by the latter procedure from the mixed anhydride of formic and acetic acids.¹⁹⁹⁷ Acyl fluorides can also be obtained by reaction of acyl chlorides with KF in acetic acid¹⁹⁹⁸ or with diethylaminosulfur trifluoride (DAST).¹⁹⁹⁹ Carboxylic esters and anhydrides can be converted to acyl halides other than fluorides by the inorganic acid halides mentioned in Reaction 16-79, as well as with Ph_3PX_2 ($\text{X} = \text{Cl}$ or Br),²⁰⁰⁰ but this is seldom done. Halide exchange can be carried out in a similar manner. When halide exchange is done, it is always acyl bromides and iodides that are made from chlorides, since chlorides are by far the most readily available.²⁰⁰¹

OS II, 528; III, 422; V, 66, 1103; IX, 13. See also, OS IV, 307.

G. Attack by Carbon at an Acyl Carbon²⁰⁰²

16-81 The Conversion of Acyl Halides to Ketones with Organometallic Compounds²⁰⁰³

Alkyl-de-halogenation



Acyl halides react cleanly and under mild conditions with lithium dialkylcopper reagents (see Reaction 10-58)²⁰⁰⁴ to give high yields of ketones.²⁰⁰⁵ The R' group may be primary, secondary, or tertiary alkyl or aryl and may contain iodo, keto, ester, nitro, or cyano groups. The R groups that have been used successfully are methyl, primary alkyl, and vinylic. Secondary and tertiary alkyl groups can be introduced by the use of PhS(R)CuLi (Reaction 10-58) instead of R_2CuLi ,²⁰⁰⁶ or by the use of either the mixed homocuprate $[(\text{R}'\text{SO}_2\text{CH}_2\text{CuR})^-\text{Li}^+]$,²⁰⁰⁷ or a magnesium dialkylcopper reagent (RMeCuMgX) .²⁰⁰⁸ Secondary alkyl groups can also be introduced with the copper–zinc

¹⁹⁹⁴ For lists of reagents converting acid derivatives to acyl halides, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1950–1951, 1955, 1968.

¹⁹⁹⁵ Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* **1979**, *44*, 3872. See also, Yin, J.; Zarkowsky, D.S.; Thomas, D.W.; Zhao, M.W.; Huffman, M.A. *Org. Lett.* **2004**, *6*, 1465.

¹⁹⁹⁶ Olah, G.A.; Kuhn, S.J. *J. Org. Chem.* **1961**, *26*, 237.

¹⁹⁹⁷ Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* **1960**, *82*, 2380.

¹⁹⁹⁸ Emsley, J.; Gold, V.; Hibbert, F.; Szeto, W.T.A. *J. Chem. Soc. Perkin Trans. 2* **1988**, 923.

¹⁹⁹⁹ Markovski, L.N.; Pashinnik, V.E. *Synthesis* **1975**, 801.

²⁰⁰⁰ Burton, D.J.; Koppes, W.M. *J. Chem. Soc., Chem. Commun.* **1973**, 425; *J. Org. Chem.* **1975**, *40*, 3026; Anderson Jr., A.G.; Kono, D.H. *Tetrahedron Lett.* **1973**, 5121.

²⁰⁰¹ See Schmidt, A.H.; Russ, M.; Grosse, D. *Synthesis* **1981**, 216; Hoffmann, H.M.R.; Haase, K. *Synthesis* **1981**, 715.

²⁰⁰² House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 691–694, 734–765.

²⁰⁰³ For a review, see Cais, M.; Mandelbaum, A. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, Vol. 1, pp. 303–330.

²⁰⁰⁴ See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, **1980**, pp. 81–85. Ryu, I.; Ikebe, M.; Sonoda, N.; Yamamoto, S.-y.; Yamamura, G.-h.; Komatsu, M. *Tetrahedron Lett.* **2002**, *43*, 1257.

²⁰⁰⁵ Posner, G.H.; Whitten, C.E.; McFarland, P.E. *J. Am. Chem. Soc.* **1972**, *94*, 5106; Luong-Thi, N.; Rivière, H. *J. Organomet. Chem.* **1974**, *77*, C52.

²⁰⁰⁶ See Bennett, G.B.; Nadelson, J.; Alden, L.; Jani, A. *Org. Prep. Proced. Int.* **1976**, *8*, 13.

²⁰⁰⁷ Johnson, C.R.; Dhanoa, D.S. *J. Org. Chem.* **1987**, *52*, 1885.

²⁰⁰⁸ Bergbreiter, D.E.; Killough, J.M. *J. Org. Chem.* **1976**, *41*, 2750.

reagents $[\text{RCu}(\text{CN})\text{ZnI}]$.²⁰⁰⁹ The R group may be alkynyl if a cuprous acetylide ($\text{R}^2\text{C}\equiv\text{CCu}$) is the reagent.²⁰¹⁰ Organocopper reagents generated *in situ* from highly reactive copper, and containing such functional groups as cyano, chloro, and ester, react with acyl halides to give ketones.²⁰¹¹

When the organometallic compound is a *Grignard reagent*,²⁰¹² ketones are generally not obtained because the initially formed ketone reacts with a second molecule of RMgX to give the salt of a tertiary alcohol (Reaction **16-82**). Ketones *have* been prepared in this manner by the use of low temperatures, inverse addition (i.e., addition of the *Grignard reagent* to the acyl halide rather than the other way), excess acyl halide, and so on, but the yields are usually low, although high yields have been reported in THF at -78°C .²⁰¹³ Pretreatment with a trialkylphosphine followed by the *Grignard reagent* gave the ketone.²⁰¹⁴ Using CuBr ²⁰¹⁵ or a Ni catalyst²⁰¹⁶ with the *Grignard reagent* can lead to the ketone. Some ketones are unreactive toward *Grignard reagents* for steric or other reasons; these can be prepared in this way.²⁰¹⁷ Other methods involve running the reaction in the presence of Me_3SiCl ²⁰¹⁸, which reacts with the initial adduct in the tetrahedral mechanism (Sec. 16.A.i), and the use of a combined *Grignard*– LiNEt_2 reagent.²⁰¹⁹ Certain metallic halides, notably ferric and cuprous halides, are catalysts that improve the yields of ketone at the expense of tertiary alcohol.²⁰²⁰ For this catalysis, both free radical and ionic mechanisms have been proposed.²⁰²¹

Grignard reagents react with ethyl chloroformate to give carboxylic esters $[\text{EtOCOC}l + \text{RMgX} \rightarrow \text{EtOCOR}]$.

The Pd catalyzed reaction of an acyl chloride and an arylboronic acid²⁰²² or an alkenylboronic acid²⁰²³ gives a ketone. Surfactants are known to promote arylboronic acid coupling reactions.²⁰²⁴ Arylboronic esters add to carbamoyl halides, in the presence of a Pd catalyst, to give the corresponding benzamide.²⁰²⁵ Arylboronic acids also react with

²⁰⁰⁹ Knochel, P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

²⁰¹⁰ Castro, C.E.; Havlin, R.; Honwad, V.K.; Malte, A.; Mojé, S. *J. Am. Chem. Soc.* **1969**, *91*, 6464. See Verkrujse, H.D.; Heus-Kloos, Y.A.; Brandsma, L. *J. Organomet. Chem.* **1988**, *338*, 289.

²⁰¹¹ Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* **1992**, *114*, 5110.

²⁰¹² See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood, NJ, **1954**, pp. 712–724. See Wang, X.-j.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C.H. *Org. Lett.* **2005**, *7*, 5593.

²⁰¹³ Föhlisch, B.; Flogaus, R. *Synthesis* **1984**, 734.

²⁰¹⁴ Maeda, H.; Okamoto, J.; Ohmori, H. *Tetrahedron Lett.* **1996**, *37*, 5381.

²⁰¹⁵ Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1996**, *52*, 13513.

²⁰¹⁶ Malanga, C.; Aronica, L.A.; Lardicci, L. *Tetrahedron Lett.* **1995**, *36*, 9185. See Lemoucheux, L.; Rouden, J.; Lasne, M.-C. *Tetrahedron Lett.* **2000**, *41*, 9997.

²⁰¹⁷ See Dubois, J.E.; Lion, C.; Arouisse, A. *Bull. Soc. Chim. Belg.* **1984**, *93*, 1083.

²⁰¹⁸ Cooke, Jr., M.P. *J. Org. Chem.* **1986**, *51*, 951.

²⁰¹⁹ Fehr, C.; Galindo, J.; Perret, R. *Helv. Chim. Acta* **1987**, *70*, 1745.

²⁰²⁰ See Fujisawa, T.; Sato, T. *Org. Synth.* **66**, 116; Babudri, F.; D'Ettole, A.; Fiandanese, V.; Marchese, G.; Naso, F. *J. Organomet. Chem.* **1991**, *405*, 53.

²⁰²¹ See MacPhee, J.A.; Boussu, M.; Dubois, J.E. *J. Chem. Soc. Perkin Trans. 2* **1974**, 1525.

²⁰²² Bandgar, B.P.; Patil, A.V. *Tetrahedron Lett.* **2005**, *46*, 7627; Ekoue-Kovi, K.; Xu, H.; Wolf, C. *Tetrahedron Lett.* **2008**, *49*, 5773. For a Cu-mediated reaction, see Nishihara, Y.; Inoue, Y.; Fujisawa, M.; Takagi, K. *Synlett* **2005**, 2309.

²⁰²³ Thimmaiah, M.; Zhang, X.; Fang, S. *Tetrahedron Lett.* **2008**, *49*, 5605.

²⁰²⁴ Xin, B.; Zhang, Y.; Cheng, K. *Synthesis* **2007**, 1970.

²⁰²⁵ Lysén, M.; Kelleher, S.; Begtrup, M.; Kristensen, J.L. *J. Org. Chem.* **2005**, *70*, 5342.

anhydrides to give a ketone in the presence of a Pd catalyst.²⁰²⁶ Similar reaction of acid chlorides, NaBPh₄, KF, and a Pd catalyst gave the aryl ketone.²⁰²⁷

Other organometallic reagents²⁰²⁸ give good yields of ketones when treated with acyl halides because, as with R₂CuLi or R₂Cd, these compounds do not generally react with the ketone product. A particularly useful class of organometallic reagent are the organo-cadmium reagents (R₂Cd), prepared from *Grignard reagents* (Reaction 12-22). In this case, R may be an aryl or primary alkyl. In general, secondary and tertiary alkylcadmium reagents are not stable enough to be useful in this reaction.²⁰²⁹ An ester group may be present in either R'COX or R₂Cd. Direct treatment of the acid chloride with an alkyl halide and Cd metal leads to the ketone in some cases.²⁰³⁰ Organozinc compounds behave similarly to dialkylcadmium reagents, but are used less often.²⁰³¹ Organotin reagents (R₄Sn) react with acyl halides to give high yields of ketones, if a Pd complex is present.²⁰³² Organolead reagents (R₄Pb) behave similarly.²⁰³³ Allylic halides and In metal react with acyl chlorides to give the ketone.²⁰³⁴ Various other groups (e.g., nitrile, ester, and aldehyde) can be present in the acyl halide without interference. Other reagents include organomanganese compounds²⁰³⁵ (R can be primary, secondary, or tertiary alkyl, vinylic, alkynyl, or aryl), organozinc,²⁰³⁶ organobismuth,²⁰³⁷ and organothallium compounds (R can be primary alkyl or aryl).²⁰³⁸ The reaction of an α -halo-ketone and an acyl chloride with SmI₂ leads to a β -diketone.²⁰³⁹

Antimony alkynes (e.g., Ph₂Sb—C \equiv C—Ph) react with acid chloride in the presence of a Pd catalyst to give the conjugated alkynyl ketone.²⁰⁴⁰ Such conjugated ketones can also be prepared from an acyl halide, a terminal alkyne, and a CuI,²⁰⁴¹ Pd,²⁰⁴² or Fe catalyst,²⁰⁴³

²⁰²⁶ Xin, B.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2006**, 71, 5725.

²⁰²⁷ Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Yang, Y. *Synth. Commun.* **2001**, 31, 3885.

²⁰²⁸ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1389–1400.

²⁰²⁹ Cason, J.; Fessenden, R. *J. Org. Chem.* **1960**, 25, 477.

²⁰³⁰ Baruah, B.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* **1996**, 37, 9087.

²⁰³¹ See Grey, R.A. *J. Org. Chem.* **1984**, 49, 2288; Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Org. Synth.* **1996**, 67, 98.

²⁰³² Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* **1983**, 105, 669, 6129; Labadie, J.W.; Tueting, D.; Stille, J.K. *J. Org. Chem.* **1983**, 48, 4634. See Inoue, K.; Shimizu, Y.; Shibata, I.; Baba, A. *Synlett* **2001**, 1659.

²⁰³³ Yamada, J.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1302.

²⁰³⁴ Yadav, J.S.; Srinivas, D.; Reddy, G.S.; Bindu, K.H. *Tetrahedron Lett.* **1997**, 38, 8745. Also see, Bryan, V.J.; Chan, T.-H. *Tetrahedron Lett.* **1997**, 38, 6493 for a similar reaction with an acyl imidazole.

²⁰³⁵ Kim, S.-H.; Rieke, R.D. *J. Org. Chem.* **1998**, 63, 6766; Cahiez, G.; Martin, A.; Delacroix, T. *Tetrahedron Lett.* **1999**, 40, 6407.

²⁰³⁶ Filon, H.; Gosmini, C.; Périchon, J. *Tetrahedron* **2003**, 59, 8199.

²⁰³⁷ Rao, M.L.N.; Venkatesh, V.; Banerjee, D. *Tetrahedron* **2007**, 63, 12917.

²⁰³⁸ Markó, I.E.; Southern, J.M. *J. Org. Chem.* **1990**, 55, 3368.

²⁰³⁹ Ying, T.; Bao, W.; Zhang, Y.; Xu, W. *Tetrahedron Lett.* **1996**, 37, 3885.

²⁰⁴⁰ Kakusawa, N.; Yamaguchi, K.; Kurita, J.; Tsuchiya, T. *Tetrahedron Lett.* **2000**, 41, 4143.

²⁰⁴¹ Chowdhury, C.; Kundu, N.G. *Tetrahedron* **1999**, 55, 7011; Wang, J.-X.; Wei, B.; Hu, Y.; Liua, Z.; Kang, L. *J. Chem. Res. (S)* **2001**, 146.

²⁰⁴² Karpov, A.S.; Müller, T.J.J. *Org. Lett.* **2003**, 5, 3451.

²⁰⁴³ Wang, B.; Wang, S.; Li, P.; Wang, L. *Chem. Commun.* **2010**, 5891.

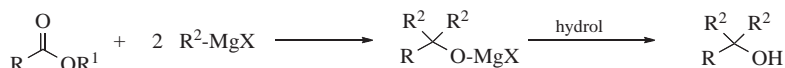
or with In metal.²⁰⁴⁴ Terminal alkynes react with chloroformates and a Pd catalyst to give the corresponding propargyl ester.²⁰⁴⁵ Similar reaction of an alkyne with an acid chloride and a Pd—Cu²⁰⁴⁶ or CuI catalyst,²⁰⁴⁷ both with microwave irradiation, gave alkynyl ketones.

Acyl halides can also be converted to ketones by treatment with Na₂Fe(CO)₄ followed by R'X (Reaction 10-76).

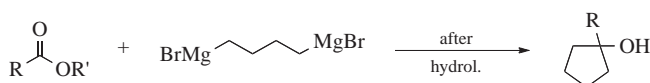
OS II, 198; III, 601; IV, 708; VI, 248, 991; VII, 226, 334; VIII, 268, 274, 371, 441, 486.

16-82 The Conversion of Anhydrides, Carboxylic Esters, or Amides to Ketones with Organometallic Compounds²⁰⁴⁸

Dialkyl,hydroxy-de-alkoxy,oxo-tersubstitution; Alkyl-de-acyloxy- or de-amido substitution



When carboxylic esters are treated with *Grignard reagents*, addition to the carbonyl (Reaction 16-24) generates a ketone. Under the reaction conditions, the initially formed ketone usually undergoes acyl substitution of R² for OR' (Reaction 16-81), so that tertiary alcohols are formed in which two R groups are the same. Isolation of the ketone as the major product is possible in some cases, particularly when the reaction is done at low temperature²⁰⁴⁹ and when there is steric hindrance to the carbonyl in the first-formed ketone. Esters (RCO₂Me) react with Zn(BH₄)₂/EtMgBr to give an alcohol [RCH(OH)Et].²⁰⁵⁰ Formates give secondary alcohols and carbonates give tertiary alcohols in which all three R groups are the same: (EtO)₂C=O + RMgX → R₃COMgX. Acyl halides and anhydrides behave similarly, though these substrates are employed less often.²⁰⁵¹ Many side reactions are possible, especially when the acid derivative or the *Grignard reagent* is branched: enolizations, reductions (not for esters, but for halides), condensations, and cleavages, but the most important is simple substitution (16-81), which in some cases can be made to predominate. When 1,4-dimagnesium compounds are used, carboxylic esters are converted to cyclopentanols.²⁰⁵² 1,5-Dimagnesium compounds give cyclohexanols, but in lower yields.²⁰⁵³



²⁰⁴⁴ Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6668.

²⁰⁴⁵ Böttcher, A.; Becker, H.; Brunner, M.; Preiss, T.; Henkelmann, J.; De Bakker, C.; Gleiter, R. *J. Chem. Soc., Perkin Trans.1* **1999**, 3555.

²⁰⁴⁶ Wang, J.-x.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. *Synth. Commun.* **2001**, *31*, 3337.

²⁰⁴⁷ Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Fu, Y. *Synth. Commun.* **2001**, *31*, 3527.

²⁰⁴⁸ See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood, NJ, **1954**, pp. 561–562, 846–908.

²⁰⁴⁹ Deskus, J.; Fan, D.; Smith, M.B. *Synth. Commun.* **1998**, *28*, 1649.

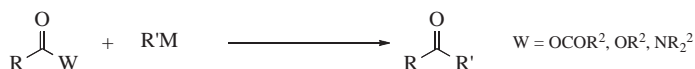
²⁰⁵⁰ Hallouis, S.; Saluzzo, C.; Amouroux, R. *Synth. Commun.* **2000**, *30*, 313.

²⁰⁵¹ See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, **1954**, pp. 549–766, 846–869.

²⁰⁵² Canonne, P.; Bernatchez, M. *J. Org. Chem.* **1986**, *51*, 2147; **1987**, *52*, 4025.

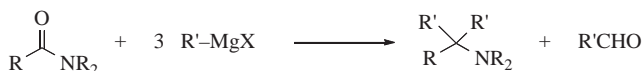
²⁰⁵³ Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* **1984**, *106*, 7140. See also, Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* **1989**, *111*, 7888, 7900.

As is the case with acyl halides (Reaction 16-81), anhydrides and carboxylic esters give tertiary alcohols (Reaction 16-82) when treated with *Grignard reagents*. Low temperatures,²⁰⁵⁴ the solvent HMPA,²⁰⁵⁵ and inverse addition have been used to increase the yields of ketone.²⁰⁵⁶ Amides give better yields of ketone at room temperature, but still not very high.²⁰⁵⁷ Anhydrides can react with arylmagnesium halides at low temperature, and in the presence of (–)-sparteine, to give a keto acid with good enantioselectivity.²⁰⁵⁸ Organo-cadmium reagents are less successful with these substrates than with acyl halides (Reaction 16-81). Esters of formic acid, dialkylformamides, and lithium or sodium formate²⁰⁵⁹ give good yields of aldehydes, when treated with *Grignard reagents*.



Organolithium compounds have been used to give ketones from carboxylic esters. The reaction must be carried out in a high-boiling solvent (e.g., toluene), since reaction at lower temperatures gives tertiary alcohols.²⁰⁶⁰ Organolithium reagents also give good yields of carbonyl compounds with *N,N*-disubstituted amides.²⁰⁶¹ Dialkylformamides react to give aldehydes, other disubstituted amides give ketones and other acid derivatives have been used.²⁰⁶²

Ketones can also be obtained by treatment of the lithium salt of a carboxylic acid with an organolithium reagent (Reaction 16-28). For an indirect way to convert carboxylic esters to ketones, see Reaction 16-82. A similar reaction with hindered aryl carboxylic acids has been reported.²⁰⁶³ Carboxylic acids can be treated with 2-chloro-4,6-dimethoxy[1,3,5] triazine and the RMgX/CuI to give ketones.²⁰⁶⁴



Disubstituted formamides can give addition of 2 molar equivalents of *Grignard reagent*. The products of this reaction (called *Bouveault reaction*) are an aldehyde and a tertiary amine.²⁰⁶⁵ The use of an amide other than a formamide can give a ketone instead of an aldehyde, but yields are generally low. The addition of 2 molar equivalents of

²⁰⁵⁴ See Newman, M.S.; Smith, A.S. *J. Org. Chem.* **1948**, *13*, 592; Edwards, Jr., W.R.; Kamman, Jr., K.P. *J. Org. Chem.* **1964**, *29*, 913; Araki, M.; Sakat, S.; Takei, H.; Mukaiyama, T. *Chem. Lett.* **1974**, 687.

²⁰⁵⁵ Huet, F.; Pellet, M.; Conia, J.M. *Tetrahedron Lett.* **1976**, 3579.

²⁰⁵⁶ For a list of reactions with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1386–1389, 1400–1419.

²⁰⁵⁷ See Olah, G.S.; Prakash, G.K.S.; Arvanaghi, M. *Synthesis* **1984**, 228; Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarraza, J. *Synlett* **1997**, 1414. Also see Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocyclic Chem.* **1995**, *32*, 25 for a related reaction.

²⁰⁵⁸ Shintani, R.; Fu, G.C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1057.

²⁰⁵⁹ Bogavac, M.; Arsenijevic, L.; Pavlov, S.; Arsenijevic, V. *Tetrahedron Lett.* **1984**, *25*, 1843.

²⁰⁶⁰ Petrov, A.D.; Kaplan, E.P.; Tsir, Ya. *J. Gen. Chem. USSR* **1962**, *32*, 691.

²⁰⁶¹ Evans, E.A. *J. Chem. Soc.* **1956**, 4691. See Clark, C.T.; Milgram, B.C.; Scheidt, K.A. *Org. Lett.* **2004**, *6*, 3977. See Wakefield, B.J. *Organolithium Methods*; Academic Press, NY, **1988**, pp. 82–88.

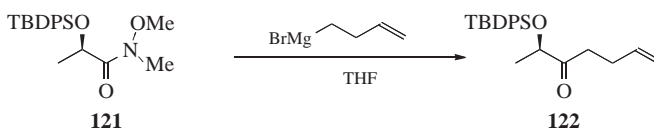
²⁰⁶² Mueller-Westerhoff, U.T.; Zhou, M. *Synlett* **1994**, 975.

²⁰⁶³ Zhang, P.; Terefenko, E.A.; Slavin, J. *Tetrahedron Lett.* **2001**, *42*, 2097.

²⁰⁶⁴ DeLuca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519.

²⁰⁶⁵ Spialtr, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, **1965**, pp. 59–63.

phenyllithium to a carbamate gave good yields of the ketone, however.²⁰⁶⁶ The reaction of *N*-(3-bromopropyl) lactams with *tert*-butyllithium gave cyclization to the bicyclic amino alcohol, and subsequent reduction with LiAlH₄ (Reaction **19-64**) gave the bicyclic amine.²⁰⁶⁷ Ketones can also be prepared by treatment of thioamides with organolithium compounds (alkyl or aryl).²⁰⁶⁸ Cerium reagents (e.g., MeCeCl₂) also add two R groups to an amide.²⁰⁶⁹ More commonly, an organolithium reagent is treated with CeCl₃ to generate the organocerium reagent *in situ*.²⁰⁷⁰ It has proven possible to add two different R groups by sequential addition of two *Grignard reagents*.²⁰⁷¹ Diketones have also been produced by using the bis(imidazole) derivative of oxalic acid.²⁰⁷² When an amide having a *gem*-dibromocyclopropyl unit elsewhere in the molecule was treated with methyllithium, Li—Br exchange was accompanied by intramolecular acyl addition to the amide carbonyl, giving a bicyclic amino alcohol.²⁰⁷³



N-Methoxy-*N*-methyl amides, (e.g., **120**) are referred to as a *Weinreb amide*.²⁰⁷⁴ When a *Weinreb amide* reacts with a *Grignard reagent* or an organolithium reagent,²⁰⁷⁵ the product is the ketone. The reaction of **121** (TBDPSO = tertiarybutyldiphenylsilyl) with 3-butenylmagnesium bromide to give ketone **122** is a typical example.²⁰⁷⁶ Aryloxy carbamates with a *Weinreb amide* unit [ArO₂C-NMe(OMe)] react with RMgBr and then R'Li to give an unsymmetrical ketone [RC(=O)R'].²⁰⁷⁷ Intramolecular displacement of a *Weinreb amide* by an organolithium reagent generated *in situ* from an iodide precursor leads to cyclic ketones.²⁰⁷⁸ Reaction with vinylmagnesium bromide led to a β-*N*-methoxy-*N*-methylamino ketone, presumably by initial formation of the conjugated ketone followed by *Michael addition* (Reaction **15-24**) of the liberated amine.²⁰⁷⁹ By the use of the compound *N*-methoxy-*N,N',N'*-trimethylurea, it is possible to add two R groups as RLi, the same or different, to a CO group.²⁰⁸⁰ Another variant used organocerium reagents with (*Z*)-α,β-unsaturated *Weinreb amides* to give (*Z*)-α,β-unsaturated ketones.²⁰⁸¹

²⁰⁶⁶ Prakash, G.K.S.; York, C.; Liao, Q.; Kotian, K.; Olah, G.A. *Heterocycles* **1995**, 40, 79.

²⁰⁶⁷ Jones, K.; Storey, J.M.D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 769.

²⁰⁶⁸ Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* **1987**, 28, 1529.

²⁰⁶⁹ Calderwood, D.J.; Davies, R.V.; Rafferty, P.; Twigger, H.L.; Whelan, H.M. *Tetrahedron Lett.* **1997**, 38, 1241.

²⁰⁷⁰ Ahn, Y.; Cohen, T. *Tetrahedron Lett.* **1994**, 35, 203.

²⁰⁷¹ Comins, D.L.; Dernell, W. *Tetrahedron Lett.* **1981**, 22, 1085.

²⁰⁷² Mitchell, R.H.; Iyer, V.S. *Tetrahedron Lett.* **1993**, 34, 3683. Also see, Sibi, M.P.; Sharma, R.; Paulson, K.L. *Tetrahedron Lett.* **1992**, 33, 1941.

²⁰⁷³ Baird, M.S.; Huber, F.A.M.; Tverezovsky, V.V.; Bolesov, I.G. *Tetrahedron* **2001**, 57, 1593.

²⁰⁷⁴ Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, 22, 3815. For a review, see Balasubramaniam, S.; Aidhen, I.S. *Synthesis* **2008**, 3707.

²⁰⁷⁵ See Tallier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, 6, 2145.

²⁰⁷⁶ Xie, W.; Zou, B.; Pei, D.; Ma, D. *Org. Lett.* **2005**, 7, 2775. For other examples see Andrés, J.M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* **2000**, 56, 1217.

²⁰⁷⁷ Lee, N.R.; Lee, J.I. *Synth. Commun.* **1999**, 29, 1249.

²⁰⁷⁸ Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* **2003**, 5, 1115.

²⁰⁷⁹ See Hansford, K.A.; Dettwiler, J.E.; Lubell, W.D. *Org. Lett.* **2003**, 5, 4887.

²⁰⁸⁰ Hlasta, D.J.; Court, J.J. *Tetrahedron Lett.* **1989**, 30, 1773. See also, Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, 22, 3815.

²⁰⁸¹ Kojima, S.; Hidaka, T.; Yamakawa, A. *Chem. Lett.* **2005**, 34, 470.

N,N-Disubstituted amides can be converted to alkynyl ketones by treatment with alkynylboranes: $\text{RCONR}_2 + (\text{R}'\text{C}\equiv\text{C})_3\text{B} \rightarrow \text{RCOC}\equiv\text{CR}'$.²⁰⁸² Lactams react with triallylborane to give cyclic 2,2-diallyl amines after treatment with methanol and then aq hydroxide.²⁰⁸³ Triallylborane reacts with the carbonyl group of lactams, and after treatment with methanol and then aq NaOH gives the *gem*-diallyl amine: 2-pyrrolidinone \rightarrow 2,2-diallylpyrrolidine.²⁰⁸⁴ *N,N*-Disubstituted carbamates ($\text{X}=\text{OR}^2$) and carbamoyl chlorides ($\text{X}=\text{Cl}$) react with 2 molar equivalents of an alkyl- or aryllithium or *Grignard reagent* to give symmetrical ketones, in which both R groups are derived from the organometallic compound: $\text{R}_2'\text{NCOX} + 2 \text{RMgX} \rightarrow \text{R}_2\text{CO}$.²⁰⁸⁵ *N,N*-Disubstituted amides give ketones in high yields when treated with alkylaluminum triflates $[\text{RLa}(\text{OTf})_2]$.²⁰⁸⁶

Other organometallic reagents give acyl substitution. Sodium naphthalenide reacts with esters to give naphthyl ketones.²⁰⁸⁷ Trimethylaluminum, which exhaustively methylates ketones (Reaction 16-24), also exhaustively methylates carboxylic acids to give *tert*-butyl compounds²⁰⁸⁸ (see also, Reaction 10-63). Trimethylaluminum reacts with esters to form ketones, in the presence of *N,N*-dimethylethylenediamine.²⁰⁸⁹ Trialkylboranes have been used to convert thioesters to ketones.²⁰⁹⁰ Thioesters (RCOSR') react with arylboronic acids, in the presence of a Pd catalyst, to give the corresponding ketone,²⁰⁹¹ and esters react similarly with arylboronic acids (a Pd catalyst)²⁰⁹² or arylboronates (a Ru catalyst).²⁰⁹³ Arylboronic acids also react with dialkyl anhydrides, with a Rh²⁰⁹⁴ or a Pd catalyst,²⁰⁹⁵ to give the ketone. Thioesters are converted to ketones with organoindium compounds.²⁰⁹⁶ Thioesters give good yields of ketones when treated with lithium dialkylcopper reagents ($\text{R}_2'\text{CuLi}$, R'' = primary or secondary alkyl or aryl).²⁰⁹⁷ Organozinc reagents convert thioesters to ketones.²⁰⁹⁸ Diaryl- or dialkylzinc reagents react with anhydrides and a Pd²⁰⁹⁹ or a Ni catalyst²¹⁰⁰ to give the ketone. The reaction of alkylzinc halides and thioesters leads to ketones in the presence of 1.5% Pd/C,²¹⁰¹ in what has been called *Fukuyama coupling*.²¹⁰² Note that in the presence of a SmI_2 catalyst and 2 molar equivalents of

²⁰⁸² Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.* **1983**, 35.

²⁰⁸³ Bubnov, Y.N.; Pastukhov, F.V.; Yampolsky, I.V.; Ignatenko, A.V. *Eur. J. Org. Chem.* **2000**, 1503; Li, Z.; Zhang, Y. *Tetrahedron Lett.* **2001**, 42, 8507.

²⁰⁸⁴ Bubnov, Yu.N.; Klimkina, E.V.; Zhun', I.V.; Pastukhov, F.V.; Yampolsky, I.V. *Pure Appl. Chem.* **2000**, 72, 1641.

²⁰⁸⁵ Michael, U.; Hörnfeldt, A. *Tetrahedron Lett.* **1970**, 5219; Scilly, N.F. *Synthesis* **1973**, 160.

²⁰⁸⁶ Collins, S.; Hong, Y. *Tetrahedron Lett.* **1987**, 28, 4391.

²⁰⁸⁷ Periasamy, M.; Reddy, M.R.; Bharathi, P. *Synth. Commun.* **1999**, 29, 677.

²⁰⁸⁸ Meisters, A.; Mole, T. *Aust. J. Chem.* **1974**, 27, 1665.

²⁰⁸⁹ Chung, E.-A.; Cho, C.-W.; Ahn, K.H. *J. Org. Chem.* **1998**, 63, 7590.

²⁰⁹⁰ Yu, Y.; Liebeskind, L.S. *J. Org. Chem.* **2004**, 69, 3554.

²⁰⁹¹ Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L.S. *Org. Lett.* **2003**, 5, 3033.

²⁰⁹² Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, 6, 3597.

²⁰⁹³ Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, 69, 5615.

²⁰⁹⁴ Frost, C.G.; Wadsworth, K.J. *Chem. Commun.* **2001**, 2316.

²⁰⁹⁵ Gooßen, L.J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, 3254.

²⁰⁹⁶ Fausett, B.W.; Liebeskind, L.S. *J. Org. Chem.* **2005**, 70, 4851.

²⁰⁹⁷ Anderson, R.J.; Henrick, C.A.; Rosenblum, L.D. *J. Am. Chem. Soc.* **1974**, 96, 3654. See also, Kim, S.; Lee, J. *J. Org. Chem.* **1983**, 48, 2608.

²⁰⁹⁸ Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2002**, 43, 1039.

²⁰⁹⁹ Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* **2004**, 126, 10248.

²¹⁰⁰ O'Brien, E.M.; Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* **2003**, 125, 10498.

²¹⁰¹ Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2001**, 42, 429.

²¹⁰² See Mori, Y.; Seki, M. *Tetrahedron Lett.* **2004**, 45, 7343. For a different but related cross-coupling, see Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, 126, 15964.

allyl bromide, lactones were converted to the diallyl diol.²¹⁰³ Aryl iodides react with acetic anhydride, with a Pd catalyst, to give the aryl methyl ketone.²¹⁰⁴

Carboxylic esters can be converted to their homologues ($\text{RCOOEt} \rightarrow \text{RCH}_2\text{COOEt}$) by treatment with Br_2CHLi followed by BuLi at -90°C . The ynolate ($\text{RC}\equiv\text{COLi}$) is an intermediate.²¹⁰⁵ If the ynolate is treated with 1,3-cyclohexadiene, followed by NaBH_4 , the product is the alcohol $\text{RCH}_2\text{CH}_2\text{OH}$.²¹⁰⁶

Note that acyl benzotriazoles react with β -keto esters to give diketones via acyl substitution.²¹⁰⁷ Acyl cyanides [$\text{RC}(=\text{O})\text{CN}$] react with allylic bromides and In metal to give the corresponding ketone.²¹⁰⁸ Acyl benzotriazoles have been coupled with SmI_2 to give the 1,2-diketone.²¹⁰⁹ α -Cyanoketones (acyl nitriles) were coupled with YbI_2 in a similar manner.²¹¹⁰

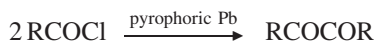
Vinyl organometallic reagents can be added to acyl derivatives. Reaction of an alkyne with Cp_2ZrEt_2 generates the vinyl zirconium reagent, which react with ethyl chloroformate to give an α,β -unsaturated ester.²¹¹¹

OS I, 226; II, 179, 602; III, 237, 831, 839; IV, 601; VI, 240, 278; VIII, 474, 505.

OS II, 282; 72, 32; III, 353; IV, 285; VI, 611; VII, 323, 451; 81, 14.

16-83 The Coupling of Acyl Halides

De-halogen-coupling



Acyl halides can be coupled with pyrophoric lead to give symmetrical α -diketones in a *Wurtz-type reaction*.²¹¹² The reaction has been performed with $\text{R} = \text{Me}$ and Ph . Samarium iodide²¹¹³ gives the same reaction. The photochemical coupling of acyl iodides gives α -diketones.²¹¹⁴ Benzoyl chloride was coupled to give benzil by subjecting it to ultrasound in the presence of Li wire: $2 \text{PhCOCl} + \text{Li} \rightarrow \text{PhCOCOPh}$.²¹¹⁵

Unsymmetrical α -diketones (RCOCOR') have been prepared by treatment of an acyl halide (RCOCl) with an acyltin reagent $\text{R}'\text{COSnBu}_3$, with a Pd complex catalyst.²¹¹⁶

²¹⁰³ Lannou, M.-I.; Hélicon, F.; Namy, J.-L. *Tetrahedron Lett.* **2002**, 43, 8007.

²¹⁰⁴ Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. *Org. Lett.* **2003**, 5, 289.

²¹⁰⁵ Kowalski, C.J.; Haque, M.S.; Fields, K.W. *J. Am. Chem. Soc.* **1985**, 107, 1429; Kowalski, C.J.; Haque, M.S. *J. Org. Chem.* **1985**, 50, 5140.

²¹⁰⁶ Kowalski, C.J.; Haque, M.S. *J. Am. Chem. Soc.* **1986**, 108, 1325.

²¹⁰⁷ Katritzky, A.R.; Wang, Z.; Wang, M.; Wilkerson, C.R.; Hall, C.D.; Akhmedov, N.G. *J. Org. Chem.* **2004**, 69, 6617.

²¹⁰⁸ Yoo, B.W.; Choi, K.H.; Lee, S.J.; Nam, G.S.; Chang, K.Y.; Kim, S.H.; Kim, J.H. *Synth. Commun.* **2002**, 32, 839.

²¹⁰⁹ Wang, X.; Zhang, Y. *Tetrahedron Lett.* **2002**, 43, 5431.

²¹¹⁰ Saikia, P.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* **2002**, 43, 7525.

²¹¹¹ Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, 122, 3228.

²¹¹² Mészáros, L. *Tetrahedron Lett.* **1967**, 4951.

²¹¹³ Souppe, J.; Namy, J.; Kagan, H.B. *Tetrahedron Lett.* **1984**, 25, 2869. See also, Collin, J.; Namy, J.; Dallemer, F.; Kagan, H.B. *J. Org. Chem.* **1991**, 56, 3118.

²¹¹⁴ Voronkov, M.G.; Belousova, L.I.; Vlasov, A.V.; Vlasova, N.N. *Russ. J. Org. Chem.* **2008**, 44, 929.

²¹¹⁵ Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* **1981**, 22, 2757.

²¹¹⁶ Verlhac, J.; Chanson, E.; Jousseau, B.; Quintard, J. *Tetrahedron Lett.* **1985**, 26, 6075. For another procedure, see Olah, G.A.; Wu, A. *J. Org. Chem.* **1991**, 56, 902.

16-84 Acylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on



This reaction is similar to **10-67**, but there are fewer examples.²¹¹⁷ Either Z or Z' may be any of the electron-withdrawing groups listed in Reaction **10-67** (CO₂R, COR, CN, etc.)²¹¹⁸ Anhydrides react similarly but are used less often. The product contains three Z groups, since RCO is a Z group. One or two of these can be cleaved (Reactions **12-40** and **12-43**). In this way, a compound ZCH₂Z' can be converted to ZCH₂Z² or an acyl halide (RCOCl) to a methyl ketone (RCOCH₃). O-Acylation is sometimes a side reaction.²¹¹⁹ When thallium(I) salts of ZCH₂Z' are used, it is possible to achieve regioselective acylation at either the C or the O position. For example, treatment of the thallium(I) salt of MeCOCH₂COMe with acetyl chloride at -78 °C gave >90% O-acylation, while acetyl fluoride at room temperature gave >95% C-acylation.²¹²⁰ The use of an alkyl chloroformate gives triesters.²¹²¹

The application of this reaction to simple ketones²¹²² (in parallel with Reaction **10-68**) requires a strong base (e.g., NaNH₂ or Ph₃CNa) and is often complicated by O-acylation, which in many cases becomes the principal pathway because acylation at the oxygen is usually much faster. It is possible to increase the proportion of C-acylated product by employing an excess (2–3 molar equivalents) of enolate anion (and adding the substrate to this, rather than vice versa), by the use of a relatively nonpolar solvent and a metal ion (e.g., Mg²⁺), which is tightly associated with the enolate oxygen atom, by the use of an acyl halide rather than an anhydride,²¹²³ and by working at low temperatures.²¹²⁴ In cases where the use of an excess of enolate anion results in C-acylation, it is because O-acylation takes place first, and the O-acylated product (an enol ester) is then C-acylated. Simple ketones can also be acylated by treatment of their silyl enol ethers with an acyl chloride in the presence of ZnCl₂ or SbCl₃.²¹²⁵ Ketones can be acylated by anhydrides to give β-diketones, with BF₃ as catalyst.²¹²⁶ Simple esters (RCH₂CO₂Et) can be acylated at the α carbon (at -78 °C) if a strong base (e.g., lithium *N*-isopropylcyclohexylamide) is used to remove the proton.²¹²⁷

²¹¹⁷ For examples of reactions in this section, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1484–1485, 1522–1527.

²¹¹⁸ For an improved procedure, see Rathke, M.W.; Cowan, P.J. *J. Org. Chem.* **1985**, *50*, 2622.

²¹¹⁹ When phase-transfer catalysts are used, O-acylation becomes the main reaction: Jones, R.A.; Nokkeo, S.; Singh, S. *Synth. Commun.* **1977**, *7*, 195.

²¹²⁰ Taylor, E.C.; Hawks, III, G.H.; McKillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2421.

²¹²¹ See Skarzewski, J. *Tetrahedron* **1989**, *45*, 4593; Newkome, G.R.; Baker, G.R. *Org. Prep. Proced. Int.* **1986**, *19*, 117.

²¹²² Hegedus, L.S.; Williams, R.E.; McGuire, M.A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973.

²¹²³ See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 762–765; House, H.O.; Auerbach, R.A.; Gall, M.; Peet, N.P. *J. Org. Chem.* **1973**, *38*, 514.

²¹²⁴ Seebach, D.; Weller, T.; Protschuk, G.; Beck, A.K.; Hoekstra, M.S. *Helv. Chim. Acta* **1981**, *64*, 716.

²¹²⁵ Tirpak, R.E.; Rathke, M.W. *J. Org. Chem.* **1982**, *47*, 5099.

²¹²⁶ See Hauser, C.R.; Swamer, F.W.; Adams, J.T. *Org. React.* **1954**, *8*, 59, pp. 98–106.

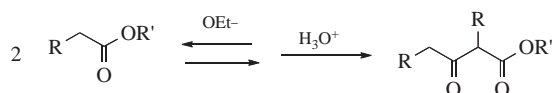
²¹²⁷ See Hayden, W.; Pucher, R.; Griengl, H. *Monatsh. Chem.* **1987**, *118*, 415.

Silyl enol esters react with acetic anhydride, in the presence of a chiral Fe complex, to give a chiral β -keto ester.²¹²⁸

OS **II**, 266, 268, 594, 596; **III**, 16, 390, 637; **IV**, 285, 415, 708; **V**, 384, 937; **VI**, 245; **VII**, 213, 359; **VIII**, 71, 326, 467. See also, OS **VI**, 620.

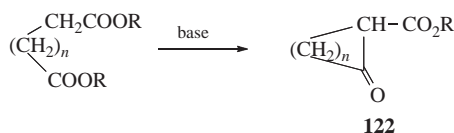
16-85 Acylation of Carboxylic Esters by Carboxylic Esters: The Claisen and Dieckmann Condensations

Alkoxy-carbonyl-alkyl-de-alkoxy-substitution



When carboxylic esters containing an α hydrogen are treated with a strong base (e.g., sodium ethoxide), a condensation occurs to give a β -keto ester via an ester enolate anion.²¹²⁹ This reaction is called the *Claisen condensation*. When it is carried out with a mixture of two different esters, each of which possesses an α hydrogen (this reaction is called a *mixed-Claisen* or a *crossed-Claisen condensation*), a mixture of all four products is generally obtained and the reaction is seldom useful synthetically.²¹³⁰ However, if only one of the esters has an α hydrogen, the mixed reaction is frequently satisfactory. Among esters lacking α hydrogen atoms (hence acting as the substrate ester) that are commonly used in this way are esters of aromatic acids, and ethyl carbonate and ethyl oxalate. When the ester enolate reacts with ethyl carbonate, the product is a malonic ester, and reaction with ethyl formate introduces a formyl group. *Claisen condensation* of phenyl esters with ZrCl_4 and diisopropylethylamine (*Hünigs base*) give the corresponding keto ester.²¹³¹ Titanium compounds catalyze a *crossed-Claisen condensation*.²¹³² Boron(III) compounds also catalyzed ester condensation reactions.²¹³³

As with ketone enolate anions (see Reaction 16-34), the use of amide bases under kinetic control conditions (strong base with a weak conjugate acid, aprotic solvents, low temperatures), allows the *mixed-Claisen condensation* to proceed. Self-condensation of the lithium enolate with the parent ester is a problem when LDA is used as a base,²¹³⁴ but this is minimized with LICA.²¹³⁵ Note that solvent-free *Claisen condensation* reactions have been reported.²¹³⁶ There is a *retro-Claisen condensation*, catalyzed by indium.²¹³⁷



When the two ester groups involved in the condensation are in the same molecule, the product is a cyclic β -keto ester (**122**) and the reaction is called the *Dieckmann*

²¹²⁸ Mermerian, A.H.; Fu, G.C. *J. Am. Chem. Soc.* **2005**, 127, 5604.

²¹²⁹ See Rablen, P.R.; Bentrup, K.L.H. *J. Am. Chem. Soc.* **2003**, 125, 2142.

²¹³⁰ See Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1989**, 62, 1917.

²¹³¹ Tanabe, Y.; Hamasaki, R.; Funakoshi, S. *Chem. Commun.* **2001**, 1674.

²¹³² Misaki, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2005**, 127, 2854.

²¹³³ Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron* **2007**, 63, 8645.

²¹³⁴ Sullivan, D.F.; Woodbury, R.P.; Rathke, M.W. *J. Org. Chem.* **1977**, 42, 2038.

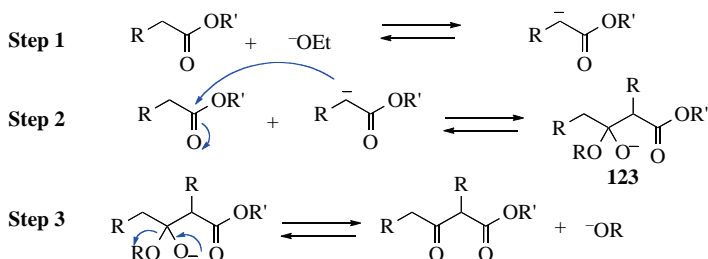
²¹³⁵ Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, 93, 2318.

²¹³⁶ Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* **2001**, 42, 7983.

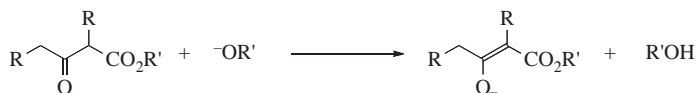
²¹³⁷ Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. *Angew. Chem. Int. Ed.* **2007**, 46, 7793.

condensation.²¹³⁸ The *Dieckmann condensation* is most successful for the formation of 5-, 6-, and 7-membered rings, but yields for rings of 9–12 members are very low or nonexistent. Reactions that form large rings are generally assisted by high dilution. A solvent-free *Dieckmann condensation* has been reported on solid potassium *tert*-butoxide.²¹³⁹ *Dieckmann condensation* of unsymmetrical substrates can be made regioselective by the use of solid-phase supports.²¹⁴⁰ The *Dieckmann condensation* has also been done using $\text{TiCl}_3/\text{NBu}_3$ with a TMSOTf catalyst.²¹⁴¹ A *Dieckmann-like condensation* was reported where an α,ω -dicarboxylic acid was heated to 450 °C on graphite, with microwave irradiation, to give the cyclic ketone.²¹⁴²

The mechanism of the *Claisen* and *Dieckmann condensations* (steps 1–3) is the ordinary *tetrahedral mechanism*,²¹⁴³ with one molecule of ester being converted to a nucleophile by the base and the other serving as the substrate. This reaction illustrates the striking difference in behavior between carboxylic esters on the one hand and aldehydes and ketones on the other. When a carbanion (e.g., an enolate anion) is added to the carbonyl group of an aldehyde or ketone (Reaction 16-38), the H or R is not lost, since these groups are much poorer leaving groups than OR. Instead, the intermediate similar to **123** adds a proton at the oxygen to give a hydroxy compound.



In contrast to Reaction 10-67, ordinary esters react quite well; that is, two Z groups are not needed. A lower degree of acidity is satisfactory because it is not necessary to convert the attacking ester entirely to its ion. Step 1 is an equilibrium that lies well to the left, but the small amount of enolate anion formed is sufficient to attack the readily approachable ester substrate. All the steps are in equilibria. The reaction proceeds because the product is converted to its conjugate base by the base present (i.e., a β -keto ester is a stronger acid than an alcohol):



The use of a stronger base (e.g., NaNH_2 , NaH , or KH),²¹⁴⁴ often increases the yield. For some esters, stronger bases *must* be used, since sodium ethoxide is ineffective. Among these are

²¹³⁸ See Schaefer, J.P.; Bloomfield, J.J. *Org. React.* **1967**, 15, 1.

²¹³⁹ Toda, F.; Suzuki, T.; Higa, S. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3521.

²¹⁴⁰ Crowley, J.I.; Rapoport, H. *J. Org. Chem.* **1980**, 45, 3215. For another method, see Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K. *Tetrahedron Lett.* **1981**, 22, 1353.

²¹⁴¹ Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, 38, 8727.

²¹⁴² Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* **2001**, 493.

²¹⁴³ In some cases, an SET mechanism may be involved: Ashby, E.C.; Park, W. *Tetrahedron Lett.* **1983**, 1667. See Nishimura, T.; Sunagawa, M.; Okajima, T.; Fukazawa, Y. *Tetrahedron Lett.* **1997**, 38, 7063.

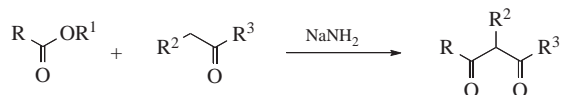
²¹⁴⁴ Brown, C.A. *Synthesis* **1975**, 326.

esters of the type $R_2CHCOOEt$, the products of which ($R_2CHCOCR_2CO_2Et$) lack an acidic hydrogen, so that they cannot be converted to enolate anions by sodium ethoxide.²¹⁴⁵

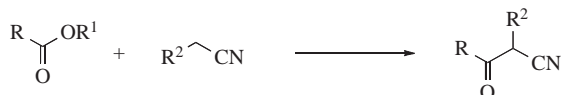
OS I, 235; II, 116, 194, 272, 288; III, 231, 300, 379, 510; IV, 141; V, 288, 687, 989; VIII, 112.

16-86 Acylation of Ketones and Nitriles by Carboxylic Esters

α -Acylalkyl-de-alkoxy-substitution



Carboxylic esters can be treated with ketones to give β -diketones. The reaction is so similar that it is sometimes also called the *Claisen reaction*, but this usage may be confusing. A strong base (e.g., sodium amide or sodium hydride) is required. Yields can be increased by the catalytic addition of crown ethers.²¹⁴⁶ Esters of formic acid ($R = H$) give β -keto aldehydes and ethyl carbonate gives β -keto esters. β -Keto esters can also be obtained by treating the lithium enolates of ketones with methyl cyanofornate (MeOCOCN ,²¹⁴⁷ in this case CN is the leaving group) and by treating ketones with KH and diethyl dicarbonate $[(\text{EtOCO})_2\text{O}]$.²¹⁴⁸ This reaction has been used to effect cyclization, especially to prepare five- and six-membered rings. Nitriles are frequently used instead of ketones, the products being β -keto nitriles, as shown.



Other nucleophilic carbon reagents (e.g., acetylide ions) and ions derived from α -methylpyridines have also been used. A particularly useful nucleophile is the methylsulfinyl carbanion ($\text{CH}_3\text{SOCH}_2^-$),²¹⁴⁹ the conjugate base of DMSO, since the β -keto sulfoxide produced can easily be reduced to a methyl ketone (see Reaction 10-67). The methylsulfonyl carbanion ($\text{CH}_2\text{SO}_2\text{CH}_2^-$), the conjugate base of dimethyl sulfone, behaves similarly,²¹⁵⁰ and the product can be similarly reduced. Certain carboxylic esters, acyl halides, and DMF will acylate 1,3-dithianes²¹⁵¹ (see Reaction 10-71) to give, after oxidative hydrolysis with NBS or NCS, α -keto aldehydes or α -diketones.²¹⁵²

As in Reaction 10-67, a ketone is deprotonated at the most acidic proton first and the second most acidic position after that if 2 equivs of base are used, to give dianion 124.

²¹⁴⁵ See Garst, J.F. *J. Chem. Educ.* **1979**, 56, 721.

²¹⁴⁶ Popik, V.V.; Nikolaev, V.A. *J. Org. Chem. USSR* **1989**, 25, 1636.

²¹⁴⁷ Mander, L.N.; Sethi, P. *Tetrahedron Lett.* **1983**, 24, 5425.

²¹⁴⁸ Hellou, J.; Kingston, J.F.; Fallis, A.G. *Synthesis* **1984**, 1014.

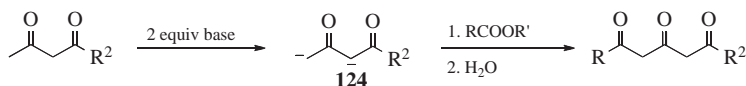
²¹⁴⁹ See Durst, T. *Adv. Org. Chem.* **1969**, 6, 285, pp. 296–301.

²¹⁵⁰ Schank, K.; Hasenfratz, H.; Weber, A. *Chem. Ber.* **1973**, 106, 1107; House, H.O.; Larson, J.K. *J. Org. Chem.* **1968**, 33, 61.

²¹⁵¹ Corey, E.J.; Seebach, D. *J. Org. Chem.* **1975**, 40, 231

²¹⁵² See Corey, E.J.; Erickson, B.W. *J. Org. Chem.* **1971**, 36, 3553.

Thus, β -diketones have been converted to 1,3,5-triketones.²¹⁵³

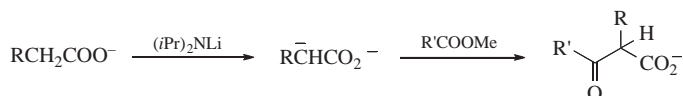


Side reactions are condensation of the ketone with itself (**16-34**), of the ester with itself, and of the ketone with the ester but with the ester supplying the α -position (**16-36**). The mechanism is the same as in Reaction **16-85**.²¹⁵⁴

OS **I**, 238; **II**, 126, 200, 287, 487, 531; **III**, 17, 251, 291, 387, 829; **IV**, 174, 210, 461, 536; **V**, 187, 198, 439, 567, 718, 747; **VI**, 774; **VII**, 351.

16-87 Acylation of Carboxylic Acid Salts

α -Carboxyalkyl-de-alkoxy-substitution



As seen previously (Reaction **10-70**), dianions of carboxylic acids can be alkylated in the α position. These ions can also be acylated on treatment with a carboxylic ester²¹⁵⁵ to give salts of β -keto acids. As in Reaction **10-70**, the carboxylic acid can be of the form $\text{RCH}_2\text{CO}_2\text{H}$ or $\text{RR}^2\text{CHCO}_2\text{H}$. Since β -keto acids are so easily converted to ketones (Reaction **12-40**), this is also a method for the preparation of ketones ($\text{R}'\text{COCH}_2\text{R}$ and $\text{R}'\text{COCHRR}^2$), where R' can be primary, secondary, or tertiary alkyl, or aryl. If the ester is ethyl formate, an α -formyl carboxylate salt ($\text{R}' = \text{H}$) is formed, which on acidification spontaneously decarboxylates into an aldehyde.²¹⁵⁶ This method accomplishes the conversion $\text{RCH}_2\text{CO}_2\text{H} \rightarrow \text{RCH}_2\text{CHO}$, and is an alternative to the reduction methods discussed in Reaction **19-39**. When the carboxylic acid is of the form $\text{RR}^2\text{CHCO}_2\text{H}$, better yields are obtained by acylating with acyl halides rather than esters.²¹⁵⁷

16-88 Preparation of Acyl Cyanides

Cyano-de-halogenation



Acyl cyanides²¹⁵⁸ can be prepared by treatment of acyl halides with copper cyanide. The mechanism could be free radical or nucleophilic substitution. The reaction has also been accomplished with thallium(I) cyanide,²¹⁵⁹ with Me_3SiCN and an SnCl_4 catalyst,²¹⁶⁰ and with Bu_3SnCN ,²¹⁶¹ but these reagents are successful only when $\text{R} = \text{aryl}$ or tertiary alkyl.

²¹⁵³ Miles, M.L.; Harris, T.M.; Hauser, C.R. *J. Org. Chem.* **1965**, 30, 1007.

²¹⁵⁴ Hill, D.G.; Burkus, T.; Hauser, C.R. *J. Am. Chem. Soc.* **1959**, 81, 602.

²¹⁵⁵ Kuo, Y.; Yahner, J.A.; Ainsworth, C. *J. Am. Chem. Soc.* **1971**, 93, 6321; Angelo, B. *C.R. Seances Acad. Sci. Ser. C* **1973**, 276, 293.

²¹⁵⁶ Koch, G.K.; Kop, J.M.M. *Tetrahedron Lett.* **1974**, 603.

²¹⁵⁷ Krapcho, A.P.; Kashdan, D.S.; Jahngen, Jr., E.G.E.; Lovey, A.J. *J. Org. Chem.* **1977**, 42, 1189; Lion, C.; Dubois, J.E. *J. Chem. Res. (S)* **1980**, 44.

²¹⁵⁸ See Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* **1982**, 21, 36.

²¹⁵⁹ Taylor, E.C.; Andrade, J.G.; John, K.C.; McKillop, A. *J. Org. Chem.* **1978**, 43, 2280.

²¹⁶⁰ Olah, G.A.; Arvanaghi, M.; Prakash, G.K.S. *Synthesis* **1983**, 636.

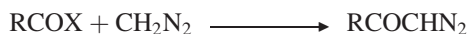
²¹⁶¹ Tanaka, M. *Tetrahedron Lett.* **1980**, 21, 2959. See also, Tanaka, M.; Koyanagi, M. *Synthesis* **1981**, 973.

Potassium cyanide has also been used, along with ultrasound,²¹⁶² as has NaCN with phase-transfer catalysts.²¹⁶³

OS III, 119.

16-89 Preparation of Diazo Ketones

Diazomethyl-de-halogenation

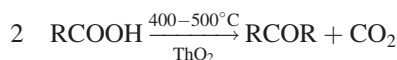


The reaction between acyl halides and diazomethane is of wide scope and is the best way to prepare diazo ketones.²¹⁶⁴ Diazomethane must be present in excess or the HX produced will react with the diazo ketone (Reaction 10-52). This reaction is the first step of the *Arndt–Eistert synthesis* (18-8). Diazo ketones can also be prepared directly from a carboxylic acid and diazomethane or diazoethane in the presence of DCC.²¹⁶⁵

OS III, 119; VI, 386, 613; VIII, 196.

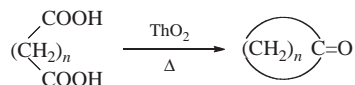
16-90 Ketonic Decarboxylation²¹⁶⁶

Alkyl-de-hydroxylation



Carboxylic acids can be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. In a mixed reaction, formic acid and another acid heated over thorium oxide give aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.²¹⁶⁷ When the R group is large, the methyl ester rather than the acid can be decarbomethoxylated over thorium oxide to give the symmetrical ketone.

The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained:



This process, called *Ruzicka cyclization*, is good for the preparation of rings of six and seven members and, with lower yields, of C₈–C₁₀ to C₃₀ cyclic ketones.²¹⁶⁸

Not much work has been done on the mechanism of this reaction. However, a free radical mechanism has been suggested on the basis of a thorough study of all the side products.²¹⁶⁹

OS I, 192; II, 389; IV, 854; V, 589. Also see, OS IV, 55, 560.

²¹⁶² Ando, T.; Kawate, T.; Yamawaki, J.; Hanafusa, T. *Synthesis* **1983**, 637.

²¹⁶³ Koenig, K.E.; Weber, W.P. *Tetrahedron Lett.* **1974**, 2275. See also, Sukata, K. *Bull. Chem. Soc. Jpn.* **1987**, 60, 1085.

²¹⁶⁴ See Fridman, A.L.; Ismagilova, G.S.; Zalesov, V.S.; Novikov, S.S. *Russ. Chem. Rev.* **1972**, 41, 371; Ried, W.; Mengler, H. *Fortshr. Chem. Forsch.*, **1965**, 5, 1.

²¹⁶⁵ Hodson, D.; Holt, G.; Wall, D.K. *J. Chem. Soc. C* **1970**, 971.

²¹⁶⁶ See Kwart, H.; King, K. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, **1969**, pp. 362–370.

²¹⁶⁷ Granito, C.; Schultz, H.P. *J. Org. Chem.* **1963**, 28, 879.

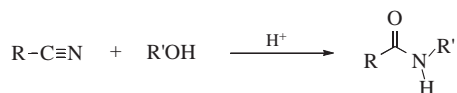
²¹⁶⁸ See Ruzicka, L.; Stoll, M.; Schinz, H. *Helv. Chim. Acta* **1926**, 9, 249; **1928**, 11, 1174; Ruzicka, L.; Brugger, W.; Seidel, C.F.; Schinz, H. *Helv. Chim. Acta* **1928**, 11, 496.

²¹⁶⁹ Hites, R.A.; Biemann, K. *J. Am. Chem. Soc.* **1972**, 94, 5772. See also, Bouchoule, C.; Blanchard, M.; Thomassin, R. *Bull. Soc. Chim. Fr.* **1973**, 1773.

16.B.iii. Reactions in which Carbon Adds to the Heteroatom

A. Oxygen Adding to the Carbon

16-91 The Ritter Reaction

N-Hydro,*N*-alkyl-*C*-oxo-biaddition

Alcohols can be added to nitriles in an entirely different manner from that seen in Reaction 16-9. In this reaction, the alcohol is converted by a strong acid to a carbocation, which is attacked by the nucleophilic nitrogen atom to give **125**. Subsequent addition of water to the electrophilic carbon atom leads to the enol form of the amide (see Reaction 126), which tautomerizes (Sec. 2.N.i) to the *N*-alkyl amide.



Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); non-benzylic primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol, but may come from protonation of an alkene or from other sources. In any case, the reaction is called the *Ritter reaction*.²¹⁷⁰ Lewis acids [e.g., $\text{Mg}(\text{HSO}_4)_2$] have been used to promote the reaction.²¹⁷¹ Highly sterically hindered nitriles have been converted to *N*-methyl amides by heating with methanol and sulfuric acid.²¹⁷² Hydrogen cyanide also gives the reaction, the product being a formamide. Trimethylsilyl cyanide has also been used.²¹⁷³

Since the amides (especially the formamides) are easily cleaved to amines under hydrolysis conditions, the *Ritter reaction* provides a method for achieving the conversions $\text{R}'\text{OH} \rightarrow \text{R}'\text{NH}_2$ (see 10-32) and $\text{alkene} \rightarrow \text{R}'\text{NH}_2$ (see 15-8) in those cases, where R' can form a relatively stable carbocation. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to primary alcohols by treatment with triflic anhydride²¹⁷⁴ or $\text{Ph}_2\text{CCl}^+ \text{SbCl}_6^-$ or a similar salt²¹⁷⁵ in the presence of the nitrile. A mixture of P_2O_5 and silica gel has been used to mediate the *Ritter reaction*.²¹⁷⁶ There is a Nafion-catalyzed,

²¹⁷⁰ Ritter, J.J.; Minieri, P.P. *J. Am. Chem. Soc.* **1948**, 70, 4045. See Krimen, L.I.; Cota, D.J. *Org. React.* **1969**, 17, 213; Johnson, F.; Madroñero, R. *Adv. Heterocycl. Chem.* **1966**, 6, 95; Tongco, E.C.; Prakash, G.K.S.; Olah, G.A. *Synlett* **1997**, 1193.

²¹⁷¹ Salehi, P.; Khodaei, M.M.; Zolfigol, M.A.; Keyvan, A. *Synth. Commun.* **2001**, 31, 1947.

²¹⁷² Lebedev, M.Y.; Erman, M.B. *Tetrahedron Lett.* **2002**, 43, 1397.

²¹⁷³ Chen, H.G.; Goel, O.P.; Kesten, S.; Knobelsdorf, J. *Tetrahedron Lett.* **1996**, 37, 8129.

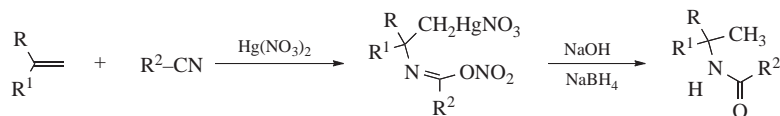
²¹⁷⁴ Martinez, A.G.; Alvarez, R.M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *Tetrahedron Lett.* **1989**, 30, 581.

²¹⁷⁵ Barton, D.H.R.; Magnus, P.D.; Garbarino, J.A.; Young, R.N. *J. Chem. Soc. Perkin Trans. 1* **1974**, 2101. See also, Top, S.; Jaouen, G. *J. Org. Chem.* **1981**, 46, 78.

²¹⁷⁶ Tamaddon, F.; Khoobi, M.; Keshavarz, E. *Tetrahedron Lett.* **2007**, 48, 3643.

microwave assisted variation,²¹⁷⁷ as well as FeCl₃ catalyzed²¹⁷⁸ and iodine-catalyzed²¹⁷⁹ reactions.

Alkenes of the form RCH=CHR' and RR'C=CH₂ add to nitriles in the presence of mercuric nitrate to give, after treatment with NaBH₄, the same amides that would be obtained by the *Ritter reaction*.²¹⁸⁰ This method has the advantage of avoiding strong acids.

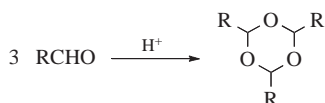


Benzylic compounds (e.g., ethylbenzene) react with alkyl nitriles, ceric ammonium nitrate, and a catalytic amount of *N*-hydroxysuccinimide to give the *Ritter* product, the amide.²¹⁸¹

The *Ritter reaction* can be applied to cyanamides RNHCN to give ureas (RNHCONHR').²¹⁸²

OS V, 73, 471.

16-92 The Addition of Aldehydes to Aldehydes



When catalyzed by acids, low-molecular-weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.²¹⁸³ The cyclic trimer of formaldehyde is called *trioxane*,²¹⁸⁴ and that of acetaldehyde is known as *paraldehyde*. Under certain conditions, it is possible to get tetramers²¹⁸⁵ or dimers. Aldehydes can also polymerize to linear polymers, but a small amount of water is required to form hemiacetal groups at the ends of the chains. The linear polymer formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers of aldehydes are acetals, they are stable to bases, but can be hydrolyzed by acids. Because formaldehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.

A slightly related reaction involves nitriles, which can be trimerized with various acids, bases, or other catalysts to give triazines (see OS III, 71).²¹⁸⁶ Here HCl is most often used. Most nitriles with an α hydrogen do not give the reaction.

²¹⁷⁷ Polshettiwar, V.; Varma, R.S. *Tetrahedron Lett.* **2008**, 49, 2661.

²¹⁷⁸ Anxionnat, B.; Guérinot, A.; Reymond, S.; Cossy, J. *Tetrahedron Lett.* **2009**, 50, 3470.

²¹⁷⁹ Theerthagiri, P.; Lalitha, A.; Arunachalam, P.N. *Tetrahedron Lett.* **2010**, 51, 2813.

²¹⁸⁰ See Fry, A.J.; Simon, J.A. *J. Org. Chem.* **1982**, 47, 5032.

²¹⁸¹ Sakaguchi, S.; Hirabayashi, T.; Ishii, Y. *Chem. Commun.* **2002**, 516.

²¹⁸² Anatol, J.; Berecoechea, J. *Bull. Soc. Chim. Fr.* **1975**, 395; *Synthesis* **1975**, 111.

²¹⁸³ See Bevington, J.C. *Q. Rev. Chem. Soc.* **1952**, 6, 141.

²¹⁸⁴ See Camarena, R.; Cano, A.C.; Delgado, F.; Zúñiga, N.; Alvarez, C. *Tetrahedron Lett.* **1993**, 34, 6857.

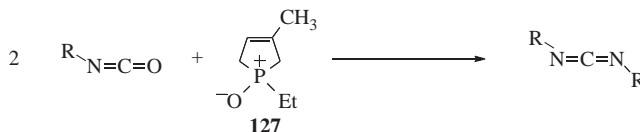
²¹⁸⁵ Barón, M.; de Manderola, O.B.; Westerkamp, J.F. *Can. J. Chem.* **1963**, 41, 1893.

²¹⁸⁶ See Martin, D.; Bauer, M.; Pankratov, V.A. *Russ. Chem. Rev.* **1978**, 47, 975. See Pankratov, V.A.; Chesnokova, A.E. *Russ. Chem. Rev.* **1989**, 58, 879.

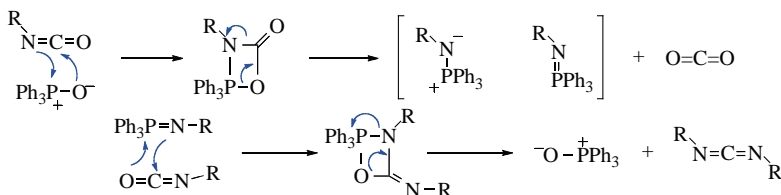
B. Nitrogen Adding to the Carbon

16-93 The Addition of Isocyanates to Isocyanates (Formation of Carbodiimides)

Alkylimino-de-oxo-bisubstitution



The treatment of isocyanates with 3-methyl-1-ethyl-3-phospholene-1-oxide (**127**) is a useful method for the synthesis of carbodiimides²¹⁸⁷ in good yields.²¹⁸⁸ The mechanism does not simply involve the addition of one molecule of isocyanate to another, since the kinetics are first order in isocyanate and first order in catalyst. The following mechanism has been proposed (the catalyst is here represented as $\text{R}_3\text{P}^+ - \text{O}^-$):²¹⁸⁹

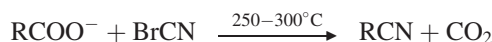


According to this mechanism, one molecule of isocyanate undergoes addition to $\text{C}=\text{O}$, and the other addition to $\text{C}=\text{N}$. Evidence is that ^{18}O labeling experiments have shown that each molecule of CO_2 produced contains one oxygen atom derived from the isocyanate and one from **127**,²¹⁹⁰ precisely what is predicted by this mechanism. Certain other catalysts are also effective.²¹⁹¹ High load, soluble oligomeric carbodiimides have been prepared.²¹⁹²

OS V, 501.

16-94 The Conversion of Carboxylic Acid Salts to Nitriles

Nitrilo-de-oxido,oxo-tersubstitution



Salts of aliphatic or aromatic carboxylic acids can be converted to the corresponding nitriles by heating with BrCN or ClCN . Heating with acetonitrile in sulfuric acid also gave the nitrile.²¹⁹³ Despite appearances, this is not a substitution reaction. When $\text{R}^{14}\text{COO}^-$ was used, the label appeared in the nitrile, not in the CO_2 ,²¹⁹⁴ and optical activity in R was retained.²¹⁹⁵ The acyl isocyanate ($\text{RCON}=\text{C}=\text{O}$) could be isolated from the reaction

²¹⁸⁷ Williams, A.; Ibrahim, I.T. *Chem. Rev.* **1981**, 81, 589; Mikołajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, 37, 233; Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* **1967**, 67, 107.

²¹⁸⁸ Campbell, T.W.; Monagle, J.J.; Foldi, V.S. *J. Am. Chem. Soc.* **1962**, 84, 3673.

²¹⁸⁹ Monagle, J.J.; Campbell, T.W.; McShane Jr., H.F. *J. Am. Chem. Soc.* **1962**, 84, 4288.

²¹⁹⁰ Monagle, J.J.; Mengenhauser, J.V. *J. Org. Chem.* **1966**, 31, 2321.

²¹⁹¹ See Ostrogovich, G.; Kerek, F.; Buzás, A.; Doca, N. *Tetrahedron* **1969**, 25, 1875.

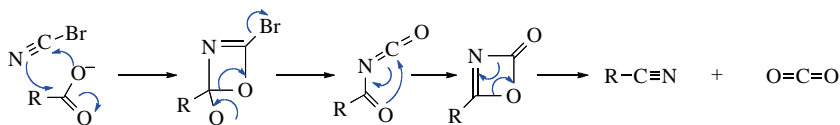
²¹⁹² Zhang, M.; Vedantham, P.; Flynn, D.L.; Hanson, P.R. *J. Org. Chem.* **2004**, 69, 8340.

²¹⁹³ Mlinarić-Majerski, K.; Margeta, R.; Veljković, J. *Synlett* **2005**, 2089.

²¹⁹⁴ Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* **1958**, 36, 1256.

²¹⁹⁵ Barltrop, J.A.; Day, A.C.; Bigley, D.B. *J. Chem. Soc.* **1961**, 3185.

mixture; hence the following mechanism was proposed:²¹⁹⁴

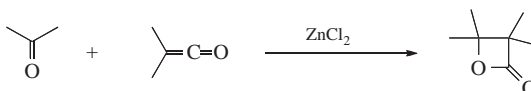


C. Carbon Adding to the Carbon

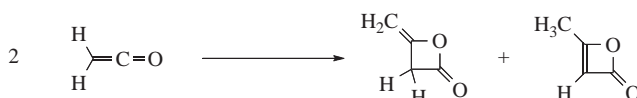
The reactions in this group are cycloadditions.

16-95 The Formation of β -Lactones and Oxetanes

(2+2)OC,CC-cyclo-[oxoethylene]-1/2/addition



Aldehydes, ketones, and quinones react with ketenes to give β -lactones,²¹⁹⁶ diphenylketene being used most often.²¹⁹⁷ The reaction is catalyzed by Lewis acids, and without them most ketenes do not give adducts because the adducts decompose at the high temperatures necessary when no catalyst is used. When ketene was added to chloral (Cl_3CCHO) in the presence of the chiral catalyst (+)-quinidine, one enantiomer of the β -lactone was produced with excellent enantioselectivity.²¹⁹⁸ Enantioselective β -lactone formation was accomplished using chiral oxazaborolidines.²¹⁹⁹ The use of a chiral Al catalyst also led to β -lactones with good syn selectivity and good enantioselectivity.²²⁰⁰ Other di- and trihalo aldehydes and ketones also give the reaction enantioselectively, with somewhat lower enantioselectivity.²²⁰¹ Ketene adds to another molecule of itself:



This dimerization is so rapid that ketene does not form β -lactones with aldehydes or ketones, except at low temperatures. Other ketenes dimerize more slowly. In these cases, the major dimerization product is not the β -lactone, but a cyclobutanedione (see Reaction 15-63). However, the proportion of ketene that dimerizes to β -lactone can be increased by the addition of catalysts (e.g., triethylamine or triethyl phosphite).²²⁰² Ketene acetals [$\text{R}_2\text{C}=\text{C}(\text{OR}')_2$] add to aldehydes and ketones in the presence of ZnCl_2 to give the

²¹⁹⁶ See Calter, M.A.; Tretyak, O.A.; Flaschenriem, C. *Org. Lett.* **2005**, 7, 1809.

²¹⁹⁷ Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, **1967**, pp. 139–168; Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*, Academic Press, NY, **1967**, pp. 39–45, 64–74.

²¹⁹⁸ Wynberg, H.; Staring, E.G.J. *J. Am. Chem. Soc.* **1982**, 104, 166; *J. Chem. Soc., Chem. Commun.* **1984**, 1181.

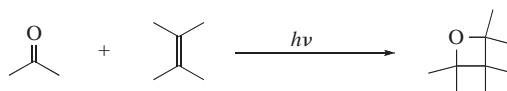
²¹⁹⁹ Gnanadesikan, V.; Corey, E.J. *Org. Lett.* **2006**, 8, 4943.

²²⁰⁰ Nelson, S.G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, 126, 14.

²²⁰¹ Wynberg, H.; Staring, E.G.J. *J. Org. Chem.* **1985**, 50, 1977.

²²⁰² Elam, E.U. *J. Org. Chem.* **1967**, 32, 215.

corresponding oxetanes.²²⁰³



Ordinary aldehydes and ketones can add to alkenes, under the influence of UV light, to give oxetanes. Quinones also react to give spirocyclic oxetanes.²²⁰⁴ This reaction, called the *Paterno-Büchi reaction*,²²⁰⁵ is similar to the photochemical dimerization of alkenes discussed at Reaction 15-63. In general, the mechanism consists of the addition of an excited state of the carbonyl compound to the ground state of the alkene. Both singlet (S_1)²²⁰⁶ and n,π^* triplet²²⁰⁷ states have been shown to add to alkenes to give oxetanes. A diradical intermediate $\cdot\text{O}-\text{C}-\text{C}-\text{C}\cdot$ ²²⁰⁸ has been detected by spectroscopic methods.²²⁰⁹ Yields in the *Paterno-Büchi reaction* are variable, ranging from very low to fairly high (90%). The reaction can be highly diastereoselective,²²¹⁰ and allylic alcohols were shown to react with aldehydes to give an oxetane with syn selectivity.²²¹¹ There are several side reactions. When the reaction proceeds through a triplet state, it can in general be successful only when the alkene possesses a triplet energy comparable to, or higher than, the carbonyl compound; otherwise energy transfer from the excited carbonyl group to the ground-state alkene can take place (triplet-triplet photosensitization, see Sec. 7.A.vi).²²¹² In most cases, quinones react normally with alkenes, giving oxetane products, but other α,β -unsaturated ketones usually give preferential cyclobutane formation (Reaction 15-63). Aldehydes and ketones also add photochemically to allenes to give the corresponding alkylideneoxetanes and dioxaspiro compounds.²²¹³ Aldehydes add to silyl enol ethers.²²¹⁴ An intramolecular reaction of ketones was reported to give a bicyclic oxetane via

²²⁰³ Aben, R.W.; Hofstraet, R.; Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 355. For a discussion of oxetane cycloreversion, see Miranda, M.A.; Izquierdo, M.A.; Galindo, F. *Org. Lett.* **2001**, *3*, 1965.

²²⁰⁴ Ciufolini, M.A.; Rivera-Fortin, M.A.; Byrne, N.E. *Tetrahedron Lett.* **1993**, *34*, 3505.

²²⁰⁵ Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, **1989**, pp. 138–152; Carless, H.A.J. in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, **1986**, pp. 95–117; Carless, H.A.J. in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, **1984**, pp. 425–487; Jones II, M. *Org. Photochem.* **1981**, *5*, 1; Arnold, D.R. *Adv. Photochem.* **1968**, *6*, 301–423; Chapman, O.L.; Lenz, G. *Org. Photochem.* **1967**, *1*, 283, pp. 283–294; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, **1967**, pp. 111–139. Also see, Bosch, E.; Hubig, S.M.; Kochi, J.K. *J. Am. Chem. Soc.* **1998**, *120*, 386.

²²⁰⁶ Turro, N.J. *Pure Appl. Chem.* **1971**, *27*, 679; Yang, N.C.; Kimura, M.; Eisenhardt, W. *J. Am. Chem. Soc.* **1973**, *95*, 5058; Barltrop, J.A.; Carless, H.A.J. *J. Am. Chem. Soc.* **1972**, *94*, 1951, 8761.

²²⁰⁷ Arnold, D.R.; Hinman, R.L.; Glick, A.H. *Tetrahedron Lett.* **1964**, 1425; Yang, N.C.; Nussim, M.; Jorgenson, M.J.; Murov, S. *Tetrahedron Lett.* **1964**, 3657.

²²⁰⁸ See references cited in Griesbeck, A.G.; Stadtmüller, S. *J. Am. Chem. Soc.* **1990**, *112*, 1281. See also, Kutateladze, A.G. *J. Am. Chem. Soc.* **2001**, *123*, 9279.

²²⁰⁹ Freilich, S.C.; Peters, K.S. *J. Am. Chem. Soc.* **1985**, *107*, 3819; Griesbeck, A.G.; Mauder, H.; Stadtmüller, S. *Accs. Chem. Res.* **1994**, *27*, 70.

²²¹⁰ Adam, W.; Stegmann, V.R. *J. Am. Chem. Soc.* **2002**, *124*, 3600. See Ciufolini, M.A.; Rivera-Fortin, M.A.; Zuzukin, V.; Whitmire, K.H. *J. Am. Chem. Soc.* **1994**, *116*, 1272.

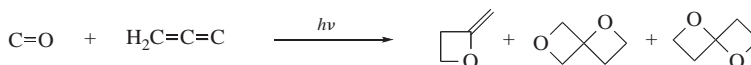
²²¹¹ Griesbeck, A.G.; Bondock, S. *J. Am. Chem. Soc.* **2001**, *123*, 6191. See also, Adam, W.; Stegmann, V.R. *Synthesis* **2001**, 1203.

²²¹² For a spin-directed reaction, see Griesbeck, A.G.; Fiege, M.; Bondock, S.; Gudipati, M.S. *Org. Lett.* **2000**, *2*, 3623.

²²¹³ Howell, A.R.; Fan, R.; Truong, A. *Tetrahedron Lett.* **1996**, *37*, 8651. See Schuster, H.F.; Coppola, G.M. *Allenenes in Organic Synthesis*, Wiley, NY, **1984**, pp. 317–326.

²²¹⁴ Abe, M.; Tachibana, K.; Fujimoto, K.; Nojima, M. *Synthesis* **2001**, 1243.

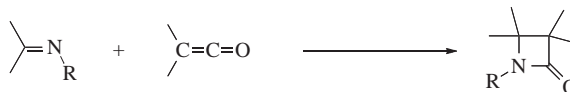
photolysis on the solid state.²²¹⁵



OS III, 508; V, 456. For the reverse reaction, see OS V, 679.

16-96 The Formation of β -Lactams

(2+2)NC,CC-cyclo-[oxoethylene]-1/2/addition



Ketenes add to imines to give β -lactams.²²¹⁶ The reaction is generally carried out with ketenes of the form $\text{R}_2\text{C}=\text{C}=\text{O}$. It has not been successfully applied to $\text{RCH}=\text{C}=\text{O}$, except when these are generated *in situ* by decomposition of a diazo ketone (the *Wolff rearrangement*, Reaction 18-8) in the presence of the imine. It has been done with ketene, but the more usual course with this reagent is an addition to the enamine tautomer of the substrate. Thioketenes²²¹⁷ ($\text{R}_2\text{C}=\text{C}=\text{S}$) give β -thiolactams.²²¹⁸ Imines also form β -lactams when treated with (1) zinc (or another metal²²¹⁹) and an α -bromo ester (*Reformatsky* conditions, 16-28),²²²⁰ or (2) the chromium carbene complexes $[(\text{CO})_5\text{Cr}=\text{C}(\text{Me})\text{OMe}]$.²²²¹ The latter method has been used to prepare optically active β -lactams.²²²² Ketenes have also been added to certain hydrazones (e.g., $\text{PhCH}=\text{NNMe}_2$) to give N-amino β -lactams.²²²³ A polymer-bound pyridinium salt facilitates β -lactam formation from carboxylic acids and imines.²²²⁴ α -Chloroimines have been used as chiral inductors in this reaction.²²²⁵

N-Tosyl imines react with ketenes, Proton Sponge (Sec. 8.A.i) and a chiral amine to give the N-tosyl β -lactam with good enantioselectivity.²²²⁶ A chiral ferrocenyl catalyst also

²²¹⁵ Kang, T.; Scheffer, J.R. *Org. Lett.* **2001**, 3, 3361.

²²¹⁶ For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1919–1921. See Fu, N.; Tidwell, T.T. *Tetrahedron* **2008**, 64, 10465; Brown, M.J. *Heterocycles* **1989**, 29, 2225; Isaacs, N.S. *Chem. Soc. Rev.* **1976**, 5, 181; Mukerjee, A.K.; Srivastava, R.C. *Synthesis* **1973**, 327; Muller, L. L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, **1967**, pp. 173–206; Anselme, J. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 305–309; Sandhu, J.S.; Sain, B. *Heterocycles* **1987**, 26, 777.

²²¹⁷ See Schaumann, E. *Tetrahedron* **1988**, 44, 1827.

²²¹⁸ Schaumann, E. *Chem. Ber.* **1976**, 109, 906.

²²¹⁹ With indium: Banik, B.K.; Ghatak, A.; Becker, F.F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2179.

²²²⁰ For a review, see Hart, D.J.; Ha, D. *Chem. Rev.* **1989**, 89, 1447.

²²²¹ Hegedus, L.S.; McGuire, M.A.; Schultze, L.M.; Yijun, C.; Anderson, O.P. *J. Am. Chem. Soc.* **1984**, 106, 2680; Hegedus, L.S.; McGuire, M.A.; Schultze, L.M. *Org. Synth.* 65, 140.

²²²² Hegedus, L.S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, 112, 1109.

²²²³ Sharma, S.D.; Pandhi, S.B. *J. Org. Chem.* **1990**, 55, 2196.

²²²⁴ Donati, D.; Morelli, C.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **2004**, 69, 9316.

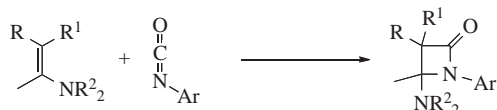
²²²⁵ D'hooghe, M.; Brabandt, W.V.; Dekeukeleire, S.; Dejaegher, Y.; De Kimpe, N. *Chemistry: European J.* **2008**, 14, 6336.

²²²⁶ Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* **2000**, 122, 7831.

gives good enantioselectivity,²²²⁷ and chiral ammonium salts²²²⁸ or chiral cinchona alkaloids²²²⁹ have been used as catalysts. A catalytic amount of benzoyl quinine gives β -lactams with good enantioselectivity.²²³⁰

An intramolecular version of this ketene–imine reaction is known.²²³¹

Like the similar cycloaddition of ketenes to alkenes (Reaction **15-63**), most of these reactions probably take place by the diionic mechanism *c* (See **15-63**).²²³² β -Lactams have also been prepared in the opposite manner by the addition of enamines to isocyanates:²²³³



The reactive compound chlorosulfonyl isocyanate²²³⁴ (ClSO_2NCO) forms β -lactams even with unactivated alkenes,²²³⁵ as well as with imines,²²³⁶ allenes,²²³⁷ conjugated dienes,²²³⁸ and cyclopropenes.²²³⁹ With microwave irradiation, alkyl isocyanates also react.²²⁴⁰

α -Diazo ketones react with imines and microwave irradiation to give β -lactams.²²⁴¹ Allylic phosphonate esters react with imines, in the presence of a Pd catalyst, to give β -lactams.²²⁴² Alkynyl reagents (e.g., $\text{BuC}\equiv\text{CO}^-\text{Li}^+$) react with imines to form β -lactams.²²⁴³ Imines and benzylic halides react to give β -lactams in the presence of CO and a Pd catalyst.²²⁴⁴ Conjugated amides react with NBS and 20% sodium acetate to give an α -bromo β -lactam.²²⁴⁵ A different approach to β -lactams heated aziridines with CO and a Co catalyst.²²⁴⁶ Aziridines also react with CO and a dendrimer catalyst to such a β -lactam.²²⁴⁷

β -Thiolactams are prepared from aryl isothiocyanates.²²⁴⁸

OS V, 673; **VIII**, 3, 216.

²²²⁷ Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* **2002**, *124*, 1578.

²²²⁸ Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626.

²²²⁹ France, S.; Shah, M.H.; Weatherwax, A.; Wack, H.; Roth, J.P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206.

²²³⁰ Shah, M.H.; France, S.; Lectka, T. *Synlett* **2003**, 1937.

²²³¹ Clark, A.J.; Battle, G.M.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 4409.

²²³² See Brady, W.T.; Shieh, C.H. *J. Org. Chem.* **1983**, *48*, 2499.

²²³³ See Opitz, G.; Koch, J. *Angew. Chem. Int. Ed.* **1963**, *2*, 152.

²²³⁴ Kamal, A.; Sattur, P.B. *Heterocycles* **1987**, *26*, 1051; Szabo, W.A. *Aldrichimica Acta* **1977**, *10*, 23;

Rasmussen, J.K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389; Graf, R. *Angew. Chem. Int. Ed.* **1968**, *7*, 172.

²²³⁵ Bestian, H. *Pure Appl. Chem.* **1971**, *27*, 611. See also, Barrett, A.G.M.; Betts, M.J.; Fenwick, A. *J. Org. Chem.* **1985**, *50*, 169.

²²³⁶ See McAllister, M.A.; Tidwell, T.T. *J. Chem. Soc. Perkin Trans. 2* **1994**, 2239.

²²³⁷ Moriconi, E.J.; Kelly, J.F. *J. Org. Chem.* **1968**, *33*, 3036. See also, Martin, J.C.; Carter, P.L.; Chitwood, J.L. *J. Org. Chem.* **1971**, *36*, 2225.

²²³⁸ Malpass, J.R.; Tweddle, N.J. *J. Chem. Soc. Perkin Trans. 1* **1977**, 874.

²²³⁹ Moriconi, E.J.; Kelly, J.F.; Salomone, R.A. *J. Org. Chem.* **1968**, *33*, 3448.

²²⁴⁰ Taguchi, Y.; Tsuchiya, T.; Oishi, A.; Shibuya, I. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1667.

²²⁴¹ Linder, M.R.; Podlech, J. *Org. Lett.* **2001**, *3*, 1849.

²²⁴² Torii, S.; Okumoto, H.; Sadakane, M.; Hai, A.K.M.A.; Tanaka, H. *Tetrahedron Lett.* **1993**, *34*, 6553.

²²⁴³ Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **1998**, *49*, 113.

²²⁴⁴ Cho, C.S.; Jiang, L.H.; Shim, S.C. *Synth. Commun.* **1999**, *29*, 2695.

²²⁴⁵ Naskar, D.; Roy, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2435.

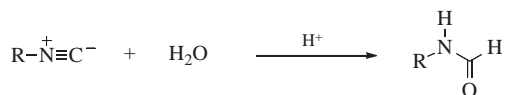
²²⁴⁶ See Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* **2001**, *57*, 1801.

²²⁴⁷ Lu, S.-M.; Alper, H. *J. Org. Chem.* **2004**, *69*, 3558.

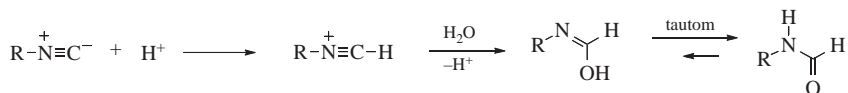
²²⁴⁸ Awasthi, C.; Yadav, L.D.S. *Synlett* **2010**, 1783.

16.B.iv. Addition to Isocyanides²²⁴⁹

Addition to $\text{R}-\text{N}^+\equiv\text{C}^-$ is not a matter of a species with an electron pair adding to one atom and a species without a pair adding to the other, as is addition to the other types of double and triple bonds in this chapter and Chapter 15. In these additions, the electrophile and the nucleophile *both add to the carbon*. No species add to the nitrogen, which, however, loses its positive charge by obtaining as an unshared pair one of the triple-bond pairs of electrons to give **128**. In most of the reactions considered below, **128** undergoes a further reaction, so the product is of the form $\text{R}-\bar{\text{N}}\text{H}-\text{CR}_3$.

**16-97 The Addition of Water to Isocyanides****1/ N,2/C-Dihydro-2/C-oxo-biaddition**

Formamides can be prepared by the acid-catalyzed addition of water to isocyanides. The mechanism is probably²²⁵⁰



The reaction has also been carried out under alkaline conditions, with hydroxide in aq dioxane.²²⁵¹ The mechanism here involves nucleophilic attack by hydroxide at the carbon atom. An intramolecular addition of an alkyne (in an ortho alkynyl phenyl isonitrile) to the carbon of an isonitrile occurred with heating in methanol to give quinoline derivatives.²²⁵²

16-98 The Passerini and Ugi Reactions²²⁵³**1/N-Hydro-2/C-(α -acyloxyalkyl),2/C-oxo-biaddition**

²²⁴⁹ Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, **1971**; Walborsky, H.M.; Periasamy, M.P. in Patai, S.; Rappaport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, **1983**, pp. 835–887; Hoffmann, P.; Marquarding, D.; Kliemann, H.; Ugi, I. in Rappaport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 853–883.

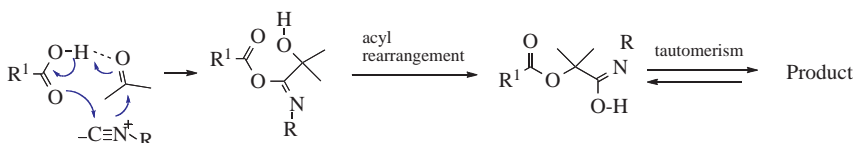
²²⁵⁰ Lim, Y.Y.; Stein, A.R. *Can. J. Chem.* **1971**, *49*, 2455.

²²⁵¹ Cunningham, I.D.; Buist, G.J.; Arkle, S.R. *J. Chem. Soc. Perkin Trans. 2* **1991**, 589.

²²⁵² Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1977.

²²⁵³ Ugi, I. *Angew. Chem. Int. Ed.* **1982**, *21*, 810; Marquarding, D.; Gokel, G.W.; Hoffmann, P.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, **1971**, pp. 133–143; Gokel, G.W.; Lüdke, G.; Ugi, I. in Ugi, I. Ref. 936, pp. 145–199, 252–254.

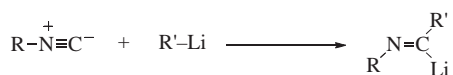
When an isocyanide is treated with a carboxylic acid and an aldehyde or ketone, an α -acyloxy amide is the product in what is called the *Passerini reaction*. A SiCl_4 mediated reaction in the presence of a chiral bis(phosphoramidate) gives an α -hydroxy amide with good enantioselectivity.²²⁵⁴ There is a solvent-free *Passerini reaction*²²⁵⁵ and ionic liquids²²⁵⁶ can be used. The following mechanism has been postulated for the basic reaction:²²⁵⁷



If ammonia or an amine is also added to the mixture (in which case the reaction is known as the *Ugi reaction*, or the *Ugi four-component condensation*), the product is $\text{R}'(\text{C}=\text{C})\text{NH}-\text{C}-(\text{C}=\text{O})\text{NHR}$ [the corresponding bis(amide) from NH_3] or $\text{R}'(\text{C}=\text{C})\text{NR}'-\text{C}-(\text{C}=\text{O})\text{NHR}$ (from a primary amine R^2NH_2). There is a catalytic *three-component Ugi reaction*.²²⁵⁸ Repetitive *Ugi reactions* are known.²²⁵⁹ This product probably arises from a reaction between the carboxylic acid, the isocyanide, and the *imine* formed from the aldehyde or ketone and ammonia or the primary amine. “Isocyanide-free” *Ugi reactions* use alkyl halides/silver cyanide and KCN to generate the isocyanide *in situ*.²²⁶⁰ The use of an *N*-protected amino acid²²⁶¹ or peptide as the carboxylic acid component and/or the use of an isocyanide containing a C-protected carboxyl group allows the reaction to be used for peptide synthesis.²²⁶² Rare earth metal triflates catalyze this reaction.²²⁶³

16-99 The Formation of Metalated Aldimines

1/1/Lithio-alkyl-addition



Isocyanides that do not contain an α hydrogen react with alkyllithium compounds,²²⁶⁴ as well as with *Grignard reagents*, to give lithium (or magnesium) aldimines.²²⁶⁵ These

²²⁵⁴ Denmark, S.E.; Fan, Y. *J. Org. Chem.* **2005**, 70, 9667.

²²⁵⁵ Koszelewski, D.; Szymanski, W.; Krysiak, J.; Ostaszewski, R. *Synth. Commun.* **2008**, 38, 1120.

²²⁵⁶ Fan, X.; Li, Y.; Zhang, X.; Qu, G.; Wang, J. *Can. J. Chem.* **2006**, 84, 794.

²²⁵⁷ See Jenner, G. *Tetrahedron Lett.* **2000**, 43, 1235.

²²⁵⁸ Pan, S.C.; List, B. *Angew. Chem. Int. Ed.* **2008**, 47, 3622.

²²⁵⁹ Constabel, F.; Ugi, I. *Tetrahedron* **2001**, 57, 5785.

²²⁶⁰ El Kaïm, L.; Grimaud, L.; Schiltz, A. *Org. Biomol. Chem.* **2009**, 7, 3024.

²²⁶¹ Godet, T.; Bovin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M.A. *Org. Lett.* **2004**, 6, 3281.

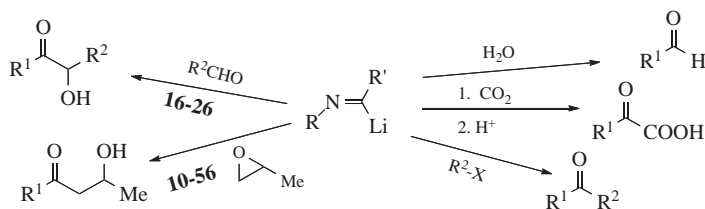
²²⁶² Ugi, I. in Gross, E.; Meienhofer, J. *The Peptides*, Vol. 2, Academic Press, NY, **1980**, pp. 365–381, *Intra-Sci. Chem. Rep.* **1971**, 5, 229; Gokel, G.W.; Hoffmann, P.; Kleimann, H.; Klusacek, H.; Lüdke, G.; Marquarding, D.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, **1971**, pp. 201–215. See also, Kunz, H.; Pfengle, W. *J. Am. Chem. Soc.* **1988**, 110, 651.

²²⁶³ Okandeji, B.O.; Gordon, J.R.; Sello, J.K. *J. Org. Chem.* **2008**, 73, 5595.

²²⁶⁴ See Ito, Y.; Murakami, M. *Synlett* **1990**, 245.

²²⁶⁵ Walborsky, H.M. *J. Org. Chem.* **1981**, 46, 5405; **1982**, 47, 52. See also, Murakami, H.; Ito, H.; Ito, Y. *J. Org. Chem.* **1988**, 53, 4158.

metalated aldimines are versatile nucleophiles and react with various substrates as follows:



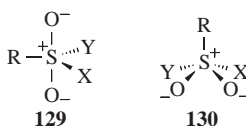
The reaction therefore constitutes a method for converting an organometallic compound ($R'M$) to an aldehyde ($R'CHO$, see also, Reaction **12-33**), an α -keto acid,²²⁶⁶ a ketone $R'COR$ (see also, Reaction **12-33**), an α -hydroxy ketone, or a β -hydroxy ketone. In each case, the $C=N$ bond is hydrolyzed to a $C=O$ bond (Reaction **16-2**).

In a related reaction, isocyanides can be converted to aromatic aldimines by treatment with an iron complex followed by irradiation in benzene solution: $RNC + C_6H_6 \rightarrow PhCH=NR$.²²⁶⁷

OS VI, 751.

16.B.v. Nucleophilic Substitution at a Sulfonyl Sulfur Atom²²⁶⁸

Nucleophilic substitution at RSO_2X is similar to attack at $RCOX$. Many of the reactions are essentially the same, though sulfonyl halides are less reactive than halides of carboxylic acids.²²⁶⁹ The mechanisms²²⁷⁰ are not identical, because a “tetrahedral” intermediate in this case (**129**) would have five groups on the central atom. This is possible since sulfur can accommodate up to 12 electrons in its valence shell, but it seems more likely that these mechanisms more closely resemble the S_N2 mechanism, with a trigonal-bipyramidal transition state (**130**). There are two major experimental results leading to this conclusion.



1. The stereospecificity of this reaction is more difficult to determine than that of nucleophilic substitution at a saturated carbon, where chiral compounds are relatively easy to prepare. Recall (Sec. 4.C, category 2) that optical activity is possible in a compound of the form RSO_2X if one oxygen is ^{16}O and the other is ^{18}O . When a sulfonate ester possessing this type of chirality was converted to a sulfone by reaction with a *Grignard reagent* (**16-105**), inversion of configuration was found.²²⁷¹ This is not incompatible with an intermediate (e.g., **129**), but it is in good accord with an S_N2 -like mechanism with backside attack.

²²⁶⁶ See Cooper, A.J.L.; Ginos, J.Z.; Meister, A. *Chem. Rev.* **1983**, 83, 321.

²²⁶⁷ Jones, W.D.; Foster, G.P.; Putinas, J.M. *J. Am. Chem. Soc.* **1987**, 109, 5047.

²²⁶⁸ See Ciuffarin, E.; Fava, A. *Prog. Phys. Org. Chem.* **1968**, 6, 81.

²²⁶⁹ For a comparative reactivity study, see Hirata, R.; Kiyan, N.Z.; Miller, J. *Bull. Soc. Chim. Fr.* **1988**, 694.

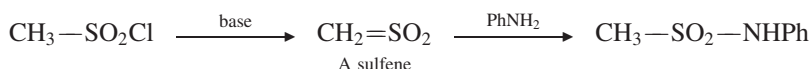
²²⁷⁰ See Gordon, I.M.; Maskill, H.; Ruasse, M. *Chem. Soc. Rev.* **1989**, 18, 123.

²²⁷¹ Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* **1969**, 91, 3603. See also, Jones, M.R.; Cram, D.J. *J. Am. Chem. Soc.* **1974**, 96, 2183.

2. More direct evidence against **129** (though still not conclusive) was found in an experiment involving acidic and basic hydrolysis of aryl arenesulfonates, where it has been shown by the use of ^{18}O that an intermediate like **129** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.²²⁷²

Other evidence favoring the $\text{S}_{\text{N}}2$ -like mechanism comes from kinetics and substituent effects.²²⁷³ However, evidence for the mechanism involving **129** is that the rates did not change much with changes in the leaving group²²⁷⁴ and the ρ values were large, indicating that a negative charge builds up in the transition state.²²⁷⁵

In certain cases in which the substrate carries an α hydrogen, there is strong evidence²²⁷⁶ that at least some of the reaction takes place by an elimination–addition mechanism (E1cB , similar to the one shown in Reaction **16-69**), going through a *sulfene* intermediate,²²⁷⁷ as in the reaction between methanesulfonyl chloride and aniline.



In the special case of nucleophilic substitution at a sulfonic ester ($\text{RSO}_2\text{OR}'$), where R' is alkyl, $\text{R}'\text{—O}$ cleavage is much more likely than S—O cleavage because the OSO_2R group is such a good leaving group (Sec. 10.G.iii).²²⁷⁸ Many of these reactions have been considered previously (e.g., Reactions **10-4** and **10-10**) as nucleophilic substitutions at an alkyl carbon atom and not at a sulfur atom. However, when R' is aryl, then the S—O bond is much more likely to cleave because of the low tendency of aryl substrates for nucleophilic substitution.²²⁷⁹

The order of nucleophilicity toward a sulfonyl sulfur has been reported as $\text{OH}^- > \text{RNH}_2 > \text{N}_3 > \text{F}^- > \text{AcO}^- > \text{Cl}^- > \text{H}_2\text{O} > \text{I}^-$.²²⁸⁰ This order is similar to that at a carbonyl carbon (Sec. 10.G.ii). Both of these substrates can be regarded as relatively hard acids, compared to a saturated carbon that is considerably softer and has a different order of nucleophilicity (Sec. 10.G.ii).

16-100 Attack by OH^- : Hydrolysis of Sulfonic Acid Derivatives

S -Hydroxy-de-chlorination, and so on



²²⁷² Kaiser, E.T.; Zaborsky, O.R. *J. Am. Chem. Soc.* **1968**, 90, 4626.

²²⁷³ Lee, I.; Kang, H.K.; Lee, H.W. *J. Am. Chem. Soc.* **1987**, 109, 7472; Arcoria, A.; Ballistreri, F.P.; Spina, E.; Tomaselli, G.A.; Maccarone, E. *J. Chem. Soc. Perkin Trans. 2* **1988**, 1793; Gnedin, B.G.; Ivanov, S.N.; Shchukina, M.V. *J. Org. Chem. USSR* **1988**, 24, 731.

²²⁷⁴ Ciuffarin, E.; Senatore, L.; Isola, M. *J. Chem. Soc. Perkin Trans. 2* **1972**, 468.

²²⁷⁵ Ciuffarin, E.; Senatore, L. *Tetrahedron Lett.* **1974**, 1635.

²²⁷⁶ Opitz, G. *Angew. Chem. Int. Ed.* **1967**, 6, 107. See Thea, S.; Guanti, G.; Hopkins, A.; Williams, A. *J. Org. Chem.* **1985**, 50, 5592; Skonieczny, S. *Tetrahedron Lett.* **1987**, 28, 5001; Pregel, M.J.; Buncel, E. *J. Chem. Soc. Perkin Trans. 2* **1991**, 307.

²²⁷⁷ King, J.F. *Acc. Chem. Res.* **1975**, 8, 10; Nagai, T.; Tokura, N. *Int. J. Sulfur Chem. Part B* **1972**, 207; Opitz, G. *Angew. Chem. Int. Ed.* **1967**, 6, 107; Wallace, T.J. *Q. Rev. Chem. Soc.* **1966**, 20, 67.

²²⁷⁸ See Netscher, T.; Prinzbach, H. *Synthesis* **1987**, 683.

²²⁷⁹ See Tagaki, W.; Kurusu, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1969**, 42, 2894.

²²⁸⁰ Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* **1973**, 95, 3912.

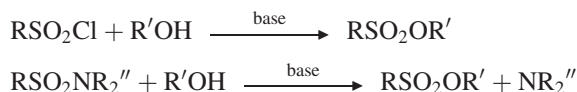
Sulfonyl chlorides as well as esters and amides of sulfonic acids can be hydrolyzed to the corresponding acids. Sulfonyl chlorides can be hydrolyzed with water or with an alcohol in the absence of acid or base. Basic catalysis is also used, though of course the salt is the product obtained. Esters are readily hydrolyzed, many with water or dilute alkali. This is the same reaction as **10-4**, and usually involves R'—O cleavage, except when R' is aryl. In some cases, retention of configuration has been shown at alkyl R', indicating S—O cleavage.²²⁸¹ Sulfonamides are generally *not* hydrolyzed by alkaline treatment, not even with hot concentrated alkali. Acids, however, do hydrolyze sulfonamides, but less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt. However, sulfonamides can be hydrolyzed with base if the solvent is HMPA.²²⁸²

Magnesium in methanol has been used to convert sulfonate esters to the parent alcohol.²²⁸³ Likewise, $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O} - \text{NaI}$ in acetonitrile converted aryl tosylates to the parent phenol derivative.²²⁸⁴

OS I, 14; II, 471; III, 262; IV, 34; V, 406; VI, 652, 727. Also see, OS V, 673; VI, 1016.

16-101 Attack by OR: Formation of Sulfonic Esters

S-Alkoxy-de-chlorination, and so on



Sulfonic esters are most frequently prepared by treatment of the corresponding sulfonyl halides with alcohols in the presence of a base.²²⁸⁵ This procedure is the most common method for the conversion of alcohols to tosylates, brosylates, and similar sulfonic esters. Both R and R' may be alkyl or aryl. The base is often pyridine or another amine, which functions as a nucleophilic catalyst,²²⁸⁶ as in the similar alcoholysis of carboxylic acyl halides (Reaction **16-61**). Primary alcohols react most rapidly, and it is often possible to sulfonate a primary OH group selectively in a molecule that also contains secondary or tertiary OH groups. The reaction with sulfonamides has been much less frequently used and is limited to *N,N*-disubstituted sulfonamides; that is, R may not be hydrogen. However, within these limits it is a useful reaction. The nucleophile in this case is actually RO^- . The R' may be hydrogen (as well as alkyl) if the nucleophile is a phenol, so that the product is RSO_2OAr . Acidic catalysts are used in this case.²²⁸⁷ Sulfonic acids have been converted directly to sulfonates by treatment with triethyl or trimethyl orthoformate $[\text{HC}(\text{OR})_3]$, without catalyst or solvent,²²⁸⁸ and with a trialkyl phosphite $[\text{P}(\text{OR})_3]$.²²⁸⁹

Mono-tosylation of a 1,2-diol was achieved using tosyl chloride and triethylamine, with a tin oxide catalyst.²²⁹⁰

²²⁸¹ Chang, F.C. *Tetrahedron Lett.* **1964**, 305.

²²⁸² Cuvigny, T.; Larchevêque, M. *J. Organomet. Chem.* **1974**, 64, 315.

²²⁸³ Sridhar, M.; Kumar, B.A.; Narender, R. *Tetrahedron Lett.* **1998**, 39, 2847.

²²⁸⁴ Reddy, G.S.; Mohan, G.H.; Iyengar, D.S. *Synth. Commun.* **2000**, 30, 3829.

²²⁸⁵ See Simpson, L.S.; Widlanski, T.S. *J. Am. Chem. Soc.* **2006**, 128, 1605.

²²⁸⁶ Rogne, O. *J. Chem. Soc. B* **1971**, 1334. See also, Litvinenko, M.; Shatskaya, V.A.; Savelova, V.A. *Doklad. Chem.* **1982**, 265, 199.

²²⁸⁷ Klamann, D.; Fabienke, E. *Chem. Ber.* **1960**, 93, 252.

²²⁸⁸ Padmapriya, A.A.; Just, G.; Lewis, N.G. *Synth. Commun.* **1985**, 15, 1057.

²²⁸⁹ Karaman, R.; Leader, H.; Goldblum, A.; Breuer, E. *Chem. Ind. (London)* **1987**, 857.

²²⁹⁰ Martinelli, M.J.; Vaidyanathan, R.; Khau, V.V. *Tetrahedron Lett.* **2000**, 41, 3773; Bucher, B.; Curran, D.P. *Tetrahedron Lett.* **2000**, 41, 9617.

OS I, 145; **III**, 366; **IV**, 753; **VI**, 56, 482, 587, 652; **VII**, 117; **66**, 1; **68**, 188. Also see, OS **IV**, 529; **VI**, 324, 757; **VII**, 495; **VIII**, 568.

16-102 Attack by Nitrogen; Formation of Sulfonamides

S-Amino-de-chlorination



Microwave assisted conversion of sulfonic acids to a 2,4,6-trichloro[1,3,5]triazine derivative is followed by formation of the sulfonamide.²²⁹¹ The treatment of sulfonyl chlorides with ammonia or amines is the usual way of preparing sulfonamides.²²⁹² Primary amines give *N*-alkyl sulfonamides, and secondary amines give *N,N*-dialkyl sulfonamides. The reaction is the basis of the *Hinsberg test* for distinguishing between primary, secondary, and tertiary amines. *N*-Alkyl sulfonamides, having an acidic hydrogen, are soluble in alkali, while *N,N*-dialkyl sulfonamides are not. Since tertiary amines are usually recovered unchanged, primary, secondary, and tertiary amines can be told apart. However, the test is limited for at least two reasons.²²⁹³ (1) Many *N*-alkyl sulfonamides in which the alkyl group has six or more carbons are insoluble in alkali, despite their acidic hydrogen,²²⁹⁴ so that a primary amine may appear to be a secondary amine. (2) If the reaction conditions are not carefully controlled, tertiary amines may not be recovered unchanged.²²⁸⁹

A primary or a secondary amine can be protected by reaction with phenacysulfonyl chloride ($\text{PhCOCH}_2\text{SO}_2\text{Cl}$) to give a sulfonamide ($\text{RNHSO}_2\text{CH}_2\text{COPh}$ or $\text{R}_2\text{NSO}_2\text{CH}_2\text{COPh}$).²²⁹⁵ The protecting group can be removed when desired with zinc and acetic acid. Sulfonyl chlorides react with azide ion to give sulfonyl azides (RSO_2N_3).²²⁹⁶ Chlorothioformates, $[\text{ROC}(=\text{S})\text{Cl}]$ react with triethylamine to give the *N,N*-diethylthioamide.²²⁹⁷

A quite different synthesis of sulfonamides treated allyltributyltin with $\text{PhI}=\text{NTs}$, in the presence of copper(II) triflate.²²⁹⁸ Another alternative method treats silyl enol ethers with sulfur dioxide, and subsequent reaction with a secondary amine gave the β -sulfonamido ester.²²⁹⁹

OS **IV**, 34, 943; **V**, 39, 179, 1055; **VI**, 78, 652; **VII**, 501; **VIII**, 104. See also, OS **VI**, 788.

16-103 Attack by Halogen: Formation of Sulfonyl Halides

S-Halo-de-hydroxylation



This reaction, parallel with **16-79**, is the standard method for the preparation of sulfonyl halides. Both PCl_3 and SOCl_2 have been used, and sulfonic acid salts can also serve as

²²⁹¹ De Luca, L.; Giacomelli, G. *J. Org. Chem.* **2008**, *73*, 3967.

²²⁹² See Kamal, A.; Reddy, J.S.; Bharathi, E.V.; Dastagiri, D. *Tetrahedron Lett.* **2008**, *49*, 348.

²²⁹³ See Gambill, C.R.; Roberts, T.D.; Shechter, H. *J. Chem. Educ.* **1972**, *49*, 287.

²²⁹⁴ Fanta, P.E.; Wang, C.S. *J. Chem. Educ.* **1964**, *41*, 280.

²²⁹⁵ Hendrickson, J.B.; Bergeron, R. *Tetrahedron Lett.* **1970**, 345.

²²⁹⁶ For an example, see Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Synth.* **V**, 179.

²²⁹⁷ Milan, D.S.; Prager, R.H. *Aust. J. Chem.* **1999**, *52*, 841.

²²⁹⁸ Kim, D.Y.; Kim, H.S.; Choi, Y.J.; Mang, J.Y.; Lee, K. *Synth. Commun.* **2001**, *31*, 2463.

²²⁹⁹ Bouchez, L.C.; Dubbaka, S.R.; Urks, M.; Vogel, P. *J. Org. Chem.* **2004**, *69*, 6413.

substrates. Cyanuric acid (2,4,6-trichloro[1,3,5]triazene) serves as a chlorinating agent.²³⁰⁰ Sulfonyl bromides and iodides have been prepared from sulfonyl hydrazides ($\text{ArSO}_2\text{NHNH}_2$), themselves prepared by Reaction **16-102** by treatment with bromine or iodine.²³⁰¹ Sulfonyl fluorides are generally prepared from the chlorides, by halogen exchange.²³⁰²

OS **I**, 84; **IV**, 571, 693, 846, 937; **V**, 196. See also, OS **VII**, 495.

16-104 Attack by Hydrogen: Reduction of Sulfonyl Chlorides

S-Hydro-de-chlorination or S -Dechlorination

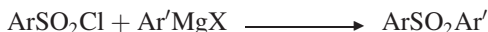


Sulfinic acids can be prepared by reduction of sulfonyl chlorides. Though mostly done on aromatic sulfonyl chlorides, the reaction has also been applied to alkyl compounds. Zinc, sodium sulfite, hydrazine, sodium sulfide, and other reducing agents have been used. For reduction of sulfonyl chlorides to thiols, see Reaction **19-78**.

OS **I**, 7, 492; **IV**, 674.

16-105 Attack by Carbon: Preparation of Sulfones

S-Aryl-de-chlorination



Grignard reagents convert aromatic sulfonyl chlorides or aromatic sulfonates to sulfones. Organolithium reagents react with sulfonyl fluorides at -78°C to give the corresponding sulfone.²³⁰³ Aromatic sulfonates have been converted to sulfones with organolithium compounds,²³⁰⁴ with aryltin compounds,²³⁰⁵ with an Fe catalyst,²³⁰⁶ and with alkyl halides and Zn metal.²³⁰⁷ Vinylic and allylic sulfones have been prepared by treatment of sulfonyl chlorides with a vinylic or allylic stannane and a Pd complex catalyst.²³⁰⁸ Alkynyl sulfones can be prepared by treatment of sulfonyl chlorides with trimethylsilylalkynes, with an AlCl_3 catalyst.²³⁰⁹ Note that trifluoromethylsulfones were converted to methyl sulfones by reaction with methylmagnesium bromide.²³¹⁰

Arylboronic acids (Reaction **12-28**) react with sulfonyl chlorides in the presence of PdCl_2 to give the corresponding sulfone.²³¹¹ Arylboronic acids also react with sulfinate anions (RSO_2Na) in the presence of $\text{Cu}(\text{OAc})_2$ to give the sulfone.²³¹²

OS **VIII**, 281.

²³⁰⁰ Blotny, G. *Tetrahedron Lett.* **2003**, 44, 1499.

²³⁰¹ Poshkus, A.C.; Herweh, J.E.; Magnotta, F.A. *J. Org. Chem.* **1963**, 28, 2766; Litvinenko, L.M.; Dadali, V.A.; Savelova, V.A.; Krichevskaya, T.I. *J. Gen. Chem. USSR* **1964**, 34, 3780.

²³⁰² See Bianchi, T.A.; Cate, L.A. *J. Org. Chem.* **1977**, 42, 2031, and references cited therein.

²³⁰³ Frye, L.L.; Sullivan, E.L.; Cusack, K.P.; Funaro, J.M. *J. Org. Chem.* **1992**, 57, 697.

²³⁰⁴ Baarschers, W.H. *Can. J. Chem.* **1976**, 54, 3056.

²³⁰⁵ Neumann, W.P.; Wicenc, C. *Chem. Ber.* **1993**, 126, 763.

²³⁰⁶ Volla, C.M.R.; Vogel, P. *Angew. Chem. Int. Ed.* **2008**, 47, 1305.

²³⁰⁷ Sun, X.; Wang, L.; Zhang, Y. *Synth. Commun.* **1998**, 28, 1785.

²³⁰⁸ Labadie, S.S. *J. Org. Chem.* **1989**, 54, 2496.

²³⁰⁹ See Waykole, L.; Paquette, L.A. *Org. Synth.* 67, 149.

²³¹⁰ Steensma, R.W.; Galabi, S.; Tagat, J.R.; McCombie, S.W. *Tetrahedron Lett.* **2001**, 42, 2281.

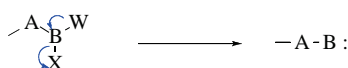
²³¹¹ Bandgar, B.P.; Bettigeri, S.V.; Phopase, J. *Org. Lett.* **2004**, 6, 2105.

²³¹² Beaulieu, C.; Guay, D.; Wang, Z.; Evans, D.A. *Tetrahedron Lett.* **2004**, 45, 3233.

Eliminations



A so-called β -*elimination* reaction occurs when two groups are lost from adjacent atoms so that a new double¹ (or triple) bond is formed. In general, the atom bearing a leaving group is the α , and the other the β atom. In an α -elimination, both groups are lost from the same atom to give a carbene (or a nitrene):



In a γ -elimination, a three-membered ring is formed:



Some of these processes were discussed in Chapter 10. Another type of elimination involves the expulsion of a fragment from within a chain or ring ($\text{X---Y---Z} \rightarrow \text{X---Z} + \text{Y}$). Such reactions are called *extrusion reactions*. This chapter discusses β -elimination and extrusion reactions (see Sec. 2.F.vi); however, β -elimination in which both X and W are hydrogen atoms are oxidation reactions. They are treated in Chapter 19.

17.A. MECHANISMS AND ORIENTATION

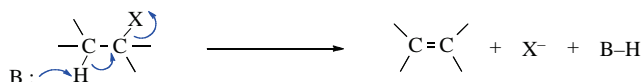
β -Elimination reactions may be divided into two types: one type taking place largely in solution, the other (pyrolytic eliminations) mostly in the gas phase. In the reactions, one group leaves with its electrons and the other without (i.e., it is pulled off), the latter most

¹ See Williams, J.M.J. *Preparation of Alkenes, A Practical Approach*, Oxford Univ. Press, Oxford, **1996**.

often being hydrogen. In these cases, the former leaves as the *leaving group or nucleofuge*. For pyrolytic eliminations, there are two principal mechanisms, one pericyclic and the other a free radical pathway. A few photochemical eliminations are also known (the most important is *Norrish-type II* cleavage of ketones, Sec. 7.A.vii), but these are not generally of synthetic importance² and will not be discussed further. In most β -eliminations, the new bonds are $C=C$ or $C\equiv C$. The discussion of mechanisms is largely confined to these cases.³ Mechanisms in solution ($E2$, $E1$)⁴ and $E1cB$ are discussed first. While standard methods are used to examine elimination reactions, new techniques (e.g., the velocity map ion imaging technique) have been used to study ultrafast elimination reactions.⁵

17.A.i. The $E2$ Mechanism

In the $E2$ mechanism (elimination, bimolecular), the proton on the β carbon is pulled off by a base, leading to near-simultaneous expulsion of the leaving group (nucleofuge):



The mechanism takes place in one step and is kinetically second order: first order in substrate and first order in base. An *ab initio* study has produced a model for the $E2$ transition state geometry.⁶ The IUPAC designation is $A_{xH}D_HD_N$, or more generally (to include cases where the electrofuge is not hydrogen), $A_nD_ED_N$. It often competes with the S_N2 mechanism (Sec. 10.A.i). With respect to the substrate, the difference between the two pathways is whether the species with the unshared pair attacks the carbon (and thus acts as a nucleophile) or the hydrogen (and thus acts as a base). As in the case of the S_N2 mechanism, the leaving group may be positive or neutral and the base may be negatively charged or neutral.

Evidence for the existence of the $E2$ mechanism includes (1) the reaction displays the proper second-order kinetics; (2) when the hydrogen is replaced by deuterium in second-order eliminations, there is an isotope effect of from 3 to 8, consistent with breaking of this

² See Neckers, D.C.; Kellogg, R.M.; Prins, W.L.; Schoustra, B. *J. Org. Chem.* **1971**, 36, 1838.

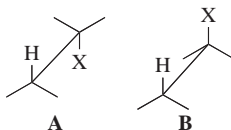
³ Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**. For reviews, see Gandler, J.R. in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, **1989**, pp. 733–797; Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, **1977**, pp. 153–221; More O'Ferrall, R.A. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, **1973**, pp. 609–675; Cockerill, A.F. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9; Elsevier, NY, **1973**, pp. 163–372; Saunders, Jr., W.H. *Acc. Chem. Res.* **1976**, 9, 19; Bordwell, F.G. *Acc. Chem. Res.* **1972**, 5, 374; Fry, A. *Chem. Soc. Rev.* **1972**, 1, 163; LeBel, N.A. *Adv. Alicyclic Chem.* **1971**, 3, 195; Bunnett, J.F. *Surv. Prog. Chem.* **1969**, 5, 53; in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, **1964**, the articles by Saunders, Jr., W.H. pp. 149–201 (eliminations in solution); and by Maccoll, A. pp. 203–240 (pyrolytic eliminations); Köbrich, G. *Angew. Chem. Int. Ed.* **1965**, 4, 49, pp. 59–63 (for the formation of triple bonds).

⁴ Thibblin, A. *Chem. Soc. Rev.* **1993**, 22, 427.

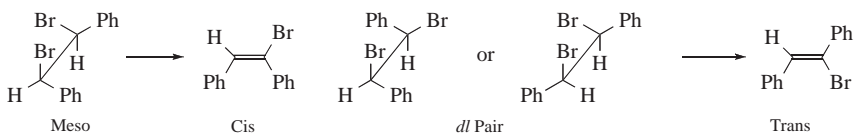
⁵ Roeterdink, W.G.; Rijs, A.M.; Janssen, M.H.M. *J. Am. Chem. Soc.* **2006**, 128, 576.

⁶ Schröder, S.; Jensen, F. *J. Org. Chem.* **1997**, 62, 253. See Wu, W.; Shaik, S.; Saunders, Jr., W.H. *J. Org. Chem.* **2010**, 75, 3722.

bond in the rate-determining step.⁷ However, neither of these results alone could prove an E2 mechanism, since both are compatible with other mechanisms also (e.g., see E1cB, Sec. 17.A.iii). The most compelling evidence for the E2 mechanism is found in stereochemical studies.⁸



As will be illustrated in the examples below, the E2 mechanism is stereospecific: The five atoms involved (including the base) in the transition state must be in one plane. There are two ways for this to happen. The H and X may be trans to one another (**A**) with a dihedral angle of 180° , or they may be cis (**B**) with a dihedral angle of 0° .⁹ Conformation **A** is called *antiperiplanar*, and this type of elimination, in which H and X depart in opposite directions, is called *anti elimination*. Conformation **B** is *syn periplanar*, and this type of elimination, with H and X leaving in the same direction, is called *syn elimination*. Many examples of both kinds have been discovered. In the absence of special effects (discussed below), anti elimination is usually greatly favored over syn elimination, probably because **A** is a staggered conformation (Sec. 4.O.i) and the molecule requires less energy to reach this transition state than it does to reach the eclipsed transition state **B**. Solvent effects play an important role in the conformational preference. A few of the many known examples of predominant or exclusive anti elimination follow:



1. Elimination of HBr from *meso*-1,2-dibromo-1,2-diphenylethane gave *cis*-2-bromostilbene, while the (+) or (–) isomer gave the *trans*-alkene. This stereospecific result, which was obtained in 1904,¹⁰ demonstrates that in this case elimination is anti. Many similar examples have been discovered since. Obviously, this type of experiment need not be restricted to compounds that have a *meso* form. Anti elimination requires that an erythro *dl* pair (or either isomer) give the *cis* alkene, and the threo *dl* pair (or either isomer) give the *trans* isomer. This result has been found many times. Anti elimination has also been demonstrated in cases where the electrofuge is not hydrogen. In the reaction of 2,3-dibromobutane with iodide

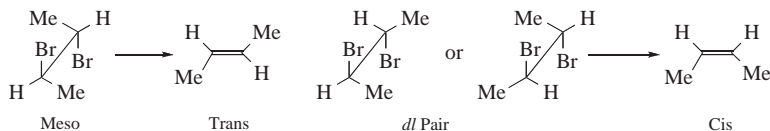
⁷ See Shiner, Jr., V.J.; Smith, M.L. *J. Am. Chem. Soc.* **1961**, *83*, 593. For a review of isotope effects, see Fry, A. *Chem. Soc. Rev.* **1972**, *1*, 163.

⁸ Bartsch, R.A.; Závada, J. *Chem. Rev.* **1980**, *80*, 453; Sicher, J. *Angew. Chem. Int. Ed.* **1972**, *11*, 200; *Pure Appl. Chem.* **1971**, *25*, 655; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**, pp. 105–163; Cockerill, A.F. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, pp. 217–235; More O'Ferrall, R.A. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, **1973**, pp. 630–640.

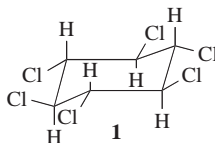
⁹ DePuy, C.H.; Morris, G.F.; Smith, J.S.; Smat, R.J. *J. Am. Chem. Soc.* **1965**, *87*, 2421.

¹⁰ Pfeiffer, P. *Z. Phys. Chem.* **1904**, *48*, 40.

ion, the two bromines are removed (**17-22**). Using iodide as a base in this manner is unusual nowadays, and common bases are discussed in several sections below, including Reaction **17-13**. In this case, the meso compound gave the trans alkene while the *dl* pair gave the cis:¹¹



- In open-chain compounds, rotation about C—C bonds usually lead to conformation in which H and X are antiperiplanar. However, in cyclic systems this is not always the case. There are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane: seven meso forms and a *dl* pair (see Sec. 4.G). Four of the meso compounds and the *dl* pair) were treated with base to initiate elimination. Only one of these (**1**) has no Cl that is trans to an H. Of the other isomers, the fastest elimination rate was about three times as fast as the slowest, but the rate for **1** was 7000 times slower than that of the slowest of the other isomers.¹² This result demonstrates that anti elimination is greatly favored over syn elimination, although the latter must be taking place on **1**, but very slowly, to be sure.

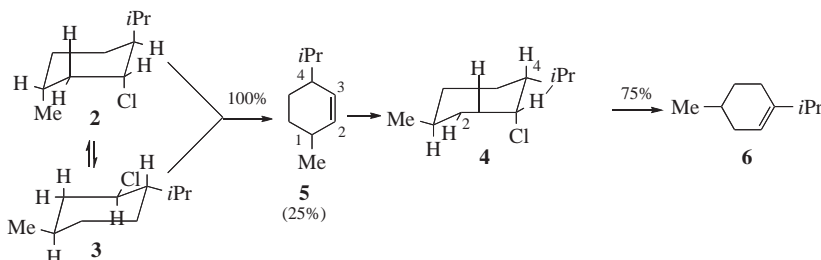


- The preceding result shows that elimination of HCl in a six-membered ring proceeds best when the H and X are trans to each other. Adjacent trans groups on a six-membered ring can be diaxial or diequatorial (Sec. 4.O.ii) and the molecule is generally free to adopt either conformation, although one may have a higher energy than the other. Antiperiplanarity of the leaving group and the proton on the adjacent carbon requires that they be diaxial, even if this is the conformation of higher energy. The results with menthyl and neomenthyl chlorides are easily interpretable on this basis. Menthyl chloride has two chair conformations, **2** and **3**. Compound **3**, in which the three substituents are all equatorial, is the more stable and less reactive. The more stable chair conformation of neomenthyl chloride is **4**, in which the chlorine is axial; there are axial hydrogen atoms on both C-2 and C-4. The results are the following: neomenthyl chloride gives rapid E2 elimination and the alkene produced is predominantly **6** (**6/5** ratio is ~ 3:1) in accord with *Zaitsev's rule* (see Reaction **12-2**, Sec. 17.B). Since an axial hydrogen is available on both sides, this factor does not control the direction of elimination and *Zaitsev's rule* is free to operate. However, for menthyl chloride, elimination is much slower and the product is entirely the *anti-Zaitsev* alkene **5**. It is slow because the unfavorable

¹¹ Winstein, S.; Pressman, D.; Young, W.G. *J. Am. Chem. Soc.* **1939**, 61, 1645.

¹² Cristol, S.J.; Hause, N.L.; Meek, J.S. *J. Am. Chem. Soc.* **1951**, 73, 674.

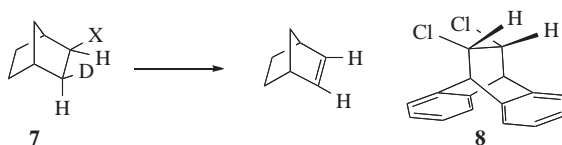
conformation (**2**) must be achieved before elimination can take place. There is an axial hydrogen only on this side as the product must be **5**.¹³



4. Anti elimination also occurs in the formation of triple bonds, as shown by elimination from *cis*- and *trans*-HO₂C-CH=C(Cl)CO₂H. In this case, the product in both cases is HO₂CC≡CCO₂H, but the *trans* isomer reacts ~ 50 times faster than the *cis* compound.¹⁴

Some examples of syn elimination have been found in molecules where H and X could not achieve an antiperiplanar conformation.

1. The deuterated norbornyl bromide (**7**, X = Br) gave 94% of the product containing no deuterium.¹⁵ Similar results were obtained with other leaving groups and with bicyclo [2.2.2] compounds.¹⁶ In these cases the *exo* X group cannot achieve a dihedral angle of 180° with the *endo* β hydrogen because of the rigid structure of the molecule. The dihedral angle here is ~ 120°. Syn elimination with a dihedral angle of ~ 0° is clearly preferred to anti elimination where the angle is restricted to ~ 120°.



2. Molecule **8** is a particularly graphic example of the need for a planar transition state. In **8**, each Cl has an adjacent hydrogen *trans* to it, and if planarity of leaving groups were not required, anti elimination could easily take place. However, the crowding of the rest of the molecule forces the dihedral angle to be ~ 120°, and elimination of HCl from **8** is much slower than from corresponding nonbridged compounds.¹⁷ Note that syn elimination from **8** is even less likely than anti elimination. Syn elimination can take place from the *trans* isomer of **8** (dihedral angle ~ 0°); this isomer reacted about eight times faster than **8**.¹⁷

¹³ Hughes, E.D.; Ingold, C.K.; Rose, J.B. *J. Chem. Soc.* **1953**, 3839.

¹⁴ Michael, A. *J. Prakt. Chem.* **1895**, 52, 308. See also, Marchese, G.; Naso, F.; Modena, G. *J. Chem. Soc. B* **1968**, 958.

¹⁵ Kwart, H.; Takeshita, T.; Nyce, J.L. *J. Am. Chem. Soc.* **1964**, 86, 2606.

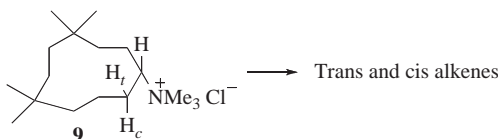
¹⁶ See Sicher, J.; Pánková, M.; Závada, J.; Kněžo, L.; Oráhovats, A. *Collect. Czech. Chem. Commun.* **1971**, 36, 3128; Bartsch, R.A.; Lee, J.G. *J. Org. Chem.* **1991**, 56, 212, 2579.

¹⁷ Cristol, S.J.; Hause, N.L. *J. Am. Chem. Soc.* **1952**, 74, 2193.

The examples given so far illustrate two points. (1) Anti elimination *requires* a dihedral angle of 180° . When this angle cannot be achieved, anti elimination is greatly slowed or prevented entirely. (2) For the simple systems so far discussed, syn elimination is not found to any significant extent unless anti elimination is greatly diminished by failure to achieve the 180° angle.

The concept of vinylogy was introduced in Section 6.B and in Reaction 10-68, category 4. Using this concept, a 1,2-elimination can be extended to give a 1,x-elimination when π bonds are incorporated between the carbon bearing the acidic proton and the leaving group (e.g., $\text{X}-\text{C}-\text{C}=\text{C}-\text{C}$, $\text{X}-\text{C}-\text{C}=\text{C}-\text{C}=\text{C}-\text{C}$ or $\text{X}-\text{C}-\text{C}\equiv\text{C}-\text{C}$).¹⁸

As noted in Section 4.Q.ii, six-membered rings are the only ones among rings of 4–13 members in which strain-free antiperiplanar conformations can be achieved. It is not surprising, therefore, that syn elimination is least common in six-membered rings. Cycloalkyltrimethylammonium hydroxides were subjected to elimination (Reaction 17-7) and the following percentages of syn elimination were found with each ring size: four-membered, 90%; five-membered, 46%; six-membered, 4% seven-membered, 31–37%.¹⁹ Note that the NMe_3^+ group has a greater tendency to syn elimination than do other common leaving groups (e.g., OTs, Cl, and Br).



Other examples of syn elimination have been found in medium-ring compounds, where both cis and trans alkenes are possible (Sec. 4.K.i). As an illustration, elimination of 1,1,4,4-tetramethyl-7-cyclodecyltrimethylammonium chloride (**9**)²⁰ gave mostly *trans*-but also some *cis*-tetramethylcyclodecenes as products. Note that *trans*-cyclodecenes, although stable, are less stable than the *cis* isomers. In order to determine the stereochemistry of the reaction, the elimination was repeated, this time using deuterated substrates. When **9** was deuterated in the *trans* position ($\text{H}_t = \text{D}$), there was a substantial isotope effect in the formation of *both* *cis* and *trans* alkenes, but when **9** was deuterated in the *cis* position ($\text{H}_c = \text{D}$), there was *no* isotope effect in the formation of either alkene. Since an isotope effect is expected for an E2 mechanism,²¹ these results indicated that *only* the *trans* hydrogen (H_t) was lost, whether the product was the *cis* or the *trans* isomer.²² This in turn means that *the cis isomer must have been formed by anti elimination and the trans isomer by syn elimination*. Anti elimination could take place from approximately the conformation shown, but for syn elimination the molecule must twist into a conformation in which the $\text{C}-\text{H}_t$ and $\text{C}-\text{NMe}_3^+$ bonds are syn periplanar. Other types of evidence have also demonstrated this remarkable result, called the syn–anti dichotomy.²³ The fact that syn

¹⁸ See Werner, C.; Hopf, H.; Dix, I.; Bubenitschek, P.; Jone, P.G. *Chemistry: European J.* **2007**, *13*, 9462.

¹⁹ Cooke, Jr., M.P.; Coke, J.L. *J. Am. Chem. Soc.* **1968**, *90*, 5556. See also, Coke, J.L.; Smith, G.D.; Britton, Jr., G. H. *J. Am. Chem. Soc.* **1975**, *97*, 4323.

²⁰ Závada, J.; Svoboda, M.; Sicher, J. *Collect. Czech. Chem. Commun.* **1968**, *33*, 4027.

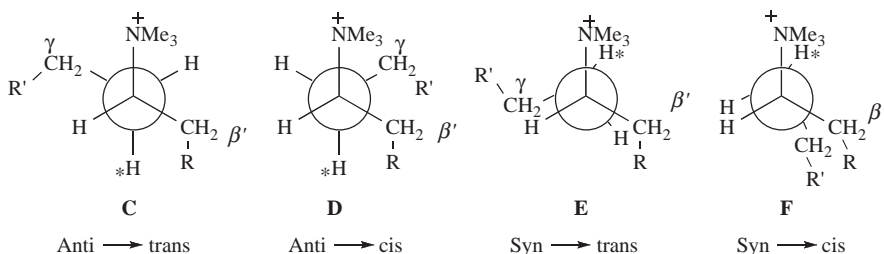
²¹ Other possible mechanisms [e.g., E1cB, Sec. 17.A.iii or α' , β -elimination (Reaction 17-8)], were ruled out in all these cases by other evidence.

²² This conclusion has been challenged by Coke, J.L. *Sel. Org. Transform* **1972**, *2*, 269.

²³ Sicher, J.; Závada, J. *Collect. Czech. Chem. Commun.* **1967**, *32*, 2122; Závada, J.; Sicher, J. *Collect. Czech. Chem. Commun.* **1967**, *32*, 3701. For a review, see Bartsch, R.A.; Závada, J. *Chem. Rev.* **1980**, *80*, 453.

elimination in this case predominates over anti (as indicated by the formation of trans-isomer in greater amounts than cis) has been explained by conformational factors.²⁴ The syn-anti dichotomy has also been found in other medium-ring systems (8–12 membered),²⁵ although the effect is greatest for 10-membered rings. With leaving groups,²⁶ the extent of this behavior decreases in the order $^+\text{NMe}_3 > \text{OTs} > \text{Br} > \text{Cl}$, which parallels steric requirements. When the leaving group is uncharged, syn elimination is favored by strong bases and by weakly ionizing solvents.²⁷

Syn elimination and the syn-anti dichotomy have also been found in open-chain systems, although to a lesser extent than in medium-ring compounds. For example, in the conversion of 3-hexyl-4-*d*-trimethylammonium ion to 3-hexene with potassium *sec*-butoxide, $\sim 67\%$ of the reaction followed the syn-anti dichotomy.²⁸ In general, syn elimination in open-chain systems is only important in cases where certain types of steric effect are present. One such type is compounds in which substituents are found on both the β' and the γ carbons (the unprimed letter refers to the branch in which the elimination takes place). The factors that cause these results are not completely understood, but the following conformational effects have been proposed as a partial explanation.²⁹ The two anti- and two syn-periplanar conformations are, for a quaternary ammonium salt:



In order for an E2 mechanism to take place, a base must approach the proton marked *. In **C**, this proton is shielded on both sides by R and R'. In **D**, the shielding is on only one side. Therefore, when anti elimination does take place in such systems, it should give more cis product than trans. Also, when the normal anti elimination pathway is hindered sufficiently to allow the syn pathway to compete, the anti \longrightarrow trans route should be diminished more than the anti \longrightarrow cis route. When syn elimination begins to appear, it seems clear that **E**, which is less eclipsed than **F**, should be the favored pathway and syn elimination should generally give the trans-isomer. In general, deviations from the synanti dichotomy are greater on the trans side than on the cis. Thus, trans-alkenes are formed partly or mainly by syn elimination, but *cis*-alkenes are formed entirely by anti elimination.

²⁴ Bartsch, R.A.; Závada, J. *Chem. Rev.* **1980**, 80, 453; Coke, J.L. *Sel. Org. Transform.* **1972**, 2, 269; Sicher, J. *Angew. Chem. Int. Ed.* **1972**, 11, 200; *Pure Appl. Chem.* **1971**, 25, 655.

²⁵ See Coke, J.L.; Mourning, M.C. *J. Am. Chem. Soc.* **1968**, 90, 5561.

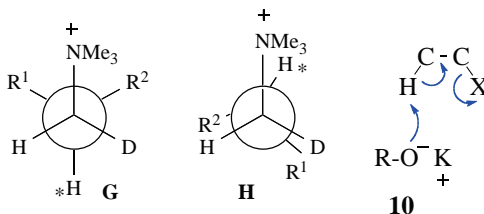
²⁶ See Sicher, J.; Jan, G.; Schlosser, M. *Angew. Chem. Int. Ed.* **1971**, 10, 926; Závada, J.; Pánková, M. *Collect. Czech. Chem. Commun.* **1980**, 45, 2171 and references cited therein.

²⁷ See Sicher, J.; Závada, J. *Collect. Czech. Chem. Commun.* **1968**, 33, 1278.

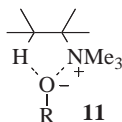
²⁸ Bailey, D.S.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* **1970**, 92, 6904. See Schlosser, M.; An, T.D. *Helv. Chim. Acta* **1979**, 62, 1194; Pánková, M.; Kocián, O.; Krupicka, J.; Závada, J. *Collect. Czech. Chem. Commun.* **1983**, 48, 2944.

²⁹ Chiao, W.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* **1977**, 99, 6699.

Predominant syn elimination has also been found in compounds of the form $R^1R^2CHCHDNMe_3^+$, where R^1 and R^2 are both bulky.³⁰ In this case, the conformation leading to syn elimination (**H**) is also less strained than **G**, which gives anti elimination. The **G** compound has three bulky groups (including NMe_3^+) in the *gauche* position to each other.



It was mentioned above that weakly ionizing solvents promote syn elimination when the leaving group is uncharged. This is probably caused by ion pairing, which is greatest in nonpolar solvents.³¹ Ion pairing can cause syn elimination with an uncharged leaving group by means of the transition state shown in **10**. This effect was graphically illustrated by elimination from 1,1,4,4-tetramethyl-7-cyclodecyl bromide.³² The ratio of syn to anti elimination when this compound was treated with *t*-BuOK in the nonpolar benzene was 55.0. When the crown ether dicyclohexano-18-crown-6 was added (this compound selectively removes K^+ from the $t-BuO^- K^+$ ion pair and thus leaves $t-BuO^-$ as a free ion), the syn/anti ratio decreased to 0.12. Large decreases in the syn/anti ratio on addition of the crown ether were also found with the corresponding tosylate and with other nonpolar solvents.³³ However, with positively charged leaving groups the effect is reversed. Here, ion pairing *increases* the amount of anti elimination.³⁴ In this case, a relatively free base (e.g., PhO^-) can be attracted to the leaving group (see **11**), putting it in a favorable position for attack on the syn β hydrogen, while ion pairing would reduce this attraction.



It can be concluded that anti elimination is generally favored in the E2 mechanism, but that steric (inability to form the antiperiplanar transition state), conformational, ion pairing, and other factors cause syn elimination to intervene (and even predominate) in some cases.

³⁰ Dohner, B.R.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* **1986**, 108, 245.

³¹ Bartsch, R.A.; Závada, J. *Chem. Rev.* **1980**, 80, 453; Bartsch, R.A. *Acc. Chem. Res.* **1975**, 8, 239.

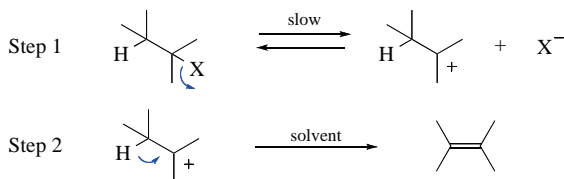
³² Svoboda, M.; Hapala, J.; Závada, J. *Tetrahedron Lett.* **1972**, 265.

³³ See Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* **1979**, 44, 3718; Croft, A.P.; Bartsch, R.A. *Tetrahedron Lett.* **1983**, 24, 2737; Kwart, H.; Gaffney, A.H.; Wilk, K.A. *J. Chem. Soc. Perkin Trans. 2* **1984**, 565.

³⁴ Borchardt, J.K.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* **1974**, 96, 3912.

17.A.ii. The E1 Mechanism

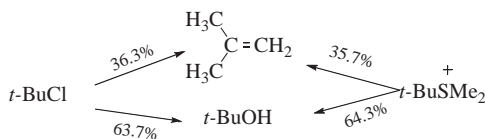
The E1 mechanism is a two-step process in which the rate-determining step is ionization of the substrate to give a carbocation that rapidly loses a β proton to a base, usually the solvent:



The IUPAC designation is $\text{D}_\text{N} + \text{D}_\text{E}$ (or $\text{D}_\text{N} + \text{D}_\text{H}$). This mechanism normally operates without an *added* base. Just as the E2 mechanism competes with the $\text{S}_\text{N}2$,³⁵ so the E1 mechanism competes with the $\text{S}_\text{N}1$. In fact, the first step of the E1 is exactly the same as that of the $\text{S}_\text{N}1$ mechanism. The second step differs in that the solvent pulls a proton from the β carbon of the carbocation rather than attacking it at the positively charged carbon, as in the $\text{S}_\text{N}1$ process. In a pure E1 reaction (without ion pairs, etc.), the product should be completely nonstereospecific, since bond rotation is possible in the carbocation before deprotonation.

Some of the evidence for the E1 mechanism is as follows:

1. The reaction exhibits first-order kinetics (in substrate) as expected. Of course, the solvent is not expected to appear in the rate equation, even if it were involved in the rate-determining step (Sec. 6.J.vi), but this point can be checked easily by adding a small amount of the conjugate base of the solvent. It is generally found that such an addition does not increase the rate of the reaction. If this more powerful base does not enter into the rate-determining step, it is unlikely that the solvent does. An example of an E1 mechanism with a rate-determining second step (proton transfer) has been reported.³⁶
2. If the reaction is performed on two molecules that differ only in the leaving group (e.g., $t\text{-BuCl}$ and $t\text{-BuSM}_2^+$), the rates should obviously be different, since they depend on the ionizing ability of the molecule. However, once the carbocation is formed, if the solvent and the temperature are the same, it should suffer the same fate in both cases. This means that the nature of the leaving group does not affect the second step, and *the ratio of elimination to substitution should be the same*. The compounds mentioned in the example were solvolyzed at 65.3°C in 80% aq ethanol with the following results:³⁷



³⁵ See Villano, S.M.; Eyet, N.; Lineberger, W.C.; Bierbaum, V.M. *J. Am. Chem. Soc.* **2009**, *131*, 8227.

³⁶ Baciocchi, E.; Clementi, S.; Sebastiani, G.V.; Ruzziconi, R. *J. Org. Chem.* **1979**, *44*, 32.

³⁷ Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J. *J. Chem. Soc.* **1948**, 2038.

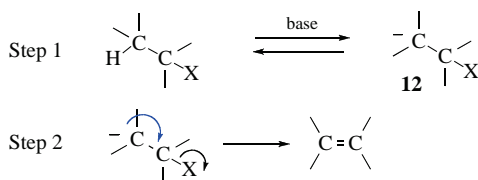
Although the rates were greatly different (as expected with such different leaving groups), the product ratios were the same, within 1%. If this had taken place by a second-order mechanism, the nucleophile would not be expected to have the same ratio of preference for attack at the β hydrogen compared to attack at a *neutral* chloride as for attack at the β hydrogen compared to attack at a *positive* SMe_2 group.

- Many reactions carried out under first-order conditions on systems where E2 elimination is anti proceed quite readily to give alkenes where a *cis* hydrogen must be removed, often in preference to the removal of a *trans* hydrogen. For example, menthyl chloride (**2**), which by the E2 mechanism gave only **5**, under E1 conditions gave 68% **6** and 32% **5**, since the steric nature of the hydrogen is no longer a factor here, and the more stable alkene (*Zaitsev's rule*, Reaction **12-2**) is predominantly formed.
- If carbocations are intermediates, rearrangements should occur with suitable substrates. These have often been found in elimination reactions performed under E1 conditions.

E1 reactions can involve ion pairs, just as is true for $\text{S}_{\text{N}}1$ reactions (Sec. 10A.iii).³⁸ This effect is naturally greatest for nondissociating solvents: It is least in water, greater in ethanol, and greater still in acetic acid. It has been proposed that the ion-pair mechanism (Sec. 10A.iii, category 1) extends to elimination reactions too, and that the $\text{S}_{\text{N}}1$, $\text{S}_{\text{N}}2$, E1, and E2 mechanisms possess in common an ion-pair intermediate, at least occasionally.³⁹

17.A.iii. The E1cB Mechanism⁴⁰

In the E1 mechanism, X leaves first and then H is removed. In the E2 mechanism, H is removed, which triggers the expulsion of X. There is a third possibility: The H is removed first to form **12**, and then X leaves. This reaction is a two-step process, called the E1cB mechanism,⁴¹ or the *carbanion mechanism*, since the intermediate is a carbanion, (**12**). The



name E1cB comes from the fact that it is the conjugate base of the substrate that is giving up the leaving group (see the $\text{S}_{\text{N}}1\text{cB}$ mechanism, Sec. 10.G.iii, category 1). The IUPAC designation is $\text{A}_{\text{n}}\text{D}_{\text{E}} + \text{D}_{\text{N}}$ or $\text{A}_{\text{xh}}\text{D}_{\text{H}} + \text{D}_{\text{N}}$ (see Sec. 9.F). Three limiting cases can be distinguished: (1) The carbanion returns to starting material faster than it forms product: step 1 is reversible; step 2 is slow. (2) Step 1 is the slow step, and formation of product is faster than return of the carbanion to starting material. In this case, step 1 is essentially

³⁸ See Thibblin, A. *J. Am. Chem. Soc.* **1987**, 109, 2071; *J. Phys. Org. Chem.* **1989**, 2, 15.

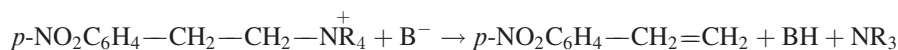
³⁹ Snee, R.A. *Acc. Chem. Res.* **1973**, 6, 46; Thibblin, A.; Sidhu, H. *J. Chem. Soc. Perkin Trans. 2* **1994**, 1423. See, however, McLennan, D.J. *J. Chem. Soc. Perkin Trans. 2* **1972**, 1577.

⁴⁰ Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, pp. 158–178; Hunter, D.H. *Intra-Sci. Chem. Rep.* **1973**, 7(3), 19; McLennan, D.J. *Q. Rev. Chem. Soc.* **1967**, 21, 490. For a general discussion, see Koch, H.F. *Acc. Chem. Res.* **1984**, 17, 137.

⁴¹ See Ryberg, P.; Matsson, O. *J. Org. Chem.* **2002**, 67, 811.

irreversible. (3) Step 1 is rapid, and the carbanion goes slowly to product. This case occurs only with the most stable carbanions. Here, too, step 1 is essentially irreversible. These cases have been given the designations: (1) (E1cB)_R, (2) (E1cB)_I (or E1cB_{irr}), and (3) (E1)_{anion}. Their characteristics are listed in Table 17.1.⁴² Investigations of the reaction order are generally not very useful (except for case 3, which is first order), because cases 1 and 2 are second order and thus difficult or impossible to distinguish from the E2 mechanism by this procedure.⁴³ The greatest likelihood of finding the E1cB mechanism is expected in substrates that have (a) a poor nucleofuge and (b) an acidic hydrogen. In addition, most investigations have concerned such substrates. The following is some of the evidence in support of the E1cB mechanism:

1. The first step of the (E1cB)_R mechanism involves a reversible exchange of protons between the substrate and the base. In that case, if deuterium is present in the base, recovered starting material should contain deuterium. This was found to be the case in the treatment of Cl₂C=CHCl with NaOD to give ClC≡CCl. When the reaction was stopped before completion, there *was* deuterium in the recovered alkene.⁴⁴ A similar result was found for pentahaloethanes.⁴⁵ These substrates are relatively acidic. In both cases, the electron-withdrawing halogens increase the acidity of the hydrogen, and in the case of trichloroethylene there is the additional factor that a hydrogen on an *sp*² carbon is more acidic than one on an *sp*³ carbon (Sec. 8.F, category 7). Thus, the E1cB mechanism is more likely to be found in eliminations yielding triple bonds than in those giving double bonds. Another likely place for the E1cB mechanism should be in reaction of a substrate like PhCH₂CH₂Br, since the carbanion is stabilized by resonance with the phenyl group. Nevertheless, no deuterium exchange was found here.⁴⁶ If this type of evidence is a guide, then it may be inferred that the (E1cB)_R mechanism is quite rare, at least for eliminations with common leaving groups (e.g., Br, Cl, or OTs), which yield C=C double bonds.
2. When the reaction shown was carried out in water containing acetohydroxamate buffers, a plot of the rate against the buffer concentration was curved and the rate leveled off at high buffer concentrations, indicating a change in rate-determining step.⁴⁷ This rules out an E2 mechanism, which has only one step.⁴⁸ When D₂O was used instead of H₂O as solvent, there was an initial inverse solvent isotope effect of 7.7 (the highest inverse solvent isotope effect yet reported).



⁴² This table, which appears in Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, p. 161, was adapted from a longer one in Bordwell, F.G. *Acc. Chem. Res.* **1972**, 5, 374, see p. 375.

⁴³ The (E1cB)_I mechanism cannot be distinguished from E2 by this means, because it has the identical rate law: Rate = *k*[substrate][B[−]]. The rate law for (E1cB)_R is different: Rate = *k*[substrate][B[−]]/[BH], but this is often not useful because the only difference is that the rate is also dependent (inversely) on the concentration of the conjugate acid of the base, and this is usually the solvent, so that changes in its concentration cannot be measured.

⁴⁴ Houser, J.J.; Bernstein, R.B.; Miekka, R.G.; Angus, J.C. *J. Am. Chem. Soc.* **1955**, 77, 6201.

⁴⁵ Hine, J.; Wiesboeck, R.; Ghirardelli, R.G. *J. Am. Chem. Soc.* **1961**, 83, 1219; Hine, J.; Wiesboeck, R.; Ramsay, O.B. *J. Am. Chem. Soc.* **1961**, 83, 1222.

⁴⁶ Skell, P.S.; Hauser, C.R. *J. Am. Chem. Soc.* **1945**, 67, 1661.

⁴⁷ Keeffe, J.R.; Jencks, W.P. *J. Am. Chem. Soc.* **1983**, 105, 265.

⁴⁸ For a borderline E1cB–E2 mechanism, see Jia, Z.S.; Rudzinski, J.; Paneth, P.; Thibblin, A. *J. Org. Chem.* **2002**, 67, 177.

TABLE 17.1 Kinetic Predictions for Base-Induced β -Eliminations^a

Mechanism	Kinetic ^b Order	β -Hydrogen Exchange Faster Than Elimination	General or Specific Base Catalysis	$\text{B:} + (\text{D}) \text{H}-\overset{\beta}{\underset{\alpha}{\text{C}}}-\overset{\gamma}{\text{C}}-\text{X} \longrightarrow \text{B-H} + \overset{\gamma}{\text{C}}=\overset{\beta}{\text{C}} + \text{X}^-$			
				$k_{\text{H}}/k_{\text{D}}$	Electron Withdrawal at C_{β} ^c	Electron Release at C_{α} ^c	Leaving Group Isotope Effect or Element Effect
(E1) _{anion}	1	Yes	General ^d	1.0	Rate decrease	Rate increase	Substantial
(E1cB) _R	2	Yes	Specific	1.0	Small rate increase	Small rate increase	Substantial
(E1cB) _{IP}	2	No	General ^f	1.0 \rightarrow 1.2	Small rate increase	Small rate increase	Substantial
(E1cB) _I	2	No	General	2 \rightarrow 8	Rate increase	Little effect	Small to negligible
E2 ^e	2	No	General	2 \rightarrow 8	Rate increase	Small rate increase	Small

^aSee Ref. 42.

^bAll mechanisms exhibit first-order kinetics in substrate.

^cEffect on rate assuming no change in mechanism is caused; steric factors upon substitution at C_{α} and rise to C_{β} have not been considered. The rate reductions are geared to substituent effects (e.g., those giving rise to Hammett reaction constants on β - and α -aryl substitution).

^dSpecific base catalysis predicted if extent of substrate ionization reduced from almost complete.

^eOnly transition states with considerable carbanion character considered in this table.

^fDepends on whether an ion pair assists in removal of leaving group.

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That is, the reaction took place faster in D_2O than in H_2O . This is compatible only with an $E1cB$ mechanism in which the proton-transfer step is not entirely rate determining. The isotope effect arises from a partitioning of the carbanion intermediate (**12**). This intermediate either can go to product or it can revert to starting compound, which requires taking a proton from the solvent. In D_2O , the latter process is slower (because the $O-D$ bond of D_2O , cleaves less easily than the $O-H$ bond of H_2O), reducing the rate at which **12** returns to starting compound. With the return reaction competing less effectively, the rate of conversion of **12** to product is increased.

3. Substrates containing acidic hydrogen atoms and poor leaving groups are most likely to proceed by the $E1cB$ mechanism. Compounds of the type ZCH_2CH_2OPh , where Z is an electron-withdrawing group (e.g., NO_2 , SMe_2^+ , $ArSO_2$, CN , CO_2R), belong to this category, because OPh is a very poor leaving group (Sec. 10.A.iii, category 1). There is much evidence to show that the mechanism here is indeed $E1cB$.⁴⁹ Isotope effects, measured for $MeSOCD_2CH_2OPh$ and $Me_2S^+CD_2CH_2OPh$ with $NaOD$ in D_2O , are ~ 0.7 . This is compatible with an $(E1cB)_R$ mechanism, but not with an $E2$ mechanism for which an isotope effect of perhaps 5 might be expected (of course, an $E1$ mechanism is precluded by the extremely poor nucleofugal ability of OPh). The fact that k_H/k_D is less than the expected value of 1 is attributable to solvent and secondary isotope effects. Among other evidence for an $E1cB$ mechanism in these systems is that changes in the identity of Z had a dramatic effect on the relative rates: a span of 10^{11} between NO_2 and COO^- . Note that elimination from substrates of the type $RCOCH_2CH_2Y$ is the reverse of *Michael-type addition* to $C=C$ bonds. Such addition involves initial attack by a nucleophile Y and subsequent protonation (see Sec. 15.A.ii). Thus the initial loss of a proton from substrates of this type (i.e., an $E1cB$ mechanism) is in accord with the principle of microscopic reversibility.⁵⁰ It may also be recalled that benzyne formation (Sec. 13.A.iii) can occur by such a process. It has been suggested that all base-initiated eliminations wherein the proton is activated by a strong electron-withdrawing group are $E1cB$ reactions,⁵¹ but there is evidence that this is not the case when there is a good nucleofuge, the mechanism is $E2$ even when strong electron-withdrawing groups are present.⁵² On the other hand, Cl^- has been found to be a leaving group in an $E1cB$ reaction.⁵³

Of the three cases of the $E1cB$ mechanism, the one most difficult to distinguish from $E2$ is $(E1cB)_I$. One way to make this distinction is to study the effect of a change in leaving group. This was done in the case of the three acenaphthylenes (**13**), where it was found that (1) the three rates were fairly similar, the largest being

⁴⁹ Cann, P.F.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* **1974**, 820. For other examples; see Kurazawa, J.; Leffek, K.T. *Can. J. Chem.* **1977**, *55*, 1696.

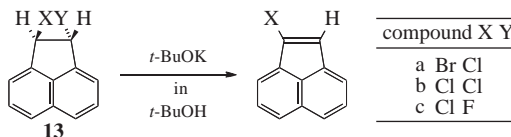
⁵⁰ Patai, S.; Weinstein, S.; Rappoport, Z. *J. Chem. Soc.* **1962**, 1741. See also, Hilbert, J.M.; Fedor, L.R. *J. Org. Chem.* **1978**, *43*, 452.

⁵¹ Bordwell, F.G. *Acc. Chem. Res.* **1972**, *5*, 374.

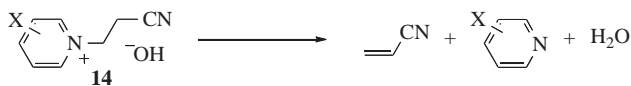
⁵² Banait, N.S.; Jencks, W.P. *J. Am. Chem. Soc.* **1990**, *112*, 6950.

⁵³ Öwegård, M.; McEwen, I.; Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* **1985**, *107*, 7494.

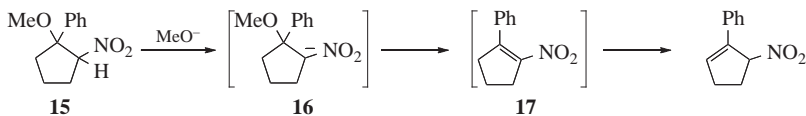
only about four times that of the smallest, and (2) in compound **c** ($X = \text{Cl}$, $Y = \text{F}$), the only product contained Cl and no F (i.e., only the poorer nucleofuge F departed



while Cl remained).⁵⁴ Result (1) rules out all the E1cB mechanisms except (E1cB)₁, because the others should all have considerable leaving group effects (Table 17.1). An ordinary E2 mechanism should also have a large leaving-group effect, but an E2 mechanism with substantial carbanionic character (see Section 17.A.iv) might not. However, no E2 mechanism can explain result (2), which can be explained by the fact that an α Cl is more effective than an α F in stabilizing the planar carbanion that remains when the proton is lost. Thus (as in the somewhat similar case of aromatic nucleophilic substitution, see Sec. 13.B.ii), when X^- leaves in the second step, the one that leaves is not determined by which is the better nucleofuge, but by which has had its β hydrogen removed.⁵⁵ Additional evidence for the existence of the (E1cB)₁ mechanism was the observation of a change in the rate-determining step in the elimination reaction of *N*-(2-cyanoethyl)pyridinium ions (**14**), treated with base, when X was changed.⁵⁶ Once again, the demonstration that two steps are involved precludes the one-step E2 mechanism. Note that pyridyl systems appear to be a borderline case, and it is not obvious if the reaction involves a carbanion intermediate (E1cb, $A_{\text{XH}}D_{\text{H}} + D_{\text{N}}$) or if the reaction proceeds by concerted loss of a proton and the halide (E2, $A_{\text{N}}D_{\text{E}}D_{\text{N}}$) with attack by the base.⁵⁷



4. An example of an (E1)_{anion} mechanism has been found with the substrate **15**, which when treated with methoxide ion undergoes elimination to **17**, which is unstable under the reaction conditions and rearranges as shown.⁵⁸ Among the evidence for the proposed mechanism in this case were kinetic and isotope-effect results, as well as the spectral detection of **16**.⁵⁹



⁵⁴ Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* **1982**, 47, 3237.

⁵⁵ See Gula, M.J.; Vitale, D.E.; Dostal, J.M.; Trometer, J.D.; Spencer, T.A. *J. Am. Chem. Soc.* **1988**, 110, 4400; Garay, R.O.; Cabaleiro, M.C. *J. Chem. Res. (S)*, **1988**, 388; Gandler, J.R.; Storer, J.W.; Ohlberg, D.A.A. *J. Am. Chem. Soc.* **1990**, 112, 7756.

⁵⁶ Bunting, J.W.; Toth, A.; Heo, C.K.M.; Moors, R.G. *J. Am. Chem. Soc.* **1990**, 112, 8878. See also, Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* **1991**, 113, 6950.

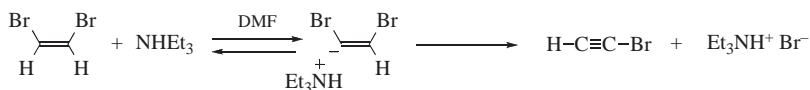
⁵⁷ Alunni, S.; De Angelis, F.; Ottavi, L.; Papavasileiou, M.; Tarantelli, F. *J. Am. Chem. Soc.* **2005**, 127, 15151. See also, Mosconi, E.; De Angelis, F.; Belpassi, L.; Tarantelli, F.; Alunni, S. *Eur. J. Org. Chem.* **2009**, 5501.

⁵⁸ Bordwell, F.G.; Yee, K.C.; Knipe, A.C. *J. Am. Chem. Soc.* **1970**, 92, 5945.

⁵⁹ See Berndt, A. *Angew. Chem. Int. Ed.* **1969**, 8, 613; Albeck, M.; Hoz, S.; Rappoport, Z. *J. Chem. Soc. Perkin Trans. 2* **1972**, 1248; **1975**, 628.

5. In many eliminations to form C=O and C≡N bonds, the initial step is loss of a positive group (normally a proton) from the oxygen or nitrogen. These may also be regarded as E1cB processes.

There is evidence that some E1cB mechanisms can involve carbanion ion pairs, for example,⁶⁰



This case is designated (E1cB)_{ip}; its characteristics are shown in Table 17.1.

17.A.iv. The E1–E2–E1cB Spectrum

In the three mechanisms so far considered, the similarities are greater than the differences. In each case, there is a leaving group that comes off with its pair of electrons and another group (usually hydrogen) that comes off without them. The only difference is in the order of the steps. It is now generally accepted that there is a spectrum of mechanisms ranging from one extreme, in which the leaving group departs well before the proton (pure E1), to the other extreme, in which the proton is removed first and then, after some time, the leaving group follows (pure E1cB). The *pure* E2 case would be somewhere in the middle, with both groups leaving simultaneously. However, most E2 reactions are not exactly in the middle, but somewhere to one side or the other. For example, the nucleofuge might depart just before the proton. This case may be described as an E2 reaction with a small amount of E1 character. The concept can be expressed by the question: In the transition state, which bond (C–H or C–X) has undergone more cleavage?⁶¹

Note that in both E1 and E2 reactions, removal of the hydrogen atom is an acid–base reaction, requiring a base. A stronger base is required for the E2, and a weaker base for E1. Further, the E1 reaction requires a solvent that facilitates ionization to a carbocation (e.g., aqueous media), whereas the E2 reaction is usually done in a protic solvent (e.g., an alcohol).

One way to determine just where a given reaction stands on the E1–E2–E1cB spectrum is to study isotope effects, which ought to tell something about the behavior of bonds in the transition state.⁶² For example, CH₃CH₂NMe₃⁺ showed a nitrogen isotope effect (k^{14}/k^{15}) of 1.017, while PhCH₂CH₂NMe₃⁺ gave a corresponding value of 1.009.⁶³ It would be expected that the phenyl group would move the reaction toward the E1cB side of the line, which means that for this compound the C–N bond is not as greatly broken in the

⁶⁰ Kwok, W.K.; Lee, W.G.; Miller, S.I. *J. Am. Chem. Soc.* **1969**, *91*, 468. See also, Petrillo, G.; Novi, M.; Garbarino, G.; Dell'Erba, C.; Mugnoli, A. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1291.

⁶¹ See Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, pp. 178–189; Saunders, Jr., W.H. *Acc. Chem. Res.* **1976**, *9*, 19; Bunnett, J.F. *Surv. Prog. Chem.* **1969**, *5*, 53; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**, pp. 47–104; Bordwell, F.G. *Acc. Chem. Res.* **1972**, *5*, 374.

⁶² Fry, A. *Chem. Soc. Rev.* **1972**, *1*, 163. See also, Hasan, T.; Sims, L.B.; Fry, A. *J. Am. Chem. Soc.* **1983**, *105*, 3967; Pulay, A.; Fry, A. *Tetrahedron Lett.* **1986**, *27*, 5055.

⁶³ Ayrey, G.; Bourns, A.N.; Vyas, V.A. *Can. J. Chem.* **1963**, *41*, 1759. Also see, Simon, H.; Müllhofer, G. *Pure Appl. Chem.* **1964**, *8*, 379, 536; Smith, P.J.; Bourns, A.N. *Can. J. Chem.* **1970**, *48*, 125.

transition state as it is for the unsubstituted one. The isotope effect bears this out, for it shows that in the phenyl compound, the mass of the nitrogen has less effect on the reaction rate than it does in the unsubstituted compound. Similar results have been obtained with SR_2^+ leaving groups by the use of $^{32}\text{S}/^{34}\text{S}$ isotope effects⁶⁴ and with Cl ($^{35}\text{Cl}/^{37}\text{Cl}$).⁶⁵ The position of reactions along the spectrum has also been studied from the other side of the newly forming double bond by the use of H/D and H/T isotope effects,⁶⁶ although interpretation of these results is clouded by the fact that β hydrogen isotope effects are expected to change smoothly from small to large to small again as the degree of transfer of the β hydrogen from the β carbon to the base increases⁶⁷ (in Sec. 6.B, it was noted that isotope effects are greatest when the proton is half-transferred in the transition state), by the possibility of secondary isotope effects (e.g., the presence of a β deuterium or tritium may cause the leaving group to depart more slowly), and by the possibility of tunneling.⁶⁸ Other isotope-effect studies have involved labeled α or β carbon, labeled α hydrogen, or labeled base.⁵⁸

Another way to study the position of a given reaction on the spectrum involves the use of β aryl substitution. Since a positive *Hammett* ρ value is an indication of a negatively charged transition state, the ρ value for substituted β aryl groups should increase as a reaction moves from E1-to-E1cB-like along the spectrum. This has been shown to be the case in a number of studies;⁶⁹ for example, ρ values of $\text{ArCH}_2\text{CH}_2\text{X}$ increase as the leaving-group ability of X decreases. A typical set of ρ values was X = I, 2.07; Br, 2.14; Cl, 2.61; SMe_2^+ , 2.75; F, 3.12.⁷⁰ As seen previously, decreasing leaving-group ability correlates with increasing E1cB character.

Still another method measures volumes of activation.⁷¹ These are negative for E2 and positive for E1cB mechanisms. Measurement of the activation volume therefore provides a continuous scale for deciding just where a reaction lies on the spectrum.

17.A.v. The E2C Mechanism⁷²

Certain alkyl halides and tosylates undergo E2 eliminations faster when treated with such weak bases as Cl^- in polar aprotic solvents or PhS^- than with the usual E2 strong bases (e.g., RO^- in ROH).⁷³ In order to explain these results, it was proposed⁷⁴ that there is a spectrum⁷⁵ of E2 transition states in which the base can interact in the transition state with the α carbon, as well as with the β hydrogen. At one end of this spectrum is a mechanism (called E2C) in which, in the transition state, the base interacts mainly with the carbon. The

⁶⁴ Wu, S.; Hargreaves, R.T.; Saunders, Jr., W.H. *J. Org. Chem.* **1985**, *50*, 2392 and references cited therein.

⁶⁵ Grout, A.; McLennan, D.J.; Spackman, I.H. *J. Chem. Soc. Perkin Trans. 2* **1977**, 1758.

⁶⁶ See Thibblin, A. *J. Am. Chem. Soc.* **1988**, *110*, 4582; Smith, P.J.; Amin, M. *Can. J. Chem.* **1989**, *67*, 1457.

⁶⁷ However, see Blackwell, L.F. *J. Chem. Soc. Perkin Trans. 2* **1976**, 488.

⁶⁸ See Miller, D.J.; Saunders, Jr., W.H. *J. Org. Chem.* **1981**, *46*, 4247 and previous papers in this series. See also, Amin, M.; Price, R.C.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* **1990**, *112*, 4467.

⁶⁹ Blackwell, L.F.; Buckley, P.D.; Jolley, K.W.; MacGibbon, A.K.H. *J. Chem. Soc. Perkin Trans. 2* **1973**, 169;

Smith, P.J.; Tsui, S.K. *J. Am. Chem. Soc.* **1973**, *95*, 4760; *Can. J. Chem.* **1974**, *52*, 749.

⁷⁰ DePuy, C.H.; Bishop, C.A. *J. Am. Chem. Soc.* **1960**, *82*, 2532, 2535.

⁷¹ Brower, K.R.; Muhsin, M.; Brower, H.E. *J. Am. Chem. Soc.* **1976**, *98*, 779. For a review, see van Eldik, R.; Asano, T.; le Noble, W.J. *Chem. Rev.* **1989**, *89*, 549.

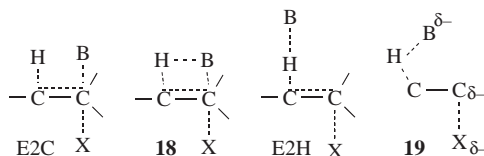
⁷² McLennan, D.J. *Tetrahedron* **1975**, *31*, 2999; Ford, W.T. *Acc. Chem. Res.* **1973**, *6*, 410.

⁷³ See Hayami, J.; Ono, N.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1628.

⁷⁴ Parker, A.J.; Ruane, M.; Biale, G.; Winstein, S. *Tetrahedron Lett.* **1968**, 2113.

⁷⁵ This is apart from the E1-E2-E1cB spectrum.

E2C mechanism is characterized by strong nucleophiles that are weak bases. At the other extreme is the normal E2 mechanism, here called E2H to distinguish it from E2C, characterized by strong bases. Transition state **18** represents a transition state between these extremes. Additional evidence⁷⁶ for the E2C mechanism is derived from *Brønsted equation* considerations (Sec. 8.D), from substrate effects, from isotope effects, and from the effects of solvents on rates.



However, the E2C mechanism has been criticized, and it has been contended that all the experimental results can be explained by the normal E2 mechanism.⁷⁷ McLennan and Lim⁷⁸ suggested that the transition state is that shown as **19**. An ion-pair mechanism has also been proposed.⁷⁹ Although the actual mechanisms involved may be a matter of controversy, there is no doubt that a class of elimination reactions exists that is characterized by second-order attack by weak bases.⁸⁰ These reactions also have the following general characteristics:⁸¹ (1) they are favored by good leaving groups; (2) they are favored by polar aprotic solvents; (3) the reactivity order is tertiary > secondary > primary, the opposite of the normal E2 order (Sec. 17.D.i); (4) the elimination is always anti (syn elimination is not found), but in cyclohexyl systems, a diequatorial anti elimination is about as favorable as a diaxial anti elimination (unlike the normal E2 reaction, Sec. 17.A.i, categories 2,3); (5) they follow *Zaitsev's rule* (see below), where this does not conflict with the requirement for anti elimination.

17.B. REGIOCHEMISTRY OF THE DOUBLE BOND

With some substrates, a β hydrogen is present on only one carbon and (barring rearrangements) there is no doubt as to the identity of the product. For example, PhCH₂CH₂Br can give only PhCH=CH₂. However, in many other cases two or three alkenyl products are possible. In the simplest such case, a *sec*-butyl compound can give either 1- or 2-butene. There are a number of rules that enable a prediction, in many instances, of which product will predominantly form.⁸²

1. No matter the mechanism, a double bond does not go to a bridgehead carbon unless the ring sizes are large enough (*Bredt's rule*, see Sec. 4.P.iii). This means, for

⁷⁶ See Kwart, H.; Wilk, K.A. *J. Org. Chem.* **1985**, *50*, 3038.

⁷⁷ See Bunnett, J.F.; Migdal, C.A. *J. Org. Chem.* **1989**, *54*, 3037, 3041 and references cited therein.

⁷⁸ McLennan, D.J.; Lim, G. *Aust. J. Chem.* **1983**, *36*, 1821. For an opposing view, see Kwart, H.; Gaffney, A. *J. Org. Chem.* **1983**, *48*, 4502.

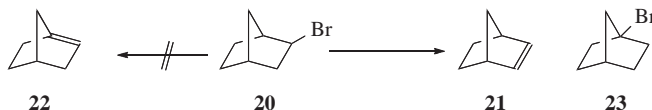
⁷⁹ Ford, W.T. *Acc. Chem. Res.* **1973**, *6*, 410.

⁸⁰ For convenience, these are called E2C reactions, although the actual mechanism is in dispute.

⁸¹ Beltrame, P.; Biale, G.; Lloyd, D.J.; Parker, A.J.; Ruane, M.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2240; Beltrame, P.; Ceccon, A.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2315.

⁸² See Hückel, W.; Hanack, M. *Angew. Chem. Int. Ed.* **1967**, *6*, 534.

example, not only that **20** gives only **21** and not **22** (indeed **22** is not a known compound), but also that **23** does *not* undergo elimination.



- No matter the mechanism, if there is a double bond (C=C or C=O) or an aromatic ring already in the molecule that can be in conjugation with the new double bond, the conjugated product usually predominates, sometimes even when the stereochemistry is unfavorable (for an exception, see Sec. 17.C).
- In the E1 mechanism, the leaving group is gone before the choice is made as to which direction the new double bond takes. Therefore the direction is determined almost entirely by the relative stabilities of the two (or three) possible alkenes. In such cases, *Zaitsev's rule*⁸³ operates. This rule states that *the double bond goes mainly toward the most highly substituted carbon*. That is, 3-bromo-2,3-dimethylpentane gives more 2,3-dimethyl-2-pentene than either 3,4-dimethyl-2-pentene or 2-ethyl-3-methyl-1-butene. Thus *Zaitsev's rule* predicts that the alkene predominantly formed will be the one with the largest possible number of alkyl groups on the C=C carbons, and in most cases this is what is found. From heat of combustion data (see Sec. 1.L), it is known that alkene stability increases with alkyl substitution, although just why this should be is a matter of conjecture. The most common explanation is hyperconjugation. For E1 eliminations, *Zaitsev's rule* governs the orientation whether the leaving group is neutral or positive, since, as already mentioned, the leaving group is not present when the choice of direction is made. This statement does not hold for E2 eliminations, and it may be mentioned here, for contrast with later results, that E1 elimination of $\text{Me}_2\text{CHCHMeSMe}_2^+$ gave 91% of the *Zaitsev* product and 9% of the other.⁸⁴ However, there *are* cases in which the leaving group affects the direction of the double bond in E1 eliminations.⁸⁵ This may be attributed to ion pairs; that is, the leaving group is not completely gone when the hydrogen departs. *Zaitsev's rule* breaks down in cases where the non-*Zaitsev* product is more stable for steric reasons. For example, E1 or E1-like eliminations of 1,2-diphenyl-2-X-propanes ($\text{PhMeCXCH}_2\text{Ph}$) were reported to give $\sim 50\%$ $\text{CH}_2=\text{CPhCH}_2\text{Ph}$, despite the fact that the double bond of the *Zaitsev* product ($\text{PhMeC}=\text{CHPh}$) is conjugated with two benzene rings.⁸⁶
- For the anti E2 mechanism, a trans β proton is necessary; if this is available in only one direction, that is the way the double bond will form. Because of the free rotation in acyclic systems (except where steric hindrance is great), this is a factor only in cyclic systems. Where trans β hydrogen atoms are available on two or three carbons, two types of behavior are found, depending on substrate structure and the nature of the leaving group. Some compounds follow *Zaitsev's rule* and give predominant formation of the most highly substituted alkene, but others follow *Hofmann's rule*: *The double bond goes mainly toward the least highly substituted carbon*. Although many exceptions are known, the following general statements can be made: In most

⁸³ Often given the German spelling: Saytzeff, or Saytseff, or Saytzev.

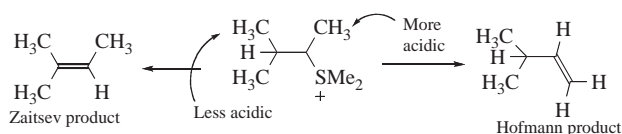
⁸⁴ de la Mare, P.B.D. *Prog. StereoChem.* **1954**, 1, 112.

⁸⁵ See Cram, D.J.; Sahyun, M.R.V. *J. Am. Chem. Soc.* **1963**, 85, 1257.

⁸⁶ Ho, I.; Smith, J.G. *Tetrahedron* **1970**, 26, 4277.

cases, compounds containing uncharged nucleofuges (those that come off as negative ions) follow *Zaitsev's rule*, just as they do in E1 elimination, no matter what the structure of the substrate. However, elimination from compounds with charged nucleofuges (e.g., NR_3^+ , SR_2^+ , those that come off as neutral molecules), follow *Hofmann's rule* if the substrate is acyclic,⁸⁷ but *Zaitsev's rule* if the leaving group is attached to a six-membered ring.⁸⁸

Much work has been devoted to searching for reasons for the differences in orientation. Since *Zaitsev* orientation almost always gives the thermodynamically more stable isomer, we must explain why in some cases the less stable *Hofmann* product predominates. Three explanations have been offered for the change in orientation in acyclic systems with a change from uncharged to charged nucleofuges. The first of these⁸⁹ is that *Hofmann orientation* is caused by the fact that the acidity of the β hydrogen is decreased by the presence of the electron-donating alkyl groups. For example, under E2 conditions $\text{Me}_2\text{CHCHMeSMe}_2^+$ gives more of the



Hofmann product; it is the more acidic hydrogen that is removed by the base. Of course, the CH_3 hydrogen atoms would still be more acidic than the Me_2CH hydrogen even if a neutral leaving group were present, but the explanation presented was that acidity matters with charged and not with neutral leaving groups, because the charged groups exert a strong electron-withdrawing effect, making differences in acidity greater than they are with the less electron-withdrawing neutral groups.^{85,90} According to this, the change to a positive leaving group causes the mechanism to shift toward the E1cB end of the spectrum, where there is more $\text{C}-\text{H}$ bond breaking in the rate-determining step and where, consequently, acidity is more important. In this view, when there is a neutral leaving group, the mechanism is more E1 -like, $\text{C}-\text{X}$ bond breaking is more important, and alkene stability determines the direction of the new double bond.

The third explanation is completely different: Field effects are unimportant, and the difference in orientation is largely a steric effect caused by the fact that charged groups are usually larger than neutral ones. A CH_3 group is more open to attack than a CH_2R group and a CHR_2 group is still less easily attacked. Of course, these considerations also apply when the leaving group is neutral, but they are proposed to be much less important here because the neutral groups are smaller and do not block access to the hydrogen atoms as much. Experiments showed that *Hofmann elimination* increases with the size of the leaving group. Thus the percentage of 1-ene obtained from $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHXCH}_3$ was as follows (X listed in order of

⁸⁷ See Feit, I.N.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* **1970**, *92*, 5615.

⁸⁸ See Booth, H.; Franklin, N.C.; Gidley, G.C. *J. Chem. Soc. C*, **1968**, 1891; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**, pp. 192–193.

⁸⁹ See Ingold, C.K. *Proc. Chem. Soc.* **1962**, 265.

⁹⁰ Bunnett, J.F. *Surv. Prog. Chem.* **1969**, 5, 53.

increasing size): Br, 31%; I, 30%; OTs, 48%; SMe_2^+ , 87%; SO_2Me , 89%; NMe_3^+ , 98%.⁹¹ *Hofmann elimination* was also shown to increase with increase in bulk of the substrate.⁹² With large enough compounds, *Hofmann orientation* can be obtained even with halides. *tert*-Amyl bromide gave 89% of the *Hofmann* product, for example. Even those who believe in the acidity explanations concede that these steric factors operate in extreme cases.⁹³

There is one series of results incompatible with the steric explanation that E2 elimination from the four 2-halopentanes gave the following percentages of 1-pentene: F, 83%; Cl, 37%; Br, 25%; I, 20%.⁹⁴ The same order was found for the four 2-halohexanes.⁹⁵ Although there is some doubt about the relative steric requirements of Br, Cl, and I, there is no doubt that F is the smallest of the halogens, and if the steric explanation were the only valid one, the fluoroalkanes could not give predominant *Hofmann orientation*. Another result that argues against the steric explanation is the effect of changing the nature of the base. An experiment in which the effective size of the base was kept constant while its basicity was increased (by using as bases a series of $\text{XC}_6\text{H}_4\text{O}^-$ ions) showed that the percentage of *Hofmann elimination* increased with increasing base strength, although the size of the base did not change.⁹⁶ These results are in accord with the previous explanation, since an increase in base strength moves an E2 reaction closer to the E1cB end of the spectrum. In further experiments, a large series of bases of different kinds was shown to obey linear free energy relationships between basicity and percentage of *Hofmann elimination*.⁹⁷ Certain very large bases (e.g., 2,6-di-*tert*-butyl-phenoxide) did not obey the relationships and steric effects are important in these cases. How large the base must be before steric effects are observed depends on the pattern of alkyl substitution in the substrate, but not on the nucleofuge.⁹⁸ One further result may be noted. In the gas phase, elimination of H and BrH^+ or H and ClH^+ using Me_3N as the base predominantly followed *Hofmann's rule*,⁹⁹ although BrH^+ and ClH^+ are not very large.

5. Only a few investigations on the orientation of syn E2 eliminations have been carried out, but these show that *Hofmann orientation* is greatly favored over *Zaitsev*.¹⁰⁰
6. In the E1cB mechanism, the question of orientation seldom arises because the mechanism is generally found only where there is an electron-withdrawing group in the β position, and that is where the double bond goes.

⁹¹ Brown, H.C.; Wheeler, O.H. *J. Am. Chem. Soc.* **1956**, 78, 2199.

⁹² See Bartsch, R.A. *J. Org. Chem.* **1970**, 35, 1334; Charton, M. *J. Am. Chem. Soc.* **1975**, 97, 6159.

⁹³ See Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* **1960**, 4054.

⁹⁴ Saunders, Jr., W.H.; Fahrenholtz, S.R.; Caress, E.A.; Lowe, J.P.; Schreiber, M.R. *J. Am. Chem. Soc.* **1965**, 87, 3401; Brown, H.C.; Klimisch, R.L. *J. Am. Chem. Soc.* **1966**, 88, 1425.

⁹⁵ Bartsch, R.A.; Bunnett, J.F. *J. Am. Chem. Soc.* **1968**, 90, 408.

⁹⁶ Froemsdorf, D.H.; Robbins, M.D. *J. Am. Chem. Soc.* **1967**, 89, 1737. See also, Feit, I.N.; Breger, I.K.; Capobianco, A.M.; Cooke, T.W.; Gitlin, L.F. *J. Am. Chem. Soc.* **1975**, 97, 2477.

⁹⁷ Bartsch, R.A.; Roberts, D.K.; Cho, B.R. *J. Org. Chem.* **1979**, 44, 4105.

⁹⁸ Bartsch, R.A.; Read, R.A.; Larsen, D.T.; Roberts, D.K.; Scott, K.J.; Cho, B.R. *J. Am. Chem. Soc.* **1979**, 101, 1176.

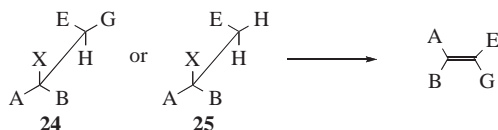
⁹⁹ Angelini, G.; Lilla, G.; Speranza, M. *J. Am. Chem. Soc.* **1989**, 111, 7393.

¹⁰⁰ Sicher, J.; Svoboda, M.; Pánková, M.; Závada, J. *Collect. Czech. Chem. Commun.* **1971**, 36, 3633; Bailey, D.S.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* **1970**, 92, 6904.

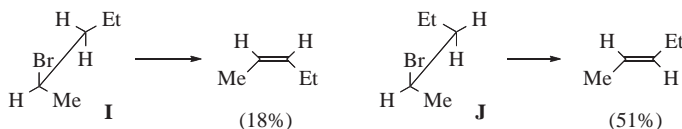
7. As already mentioned, E2C reactions show a strong preference for Zaitsev orientation.¹⁰¹ In some cases, this can be put to preparative use. For example, the compound $\text{PhCH}_2\text{CHOTsCHMe}_2$ gave $\sim 98\%$ $\text{PhCH}=\text{CHCHMe}_2$ under the usual E2 reaction conditions ($t\text{-BuOK}$ in $t\text{-BuOH}$). In this case, the double bond goes to the side with more hydrogen atoms because on that side it will be able to conjugate with the benzene ring. However, with the weak base $\text{Bu}_4\text{N}^+ \text{Br}^-$ in acetone the *Zaitsev* product ($\text{PhCH}_2\text{CH}=\text{CMe}_2$) was formed in 90% yield.¹⁰²

17.C. STEREOCHEMISTRY OF THE DOUBLE BOND

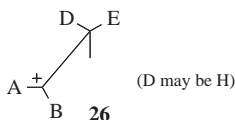
When elimination takes place on a compound of the form $\text{CH}_3\text{—CABX}$ or CHAB—CGGX , the new alkene does not have cis–trans isomerism, but for compounds of the form CHEG—CABX (E and G *not* H) (**24**) and $\text{CH}_2\text{E—CABX}$ (**25**), cis and trans isomers are possible. When the anti E2 mechanism is in operation, **24** gives the isomer



arising from trans orientation of X and H. As seen previously (Sec. 17.A.i), an erythro compound gives the cis alkene and a threo compound gives the trans. For **25**, two conformations are possible for the transition state; these lead to different isomers and often both are obtained. However, the one that predominates is often determined by an eclipsing effect.¹⁰³ For example, *Zaitsev elimination* from 2-bromopentane can occur as follows: In conformation **I**, the ethyl group is between Br and Me, while in **J** it is between Br and H. This means that **J** is more stable, and most of the elimination should occur from this conformation. This is indeed what happens, and 51% of the trans isomer is formed (with KOEt) compared to 18% of the cis (the rest is the *Hofmann* product).¹⁰⁴ These effects become larger with increasing size of groups A, B, and E.



However, eclipsing effects are not the only factors that affect the cis/trans ratio in anti E2 eliminations. Other factors are the nature of the leaving group, the base, the solvent, and the substrate. Not all of these effects are completely understood.¹⁰⁵



¹⁰¹ Muir, D.M.; Parker, A.J. *J. Org. Chem.* **1976**, *41*, 3201.

¹⁰² Lloyd, D.J.; Muir, D.M.; Parker, A.J. *Tetrahedron Lett.* **1971**, 3015.

¹⁰³ See Cram, D.J.; Greene, F.D.; DePuy, C.H. *J. Am. Chem. Soc.* **1956**, *78*, 790; Cram, D.G. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, **1956**, pp. 338–345.

¹⁰⁴ Brown, H.C.; Wheeler, O.H. *J. Am. Chem. Soc.* **1956**, *78*, 2199.

¹⁰⁵ Alunni, S.; Baciocchi, E. *J. Chem. Soc. Perkin Trans. 2* **1976**, 877; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**, pp. 165–193.

For E1 eliminations, if there is a free carbocation (**26**), it is free to rotate, and no matter the geometry of the original compound, the more stable situation is the one where the larger of the D—E pair is opposite the smaller of the A—B pair and the corresponding alkene should form. If the carbocation is not completely free, then to that extent, E2-type products are formed. Similar considerations apply in E1cB eliminations.¹⁰⁶

17.D. REACTIVITY

In this section, we examine the effects of changes in the substrate, base, leaving group, and medium on (1) overall reactivity, (2) E1 versus E2 versus E1cB,¹⁰⁷ and (3) elimination versus substitution.

17.D.i. Effect of Substrate Structure

1. *Effect on Reactivity.* The carbon containing the nucleofuge (X) is referred to as the α carbon and the carbon that loses the positive species (usually a proton) as the β carbon. Groups attached to the α or β carbons can exert at least four kinds of influence:
 - a. They can stabilize or destabilize the incipient double bond (both α and β groups).
 - b. They can stabilize or destabilize an incipient negative charge, affecting the acidity of the proton (β groups only).
 - c. They can stabilize or destabilize an incipient positive charge (α groups only).
 - d. They can exert steric effects (e.g., eclipsing effects) (both α and β groups).

Effects *a* and *d* can apply in all three mechanisms, although steric effects are greatest for the E2 mechanism. Effect *b* does not apply in the E1 mechanism, and effect *c* does not apply in the E1cB mechanism. Groups such as Ar and C=C increase the rate by any mechanism, except perhaps when formation of the C=C bond is not the rate-determining step, whether they are α or β (effect *a*). Electron-withdrawing groups increase the acidity when in the β position, but have little effect in the α position unless they also conjugate with the double bond. Thus Br, Cl, CN, Ts, NO₂, CN, and SR in the β position all increase the rate of E2 eliminations.

2. *Effect on E1 versus E2 versus E1cB.* The α alkyl and α aryl groups stabilize the carbocation character of the transition state, shifting the spectrum toward the E1 end. β Alkyl groups also shift the mechanism toward E1, since they *decrease* the acidity of the hydrogen. However, β aryl groups shift the mechanism the other way (toward E1cB) by stabilizing the carbanion. Indeed, as seen in Section 17.A.iii, all electron-withdrawing groups in the β position shift the mechanism toward E1cB.¹⁰⁸ α alkyl groups also increase the extent of elimination with weak bases (E2C reactions).

¹⁰⁶ See Redman, R.P.; Thomas, P.J.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* **1978**, 43.

¹⁰⁷ See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups*, Supplement A, pt. 1, Wiley, NY, **1977**, pp. 178–189.

¹⁰⁸ See Butskus, P.F.; Denis, G.I. *Russ. Chem. Rev.* **1966**, 35, 839.

TABLE 17.2 The Effect of α and β Branching on the Rate of E2 Elimination and the Amount of Alkene Formed^a

Substrate	Temperature (°C)	Alkene (%)	Rate $\times 10^5$ of E2 reaction	Reference
CH ₃ CH ₂ Br	55	0.9	1.6	109
(CH ₃) ₂ CHBr	24	80.3	0.237	110
(CH ₃) ₃ Br	25	97	4.17	111
CH ₃ CH ₂ CH ₂ Br	55	8.9	5.3	109
(CH ₃) ₂ CHCH ₂ Br	55	59.5	8.5	109

^aThe reactions were between the alkyl bromide and ⁻OEt. The rate for isopropyl bromide was actually greater than that for ethyl bromide, if the temperature difference is considered. Neopentyl bromide, the next compound in the β -branching series, cannot be compared because it has no β hydrogen and cannot give an elimination product without rearrangement.

3. *Effect on Elimination versus Substitution.* Under second-order conditions, increased branching increases elimination, to the point where tertiary substrates undergo few S_N2 reactions, as seen in Chapter 10. For example, Table 17.2 shows results on some simple alkyl bromides. Similar results were obtained with SMe₂⁺ as the leaving group.¹¹¹ Two reasons can be presented for this trend. One is statistical: As α branching increases, there are usually more hydrogen atoms for the base to attack. The other is that α branching presents steric hindrance to attack of the base at the carbon. Under first-order conditions, increased α branching also increases the amount of elimination (E1 vs S_N1), although not so much, and usually the substitution product predominates. For example, solvolysis of *tert*-butyl bromide gave only 19% elimination¹¹² (cf. with Table 17.2). β Branching also increases the amount of E2 elimination with respect to S_N2 substitution (Table 17.2), not because elimination is faster, but because the S_N2 mechanism is so greatly slowed (Sec. 10.G. i). Under first-order conditions too, β branching favors elimination over substitution, probably for steric reasons.¹¹³ However, E2 eliminations from compounds with charged leaving groups are slowed by β branching. This is related to *Hofmann's rule* (Sec. 17.B, category 4). Electron-withdrawing groups in the β position not only increase the rate of E2 eliminations and shift the mechanisms toward the E1cB end of the spectrum, but also increase the extent of elimination as opposed to substitution.

Another method that compares E2 and S_N2 reactions is called the *activation-strain model*. In this model, the activation energy = activation strain + transition state interaction, and corresponds directly to the strength of the Lewis acid or base. A more basic nucleophile or base, with a higher energy HOMO, and a more acidic substrate, with a lower energy LUMO, interact more strongly.¹¹⁴ Activation strain is connected with the strength of the bonds broken: A strong C-leaving group bond has a higher activation strain and a higher barrier. Using this model, the E2 reaction has

¹⁰⁹ Hughes, E.D.; Ingold, C.K.; Maw, G.A. *J. Chem. Soc.* **1948**, 2072; Hughes, E.D.; Ingold, C.K.; Woolf, L.I. *J. Chem. Soc.* **1948**, 2084.

¹¹⁰ Brown, H.C.; Berneis, H.L. *J. Am. Chem. Soc.* **1953**, 75, 10.

¹¹¹ Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; Masterman, S. *J. Chem. Soc.* **1948**, 2055.

¹¹² Dhar, M.L.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* **1948**, 2058.

¹¹³ Hughes, M.L.; Ingold, C.K.; Maw, G.A. *J. Chem. Soc.* **1948**, 2065.

¹¹⁴ See van Zeist, W.-J.; Bickelhaupt, F.M. *Org. Biomol. Chem.* **2010**, 8, 3118; de Jong, G.Th.; Bickelhaupt, F.M. *ChemPhysChem* **2007**, 8, 1170.

a higher activation strain than S_N2 because two bonds are broken, and with weak bases, S_N2 dominates E2 because S_N2 has less activation strain.¹¹⁵ With strong bases, a favorable interaction of the more acidic transition state for the E2 reaction leads to a preference for E2.

17.D.ii. Effect of the Attacking Base

1. *Effect on E1 versus E2 versus E1cB.* In the E1 mechanism, an external base is generally not required: The solvent acts as the base. Hence, when external bases are added, the mechanism is shifted toward E2. Stronger bases and higher base concentrations cause the mechanism to move toward the E1cB end of the E1–E2–E1cB spectrum.¹¹⁶ However, weak bases in polar aprotic solvents can also be effective in elimination reactions with certain substrates (the E2C reaction). Normal E2 elimination has been accomplished with the following bases:¹¹⁷ H_2O , NR_3 , ^-OH , ^-OAc , ^-OR , ^-OAr , $^-NH_2$, CO_3^{2-} , $LiAlH_4$, I^- , ^-CN , and organic bases. However, the only bases of preparative importance in the normal E2 reaction are ^-OH , ^-OR , and $^-NH_2$, usually in the conjugate acid as solvent, and certain amines. Weak bases effective in the E2C reaction are Cl^- , Br^- , F^- , ^-OAc , and RS^- . These bases are often used in the form of their R_4N^+ salts.
2. *Effect on Elimination versus Substitution.* Strong bases not only benefit E2 as against E1, but also benefit elimination as against substitution. With a high concentration of strong base in a nonionizing solvent, bimolecular mechanisms are favored and E2 predominates over S_N2 . At low-base concentrations, or in the absence of base altogether, in ionizing solvents, unimolecular mechanisms are favored, and the S_N1 mechanism predominates over the E1. Chapter 10 pointed out that some species are strong nucleophiles but weak bases (Sec. 10.G.ii). The use of these obviously favors substitution, except that, as seen, elimination can predominate if polar aprotic solvents are used. It has been shown for the base cyanide that in polar aprotic solvents, the less the base is encumbered by its counterion in an ion pair (i.e., the freer the base), the more substitution is favored at the expense of elimination.¹¹⁸

17.D.iii. Effect of the Leaving Group

1. *Effect on Reactivity.* The leaving groups in elimination reactions are similar to those in nucleophilic substitution. The E2 eliminations have been performed with the following groups: $^+NR_3$, $^+PR_3$, $^+SR_2$, ^+OHR , SO_2R , OSO_2R , $OCOR$, OOH , OOR , NO_2 ,¹¹⁹ F , Cl , Br , I , and CN (*not* $^+OH_2$). The E1 eliminations have been

¹¹⁵ See Bickelhaupt, F.M. *J. Comput. Chem.* **1999**, 20, 114. Prof. F.M. Bickelhaupt, Vrije Universiteit Amsterdam, personal communication.

¹¹⁶ Baciocchi, E. *Acc. Chem. Res.* **1979**, 12, 430. See also, Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* **1980**, 45, 827.

¹¹⁷ This list is from Banthorpe, D.V. *Elimination Reactions*, Elsevier, NY, **1963**, p. 4.

¹¹⁸ Loupy, A.; Seyden-Penne, J. *Bull. Soc. Chim. Fr.* **1971**, 2306.

¹¹⁹ See Ono, N. in Feuer, H.; Nielsen, A.T. *Nitro Compounds; Recent Advances in Synthesis and Chemistry*, VCH, NY, **1990**, pp. 1–135, pp. 86–126.

carried out with: $^+\text{NR}_3$, $^+\text{SR}_2$, $^+\text{OH}_2$, ^+OHR , OSO_2R , OCOR , Cl , Br , I , and $^+\text{N}_2$.¹²⁰ However, the major leaving groups for preparative purposes are $^+\text{OH}_2$ (always by E1) and Cl , Br , I , and $^+\text{NR}_3$ (usually by E2).

2. *Effect on E1 versus E2 versus E1cB.* Better leaving groups shift the mechanism toward the E1 end of the spectrum, *since they make ionization easier*. This effect has been studied in various ways. One way already mentioned was a study of ρ values (Sec. 17.A.iv). Poor leaving groups and positively charged leaving groups shift the mechanism toward the E1cB end of the spectrum because the strong electron-withdrawing field effects increase the acidity of the β hydrogen.¹²¹ The E2C reaction is favored by good leaving groups.
3. *Effect on Elimination versus Substitution.* As seen previously (Sec. 17.A.ii), for first-order reactions the leaving group has nothing to do with the competition between elimination and substitution, since it is gone before the decision is made as to which path to take. However, where ion pairs are involved, this is not true, and results have been found where the nature of the leaving group does affect the product.¹²² In second-order reactions, the elimination/substitution ratio is not greatly dependent on a halide leaving group, although there is a slight increase in elimination in the order $\text{I} > \text{Br} > \text{Cl}$. When OTs is the leaving group, there is usually much more substitution. For example, $n\text{-C}_{18}\text{H}_{37}\text{Br}$ treated with $t\text{-BuOK}$ gave 85% elimination, while $n\text{-C}_{18}\text{H}_{37}\text{OTs}$ gave, under the same conditions, 99% substitution.¹²³ On the other hand, positively charged leaving groups increase the amount of elimination.

17.D.iv. Effect of the Medium

1. *Effect of Solvent on E1 versus E2 versus E1cB.* With any reaction a more polar environment enhances the rate of mechanisms that involve ionic intermediates. For neutral leaving groups, it is expected that E1 and E1cB mechanisms will be aided by increasing the polarity of the solvent and by increasing the ionic strength. With certain substrates, polar aprotic solvents promote elimination with weak bases (the E2C reaction).
2. *Effect of Solvent on Elimination versus Substitution.* Increasing polarity of solvent favors $\text{S}_{\text{N}}2$ reactions at the expense of E2. In the classical example, alcoholic KOH is used to effect elimination, while the more polar aq KOH is used for substitution. Charge-dispersal discussions, similar to those in Section 10.G.iv,¹²⁴ only partially explain this. In most solvents, $\text{S}_{\text{N}}1$ reactions are favored over E1. The E1 reactions compete best in polar solvents that are poor nucleophiles, especially dipolar aprotic solvents.¹²⁵ A study made in the gas phase, where there is no solvent, has shown that

¹²⁰ These lists are from Banthorpe, D.V. *Elimination Reactions*, Elsevier, NY, **1963**, pp. 4, 7.

¹²¹ See Stirling, C.J.M. *Acc. Chem. Res.* **1979**, *12*, 198. See also, Varma, M.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* **1981**, 553.

¹²² See Wright, D.G. *J. Chem. Soc., Chem. Commun.* **1975**, 776. See, however, Cavazza, M. *Tetrahedron Lett.* **1975**, 1031.

¹²³ Veeravagu, P.; Arnold, R.T.; Eigenmann, E.W. *J. Am. Chem. Soc.* **1964**, *86*, 3072.

¹²⁴ Cooper, K.A.; Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J.; Woolf, L.I. *J. Chem. Soc.* **1948**, 2043.

¹²⁵ Aksnes, G.; Stensland, P. *Acta Chem. Scand.*, **1989**, *43*, 893, and references cited therein.

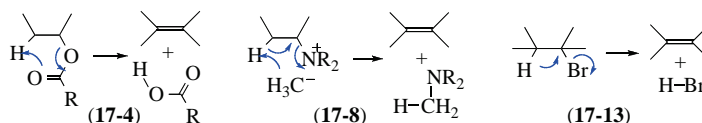
when 1-bromopropane reacts with MeO^- only elimination takes place (no substitution) even with this primary substrate.¹²⁶

3. *Effect of Temperature.* Elimination is favored over substitution by increasing temperature, whether the mechanism is first or second order.¹²⁷ The reason is that the activation energies of eliminations are higher than those of substitutions (because eliminations have greater changes in bonding).

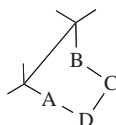
17.E. MECHANISMS AND ORIENTATION IN PYROLYTIC ELIMINATIONS

17.E.i. Mechanisms¹²⁸

Several types of compound undergo elimination on heating, with no other reagent present. Reactions of this type are often run in the gas phase. The mechanisms are obviously different from those already discussed, since all those require an external base, which may be the solvent, in one of the steps, and there is no external base or solvent present in pyrolytic elimination. Two mechanisms have been found to operate. One involves a cyclic transition state, which may be four, five, or six membered. Examples of each size are



In this mechanism, the two groups leave at about the same time and bond to each other as they are doing so. The designation is E^i in the Ingold terminology and *cyclo*- $\text{D}_\text{E}\text{D}_\text{N}\text{A}_\text{n}$ in the IUPAC system. The elimination must be syn and, for the four- and five-membered transition states, the four or five atoms making up the ring must be coplanar. Coplanarity is not required for the six-membered transition state, since there is room for the outside atoms when the leaving atoms are staggered.



As in the E_2 mechanism, it is not necessary that the $\text{C}-\text{H}$ and $\text{C}-\text{X}$ bond be broken simultaneously in the transition state. In fact, there is also a spectrum of mechanisms here, ranging from a mechanism in which $\text{C}-\text{X}$ bond breaking is a good deal more advanced

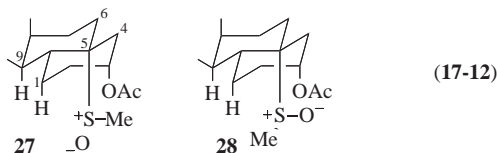
¹²⁶ Jones, M.E.; Ellison, G.B. *J. Am. Chem. Soc.* **1989**, *111*, 1645. For a different result with other reactants, see Lum, R.C.; Grabowski, J.J. *J. Am. Chem. Soc.* **1988**, *110*, 8568.

¹²⁷ Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; Maw, G.A.; MacNulty, B.J. *J. Chem. Soc.* **1948**, 2049.

¹²⁸ Taylor, R. in Patai, S. *The Chemistry of Functional Groups, Supplement B* pt. 2, Wiley, NY, **1979**, pp. 860–914; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* **1971**, *8*, 75, pp. 76–143, 207–234; in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5, Elsevier, NY, **1972**, the articles by Swinbourne, E.S. pp. 149–233 (pp. 158–188), and by Richardson, W.H.; O'Neal, H.E. pp. 381–565 (pp. 381–446); Maccoll, A. *Adv. Phys. Org. Chem.* **1965**, *3*, 91. See Egger, K.W.; Cocks, A.T. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, **1973**, pp. 677–745; Maccoll, A. *Chem. Rev.* **1969**, *69*, 33.

than C—H bond breaking to one in which the extent of bond breaking is virtually identical for the two bonds. Evidence for the existence of the E^i mechanism includes:

1. The kinetics are first order, so only one molecule of the substrate is involved in the reaction (i.e., if one molecule attacked another, the kinetics would be second order in substrate).¹²⁹
2. Free radical inhibitors do not slow the reactions, so no free radical mechanism is involved.¹³⁰
3. The mechanism predicts exclusive syn elimination, and this behavior has been found in many cases.¹³¹ The evidence is inverse to that for the anti E2 mechanism and generally involves the following facts: (1) an erythro isomer gives a *trans*-alkene and a threo isomer gives a *cis*-alkene; (2) the reaction takes place only when a *cis* β hydrogen is available; (3) if, in a cyclic compound, a *cis* hydrogen is available on only one side, the elimination goes in that direction. Another piece of evidence involves a pair of steroid molecules. In 3 β -acetoxy-(*R*)-5 α -methylsulfinylcholestane (**27** shows rings A and B of this compound) and in 3 β -acetoxy-(*S*)-5 α -methylsulfinylcholestane (**28**: rings A and B), the *only* difference is the configuration of oxygen and methyl about the sulfur. Yet pyrolysis of **27** gave only elimination to the 4-side (86% 4-ene), while **28** gave predominant elimination to the 6-side (65% 5-ene and 20% 4-ene).¹³² Models show that interference from the 1- and 9-hydrogen atoms causes the two groups on the sulfur to lie *in front of it* with respect to the rings, rather than behind it. Since the sulfur is a stereogenic center, this means that in **27** the oxygen is near the 4-hydrogen, while in **28** it is near the 6-hydrogen. This experiment is compatible only with syn elimination.¹³³



4. The ^{14}C isotope effects for the *Cope elimination* (17-9) show that both the C—H and C—N bonds have been extensively broken in the transition state.¹³⁴
5. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted in geometry in the transition state than they are in the starting compound.

Where a pyrolytic elimination lies on the mechanistic spectrum seems to depend mostly on the leaving group. When this is halogen, all available evidence suggests that in the transition state the C—X bond is cleaved to a much greater extent than the C—H bond; that is, there is a considerable amount of carbocation character in the transition state. This

¹²⁹ O'Connor, G.L.; Nace, H.R. *J. Am. Chem. Soc.* **1953**, 75, 2118.

¹³⁰ Barton, D.H.R.; Head, A.J.; Williams, R.J. *J. Chem. Soc.* **1953**, 1715.

¹³¹ See, however, Briggs, W.S.; Djerassi, C. *J. Org. Chem.* **1968**, 33, 1625; Smitsman, E.E.; Li, J.P.; Creese, M.W. *J. Org. Chem.* **1970**, 35, 1352.

¹³² Jones, D.N.; Saeed, M.A. *Proc. Chem. Soc.* **1964**, 81. See also, Goldberg, S.I.; Sahli, M.S. *J. Org. Chem.* **1967**, 32, 2059.

¹³³ See Bailey, W.J.; Bird, C.N. *J. Org. Chem.* **1977**, 42, 3895.

¹³⁴ Wright, D.R.; Sims, L.B.; Fry, A. *J. Am. Chem. Soc.* **1983**, 105, 3714.

observation is in accord with the fact that a completely nonpolar four-membered cyclic transition state violates the *Woodward–Hoffmann rules* (see the similar case of Reaction **15-63**). Evidence for the carbocation-like character of the transition state when halide is the leaving group is that relative rates are in the order $I > Br > Cl$ ¹³⁵ (see Sec. 10.G.iii), and that the effects of substituents on reaction rates are in accord with such a transition state.¹³⁶ Rate ratios for pyrolysis of some alkyl bromides at 320 °C were ethyl bromide, 1; isopropyl bromide, 280; *tert*-butyl bromide, 78,000. Also, α -phenylethyl bromide had about the same rate as *tert*-butyl bromide. On the other hand, β -phenylethyl bromide was only slightly faster than ethyl bromide.¹³⁷ This result indicates that C—Br cleavage was much more important in the transition state than C—H cleavage, since the incipient carbocation was stabilized by a alkyl and α -aryl substitution, while there was no incipient carbanion to be stabilized by β aryl substitution. These substituent effects, as well as those for other groups, are very similar to the effects found for the S_N1 mechanism and thus in very good accord with a carbocation-like transition state.

For carboxylic esters, the rate ratios were much smaller,¹³⁸ although still in the same order, so that this reaction is closer to a pure E^i mechanism, although the transition state still has some carbocationic character. Other evidence for a greater initial C—O cleavage with carboxylic esters is that a series of 1-arylethyl acetates followed σ^+ rather than σ , showing carbocationic character at the 1 position.¹³⁹ The extent of $E1$ character in the transition state increases in the following order of ester types: acetate < phenylacetate < benzoate < carbamate < carbonate.¹⁴⁰ Cleavage of xanthates (Reaction **17-5**), cleavage of sulfoxides (Reaction **17-12**), the *Cope Reaction* (**17-9**), and Reaction **17-8** are probably very close to straight E^i mechanisms.¹⁴¹

The second type of pyrolysis mechanism is completely different and involves free radicals. Initiation occurs by pyrolytic homolytic cleavage. The remaining steps may vary, and a few are shown below. Free radical mechanisms are mostly found in pyrolyses of polyhalides and of primary monohalides,¹⁴² although they also have been postulated in pyrolysis of certain carboxylic esters.¹⁴³ β -Elimination of tosyl radicals is known.¹⁴⁴ Much less is known about these mechanisms and we will not consider them further. Free radical eliminations in solution are also known, but are rare.¹⁴⁵

¹³⁵ Maccoll, A., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, **1964**, pp. 215–216.

¹³⁶ For reviews of such studies, see Maccoll, A. *Chem. Rev.* **1969**, 69, 33.

¹³⁷ See Chuchani, G.; Rotinov, A.; Dominguez, R.M.; Martin, I. *Int. J. Chem. Kinet.* **1987**, 19, 781.

¹³⁸ Scheer, J.C.; Kooyman, E.C.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* **1963**, 82, 1123. See also, Louw, R.; Vermeeren, H.P.W.; Vogelzang, M.W. *J. Chem. Soc. Perkin Trans. 2* **1983**, 1875.

¹³⁹ Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1978**, 1255. See also, August, R.; McEwen, I.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1683, and other papers in this series; Al-Awadi, N.A. *J. Chem. Soc. Perkin Trans. 2* **1990**, 2187.

¹⁴⁰ Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1975**, 1025.

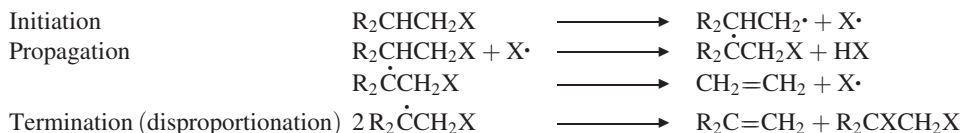
¹⁴¹ For a review of the mechanisms of Reaction **17-12** and **17-9**, and the pyrolysis of sulfilimines, see Oae, S.; Furukawa, N. *Tetrahedron* **1977**, 33, 2359.

¹⁴² See Barton, D.H.R.; Howlett, K.E. *J. Chem. Soc.* **1949**, 155, 165.

¹⁴³ See Louw, R.; Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas* **1965**, 84, 1511.

¹⁴⁴ Timokhin, V.I.; Gastaldi, S.; Bertrand, M.P.; Chatgililoglu, C. *J. Org. Chem.* **2003**, 68, 3532.

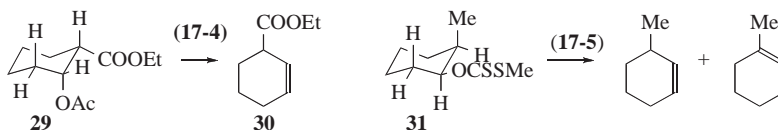
¹⁴⁵ Boothe, T.E.; Greene, Jr., J.L.; Shevlin, P.B. *J. Org. Chem.* **1980**, 45, 794; Stark, T.J.; Nelson, N.T.; Jensen, F.R. *J. Org. Chem.* **1980**, 45, 420; Kochi, J.K. *Organic Mechanisms and Catalysis*, Academic Press, NY, **1978**, pp. 346–349; Kamimura, A.; Ono, N. *J. Chem. Soc., Chem. Commun.* **1988**, 1278.



17.E.ii. Orientation in Pyrolytic Eliminations

As in the E1–E2–E1cB mechanistic spectrum, *Bredt's rule* applies; and if a double bond is present, a conjugated system will be preferred, if sterically possible. Apart from these considerations, the following statements can be made for Eⁱ eliminations:

1. In the absence of considerations mentioned below, orientation is statistical and is determined by the number of β -hydrogen atoms available (therefore *Hofmann's rule* is followed). For example, *sec*-butyl acetate gives 55–62% 1-butene and 38–45% 2-butene,¹⁴⁶ which is close to the 3:2 distribution predicted by the number of hydrogen atoms available.¹⁴⁷
2. A cis β hydrogen is required. Therefore in cyclic systems, if there is a cis hydrogen on only one side, the double bond will go that way. However, when there is a six-membered transition state, this does not necessarily mean that the leaving groups must be cis to each other, since such transition states need not be completely coplanar. If the leaving group is axial, then the hydrogen obviously must be equatorial (and consequently cis to the leaving group), since the transition state cannot be realized when the groups are both axial. But if the leaving group is equatorial, it can form a transition state with a β hydrogen that is either axial (hence, cis) or equatorial (hence, trans). Thus **29**, in which the leaving group is most likely axial, does not form a double bond in the direction of the carboxyl group, even though that would be conjugated, because there is no equatorial hydrogen on that side. Instead, it gives 100% **30**.¹⁴⁸ On the other hand, **31**, with an equatorial leaving group, gives $\sim 50\%$ of each alkene, even though, for elimination to the 1-ene, the leaving group must depart with a trans hydrogen.¹⁴⁹



3. In some cases, especially with cyclic compounds, the more stable alkene forms and *Zaitsev's rule* applies. For example, menthyl acetate gives 35% of the *Hofmann* product and 65% of the *Zaitsev*, even though a cis β hydrogen is present on both sides and the statistical distribution is the other way. A similar result was found for the pyrolysis of menthyl chloride.¹⁵⁰

¹⁴⁶ Froemsdorf, D.H.; Collins, C.H.; Hammond, G.S.; DePuy, C.H. *J. Am. Chem. Soc.* **1959**, *81*, 643; Haag, W.O.; Pines, H. *J. Org. Chem.* **1959**, *24*, 877.

¹⁴⁷ DePuy, C.H.; King, R.W. *Chem. Rev.* **1960**, *60*, 431, with tables showing product distributions.

¹⁴⁸ Bailey, W.J.; Baylouny, R.A. *J. Am. Chem. Soc.* **1959**, *81*, 2126.

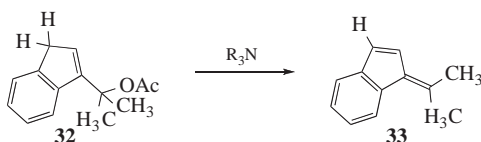
¹⁴⁹ Botteron D.G.; Shulman, G.P. *J. Org. Chem.* **1962**, *27*, 2007.

¹⁵⁰ See Bamkole, T.; Maccoll, A. *J. Chem. Soc. B* **1970**, 1159.

4. There are also steric effects. In some cases the direction of elimination is determined by the need to minimize steric interactions in the transition state or to relieve steric interactions in the ground state.

17.E.iii. 1,4-Conjugate Eliminations¹⁵¹

1,4-eliminations of the type $\text{H}-\text{C}-\text{C}=\text{CC}-\text{X} \rightarrow \text{C}=\text{C}-\text{C}=\text{C}$ are much rarer than conjugate additions (Chapter 15), but some examples are known.¹⁵² One such is the conversion of **32** to **33**.¹⁵³



17.F. REACTIONS

Reactions in which a $\text{C}=\text{C}$ or a $\text{C}\equiv\text{C}$ bond is formed will be considered first. From a synthetic point of view, the most important reactions for the formation of double bonds are **17-1** (usually by an E1 mechanism), **17-7**, **17-13**, and **17-22** (usually by an E2 mechanism), and **17-4**, **17-5**, and **17-9** (usually by an E^{i} mechanism). The only synthetically important method for the formation of triple bonds is **17-13**.¹⁵⁴ In the second section, reactions in which $\text{C}\equiv\text{N}$ bonds and $\text{C}=\text{N}$ bonds are formed will be considered, and then eliminations that give $\text{C}=\text{O}$ bonds and diazoalkanes. Finally, extrusion reactions will be discussed.

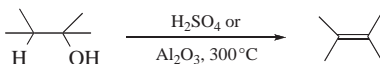
17.F.i. Reactions in which $\text{C}=\text{C}$ and $\text{C}\equiv\text{C}$ Bonds Are Formed

A. Reactions in which Hydrogen Is Removed from One Side

In Reactions **17-1**–**17-6**, the other leaving atom is oxygen. In Reactions **17-7**–**17-11**, it is nitrogen. For reactions in which hydrogen is removed from both sides, see **19-1**–**19-6**.

17-1 Dehydration of Alcohols

Hydro-hydroxy-elimination



¹⁵¹ Taylor, R. in Patai, S. *The Chemistry of Functional Groups, Supplement B*, pt. 2, Wiley, NY, **1979**, pp. 885–890; Smith, G.G.; Mutter, L.; Todd, G.P. *J. Org. Chem.* **1977**, *42*, 44; Chuchani, G.; Dominguez, R.M. *Int. J. Chem. Kinet.* **1981**, *13*, 577; Hernández, A.; Chuchani, G. *Int. J. Chem. Kinet.* **1983**, *15*, 205.

¹⁵² See Wakselman, M. *Nouv. J. Chem.* **1983**, *7*, 439.

¹⁵³ Ölwegård, M.; Ahlberg, P. *Acta Chem. Scand.*, **1990**, *44*, 642. See also, Ölwegård, M.; Ahlberg, P. *J. Chem. Soc., Chem. Commun.* **1989**, 1279.

¹⁵⁴ Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 2, Wiley, NY, **1983**; pp. 1376–1384; Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, **1978**, pp. 755–790. For a comparative study of various methods, see Mesnard, D.; Bernadou, F.; Miginiac, L. *J. Chem. Res. (S)* **1981**, 270, and references cited therein.

Dehydration of alcohols can be accomplished in several ways. Both H_2SO_4 and H_3PO_4 are common reagents, but formation of an intermediate carbocation can lead to rearrangement products and to ether formation (Reaction 10-12). If the alcohol is volatile, vapor-phase elimination over Al_2O_3 is an excellent method since side reactions are greatly reduced. This method has even been applied to such high-molecular-weight alcohols as 1-dodecanol.¹⁵⁵ Other metallic oxides (e.g., Cr_2O_3 , TiO_2 , WO_3) have been used, as have been sulfides, other metallic salts, and zeolites. The presence of an electron-withdrawing group usually facilitates elimination of water, as in the *aldol condensation* (Reaction 16-34). Similarly, 2-nitroalcohols (products of the *Henry reaction*, 16-37) give conjugated nitro compounds when heated with zeolite $\text{Y}-\text{Y}$.¹⁵⁶ Treating a 4-hydroxy lactam with DMAP and Boc anhydride leads to the conjugated lactam.¹⁵⁷ Elimination of serine derivatives to α -alkylidene amino acid derivatives was accomplished with $(\text{EtO})_2\text{POCl}$.¹⁵⁸ Another method of avoiding side reactions is the conversion of alcohols to esters, followed by pyrolysis (17-4–17-6). The ease of dehydration increases with α branching, and tertiary alcohols are dehydrated so easily with only a trace of acid that it sometimes happens even when the investigator desires otherwise. Indeed, the initial alcohol products of many base-catalyzed condensations dehydrate spontaneously after an acid workup (Chapter 16) because the new double bond can be in conjugation with one already there.

Many other dehydrating agents¹⁵⁹ have been used on occasion: P_2O_5 , I_2 , and PPh_3-I_2 ,¹⁶⁰ BF_3 -etherate, DMSO, $\text{SiO}_2-\text{Cl}/\text{Me}_3\text{SiCl}$,¹⁶¹ KHSO_4 anhydrous CuSO_4 , and phthalic anhydride, among others. Secondary and tertiary alcohols can also be dehydrated, without rearrangements, simply on refluxing in HMPA.¹⁶² With nearly all reagents, dehydration follows *Zaitsev's rule*. An exception involves the passage of hot alcohol vapors over thorium oxide at 350–450 °C, under which conditions *Hofmann's rule* is followed.¹⁶³

Transition metals can induce the dehydration of certain alcohols. β -Hydroxy ketones are converted to conjugated ketones by treatment with CeCl_3 and NaI .¹⁶⁴ In the presence of a Pd complex, alkyl cyclopropanols undergo a dehydration reaction to give a conjugated ketone.¹⁶⁵ A δ -hydroxy- α,β -unsaturated aldehyde was converted to a dienyl aldehyde with a Hf catalyst.¹⁶⁶ β -Hydroxy esters are converted to conjugated esters when treated with 2 molar equivalents of SmI_2 .¹⁶⁷ The reaction of a β -hydroxy nitrile

¹⁵⁵ Spitzin, V.I.; Michailenko, I.E.; Pirogowa, G.N. *J. Prakt. Chem.* **1964**, [4] 25, 160; Bertsch, H.; Greiner, A.; Kretzschmar, G.; Falk, F. *J. Prakt. Chem.* **1964**, [4] 25, 184.

¹⁵⁶ Anbazhagan, M.; Kumaran, G.; Sasidharan, M. *J. Chem. Res. (S)* **1997**, 336.

¹⁵⁷ Mattern, R.-H. *Tetrahedron Lett.* **1996**, 37, 291.

¹⁵⁸ Berti, F.; Ebert, C.; Gardossi, L. *Tetrahedron Lett.* **1992**, 33, 8145.

¹⁵⁹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 291–294.

¹⁶⁰ Alvarez-Manzaneda, E.J.; Chahboun, R.; Torres, E.C.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* **2004**, 45, 4453.

¹⁶¹ Firouzbadi, H.; Iranpoor, N.; Hazarkhani, H.; Karimi, B. *Synth. Commun.* **2003**, 33, 3653.

¹⁶² Monson, R.S.; Priest, D.N. *J. Org. Chem.* **1971**, 36, 3826; Lomas, J.S.; Sagatys, D.S.; Dubois, J.E. *Tetrahedron Lett.* **1972**, 165.

¹⁶³ Lundeen, A.J.; Van Hoozer, R. *J. Org. Chem.* **1967**, 32, 3386. See also, Davis, B.H. *J. Org. Chem.* **1982**, 47, 900; Iimori, T.; Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1991**, 32, 1209.

¹⁶⁴ Bartoli, G.; Bellucci, M.C.; Petrini, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Org. Lett.* **2000**, 2, 1791.

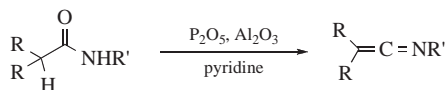
¹⁶⁵ Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629.

¹⁶⁶ Saito, S.; Nagahara, T.; Yamamoto, H. *Synlett* **2001**, 1690.

¹⁶⁷ Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Angew. Chem. Int. Ed.* **2000**, 39, 2773.

with MeMgCl ¹⁶⁸ or with MgO ¹⁶⁹ leads to a conjugated nitrile. In another variation of the dehydration reaction, vicinal bromohydrins are converted to alkenes upon treatment with In , InCl_3 , and a Pd catalyst.¹⁷⁰ Chlorohydrins react similarly when treated with Sm , and then diiodomethane.¹⁷¹

Carboxylic acids can be dehydrated by pyrolysis to give a ketene: $\text{RCH}_2\text{CO}_2\text{H} \rightarrow \text{RCH}=\text{C}=\text{O}$. Ketene itself is commercially prepared in this manner. Carboxylic acids have been converted to ketenes by treatment with certain reagents, including TsCl ,¹⁷² dicyclohexylcarbodiimide,¹⁷³ and 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).¹⁷⁴ Analogously, amides can be dehydrated with P_2O_5 , pyridine, and Al_2O_3 to give ketenimines:¹⁷⁵



There is no way in which dehydration of alcohols can be used to prepare triple bonds: *gem*-diols and vinylic alcohols are not normally stable compounds and *vic*-diols¹⁷⁶ give either conjugated dienes or lose only 1 equiv of water to give an aldehyde or ketone. Dienes can be prepared, however, by heating alkynyl alcohols with triphenylphosphine.¹⁷⁷

When proton acids catalyze alcohol dehydration, the mechanism is E1 .¹⁷⁸ The principal process involves conversion of ROH to ROH_2^+ and cleavage of the latter to R^+ and H_2O , although with some acids a secondary process probably involves conversion of the alcohol to an inorganic ester and ionization of that ester (illustrated for H_2SO_4):



Note that these mechanisms are the reverse of those involved in the acid-catalyzed hydration of double bonds (Reaction 15-3), in accord with the principle of microscopic reversibility. With anhydrides (e.g., P_2O_5 , phthalic anhydride), as well as with some other reagents (e.g., HMPA),¹⁷⁹ it is likely that an ester is formed, and the leaving group is the conjugate base of the corresponding acid. In these cases, the mechanism can be E1 or E2 . The mechanism with Al_2O_3 and other solid catalysts has been studied extensively, but is poorly understood.¹⁸⁰

¹⁶⁸ Fleming, F.F.; Shook, B.C. *Tetrahedron Lett.* **2000**, 41, 8847.

¹⁶⁹ Fleming, F.F.; Shook, B.C. *J. Org. Chem.* **2002**, 67, 3668.

¹⁷⁰ Cho, S.; Kang, S.; Keum, G.; Kang, S.B.; Han, S.-Y.; Kim, Y. *J. Org. Chem.* **2003**, 68, 180.

¹⁷¹ Concellón, J.M.; Rodríguez-Solla, H.; Huerta, M.; Pérez-Andrés, J.A. *Eur. J. Org. Chem.* **2002**, 1839.

¹⁷² Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *Synthesis* **1987**, 395; *J. Org. Chem.* **1987**, 52, 3457.

¹⁷³ Olah, G.A.; Wu, A.; Farooq, O. *Synthesis* **1989**, 568.

¹⁷⁴ Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *J. Org. Chem.* **1987**, 52, 3457; Funk, R.L.; Abelman, M.M.; Jellison, K.M. *Synlett* **1989**, 36.

¹⁷⁵ Stevens, C.L.; Singhal, G.H. *J. Org. Chem.* **1964**, 29, 34.

¹⁷⁶ See Bartók, M.; Molnár, A. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 2, Wiley, NY, **1980**, pp. 721–760.

¹⁷⁷ Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 394.

¹⁷⁸ Vinnik, M.I.; Obratsov, P.A. *Russ. Chem. Rev.* **1990**, 59, 63; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**, pp. 221–274, 317–331; Knözinger, H. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, **1971**, pp. 641–718.

¹⁷⁹ See Kawanisi, M.; Arimatsu, S.; Yamaguchi, R.; Kimoto, K. *Chem. Lett.* **1972**, 881.

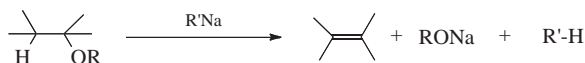
¹⁸⁰ Beránek, L.; Kraus, M. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20, Elsevier, NY, **1978**, pp. 274–295; Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed.* **1971**, 10, 172; Berteau, P.; Ruwet, M.; Delmon, B. *Bull. Soc. Chim. Belg.* **1985**, 94, 859.

Magnesium alkoxides (formed by $\text{ROH} + \text{Me}_2\text{Mg} \rightarrow \text{ROMgMe}$) have been decomposed thermally, by heating at 195–340 °C to give the alkene, CH_4 , and MgO .¹⁸¹ Syn elimination is found and an E^i mechanism is likely. Similar decomposition of aluminum and zinc alkoxides has also been accomplished.¹⁸²

OS **I**, 15, 183, 226, 280, 345, 430, 473, 475; **II**, 12, 368, 408, 606; **III**, 22, 204, 237, 312, 313, 353, 560, 729, 786; **IV**, 130, 444, 771; **V**, 294; **VI**, 307, 901; **VII**, 210, 241, 363, 368, 396; **VIII**, 210, 444. See also, OS **VII**, 63; **VIII**, 306, 474. No attempt has been made to list alkene-forming dehydration reactions accompanying condensations or rearrangements.

17-2 Cleavage of Ethers to Alkenes

Hydro-alkoxy-elimination



Alkenes can be formed by the treatment of ethers with very strong bases (e.g., alkylsodium or alkyllithium¹⁸³ compounds, sodium amide,¹⁸⁴ or LDA),¹⁸⁵ although there are side reactions with many of these reagents. The reaction is aided by electron-withdrawing groups in the β position, and, for example, $\text{EtOCH}_2\text{CH}(\text{COOEt})_2$ can be converted to $\text{CH}_2=\text{C}(\text{COOEt})_2$ without any base at all, but simply by heating.¹⁸⁶ *tert*-Butyl ethers are cleaved more easily than others. Several mechanisms are possible. In many cases, the mechanism is probably E1cB or on the E1cB side of the mechanistic spectrum,¹⁸⁷ since the base required is so strong, but it has been shown (by the use of PhCD_2OEt) that PhCH_2OEt reacts by the five-membered E^i mechanism.¹⁸⁸ Propargylic benzyl ethers are converted to conjugated dienes by heating with a Ru catalyst.¹⁸⁹ Ethers also have been converted to alkenes and alcohols by passing vapors over hot P_2O_5 or Al_2O_3 (this method is similar to Reaction 17-1), but this is not a general reaction.

Cyclic ethers (e.g., THF) react slowly with organolithium reagents with cleavage that produces a $\text{C}=\text{C}$ unit.¹⁹⁰ Fragmentation of 2,5-dihydrofuran with ethylmagnesium chloride and a chiral Zr catalyst leads to a chiral, homoallylic alcohol.¹⁹¹ Acetals can be converted to enol ethers (**34**) in this manner. When ketals react with 2 molar equivalents of tri-isobutylaluminum, the product is a vinyl ether.¹⁹² This can also be done at room temperature by treatment with trimethylsilyl triflate and a tertiary amine¹⁹³ or with Me_3SiI in the presence of hexamethyldisilazane.¹⁹⁴

¹⁸¹ Ashby, E.C.; Willard, G.F.; Goel, A.B. *J. Org. Chem.* **1979**, *44*, 1221.

¹⁸² Brieger, G.; Watson, S.W.; Barar, D.G.; Shene, A.L. *J. Org. Chem.* **1979**, *44*, 1340.

¹⁸³ Tayama, E.; Sugai, S. *Synlett* **2006**, 849.

¹⁸⁴ For a review, see Maercker, A. *Angew. Chem. Int. Ed.* **1987**, *26*, 972.

¹⁸⁵ Fleming, F.F.; Wang, Q.; Steward, O.W. *J. Org. Chem.* **2001**, *66*, 2171.

¹⁸⁶ Feely, W.; Boekelheide, V. *Org. Synth.* **IV**, 298.

¹⁸⁷ For a gas phase investigation, see DePuy, C.H.; Bierbaum, V.M. *J. Am. Chem. Soc.* **1981**, *103*, 5034.

¹⁸⁸ Letsinger, R.L.; Pollart, D.F. *J. Am. Chem. Soc.* **1956**, *78*, 6079.

¹⁸⁹ Yeh, K.-L.; Liu, B.; Lo, C.-Y.; Huang, H.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2002**, *124*, 6510.

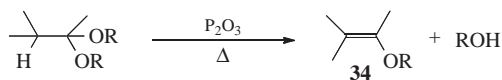
¹⁹⁰ See Cohen, T.; Stokes, S. *Tetrahedron Lett.* **1993**, *34*, 8023.

¹⁹¹ Morken, J.P.; Didiuk, M.T.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1993**, *115*, 6997.

¹⁹² Cabrera, G.; Fiaschi, R.; Napolitano, E. *Tetrahedron Lett.* **2001**, *42*, 5867.

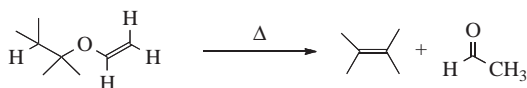
¹⁹³ Gassman, P.G.; Burns, S.J. *J. Org. Chem.* **1988**, *53*, 5574.

¹⁹⁴ Miller, R.D.; McKean, D.R. *Tetrahedron Lett.* **1982**, *23*, 323. For another method, see Marsi, M.; Gladysz, J.A. *Organometallics* **1982**, *1*, 1467.



Conversion of a carbonyl compound to an enol phosphate¹⁹⁵ or triflate¹⁹⁶ allows a subsequent elimination reaction to give an alkyne. Conversion of an aldehyde to the vinyl nonaflate (nonafluorobutane-1-sulfonyl) was followed by reaction with a phosphazene base to give the alkyne.¹⁹⁷

Enol ethers can be pyrolyzed to alkenes and aldehydes in a manner similar to that of Reaction 17-4

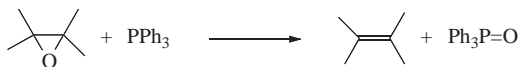


The rate of this reaction for $R-O-CH=CH_2$ increased in the order $Et < iPr < t-Bu$.¹⁹⁸ The mechanism is similar to that of Reaction 17-4.

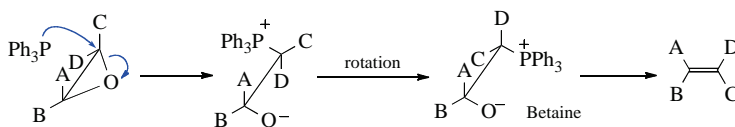
OS IV, 298, 404; V, 25, 642, 859, 1145; VI, 491, 564, 584, 606, 683, 948; VIII, 444.

17-3 The Conversion of Epoxides and Episulfides to Alkenes

epi-Oxy-elimination



Epoxides can be converted to alkenes¹⁹⁹ by treatment with triphenylphosphine²⁰⁰ or triethylphosphite $P(OEt)_3$.²⁰¹ The first step of the mechanism is nucleophilic substitution (Reaction 10-35), followed by a four-center elimination. Since inversion accompanies the substitution, the overall elimination is anti; that is, if two groups A and C are cis in the epoxide, they will be trans in the alkene:



Alternatively, the epoxide can be treated with lithium diphenylphosphide (Ph_2PLi), and the product quaternized with methyl iodide.²⁰² Alkenes have also been obtained from epoxides

¹⁹⁵ Negishi, E.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira, A. *J. Org. Chem.* **1980**, 45, 2526.

¹⁹⁶ Clasby, M. C.; Craig, D. *Synlett* **1992**, 825.

¹⁹⁷ Lyapkalo, I.M.; Vogel, M.A.K.; Boltukhina, E.V.; Vavřík, J. *Synlett* **2009**, 55.

¹⁹⁸ McEwen, I.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1982**, 1179. See also, Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1988**, 737.

¹⁹⁹ For reviews, see Wong, H.N.C.; Fok, C.C.M.; Wong, T. *Heterocycles* **1987**, 26, 1345; Sonnet, P.E. *Tetrahedron* **1980**, 36, 557, p. 576.

²⁰⁰ Wittig, G.; Haag, W. *Chem. Ber.* **1955**, 88, 1654.

²⁰¹ Scott, C.B. *J. Org. Chem.* **1957**, 22, 1118.

²⁰² Vedejs, E.; Fuchs, P.L. *J. Am. Chem. Soc.* **1971**, 93, 4070; **1973**, 95, 822.

by reaction with a large number of reagents,²⁰³ among them Li in THF,²⁰⁴ trimethylsilyl iodide,²⁰⁵ $\text{F}_3\text{COOH}-\text{NaI}$,²⁰⁶ and compounds of Sm,²⁰⁷ Mo, In,²⁰⁸ and the W reagents mentioned in Reaction 17-18. Some of these methods give syn elimination. Treatment of cyclooctane oxide with $\text{Ph}_3\text{P}-\text{OPPh}_3$ and NEt_3 gave cyclooctadiene.²⁰⁹ Sodium amalgam with a Co-salen complex converted epoxides to alkenes.²¹⁰

Epoxides can be converted to allylic alcohols²¹¹ by treatment with several reagents, including *sec*-butyllithium,²¹² and $i\text{Pr}_2\text{NLi}-t\text{-BuOK}$ (the *LIDAKOR reagent*).²¹³ These bases remove the proton from the adjacent carbon, leading to formation of a $\text{C}=\text{C}$ unit and opening of the epoxide to give an alkoxide. Phenyllithium reacts with epoxides in the presence of LTMP to give a *trans*-alkene.²¹⁴ Sulfur ylids (e.g., $\text{Me}_2\text{S}=\text{CH}_2$) also convert epoxides to allylic alcohols.²¹⁵ Bromomethyl epoxides react with $\text{InCl}_3/\text{NaBH}_4$ to give an allylic alcohol²¹⁶ or with $\text{Me}_3\text{S}^+\text{Br}^-$ and butyllithium to give a dienyl alcohol.²¹⁷ α,β -Epoxy ketones are converted to conjugated ketones by treatment with NaI in acetone in the presence of Amberlyst 15,²¹⁸ or with 2.5 molar equivalents of SmI_2 .²¹⁹

When an optically active reagent is used, optically active allylic alcohols can be produced from achiral epoxides.²²⁰ Sparteine and *sec*-butyllithium generate a chiral base that leads to formation of chiral allylic alcohols.²²¹ Chiral diamines react with organolithium reagents to produce chiral bases that convert epoxides to allylic alcohols with good enantioselectivity.²²² Chiral diamines with a mixture of LDA and DBU (Reactions 15-32 and 17-13) give similar results.²²³

²⁰³ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, 1999, pp. 272-277.

²⁰⁴ Gurudutt, K.N.; Ravindranath, B. *Tetrahedron Lett.* **1980**, 21, 1173.

²⁰⁵ Denis, J.N.; Magnane, R.; Van Eenoo, M.; Krief, A. *Nouv. J. Chim.* **1979**, 3, 705. See Caputo, R.; Mangoni, L.; Neri, O.; Palumbo, G. *Tetrahedron Lett.* **1981**, 22, 3551.

²⁰⁶ Sarma, D.N.; Sharma, R.P. *Chem. Ind. (London)* **1984**, 712.

²⁰⁷ Matsukawa, M.; Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2101.

²⁰⁸ Mahesh, M.; Murphy, J.A.; Wessel, H.P. *J. Org. Chem.* **2005**, 70, 4118.

²⁰⁹ Hendrickson, J.B.; Walker, M.A.; Varvak, A.; Hussoin, Md.S. *Synlett* **1996**, 661.

²¹⁰ Isobe, H.; Branchaud, B.P. *Tetrahedron Lett.* **1999**, 40, 8747.

²¹¹ Smith, J.G. *Synthesis* **1984**, 629, pp. 637-642; Crandall, J.K.; Appar, M. *Org. React.* **1983**, 29, 345. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, 1999, pp. 231-233. See also, Okovytyy, S.; Gorb, L.; Leszczynski, J. *Tetrahedron* **2001**, 57, 1509.

²¹² Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, 35, 7943.

²¹³ Thurner, A.; Faigl, F.; Töke, L.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, G. *Tetrahedron* **2001**, 57, 8173.

²¹⁴ Hodgson, D.M.; Fleming, M.J.; Stanway, S.J. *J. Org. Chem.* **2007**, 72, 4763.

²¹⁵ Alcaraz, L.; Cridland, A.; Kinchin, E. *Org. Lett.* **2001**, 3, 4051.

²¹⁶ Ranu, B.C.; Banerjee, S.; Das, A. *Tetrahedron Lett.* **2004**, 45, 8579.

²¹⁷ Alcaraz, L.; Cox, K.; Cridland, A.P.; Kinchin, E.; Morris, J.; Thompson, S.P. *Org. Lett.* **2005**, 7, 1399.

²¹⁸ Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron* **2000**, 56, 1733.

²¹⁹ Concellón, J.M.; Bardales, E. *J. Org. Chem.* **2003**, 68, 9492. In a similar manner, epoxy amides are converted to conjugated amides, see Concellón, J.M.; Bardales, E. *Eur. J. Org. Chem.* **2004**, 1523.

²²⁰ Su, H.; Walder, L.; Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* **1988**, 71, 1073, and references cited therein. Also see, Brookes, P.C.; Milne, D.J.; Murphy, P.J.; Spolaore, B. *Tetrahedron* **2002**, 58, 4675.

²²¹ Alexakis, A.; Vrancken, E.; Mangeney, P. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3354.

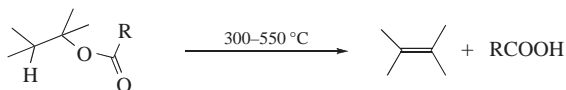
²²² Equey, O.; Alexakis, A. *Tetrahedron Asymmetry* **2004**, 15, 1069.

²²³ Bertilsson, S.K.; Södergren, M.J.; Andersson, P.G. *J. Org. Chem.* **2002**, 67, 1567; Bertilsson, S.K.; Andersson, P.G. *Tetrahedron* **2002**, 58, 4665.

Episulfides²²⁴ can be converted to alkenes.²²⁵ However, in this case the elimination is syn, so the mechanism cannot be the same as that for conversion of epoxides. The phosphite attacks sulfur rather than carbon. Among other reagents that convert episulfides to alkenes are certain Rh complexes,²²⁶ LiAlH_4 ²²⁷ (this compound behaves quite differently with epoxides, see Reaction 19-35), and MeI .²²⁸ Episulfoxides can be converted to alkenes and sulfur monoxide simply by heating.²²⁹

17-4 Pyrolysis of Carboxylic Acids and Esters of Carboxylic Acids

Hydro-acyloxy-elimination



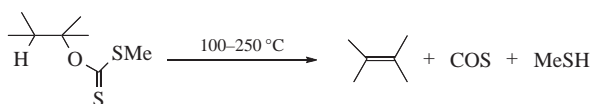
Direct elimination of a carboxylic acid (decarboxylation) to an alkene has been accomplished by heating in the presence of Pd catalysts.²³⁰ Carboxylic esters that bear an alkyl group with a β hydrogen can be pyrolyzed, most often in the gas phase, to give the corresponding acid and an alkene.²³¹ No solvent is required. Since rearrangement and other side reactions are few, the reaction is synthetically very useful and is often carried out as an indirect method of accomplishing 17-1. The yields are excellent and the workup is easy. Many alkenes have been prepared in this manner. For higher alkenes (above $\sim \text{C}_{10}$) a better method is to pyrolyze the alcohol in the presence of acetic anhydride.²³²

The mechanism is E^i (see Sec. 17.E.i). Lactones can be pyrolyzed to give unsaturated acids, provided that the six-membered transition state required for E^i reactions is available (it is not for five- and six-membered lactones, but it is for larger rings²³³). Amides give a similar reaction, but require higher temperatures.

Allylic acetates give dienes when heated with certain Pd²³⁴ or Mo²³⁵ compounds.

OS III, 30; IV, 746; V, 235; IX, 293.

17-5 The Chugaev Reaction



²²⁴ See Sonnet, P.E. *Tetrahedron* **1980**, 36, 557, see p. 587; Goodman, L.; Reist, E.J. in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, **1966**, pp. 93–113.

²²⁵ Neureiter, N.P.; Bordwell, F.G. *J. Am. Chem. Soc.* **1959**, 81, 578.

²²⁶ Calet, S.; Alper, H. *Tetrahedron Lett.* **1986**, 27, 3573.

²²⁷ See Latif, N.; Mishriky, N.; Zeid, I. *J. Prakt. Chem.* **1970**, 312, 421.

²²⁸ See Helmkamp, G.K.; Pettitt, D.J. *J. Org. Chem.* **1964**, 29, 3258.

²²⁹ Aalbersberg, W.G.L.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* **1977**, 99, 2792.

²³⁰ Gooßen, L.J.; Rodríguez, N. *Chem. Commun.* **2004**, 724.

²³¹ See DePuy, C.H.; King, R.W. *Chem. Rev.* **1960**, 60, 431, p. 432; Jenneskens, L.W.; Hoefs, C.A.M.; Wiersum, U.E. *J. Org. Chem.* **1989**, 54, 5811, and references cited therein.

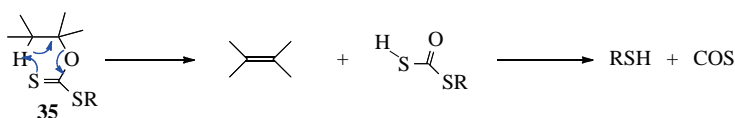
²³² Aubrey, D.W.; Barnatt, A.; Gerrard, W. *Chem. Ind. (London)* **1965**, 681.

²³³ See Bailey, W.J.; Bird, C.N. *J. Org. Chem.* **1977**, 42, 3895.

²³⁴ Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, **1985**, pp. 172–178. See Cheng, H.-Y.; Sun, C.-S.; Hou, D.-R. *J. Org. Chem.* **2007**, 72, 2674.

²³⁵ Trost, B.M.; Lautens, M.; Peterson, B. *Tetrahedron Lett.* **1983**, 24, 4525.

Methyl xanthates are prepared by treatment of alcohols with NaOH and CS₂ to give RO—C(=S)—SNa, followed by treatment of this with iodomethane.²³⁶ Pyrolysis of the xanthate to give the alkene, COS, and the thiol is called the *Chugaev reaction*.²³⁷ The reaction is like **17-4**; an indirect method of accomplishing **17-2**. The temperatures required with xanthates are lower than with ordinary esters, which is advantageous because possible isomerization of the resulting alkene is minimized. The mechanism is Eⁱ, similar to that of Reaction **17-4**. For a time, there was doubt as to which sulfur atom closed the ring, but now there is much evidence, including the study of ³⁴S and ¹³C isotope effects, to show that it is the C=S sulfur (see **35**).²³⁸ In a structural variation of this reaction, heating a propargylic xanthate with 2,4,6-trimethylpyridinium trifluoromethyl sulfonate leads to formation of an alkene.²³⁹

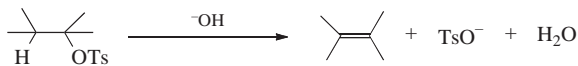


The mechanism is thus exactly analogous to that of Reaction **17-5**.

OS **VII**, 139.

17-6 Decomposition of Other Esters

Hydro-tosyloxy-elimination



Several types of inorganic ester can be cleaved to alkenes by treatment with bases. Esters of sulfuric, sulfurous, and other acids undergo elimination in solution by E1 or E2 mechanisms, as do tosylates and other esters of sulfonic acids.²⁴⁰ It has been shown that bis(tetra-*n*-butylammonium) oxalate, (Bu₄N⁺)₂ (COO[−])₂, is an excellent reagent for inducing tosylates to undergo elimination rather than substitution.²⁴¹ Aryl sulfonates have also been cleaved without a base. Esters of 2-pyridinesulfonic acid and 8-quinolinesulfonic acid gave alkenes in high yields simply on heating, without a solvent.²⁴² Phosphonate esters have been cleaved to alkenes by treatment with *Lawesson's reagent*²⁴³ (see Reaction **16-11**).

OS, **VI**, 837; **VII**, 117.

²³⁶ See Nagle, A.S.; Salvataore, R.N.; Cross, R.M.; Kapxhiu, E.A.; Sahab, S.; Yoon, C.H.; Jung, K.W. *Tetrahedron Lett.* **2003**, 44, 5695.

²³⁷ DePuy, C.H.; King, R.W. *Chem. Rev.* **1960**, 60, 431, see p. 444; Nace, H.R. *Org. React.* **1962**, 12, 57.

²³⁸ Bader, R.F.W.; Bourns, A.N. *Can. J. Chem.* **1961**, 39, 348.

²³⁹ Fauré-Tromeur, M.; Zard, S.Z. *Tetrahedron Lett.* **1999**, 40, 1305.

²⁴⁰ For a list of reagents used for sulfonate cleavages, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 294–295.

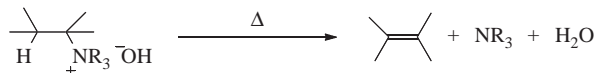
²⁴¹ Corey, E.J.; Terashima, S. *Tetrahedron Lett.* **1972**, 111.

²⁴² Corey, E.J.; Posner, G.H.; Atkinson, R.F.; Wingard, A.K.; Halloran, D.J.; Radzik, D.M.; Nash, J.J. *J. Org. Chem.* **1989**, 54, 389.

²⁴³ Shimagaki, M.; Fujieda, Y.; Kimura, T.; Nakata, T. *Tetrahedron Lett.* **1995**, 36, 719.

17-7 Cleavage of Quaternary Ammonium Hydroxides

Hydro-trialkylammonio-elimination



Cleavage of quaternary ammonium hydroxides is the final step of the process known as *Hofmann exhaustive methylation* or *Hofmann degradation* or just *Hofmann elimination*.²⁴⁴ In the first step, a primary, secondary, or tertiary amine is treated with enough iodomethane to convert it to the quaternary ammonium iodide (Reaction **10-31**). In the second step, the iodide counterion is converted to the hydroxide counterion by treatment with silver oxide. In the cleavage step, an aqueous or alcoholic solution of the ammonium hydroxide is distilled, often under reduced pressure. The decomposition generally takes place between 100 and 200 °C. Alternatively, the solution can be concentrated to a syrup by distillation or freeze-drying.²⁴⁵ When the syrup is heated at low pressures, the cleavage reaction takes place at lower temperatures than are required for the reaction in the ordinary solution, probably because the base (HO^- or RO^-) is less solvated.²⁴⁶ The reaction has never been an important synthetic tool, but has been used in the determination of the structure of unknown amines, especially alkaloids. In many of these compounds, the nitrogen is in a ring, or even at a ring junction, and in such cases formation of the alkene is incomplete. Repetitions of the process are required to remove the nitrogen completely, as in the conversion of 2-methylpiperidine to 1,5-hexadiene by two rounds of exhaustive methylation followed by pyrolysis.

A side reaction involving nucleophilic substitution to give an alcohol ($\text{R}_4\text{N}^+ \text{OH}^- \rightarrow \text{ROH} + \text{R}_3\text{N}$) generally accompanies the normal elimination reaction,²⁴⁷ but seldom causes trouble. However, when none of the four groups on the nitrogen has a β hydrogen, substitution is the only reaction possible. On heating $\text{Me}_4\text{N}^+ \text{OH}^-$ in water, methanol is obtained, although without a solvent the product is not methanol, but dimethyl ether.²⁴⁸

The mechanism of elimination is usually E2 in protic solvents. *Hofmann's rule* is generally obeyed by acyclic and *Zaitsev's rule* by cyclohexyl substrates (Sec. 17.B, category 4). In certain cases, where the molecule is highly hindered or if the ammonium hydroxide is heated without solvent (neat), a five-membered E^i mechanism, similar to that in Reaction **17-8**, has been shown to operate. That is, the hydroxide in these cases does not attract the β hydrogen, but instead removes one of the methyl hydrogen atoms (see **36**), which removes a proton from the less substituted β -carbon atom to give the less substituted alkene with loss of the amine. It is also possible that the hydroxide (rather than the *N*-ylid) removes the β -hydrogen atom via an eclipsed rotamer in which the hydroxide is tethered to the ammonium unit and a syn-transition state is lower in energy.

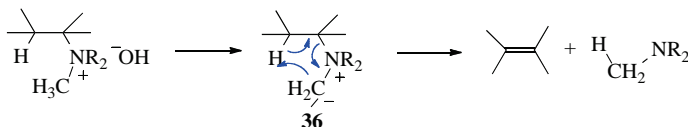
²⁴⁴ Bentley, K.W. in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, **1973**, pp. 255–289; White, E.H.; Woodcock, D.J. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, **1968**, pp. 409–416; Cope, A.C.; Trumbull, E.R. *Org. React.* **1960**, *11*, 317.

²⁴⁵ Archer, D.A. *J. Chem. Soc. C* **1971**, 1327.

²⁴⁶ Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**, pp. 4–5.

²⁴⁷ Baumgarten, R.J. *J. Chem. Educ.* **1968**, *45*, 122.

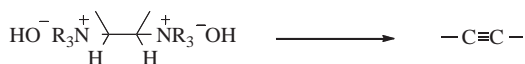
²⁴⁸ See Musker, W.K.; Stevens, R.R. *J. Am. Chem. Soc.* **1968**, *90*, 3515.



The obvious way to distinguish between this mechanism and the ordinary E2 mechanism is by the use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β carbon ($\text{R}_2\text{CDCH}_2\text{NMe}_3^+ \text{OH}^-$), the fate of the deuterium indicates the mechanism. If the E2 mechanism were in operation, the trimethylamine produced would contain no deuterium, which would be found only in the water. But if the mechanism is E^1 , the amine would contain deuterium. In the case of the highly hindered compound $(\text{Me}_3\text{C})_2\text{CDCH}_2\text{NMe}_3^+ \text{OH}^-$, the deuterium did appear in the amine, demonstrating an E^1 mechanism for this case.²⁴⁹ With simpler compounds, the mechanism is E2, since here the amine was deuterium-free.²⁵⁰

When the nitrogen bears more than one group possessing a β hydrogen, which group cleaves? The *Hofmann rule* says that *within* a group the hydrogen on the least alkylated carbon cleaves. This tendency is also carried over to the choice of which group cleaves: thus ethyl with three β -hydrogen atoms cleaves more readily than any longer n -alkyl group, all of which have two β -hydrogen atoms. "The β hydrogen is removed most readily if it is located on a methyl group, next from RCH_2 , and least readily from R_2CH ."²⁵¹ In fact, the *Hofmann rule* as first stated²⁵² in 1851 applied only to which group cleaved, not to the orientation within a group. The latter could not have been specified in 1851, since the structural theory of organic compounds was not formulated until 1857–1860. Of course, the *Hofmann rule* (applied to which group cleaves *or* to orientation within a group) is superseded by conjugation possibilities. Thus $\text{PhCH}_2\text{CH}_2\text{N}^+\text{Me}_2\text{Et}^- \text{OH}^-$ gives mostly styrene instead of ethylene.

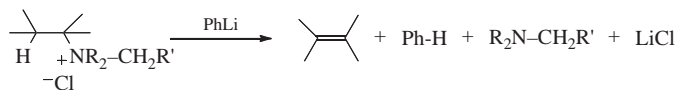
Triple bonds have been prepared by pyrolysis of 1,2-bis(ammonium) salts.²⁵³



OS IV, 980; V, 315, 608; VI, 552. Also see, OS V, 621, 883; VI, 75.

17-8 Cleavage of Quaternary Ammonium Salts with Strong Bases

Hydro-trialkylammonio-elimination



²⁴⁹ Cope, A.C.; Mehta, A.S. *J. Am. Chem. Soc.* **1963**, 85, 1949. See also, Baldwin, M.A.; Banthorpe, D.V.; Loudon, A.G.; Waller, F.D. *J. Chem. Soc. B* **1967**, 509.

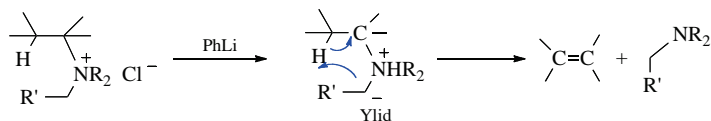
²⁵⁰ Cope, A.C.; LeBel, N.A.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* **1961**, 83, 3861.

²⁵¹ Cope, A.C.; Trumbull, E.R. *Org. React.* **1960**, 11, 317, see p. 348.

²⁵² Hofmann, A.W. *Liebigs Ann. Chem.* **1851**, 78, 253.

²⁵³ See Franke, W.; Ziegenbein, W.; Meister, H. *Angew. Chem.* **1960**, 72, 391, see pp. 397–398.

When quaternary ammonium halides are treated with strong bases (e.g., PhLi, KNH₂ in liquid NH₃²⁵⁴), an elimination can occur that is similar in products, although not in mechanism, to Reaction 17-7. This is an alternative to Reaction 17-7 and is done on the quaternary ammonium halide, so that it is not necessary to convert this to the hydroxide. The mechanism is E¹:



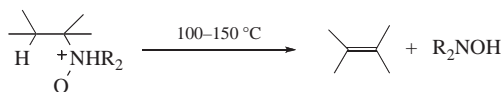
An α' hydrogen is obviously necessary in order for the ylid to be formed. This type of mechanism is called α',β elimination, since a β hydrogen is removed by the α' carbon. The mechanism has been confirmed by labeling experiments similar to those described at Reaction 17-7,²⁵⁵ and by isolation of the intermediate ylids.²⁵⁶ An important synthetic difference between this and most instances of Reaction 17-7 is that syn elimination is observed here and anti elimination in Reaction 17-7, so products of opposite configuration are formed when the alkene exhibits cis-trans isomerism.

An alternative procedure that avoids the use of a very strong base is heating the salt with KOH in polyethylene glycol monomethyl ether.²⁵⁷

Benzotriazole has been shown to be a good leaving group for elimination reactions. The reaction of an allylic benzotriazole (3-benzotriazolyl-4-trimethylsilyl-1-butene) with *n*-butyllithium, and then an alkyl halide leads to an alkylated 1,3-diene upon heating.²⁵⁸

17-9 Cleavage of Amine Oxides

Hydro-(Dialkyloxidoammonio)-elimination



Cleavage of amine oxides to produce an alkene and a hydroxylamine is called the *Cope reaction* or *Cope elimination* (not to be confused with the *Cope rearrangement*, 18-32). It is an alternative to Reactions 17-7 and 17-8.²⁵⁹ The reaction is usually performed with a mixture of amine and oxidizing agent (see 19-29) without isolation of the amine oxide. Because of the mild conditions, side reactions are few, and the alkenes do not usually rearrange. The reaction is thus very useful for the preparation of many alkenes. A limitation is that it does not open six-membered rings containing nitrogen, although it does open rings of 5 and 7–10 members.²⁶⁰ Rates of the reaction increase with increasing size of α - and

²⁵⁴ Bach, R.D.; Bair, K.W.; Andrzejewski, D. *J. Am. Chem. Soc.* **1972**, *94*, 8608; *J. Chem. Soc., Chem. Commun.* **1974**, 819.

²⁵⁵ Bach, R.D.; Knight, J.W. *Tetrahedron Lett.* **1979**, 3815.

²⁵⁶ Wittig, G.; Burger, T.F. *Liebigs Ann. Chem.* **1960**, 632, 85.

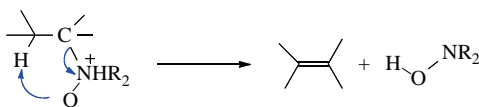
²⁵⁷ Hünig, S.; Öller, M.; Wehner, G. *Liebigs Ann. Chem.* **1979**, 1925.

²⁵⁸ Katritzky, A.R.; Serdyuk, L.; Toader, D.; Wang, X. *J. Org. Chem.* **1999**, *64*, 1888.

²⁵⁹ See Cope, A.C.; Trumbull, E.R. *Org. React.* **1960**, *11*, 317, see p. 361; DePuy, C.H.; King, R.W. *Chem. Rev.* **1960**, *60*, 431, see pp. 448–451.

²⁶⁰ Cope, A.C.; LeBel, N.A. *J. Am. Chem. Soc.* **1960**, *82*, 4656; Cope, A.C.; Ciganek, E.; Howell, C.F.; Schweizer, E.E. *J. Am. Chem. Soc.* **1960**, *82*, 4663.

β -substituents.²⁶¹ The reaction can be carried out at room temperature in dry Me_2SO or THF.²⁶² The influence of solvent effects has been examined.²⁶³ The elimination is a stereoselective syn process,²⁶⁴ and the five-membered E^i mechanism operates:



Almost all evidence indicates that the transition state must be planar. Deviations from planarity as in Reaction 17-4 (see Sec. 17.E.i) are not found here, and indeed this is why six-membered heterocyclic nitrogen compounds do not react. Because of the stereoselectivity of this reaction and the lack of rearrangement of the products, it is useful for the formation of *trans*-cycloalkenes (eight-membered and higher). A polymer-bound *Cope elimination* reaction has been reported.²⁶⁵

OS IV, 612.

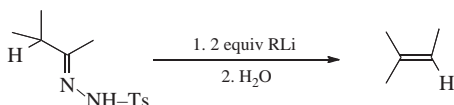
17-10 Pyrolysis of Keto-ylids

Hydro-(oxophosphoryl)-elimination



Phosphorus ylids are quite common (see Reaction 16-44) and keto-phosphorus ylids ($\text{RCOCH}=\text{PPh}_3$) are also known. When these compounds are heating (flash vacuum pyrolysis, FVP) to $> 500^\circ\text{C}$, alkynes are formed. Simple alkynes²⁶⁶ can be formed as well as keto-alkynes²⁶⁷ and en-yne.²⁶⁸ Rearrangement from ylids derived from tertiary amines and α -diazo ketones is also known.²⁶⁹

17-11 Decomposition of Toluene-p-sulfonylhydrazones



Treatment of the tosylhydrazone of an aldehyde or a ketone with a strong base leads to the formation of an alkene, the reaction being formally an elimination accompanied by a hydrogen shift.²⁷⁰ The reaction (called the *Shapiro reaction*) has been applied to

²⁶¹ Závada, J.; Pánková, M.; Svoboda, M. *Collect. Czech. Chem. Commun.* **1973**, 38, 2102.

²⁶² Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc.* **1962**, 84, 1734.

²⁶³ Acevedo, O.; Jorgensen, W.L. *J. Am. Chem. Soc.* **2006**, 128, 6141.

²⁶⁴ See, for example, Bach, R.D.; Andrzejewski, D.; Dusold, L.R. *J. Org. Chem.* **1973**, 38, 1742.

²⁶⁵ Sammelson, R.E.; Kurth, M.J. *Tetrahedron Lett.* **2001**, 42, 3419.

²⁶⁶ Aitken, R.A.; Atherton, J.I. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1281.

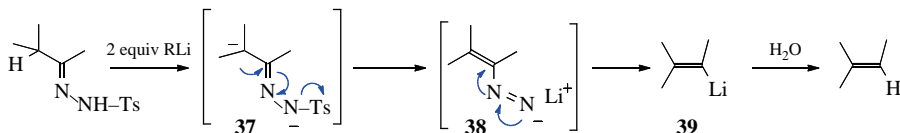
²⁶⁷ Aitken, R.A.; Hérion, H.; Janosi, A.; Karodia, N.; Raut, S.V.; Seth, S.; Shannon, I.J.; Smith, F.C. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2467.

²⁶⁸ Aitken, R.A.; Boeters, C.; Morrison, J.J. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2473.

²⁶⁹ DelZotto, A.; Baratta, W.; Miani, F.; Verardo, G.; Rigo, P. *Eur. J. Org. Chem.* **2000**, 3731.

²⁷⁰ See Adlington, R.M.; Barrett, A.G.M. *Acc. Chem. Res.* **1983**, 16, 55; Shapiro, R.H. *Org. React.* **1976**, 23, 405.

tosylhydrazones²⁷¹ of many aldehydes and ketones. The most useful synthetic method involves treatment of the substrate with at least 2 molar equivalents of an organolithium compound²⁷² (usually MeLi) in ether, hexane, or tetramethylenediamine.²⁷³ This procedure gives good yields of alkenes without side reactions and, where a choice is possible, predominantly gives the less highly substituted alkene. Tosylhydrazones of α,β -unsaturated ketones give conjugated dienes.²⁷⁴ The mechanism²⁷⁵ has been formulated as that shown.



Evidence for this mechanism is (1) two molar equivalents of RLi are required; (2) the hydrogen in the product comes from the water and not from the adjacent carbon, as shown by deuterium labeling;²⁷⁶ and (3) the intermediates **37**–**39** have been trapped.²⁷⁷ This reaction, when performed in tetramethylenediamine, can be a synthetically useful method²⁷⁸ of generating vinylic lithium compounds (**39**), which can be trapped by various electrophiles²⁷⁹ (e.g., D₂O, to give deuterated alkenes), CO₂ (to give α,β -unsaturated carboxylic acids, Reaction **16-30**), or DMF (to give α,β -unsaturated aldehydes, Reaction **16-82**). Treatment of *N*-aziridino hydrazones with LDA leads to alkenes with high *cis* selectivity.²⁸⁰

The reaction also takes place with other bases (e.g., NaH, LiH,²⁸¹ Na in ethylene glycol, NaNH₂) or with smaller amounts of RLi, but in these cases side reactions are common and the orientation of the double bond is in the other direction (to give the more highly substituted alkene). The reaction with Na in ethylene glycol is called the *Bamford–Stevens reaction*.²⁸² For these reactions, two mechanisms are possible: a carbenoid and a carbocation mechanism.²⁸³ The side reactions found are those expected of carbenes and carbocations. In general, the carbocation mechanism is chiefly found in protic solvents and the carbenoid mechanism in aprotic solvents. Both routes involve formation of a diazo compound (**40**), which in some cases can be isolated. In fact, this reaction has been used as a synthetic method for the preparation of diazo compounds.²⁸⁴ In the absence of protic solvents, **36** loses N₂, and hydrogen migrates, to give the alkene product. The migration of hydrogen may immediately follow, or be simultaneous with, the loss of N₂. In a protic

²⁷¹ See Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem. Int. Ed.* **2007**, 46, 5587.

²⁷² Shapiro, R.H. *Tetrahedron Lett.* **1968**, 345; Meinwald, J.; Uno, F. *J. Am. Chem. Soc.* **1968**, 90, 800.

²⁷³ Stemke, J.E.; Bond, F.T. *Tetrahedron Lett.* **1975**, 1815.

²⁷⁴ See Dauben, W.G.; Rivers, G.T.; Zimmerman, W.T. *J. Am. Chem. Soc.* **1977**, 99, 3414.

²⁷⁵ For a review of the mechanism, see Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* **1975**, 922.

²⁷⁶ See Ref. 272; Shapiro, R.H.; Hornaman, E.C. *J. Org. Chem.* **1974**, 39, 2302.

²⁷⁷ Lipton, M.F.; Shapiro, R.H. *J. Org. Chem.* **1978**, 43, 1409.

²⁷⁸ See Traas, P.C.; Boelens, H.; Takken, H.J. *Tetrahedron Lett.* **1976**, 2287; Stemke, J.E.; Chamberlin, A.R.; Bond, F.T. *Tetrahedron Lett.* **1976**, 2947.

²⁷⁹ For a review, see Chamberlin, A.R.; Bloom, S.H. *Org. React.* **1990**, 39, 1.

²⁸⁰ Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, 118, 2289.

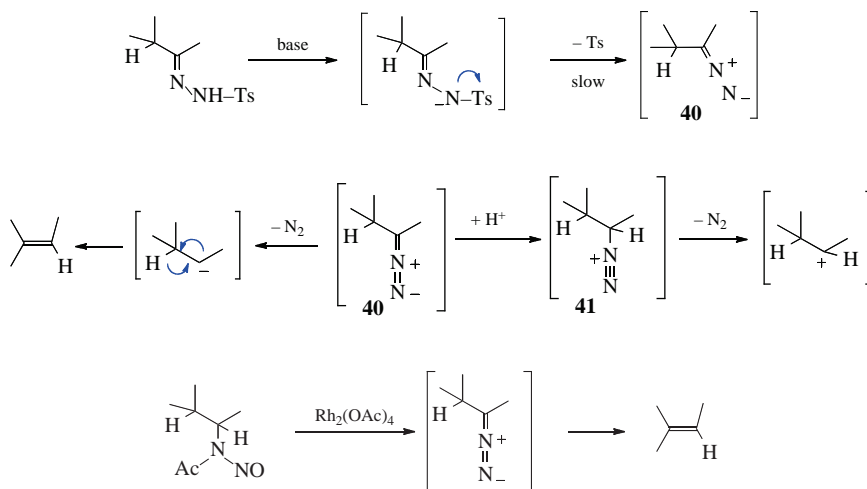
²⁸¹ Biellmann, J.F.; Pète, J. *Bull. Soc. Chim. Fr.* **1967**, 675.

²⁸² Bamford, W.R.; Stevens, R.R. *J. Chem. Soc.* **1952**, 4735. For a tandem *Bamford–Stevens–Claisen rearrangement*, see May, J.A.; Stoltz, B.M. *J. Am. Chem. Soc.* **2002**, 124, 12426.

²⁸³ See Nickon, A.; Werstiuk, N.H. *J. Am. Chem. Soc.* **1972**, 94, 7081.

²⁸⁴ See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, **1986**, pp. 257–295. For an improved procedure, see Wulfin, D.S.; Yousefian, S.; White, J.M. *Synth. Commun.* **1988**, 18, 2349.

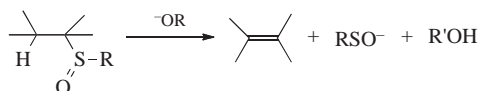
solvent, **40** becomes protonated to give the diazonium ion **41**, which loses N_2 to give the corresponding carbocation, that may then undergo elimination or give other reactions characteristic of carbocations. A diazo compound is an intermediate in the formation of alkenes by treatment of *N*-nitrosoamides with a Rh(II) catalyst.²⁸⁵



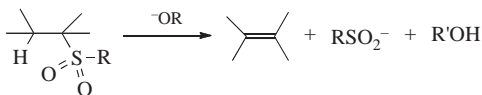
OS VI, 172; VII, 77; IX, 147. For the preparation of a diazo compound, see OS VII, 438.

17-12 Cleavage of Sulfoxides, Selenoxides, and Sulfones

Hydro-alkylsulfinyl-elimination



Hydro-alkylsulfonyl-elimination



Sulfonium compounds ($-C-SR_2^+$) undergo elimination similar to that of their ammonium counterparts (Reactions 17-7 and 17-8) in scope and mechanism, but this reaction is not of great synthetic importance. These syn-elimination reactions are related to the *Cope elimination* (Reaction 17-9) and *Hofmann elimination* (Reaction 17-7).²⁸⁶

²⁸⁵ Godfrey, A.G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, 112, 3717.

²⁸⁶ See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 161–171.

Sulfones and sulfoxides²⁸⁷ with a β hydrogen, on the other hand, undergo elimination on treatment with an alkoxide or, for sulfones,²⁸⁸ even with hydroxide.²⁸⁹ Sulfones also eliminate in the presence of an organolithium reagent and a Pd catalyst.²⁹⁰ Mechanistically, these reactions belong on the E1–E2–E1cB spectrum.²⁹¹ Although the leaving groups are uncharged, the orientation follows *Hofmann's rule*, not *Zaitsev's*. Sulfoxides (but not sulfones) also undergo elimination upon pyrolysis at $\sim 80^\circ\text{C}$ in a manner analogous to Reaction 17-9. The mechanism is also analogous, being the five-membered Eⁱ mechanism with syn elimination.²⁹²

Selenoxides²⁹³ and sulfinate esters ($\text{R}_2\text{CH}-\text{CHR}-\text{SO}-\text{OMe}$)²⁹⁴ also undergo elimination by the Eⁱ mechanism, and the selenoxide reaction takes place at room temperature. The reaction with selenoxides has been extended to the formation of triple bonds.²⁹⁵

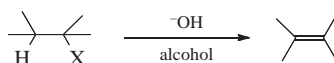
Both α -keto selenoxides²⁹⁶ and sulfoxides²⁹⁷ have been used in a method for the conversion of ketones, aldehydes, and carboxylic esters to their α,β -unsaturated derivatives. Allylic sulfoxides undergo 1,4-elimination to give dienes.²⁹⁸

A radical elimination reaction generates alkenes from sulfoxides. The reaction of a 2-bromophenyl alkylsulfoxide with Bu_3SnH and AIBN (see Sec. 14.A.i for a discussion of these standard radical conditions) leads to an alkene.²⁹⁹

OS VI, 23, 737; VIII, 543; IX, 63.

17-13 Dehydrohalogenation of Alkyl Halides

Hydro-halo-elimination



The elimination of HX from an alkyl halide is a very general reaction and can be accomplished with chlorides, fluorides, bromides, and iodides.³⁰⁰ Hot alcoholic KOH is the

²⁸⁷ See Cubbage, J.W.; Guo, Y.; McCulla, R.D.; Jenks, W.S. *J. Org. Chem.* **2001**, 66, 8722.

²⁸⁸ See Yoshida, T.; Saito, S. *Chem. Lett.* **1982**, 165.

²⁸⁹ Hofmann, J.E.; Wallace, T.J.; Argabright, P.A.; Schriesheim, A. *Chem. Ind. (London)* **1963**, 1234.

²⁹⁰ Gai, Y.; Jin, L.; Julia, M.; Verpeaux, J.-N. *J. Chem. Soc., Chem. Commun.* **1993**, 1625.

²⁹¹ Hofmann, J.E.; Wallace, T.L.; Schriesheim, A. *J. Am. Chem. Soc.* **1964**, 86, 1561.

²⁹² Schmitz, C.; Harvey, J.N.; Viehe, H.G. *Bull. Soc. Chim. Belg.* **1994**, 103, 105.

²⁹³ Back, T.G. in Patai, S. *The Chemistry of Organic Selenium and Tellurium Compounds*, Vol. 2, Wiley, NY, **1987**, pp. 91–213, pp. 95–109; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, **1986**, pp. 132–143; Reich, H.J. *Acc. Chem. Res.* **1979**, 12, 22, in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, **1978**, pp. 15–101; Sharpless, K.B.; Gordon, K.M.; Lauer, R.F.; Patrick, D.W.; Singer, S.P.; Young, M.W. *Chem. Scr.* **1975**, 8A, 9. See Liotta, D. *Organoselenium Chemistry*, Wiley, NY, **1987**.

²⁹⁴ Jones, D.N.; Higgins, W. *J. Chem. Soc. C* **1970**, 81.

²⁹⁵ Reich, H.J.; Willis Jr., W.W. *J. Am. Chem. Soc.* **1980**, 102, 5967.

²⁹⁶ Reich, H.J.; Renga, J.M.; Reich, I.L. *J. Am. Chem. Soc.* **1975**, 97, 5434 and references cited therein; Crich, D.; Barba, G.R. *Org. Lett.* **2000**, 2, 989. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 287–290.

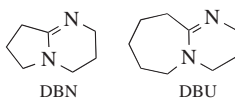
²⁹⁷ Trost, B.M.; Salzmann, T.N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, 98, 4887. For a review of this and related methods, see Trost, B.M. *Acc. Chem. Res.* **1978**, 11, 453.

²⁹⁸ de Groot, A.; Jansen, B.J.M.; Reuvers, J.T.A.; Tedjo, E.M. *Tetrahedron Lett.* **1981**, 22, 4137.

²⁹⁹ Imboden, C.; Villar, F.; Renaud, P. *Org. Lett.* **1999**, 1, 873.

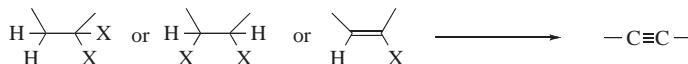
³⁰⁰ See Baciocchi, E. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, **1983**, pp. 1173–1227.

most frequently used base, although stronger bases³⁰¹ (^-OR , $^-\text{NH}_2$, etc.) or weaker ones (e.g., amines) are used where warranted.³⁰² The bicyclic amidines 1,5-diazabicyclo[3.4.0]non-5-ene (DBN)³⁰³ and DBU³⁰⁴ are good reagents for difficult cases.³⁰⁵ Solvation by HMPA promotes LDA mediated dehydrobromination.³⁰⁶



Dehydrohalogenation with the non-ionic base $(\text{Me}_2\text{N})_3\text{P}=\text{N}-\text{P}(\text{NMe}_3)_2=\text{NMe}$ is even faster.³⁰⁷ A Co catalyst with dimethylphenylsilylmethylmagnesium chloride leads to formation of terminal alkenes from 2° alkyl bromides.³⁰⁸ Phase-transfer catalysis has been used with hydroxide as base.³⁰⁹ As previously mentioned (Sec. 17.A.v), certain weak bases in dipolar aprotic solvents are effective reagents for dehydrohalogenation. Among those most often used for synthetic purposes are LiCl or LiBr-LiCO₃ in DMF.³¹⁰ Dehydrohalogenation occurs by simply heating the alkyl halide in HMPA with no other reagent present.³¹¹ As in nucleophilic substitution (Sec. 10.G.iii), the order of leaving group reactivity is $\text{I} > \text{Br} > \text{Cl} > \text{F}$.³¹² Tertiary halides undergo elimination most easily. Eliminations of chlorides, bromides, and iodides follow *Zaitsev's rule*, except for a few cases where steric effects are important (e.g., see Sec. 17.B, category 4). Eliminations of fluorides follow *Hofmann's rule* (Sec. 17.B, category 4).

This reaction is by far the most important way of introducing a triple bond into a molecule.³¹³ Alkyne formation can be accomplished with substrates of the types:³¹⁴



When the base is NaNH_2 , 1-alkynes predominate (where possible), because this base is strong enough to form the salt of the alkyne, shifting any equilibrium between 1- and

³⁰¹ See Anton, D.R.; Crabtree, R.H. *Tetrahedron Lett.* **1983**, 24, 2449.

³⁰² For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 256–258.

³⁰³ Vogel, E.; Klärner, F. *Angew. Chem. Int. Ed.* **1968**, 7, 374.

³⁰⁴ Oediger, H.; Möller, F. *Angew. Chem. Int. Ed.* **1967**, 6, 76; Wolkoff, P. *J. Org. Chem.* **1982**, 47, 1944.

³⁰⁵ See Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591.

³⁰⁶ Clayden, J. *Organolithiums: Selectivity for Synthesis*, Pergamon, New York, **2002**; For a mechanistic evaluation and an analysis of the influence of HMPA, see Ma, Y.; Ramirez, A.; Singh, K.J.; Keresztes, I.; Collum, D.B. *J. Am. Chem. Soc.* **2006**, 128, 15399.

³⁰⁷ Schwesinger, R.; Schlemper, H. *Angew. Chem. Int. Ed.* **1987**, 26, 1167.

³⁰⁸ Kobayashi, T.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2008**, 130, 11276.

³⁰⁹ Halpern, M.; Zahalka, H.A.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* **1985**, 50, 5088. See also, Barry, J.; Bram, G.; Decodts, G.; Loupy, A.; Pigeon, P.; Sansoulet, J. *J. Org. Chem.* **1984**, 49, 1138.

³¹⁰ See Fieser, L.F.; Fieser, M. *Reagents for Organic Syntheses*, Vol. 1, Wiley, NY, **1967**, pp. 606–609; Yakobson, G.G.; Akhmetova, N.E. *Synthesis* **1983**, 169, see pp. 170–173.

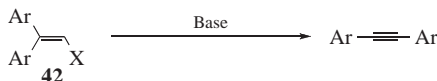
³¹¹ See Hoye, T.R.; van Deidhuizen, J.J.; Vos, T.J.; Zhao, P. *Synth. Commun.* **2001**, 31, 1367.

³¹² Matsubara, S.; Matsuda, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* **1988**, 44, 2855.

³¹³ Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, **1978**, p. 755; Köbrich, G.; Buck, P. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, **1969**, pp. 100–134; Köbrich, G. *Angew. Chem. Int. Ed.* **1965**, 4, 49, see pp. 50–53.

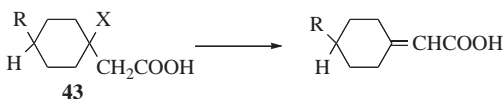
³¹⁴ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 569–571.

2-alkynes. When the base is ^-OH or ^-OR , the equilibrium tends to be shifted to the internal alkyne, which is thermodynamically more stable. If another hydrogen is suitably located (e.g., $-\text{CRH}-\text{CX}_2-\text{CH}_2-$), allene formation can compete, although alkynes are usually more stable. Tetrabutylammonium fluoride mediates the dehydrobromination of vinyl bromide to terminal alkynes.³¹⁵ Treatment of 1,1-dibromo-1-alkenes with a Pd-catalyst, followed by reaction with tetrabutylammonium hydroxide gives an internal alkyne.³¹⁶



1,1-Dibromoalkenes are converted to alkynes when treated with *n*-butyllithium.³¹⁷ This transformation is a modification of the *Fritsch–Buttenberg–Wiechell rearrangement* in which a 1,1-diaryl vinyl bromide (**42**) gives a diaryl alkyne upon treatment with base.³¹⁸ Vinyl sulfoxides that contain a leaving group (e.g., chloride) on the double bond react with *tert*-butyllithium to give a lithio alkyne, and hydrolysis leads to the final product, an alkyne.

Dehydrohalogenation is generally carried out in solution, with a base, and the mechanism is usually E2, although the E1 mechanism has been demonstrated in some cases. However, elimination of HX can be accomplished by pyrolysis of the halide, in which case the mechanism is Eⁱ (Sec. 17.E.i) or, in some instances, the free radical mechanism (Sec. 17.E.i). Pyrolysis is normally performed without a catalyst at $\sim 400^\circ\text{C}$. The pyrolysis reaction is not generally useful synthetically, because of its reversibility. Less work has been done on pyrolysis with a catalyst³¹⁹ (usually a metallic oxide or salt), but the mechanisms here are probably E1 or E2.



In the special case of the prochiral carboxylic acids (**43**), dehydrohalogenation with an optically active lithium amide gave an optically active product with %ee as high as 82%.³²⁰

OS **I**, 191, 205, 209, 438; **II**, 10, 17, 515; **III**, 125, 209, 270, 350, 506, 623, 731, 785; **IV**, 128, 162, 398, 404, 555, 608, 616, 683, 711, 727, 748, 755, 763, 851, 969; **V**, 285, 467, 514; **VI**, 87, 210, 327, 361, 368, 427, 462, 505, 564, 862, 883, 893, 954, 991, 1037; **VII**, 126, 319, 453, 491; **VIII**, 161, 173, 212, 254; **IX**, 191, 656, 662. Also see, OS **VI**, 968.

³¹⁵ Okutani, M.; Mori, Y. *Tetrahedron Lett.* **2007**, 48, 6856; Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, 74, 442.

³¹⁶ Chelucci, G.; Capitta, F.; Baldino, S. *Tetrahedron* **2008**, 64, 10250.

³¹⁷ Chernick, E.T.; Eisler, S.; Tykwinski, R.R. *Tetrahedron Lett.* **2001**, 42, 8575.

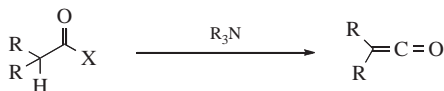
³¹⁸ Fritsch, P. *Ann.* **1894**, 279, 319; Buttenberg, W.P. *Ann.*, **1894**, 279, 324; Wiechell, H. *Ann.* **1894**, 279, 337. For a review, see Stang, P.J. *Chem. Rev.* **1978**, 78, 383. See Jahnke, E.; Tykwinski, R.R. *Chem. Commun.* **2010**, 3235; Pratt, L.M.; Nguyen, N.V.; Kwon, O. *Chem. Lett.* **2009**, 38, 574.

³¹⁹ For a review, see Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed.* **1971**, 10, 172.

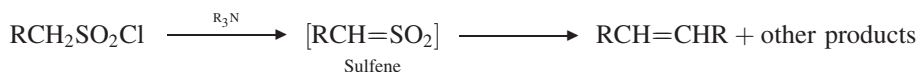
³²⁰ Duhamel, L.; Ravard, A.; Plaquevent, J.C.; Plé, G.; Davoust, D. *Bull. Soc. Chim. Fr.* **1990**, 787.

17-14 Dehydrohalogenation of Acyl Halides and Sulfonyl Halides

Hydro-halo-elimination



Ketenes can be prepared by treatment of acyl halides with tertiary amines³²¹ or with NaH and a crown ether.³²² The scope is broad, and most acyl halides possessing an α hydrogen give the reaction, but if at least one R is hydrogen, only the ketene dimer, not the ketene, is isolated. However, if a reactive ketene must be used in a reaction with a given compound, the ketene can be generated *in situ* in the presence of the given compound.³²³

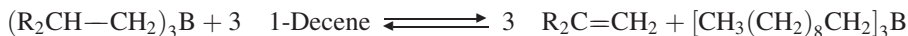


Closely related is the reaction of tertiary amines with sulfonyl halides that contain an α hydrogen. In this case, the initial product is the highly reactive sulfene, which cannot be isolated but reacts further to give products, one of which may be the alkene that is the dimer of RCH.³²⁴ Reactions of sulfenes *in situ* are also common (e.g., see 16-48).

OS IV, 560; V, 294, 877; VI, 549, 1037; VII, 232; VIII, 82.

17-15 Elimination of Boranes

Hydro-boranetriyl-elimination



Trialkylboranes are formed from an alkene and BH_3 (Reaction 15-16). When the resulting borane is treated with another alkene, an exchange reaction occurs.³²⁵ This is an equilibrium process that can be shifted by using a large excess of alkene, by using an unusually reactive alkene, or by using an alkene with a higher boiling point than the displaced alkene and removing the latter by distillation. The reaction is useful for shifting a double bond in the direction opposite to that resulting from normal isomerization methods (12-2). This cannot be accomplished simply by treatment of a borane with an alkene, because elimination in this reaction follows *Zaitsev's rule*: It is in the direction of the most stable alkene. However, heating borane (44) leads to 45 (Reaction 18-11) and when 45 is heated with a higher-boiling alkene (e.g., 1-decene), the exchange reaction gives 46. These isomerizations proceed essentially without rearrangement. The mechanism is probably the reverse of borane addition (Reaction 15-16).

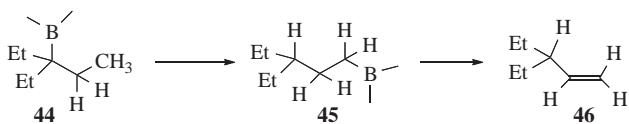
³²¹ See Tidwell, T.T. *Ketenes*, Wiley, NY, 1995.

³²² Taggi, A.E.; Wack, H.; Hafez, A.M.; France, S.; Lectka, T. *Org. Lett.* **2002**, 4, 627.

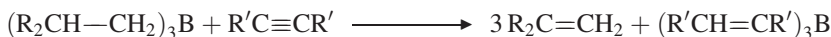
³²³ See Luknitskii, F.I.; Vovsi, B.A. *Russ. Chem. Rev.* **1969**, 38, 487.

³²⁴ See King, J.F. *Acc. Chem. Res.* **1975**, 8, 10; Nagai, T.; Tokura, N. *Int. J. Sulfur Chem. Part B* **1972**, 207; Truce, W.E.; Liu, L.K. *Mech. React. Sulfur Compd.* **1969**, 4, 145; Opitz, G. *Angew. Chem. Int. Ed.* **1967**, 6, 107; Wallace, T.J. *Q. Rev. Chem. Soc.* **1966**, 20, 67.

³²⁵ Brown, H.C.; Bhatt, M.V.; Munkata, T.; Zweifel, G. *J. Am. Chem. Soc.* **1967**, 89, 567; Taniguchi, H. *Bull. Chem. Soc. Jpn.* **1979**, 52, 2942.

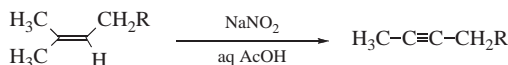


A similar reaction, but irreversible, has been demonstrated for alkynes.³²⁶



17-16 Conversion of Alkenes to Alkynes

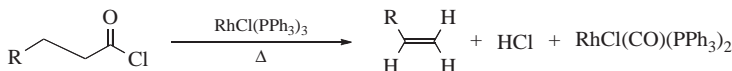
Hydro-methyl-elimination



Alkenes of the form shown lose the elements of methane when treated with sodium nitrite in acetic acid and water, to form alkynes in moderate-to-high yields.³²⁷ The R may contain additional unsaturation, as well as OH, OR, OAc, C=O, and other groups, but the $\text{Me}_2\text{C}=\text{CHCH}_2-$ portion of the substrate is necessary for the reaction to take place. The mechanism is complex, beginning with a nitration that takes place with allylic rearrangement [$\text{Me}_2\text{C}=\text{CHCH}_2\text{R} \rightarrow \text{H}_2\text{C}=\text{CMeCH}(\text{NO}_2)\text{CH}_2\text{R}$], and involving several additional intermediates.³²⁸ The CH_3 lost from the substrate appears as CO_2 , as demonstrated by the trapping of this gas.³²⁸

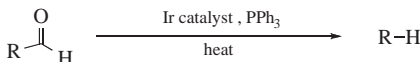
17-17 Decarbonylation of Acyl Halides or Aldehydes

Hydro-chloroformyl-elimination



Acyl chlorides containing an α hydrogen are smoothly converted to alkenes, with loss of HCl and CO, upon heating with chlorotris(triphenylphosphine)rhodium, with metallic Pt, or with certain other catalysts.³²⁹ The mechanism probably involves conversion of $\text{RCH}_2\text{CH}_2\text{COCl}$ to $\text{RCH}_2\text{CH}_2-\text{RhCO}(\text{Ph}_3\text{P})_2\text{Cl}_2$ followed by a concerted syn elimination of Rh and H^{330} (see also, Reactions **14-32** and **19-12**).

Aldehydes are decarbonylated to give the corresponding hydrocarbon in the presence of an Ir catalyst and triphenylphosphine.



³²⁶ Hubert, A.J. *J. Chem. Soc.* **1965**, 6669.

³²⁷ Abidi, S.L. *Tetrahedron Lett.* **1986**, 27, 267; *J. Org. Chem.* **1986**, 51, 2687.

³²⁸ Corey, E.J.; Seibel, W.L.; Kappos, J.C. *Tetrahedron Lett.* **1987**, 28, 4921.

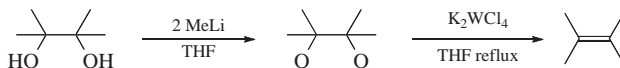
³²⁹ For a review, see Tsuji, J.; Ohno, K. *Synthesis* **1969**, 157. For extensions to certain other acid derivatives, see Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* **1987**, 992.

³³⁰ Lau, K.S.Y.; Becker, Y.; Huang, F.; Baenziger, N.; Stille, J.K. *J. Am. Chem. Soc.* **1977**, 99, 5664.

B. Reactions in which Neither Leaving Atom Is Hydrogen

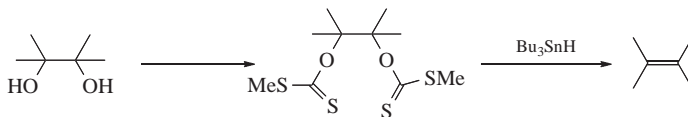
17-18 Deoxygenation of Vicinal Diols

Dihydroxy-elimination

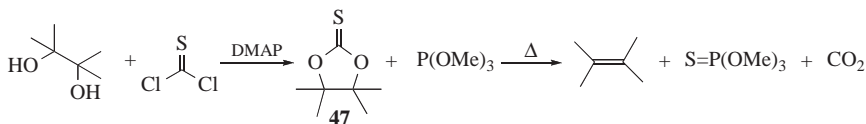


vic-Diols can be deoxygenated by treatment of the dilithium dialkoxide with the tungsten halide (K₂WCl₆), or with certain other tungsten reagents, in refluxing THF.³³¹ Tetrasubstituted diols react most rapidly. The elimination is largely, but not entirely, syn. Several other methods have been reported,³³² in which the diol is deoxygenated directly, without conversion to the dialkoxide. These include treatment with Ti metal,³³³ with TsOH—NaI,³³⁴ and by heating with CpReO₃,³³⁵ where Cp is cyclopentadienyl.

vic-Diols can also be deoxygenated indirectly, through sulfonate ester derivatives. For example, *vic*-dimesylates and *vic*-ditosylates have been converted to alkenes by treatment, respectively, with naphthalene—sodium³³⁶ and with NaI in DMF.³³⁷ In another procedure, the diols are converted to bis(dithiocarbonates) [bis(xanthates)], which undergo elimination (probably by a free radical mechanism) when treated with tri-*n*-butylstannane in toluene or benzene.³³⁸ *vic*-Diols can also be deoxygenated through cyclic derivatives (Reaction 17-19).



17-19 Cleavage of Cyclic Thionocarbonates



Cyclic thionocarbonates (**47**) can be cleaved to alkenes (the *Corey–Winter reaction*)³³⁹ by heating with trimethyl phosphite³⁴⁰ or other trivalent phosphorus compounds³⁴¹ or by treatment with bis(1,5-cyclooctadiene)nickel.³⁴² The thionocarbonates (e.g., **47**) can be

³³¹ Sharpless, K.B.; Umbreit, M.A.; Nieh, T.; Flood, T.C. *J. Am. Chem. Soc.* **1972**, *94*, 6538.

³³² For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 297–299.

³³³ McMurry, J.E. *Acc. Chem. Res.* **1983**, *16*, 405 and references cited therein.

³³⁴ Sarma, J.C.; Sharma, R.P. *Chem. Ind. (London)* **1987**, 96.

³³⁵ Cook, G.K.; Andrews, M.A. *J. Am. Chem. Soc.* **1996**, *118*, 9448.

³³⁶ Carnahan, Jr., J.C.; Closson, W.D. *Tetrahedron Lett.* **1972**, 3447.

³³⁷ Dafaye, J. *Bull. Soc. Chim. Fr.* **1968**, 2099.

³³⁸ Barrett, A.G.M.; Barton, D.H.R.; Bielski, R. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2378.

³³⁹ See Block, E. *Org. React.* **1984**, *30*, 457; Sonnet, P.E. *Tetrahedron* **1980**, *36*, 557, pp. 593–598; Mackie, R.K. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, **1979**, pp. 354–359.

³⁴⁰ Corey, E.J.; Winter, R.A.E. *J. Am. Chem. Soc.* **1963**, *85*, 2677.

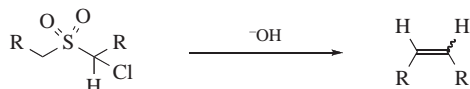
³⁴¹ Corey, E.J. *Pure Appl. Chem.* **1967**, *14*, 19, see pp. 32–33.

³⁴² Semmelhack, M.F.; Stauffer, R.D. *Tetrahedron Lett.* **1973**, 2667. For another method, see Vedejs, E.; Wu, E.S. *C. J. Org. Chem.* **1974**, *39*, 3641.

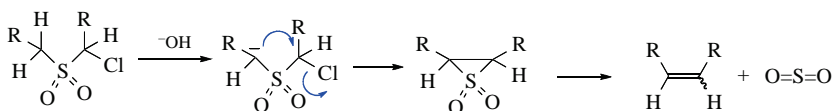
prepared by treatment of 1,2-diols with thiophosgene and DMAP.³⁴³ The elimination is of course syn, so the product is sterically controlled. Alkenes that are not sterically favored can be made this way in high yield (e.g., *cis*-PhCH₂CH=CHCH₂Ph).³⁴⁴ Certain other five-membered cyclic derivatives of 1,2-diols can also be converted to alkenes.³⁴⁵

17-20 The Ramberg–Bäcklund Reaction

Ramberg–Bäcklund halosulfone transformation



The reaction of an α -halo sulfone with a base to give an alkene is called the *Ramberg–Bäcklund reaction*.³⁴⁶ The reaction is quite general for α -halo sulfones with an α' hydrogen, despite the unreactive nature of α -halo sulfones in normal S_N2 reactions (Sec. 10.G.i, category 6). Halogen reactivity is in the order I > Br \gg Cl. Phase-transfer catalysis has been used.³⁴⁷ In general, mixtures of *cis* and *trans* isomers are obtained, but usually the less stable *cis* isomer predominates. The mechanism involves formation of an episulfone, and then elimination of SO₂. There is much evidence for this mechanism,³⁴⁸



including the isolation of the episulfone intermediate,³⁴⁹ and also the preparation of episulfones in other ways and the demonstration that they give alkenes under the reaction conditions faster than the corresponding α -halo sulfones.³⁵⁰ Episulfones synthesized in other ways (e.g., Reaction 16-48) are reasonably stable compounds, but eliminate SO₂ to give alkenes when heated or treated with base.

If the reaction is run on the unsaturated bromosulfones (RCH₂CH=CHSO₂CH₂Br, prepared by reaction of BrCH₂SO₂Br with RCH₂CH=CH₂ followed by treatment with Et₃N), RCH=CHCH=CH₂ is produced in moderate-to-good yields.³⁵¹ The compound mesyltriflone (CF₃SO₂CH₂SO₂CH₃) can be used as a synthon for the tetraion ²⁻C=C²⁻. Successive alkylation (Reaction 10-67) converts it to CF₃SO₂CR¹R²SO₂CHR³R⁴

³⁴³ Corey, E.J.; Hopkins, P.B. *Tetrahedron Lett.* **1982**, 23, 1979.

³⁴⁴ Corey, E.J.; Carey, F.A.; Winter, R.A.E. *J. Am. Chem. Soc.* **1965**, 87, 934.

³⁴⁵ See Beels, C.M.D.; Coleman, M.J.; Taylor, R.J.K. *Synlett* **1990**, 479.

³⁴⁶ Paquette, L.A. *Org. React.* **1977**, 25, 1; *Mech. Mol. Migr.* **1968**, 1, 121; *Acc. Chem. Res.* **1968**, 1, 209; Meyers, C.Y.; Matthews, W.S.; Ho, L.L.; Kolb, V.M.; Parady, T.E. in Smith, G.V. *Catalysis in Organic Synthesis*, Academic Press, NY, **1977**, pp. 197–278; Rappe, C. in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, **1973**, pp. 1105–1110; Bordwell, F.G. *Acc. Chem. Res.* **1970**, 3, 281.

³⁴⁷ Hartman, G.D.; Hartman, R.D. *Synthesis* **1982**, 504.

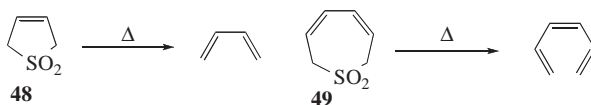
³⁴⁸ See Bordwell, F.G.; Wolfinger, M.D. *J. Org. Chem.* **1974**, 39, 2521; Bordwell, F.G.; Doomes, E. *J. Org. Chem.* **1974**, 39, 2526, 2531.

³⁴⁹ Sutherland, A.G.; Taylor, R.J.K. *Tetrahedron Lett.* **1989**, 30, 3267.

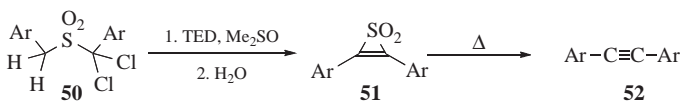
³⁵⁰ Bordwell, F.G.; Williams, Jr., J.M.; Hoyt, Jr., E.B.; Jarvis, B.B. *J. Am. Chem. Soc.* **1968**, 90, 429; Bordwell, F.G.; Williams, Jr., J.M. *J. Am. Chem. Soc.* **1968**, 90, 435.

³⁵¹ Block, E.; Aslam, M.; Eswarakrishnan, V.; Gebreyes, K.; Hutchinson, J.; Iyer, R.; Laffitte, J.; Wall, A. *J. Am. Chem. Soc.* **1986**, 108, 4568.

(anywhere from one to four alkyl groups can be put in), which, when treated with base, gives $R^1R^2C=CR^3R^4$.³⁵² The nucleofuge here is the $CF_3SO_2^-$ ion. There is an example of a *Ramberg–Bäcklund reaction* that is induced by a *Michael addition*.³⁵³



2,5-Dihydrothiophene-1,1-dioxides (**48**) and 2,17-dihydrothiepin-1,1-dioxides (**49**) undergo analogous 1,4- and 1,6-eliminations, respectively (see also, Reaction **17-36**). These are concerted reactions and, as predicted by the orbital-symmetry rules (Reaction **15-50**, A, and immediately preceding pages), the former³⁵⁴ is a suprafacial process and the latter³⁵⁵ an antarafacial process. The rules also predict that elimination of SO_2 from episulfones cannot take place by a concerted mechanism (except antarafacially, which is unlikely for such a small ring), and evidence shows that this reaction occurs by a nonconcerted pathway.³⁵⁶ The eliminations of SO_2 from **48** and **49** are examples of *cheletropic reactions*,³⁵⁷ which are defined as reactions in which two σ bonds that terminate at a single atom (in this case the sulfur atom) are made or broken in concert.³⁵⁸



α,α -Dichlorobenzyl sulfones (**50**) react with an excess of the base triethylenediamine (TED) in DMSO at room temperature to give 2,3-diarylthiiren-1,1-dioxides (**51**), which can be isolated.³⁵⁹ Thermal decomposition of **51** gives the alkynes **52**.³⁶⁰

A *Ramberg–Bäcklund-type reaction* has been carried out on the α -halo sulfides ($ArCHClSCH_2Ar$), which react with *t*-BuOK and PPh_3 in refluxing THF to give the alkenes ($ArCH=CHAr$).³⁶¹ Cyclic sulfides lead to ring-contracted cyclic alkenes upon treatment with NCS in CCl_4 followed by oxidation with *m*-chloroperoxybenzoic acid.³⁶²

³⁵² Hendrickson, J.B.; Boudreaux, G.J.; Palumbo, P.S. *J. Am. Chem. Soc.* **1986**, *108*, 2358.

³⁵³ Vasin, V.A.; Bolusheva, I.Yu.; Razin, V.V. *Russ. J. Org. Chem.* **2010**, *46*, 758.

³⁵⁴ Mock, W.L. *J. Am. Chem. Soc.* **1966**, *88*, 2857; McGregor, S.D.; Lemal, D.M. *J. Am. Chem. Soc.* **1966**, *88*, 2858.

³⁵⁵ Mock, W.L. *J. Am. Chem. Soc.* **1969**, *91*, 5682.

³⁵⁶ Bordwell, F.G.; Williams, Jr., J.M.; Hoyt, Jr., E.B.; Jarvis, B.B. *J. Am. Chem. Soc.* **1968**, *90*, 429; Bordwell, F.G.; Williams, Jr., J.M. *J. Am. Chem. Soc.* **1968**, *90*, 435. See also, Vilsmaier, E.; Tropitzsch, R.; Vostrowsky, O. *Tetrahedron Lett.* **1974**, 3987.

³⁵⁷ See Mock, W.L. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, **1977**, pp. 141–179.

³⁵⁸ Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, **1970**, pp. 152–163.

³⁵⁹ Philips, J.C.; Swisher, J.V.; Haidukewych, D.; Morales, O. *Chem. Commun.* **1971**, 22.

³⁶⁰ Philips, J.C.; Morales, O. *J. Chem. Soc., Chem. Commun.* **1977**, 713.

³⁶¹ Mitchell, R.H. *Tetrahedron Lett.* **1973**, 4395. For a similar reaction without base treatment, see Pommelet, J.; Nyns, C.; Lahousse, F.; Merényi, R.; Viehe, H.G. *Angew. Chem. Int. Ed.* **1981**, *20*, 585.

³⁶² MacGee, D.I.; Beck, E.J. *J. Org. Chem.* **2000**, *65*, 8367.

The *Ramberg–Bäcklund reaction* can be regarded as a type of extrusion reaction (see Sec. 17.F.vi).

OS V, 877; VI, 454, 555; VIII, 212.

17-21 The Conversion of Aziridines to Alkenes

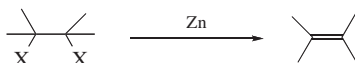
epi-Imino-elimination



Aziridines not substituted on the nitrogen atom react with nitrous acid to produce alkenes.³⁶³ An *N*-nitroso compound is an intermediate (Reaction 12-50); other reagents that produce such intermediates also give alkenes. The reaction is stereospecific: *cis*-aziridines give *cis*-alkenes and *trans*-aziridines give *trans*-alkenes.³⁶⁴ Aziridines carrying *N*-alkyl substituents can be converted to alkenes by treatment with ferrous iodide³⁶⁵ or with *m*-chloroperoxybenzoic acid.³⁶⁶ An *N*-oxide intermediate (Reaction 19-29) is presumably involved in the latter case. *N*-Tosylaziridines give allylic sulfonamides when treated with butyllithium.³⁶⁷ *N*-Tosyl aziridines are converted to *N*-tosyl imines when treated with boron trifluoride.³⁶⁸ 2-Tosylmethyl *N*-tosylaziridines react with Te^{2-} in the presence of Adogen 464 to give allylic *N*-tosyl amines.³⁶⁹ 2-Halomethyl *N*-tosyl aziridines also react with In metal in methanol to give *N*-tosyl allylic amines.³⁷⁰

17-22 Elimination of Vicinal Dihalides

Dihalo-elimination



Dehalogenation has been accomplished with many reagents, the most common being Zn, Mg, and iodide ion.³⁷¹ Heating in HMPA is often enough to convert a *vic*-dibromide to an alkene.³⁷² Among reagents used less frequently have been phenyllithium, phenylhydrazine, CrCl_2 , Na_2S in DMF,³⁷³ and LiAlH_4 .³⁷⁴ Electrochemical reduction has also

³⁶³ See Sonnet, P.E. *Tetrahedron* **1980**, 36, 557, see p. 591; Dermer, O.C.; Ham, G.E. *Ethylenimine and other Aziridines*, Academic Press, NY, **1969**, pp. 293–295.

³⁶⁴ See Carlson, R.M.; Lee, S.Y. *Tetrahedron Lett.* **1969**, 4001.

³⁶⁵ Imamoto, T.; Yukawa, Y. *Chem. Lett.* **1974**, 165.

³⁶⁶ Heine, H.W.; Myers, J.D.; Peltzer, III, E.T. *Angew. Chem. Int. Ed.* **1970**, 9, 374.

³⁶⁷ Hodgson, D.M.; Štefane, B.; Miles, T.J.; Witherington, J. *J. Org. Chem.* **2006**, 71, 8510.

³⁶⁸ Sugihara, Y.; Iimura, S.; Nakayama, J. *Chem. Commun.* **2002**, 134.

³⁶⁹ Chao, B.; Dittmer, D.C. *Tetrahedron Lett.* **2001**, 42, 5789.

³⁷⁰ Yadav, J.S.; Bandyapadhyay, A.; Reddy, B.V.S. *Synlett* **2001**, 1608.

³⁷¹ Baciocchi, E. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, **1983**, pp. 161–201. Also see, Bossier, G.; Paris, J. *J. Chem. Soc. Perkin Trans. 2* **1992**, 2057.

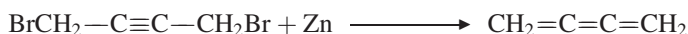
³⁷² Khurana, J.M.; Bansal, G.; Chauhan, S. *Bull. Chem. Soc. Jpn.* **2001**, 74, 1089.

³⁷³ Fukunaga, K.; Yamaguchi, H. *Synthesis* **1981**, 879. See also, Nakayama, J.; Machida, H.; Hoshino, M. *Tetrahedron Lett.* **1983**, 24 3001; Landini, D.; Milesi, L.; Quadri, M.L.; Rolla, F. *J. Org. Chem.* **1984**, 49, 152.

³⁷⁴ For a lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 259–263.

been used.³⁷⁵ Treatment with In³⁷⁶ or Sm³⁷⁷ metal in methanol, InCl₃/NaBH₄,³⁷⁸ heating with Zn in acetic acid,³⁷⁹ or reaction of a *Grignard reagent* and Ni(dppe)Cl₂ (dppe = 1,2-diphenylphosphinoethane).³⁸⁰ When the reagent is Zn, antistereospecificity has been observed in some cases,³⁸¹ but not in others.³⁸² Microwave irradiation of a *vic*-dibromide in an ionic liquid leads to the alkene.³⁸³ The reaction of a vicinal dibromide with triethylamine and DMF with microwave irradiation leads to vinyl bromide.³⁸⁴ α,β -Dibromo amides are converted to conjugated amides upon photolysis in methanol.³⁸⁵

One useful feature of this reaction is that there is no doubt about the *position* of the new double bond, so that it can be used to give double bonds exactly where they are wanted. For example, allenes, which are not easily prepared by other methods, can be prepared from X—C—CX₂—C—X or X—C—CX=C— systems.³⁸⁶ Cumulenes have been obtained from 1,4-elimination:



Cumulenes have also been prepared by treating alkynyl epoxides with boron trifluoride.³⁸⁷ 1,4-Elimination of BrC—C=C—CBr has been used to prepare conjugated dienes C=C—C=C.³⁸⁸ Allenes are formed by heating propargylic alcohols with arylboronic acids (Reaction 12-28) and a Pd catalyst.³⁸⁹ Allenes are also formed from propargylic amines using a CuI and a Pd catalyst.³⁹⁰ In addition, allenenes are formed from lithium bromocyclopropylidenoids.³⁹¹

The reaction can be carried out for any combination of halogens, except where one is fluorine. Mechanisms are often complex and depend on the reagent and reaction conditions.³⁹² For different reagents, mechanisms involving carbocations, carbanions, and free radical intermediates, as well as concerted mechanisms, have been proposed.

OS III, 526, 531; IV, 195, 268; V, 22, 255, 393, 901; VI, 310, VII, 241. Also see, OS IV, 877, 914, 964.

³⁷⁵ See Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, **1984**, pp. 145–147; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, **1989**, pp. 151–154.

³⁷⁶ Ranu, B.C.; Guchhait, S.K.; Sarkar, A. *Chem. Commun.* **1998**, 2113.

³⁷⁷ Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett.* **1996**, 37, 9313.

³⁷⁸ Ranu, B.C.; Das, A.; Hajra, A. *Synthesis* **2003**, 1012.

³⁷⁹ Gaenzler, F.C.; Smith, M.B. *Synlett* **2007**, 1299.

³⁸⁰ Malanga, C.; Aronica, L.A.; Lardicci, L. *Tetrahedron Lett.* **1995**, 36, 9189.

³⁸¹ See Gordon, M.; Hay, J.V. *J. Org. Chem.* **1968**, 33, 427.

³⁸² See Sicher, J.; Havel, M.; Svoboda, M. *Tetrahedron Lett.* **1968**, 4269.

³⁸³ Ranu, B.C.; Jana, R. *J. Org. Chem.* **2005**, 70, 8621.

³⁸⁴ Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron Lett.* **2001**, 42, 3893.

³⁸⁵ Aruna, S.; Kalyanakumar, R.; Ramakrishnan, V.T. *Synth. Commun.* **2001**, 31, 3125.

³⁸⁶ See Schuster, H.F.; Coppola, G.M. *Allenenes in Organic Synthesis*, Wiley, NY, **1984**, pp. 9–56; Landor, P.D. in Landor, S.R. *The Chemistry of the Allenenes*, Vol. 1, Academic Press, NY, **1982**; pp. 19–233; Taylor, D.R. *Chem. Rev.* **1967**, 67, 317.

³⁸⁷ Wang, X.; Ramos, B.; Rodriguez, A. *Tetrahedron Lett.* **1994**, 35, 6977.

³⁸⁸ Engman, L.; Byström, S.E. *J. Org. Chem.* **1985**, 50, 3170.

³⁸⁹ Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* **2004**, 45, 5573.

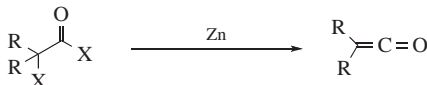
³⁹⁰ Nakamura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* **2004**, 126, 5958.

³⁹¹ Azizoglu, A.; Balci, M.; Mieusset, J.-L.; Brinker, U.H. *J. Org. Chem.* **2008**, 73, 8182.

³⁹² See Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**, pp. 332–368; Baciocchi, W. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, **1983**, p. 161.

17-23 Dehalogenation of α -Halo Acyl Halides

Dihalo-elimination

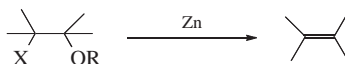


Ketenes can be prepared by dehalogenation of α -halo acyl halides with zinc or with triphenylphosphine.³⁹³ The reaction generally gives good results when the two R groups are aryl or alkyl, but not when either one is hydrogen.³⁹⁴

OS IV, 348; VIII, 377.

17-24 Elimination of a Halogen and a Hetero Group

Alkoxy-halo-elimination



The elimination of OR and halogen from β -halo ethers is called the *Boord reaction*. It can be carried out with Zn, Mg, Na, or certain other reagents.³⁹⁵ The yields are high and the reaction is of broad scope. β -Halo acetals readily yield vinylic ethers, $\text{X}-\text{C}-\text{C}(\text{OR})_2 \rightarrow \text{C}=\text{C}-\text{OR}$ and 2 molar equivalents of SmI_2 in HMPA is effective.³⁹⁶ Besides β -halo ethers, the reaction can also be carried out on compounds of the formula $\text{Z}-\text{C}-\text{C}-\text{Z}$ where X is halogen and Z is OCOR, OTs,³⁹⁷ NR_2 ,³⁹⁸ or SR.³⁹⁹ When $\text{X} = \text{Cl}$ and $\text{Z} = \text{OAc}$, heating in THF with an excess of SmI_2 followed by treatment with dilute aq HCl gives an alkene.⁴⁰⁰ When $\text{Z} = \text{I}$ and the other Z is an oxygen of an oxazolone (a carbamate unit), heating with In metal in methanol leads to an allylic amine.⁴⁰¹ The Z group may also be OH, but then X is limited to Br and I.⁴⁰² Like Reaction 17-22, this method ensures that the new double bond will be in a specific position. The fact that Mg causes elimination in these cases limits the preparation of *Grignard reagents* from these compounds. It has been shown that treatment of β -halo ethers and esters with Zn gives nonstereospecific elimination,⁴⁰³ so the mechanism was not E2. An E1cB mechanism was postulated because of the poor leaving-group ability of OR and OCOR. Bromohydrins can be converted to alkenes (elimination of Br, OH) in high yields by treatment with $\text{LiAlH}_4\text{-TiCl}_3$.⁴⁰⁴

OS III, 698, IV, 748; VI, 675.

³⁹³ Darling, S.D.; Kidwell, R.L. *J. Org. Chem.* **1968**, 33, 3974.

³⁹⁴ See McCarney, C.C.; Ward, R.S. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1600. See also, Masters, A.P.; Sorensen, T.S.; Ziegler, T. *J. Org. Chem.* **1986**, 51, 3558.

³⁹⁵ See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 263–267, for reagents that produce olefins from β -halo ethers and esters, and from halohydrins.

³⁹⁶ Park, H.S.; Kim, S.H.; Park, M.Y.; Kim, Y.H. *Tetrahedron Lett.* **2001**, 42, 3729.

³⁹⁷ Reeve, W.; Brown, R.; Steckel, T.F. *J. Am. Chem. Soc.* **1971**, 93, 4607.

³⁹⁸ Gurien, H. *J. Org. Chem.* **1963**, 28, 878.

³⁹⁹ Amstutz, E.D. *J. Org. Chem.* **1944**, 9, 310.

⁴⁰⁰ Concellón, J.M.; Bernad, P.L.; Bardales, E. *Org. Lett.* **2001**, 3, 937.

⁴⁰¹ Yadav, J.S.; Bandyopadhyay, A.; Reddy, B.V.S. *Tetrahedron Lett.* **2001**, 42, 6385.

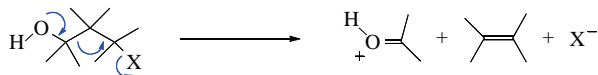
⁴⁰² Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, 7, 3062.

⁴⁰³ House, H.O.; Ro, R.S. *J. Am. Chem. Soc.* **1965**, 87, 838.

⁴⁰⁴ McMurry, J.E.; Hoz, T. *J. Org. Chem.* **1975**, 40, 3797.

17.F.ii. Fragmentations

When carbon is the positive leaving group (the electrofuge) in an elimination, the reaction is called *fragmentation*.⁴⁰⁵ These processes occur on substrates of the form $W-C-C-X$, where X is a normal nucleofuge (e.g., halogen, OH_2^+ , OTs, NR_3^+) and W is a positive-carbon electrofuge. In most of the cases, W is $HO-C-$ or R_2N-C- , so that the positive charge on the carbon atom is stabilized by the unshared pair of the oxygen or nitrogen, for example,

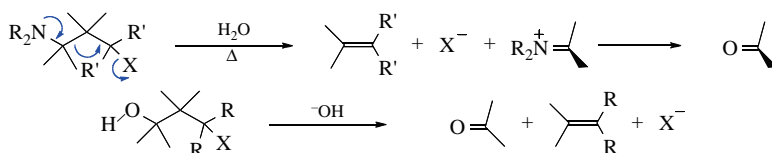


The mechanisms are mostly E1 or E2. We will discuss only a few fragmentations, since many are possible and not much work has been done on most of them. Reactions **17-25–17-28** and **17-30** may be considered fragmentations (see also, Reactions **19-12** and **19-13**).

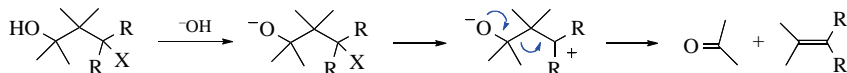
17-25 1,3-Fragmentation of γ -Amino, γ -Hydroxy Halides and 1,3-Diols

Dialkylaminoalkyl-halo-elimination, and so on

Hydroxyalkyl-hydroxy-elimination



γ -Dialkylamino halides undergo fragmentation when heated with water to give an alkene and an iminium salt, which under the reaction conditions is hydrolyzed to an aldehyde or ketone (**16-2**).⁴⁰⁶ γ -Hydroxy halides and tosylates are fragmented with base. In this instance, the base does not play its usual role in elimination reactions, but instead serves to remove a proton from the OH group, which enables the carbon leaving group to come off more easily:



Prelog and Zalán⁴⁰⁷ first observed this type of fragmentation in work that solved the structure of quinine and other Cinchona alkaloids in a 1,3-elimination ring-opening reaction. Subsequent work by Grob⁴⁰⁸ elucidated the mechanism of the reaction, and this 1,3-elimination is often referred to as *Grob fragmentation*.⁴⁰⁹ The mechanism of these

⁴⁰⁵ Becker, K.B.; Grob, C.A. in Patai, S. *The Chemistry of Functional Groups, Supplement A*, pt. 2, Wiley, NY, **1977**, pp. 653–723; Grob, C.A. *Angew. Chem. Int. Ed.* **1969**, 8, 535; Grob, C.A.; Schiess, P.W. *Angew. Chem. Int. Ed.* **1967**, 6, 1.

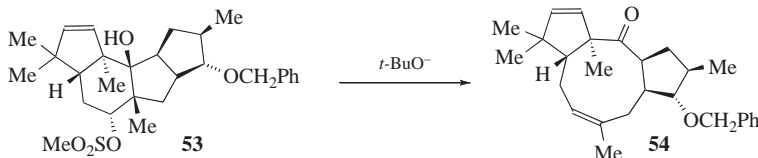
⁴⁰⁶ Grob, C.A.; Ostermayer, F.; Raudenbusch, W. *Helv. Chim. Acta* **1962**, 45, 1672.

⁴⁰⁷ Prelog, V.; Zalán, E. *Helv. Chim. Acta* **1944**, 27, 535; Prelog, V.; Häfliger, O. *Helv. Chim. Acta* **1950**, 33, 2021.

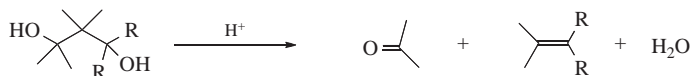
⁴⁰⁸ Grob, C.A. *Angew. Chem. Int. Ed.* **1969**, 8, 535 and references cited therein; Grob, C.A.; Kiefer, H.R.; Lutz, H. J.; Wilkens, H.J. *Helv. Chim. Acta* **1967**, 50, 416.

⁴⁰⁹ See Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, 110, 3741.

reactions is often E1, but an E2 mechanism also operates.⁴¹⁰ It has been shown that stereoisomers of cyclic γ -amino halides and tosylates in which the two leaving groups can assume an antiperiplanar conformation react by the E2 mechanism, while those isomers in which the groups cannot assume such a conformation either fragment by the E1 mechanism or do not undergo fragmentation at all, but in either case give rise to side products characteristic of carbocations.⁴¹¹ An example of a *Grob fragmentation* is the conversion of **53** to **54**.⁴¹²



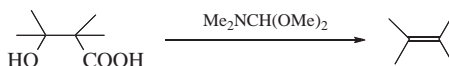
γ -Dialkylamino alcohols do not give fragmentation, since for ionization the OH group must be converted to $^+\text{OH}_2$ and this would convert NR_2 to $^+\text{NR}_2\text{H}$, which does not have the unshared pair necessary to form the double bond with the carbon.⁴¹³



1,3-Diols in which at least one OH group is tertiary or is located on a carbon with aryl substituents can be cleaved by acid treatment.⁴¹⁴ The reaction is most useful synthetically when at least one of the OH groups is on a ring.⁴¹⁵

17-26 Decarboxylation of β -Hydroxy Carboxylic Acids and of β -Lactones

Carboxy-hydroxy-elimination



An OH and a CO_2H group can be eliminated from β -hydroxy carboxylic acids by refluxing with excess DMF dimethyl acetal.⁴¹⁶ Mono-, di-, tri-, and tetrasubstituted alkenes have been prepared by this method in good yields.⁴¹⁷ There is evidence that the mechanism involves E1 or E2 elimination from the zwitterionic intermediate $^-\text{O}_2\text{C}-\text{C}-\text{O}-\text{C}=\text{N}^+\text{Me}_2$.⁴¹⁸ The reaction has also been accomplished⁴¹⁹ under extremely mild conditions (a few seconds at 0°C) with PPh_3 and $\text{EtO}_2\text{C}-\text{N}=\text{N}-\text{CO}_2\text{Et}$,

⁴¹⁰ Fischer, W.; Grob, C.A. *Helv. Chim. Acta* **1978**, *61*, 2336 and references cited therein.

⁴¹¹ Geisel, M.; Grob, C.A.; Wohl, R.A. *Helv. Chim. Acta* **1969**, *52*, 2206 and references cited therein.

⁴¹² Chass, D.A.; Buddhsukh, D.; Magnus, P.D. *J. Org. Chem.* **1978**, *43*, 1750.

⁴¹³ Grob, C.A.; Hoegerle, R.M.; Ohta, M. *Helv. Chim. Acta* **1962**, *45*, 1823.

⁴¹⁴ Zimmerman, H.E.; English Jr., J. *J. Am. Chem. Soc.* **1954**, *76*, 2285, 2291, 2294.

⁴¹⁵ For a review, see Caine, D. *Org. Prep. Proced. Int.* **1988**, *20*, 1.

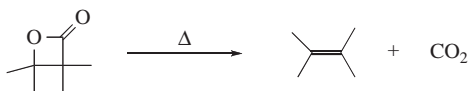
⁴¹⁶ Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, 1545.

⁴¹⁷ See Rüttimann, A.; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* **1975**, *58*, 1450.

⁴¹⁸ Mulzer, J.; Brüntrup, G. *Tetrahedron Lett.* **1979**, 1909.

⁴¹⁹ For another method, see Tanzawa, T.; Schwartz, J. *Organometallics* **1990**, *9*, 3026.

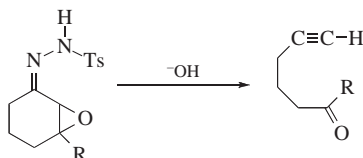
diethyl azodicarboxylate.⁴²⁰ In a related procedure, β -lactones undergo thermal decarboxylation to give alkenes in high yields. The reaction has been shown to be stereospecific syn elimination.⁴²¹ There is evidence that this reaction also involves a zwitterionic intermediate.⁴²²



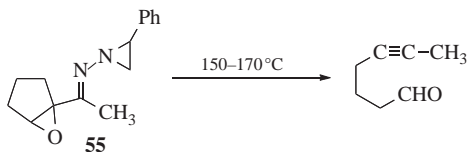
There are no OS references, but see OS VII, 172, for a related reaction.

17-27 Fragmentation of α,β -Epoxy Hydrazones

Eschenmoser–Tanabe ring cleavage



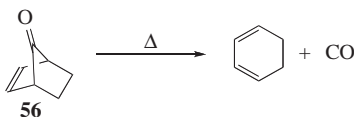
Cyclic α,β -unsaturated ketones⁴²³ can be cleaved by treatment with base of their epoxy tosylhydrazone derivatives to give acetylenic ketones,⁴²⁴ in what is known as the *Eschenmoser–Tanabe ring cleavage*. The reaction can be applied to the formation of acetylenic aldehydes ($\text{R}=\text{H}$) by using the corresponding, 2,4-dinitro-tosylhydrazone derivatives.⁴²⁵ Hydrazones (e.g., **55**) prepared from epoxy ketones and ring-substituted *N*-aminoaziridines undergo similar fragmentation when heated.⁴²⁶



OS VI, 679.

17-28 Elimination of CO and CO_2 from Bridged Bicyclic Compounds

seco-Carbonyl-1, 4-elimination



⁴²⁰ Mulzer, J.; Lammer, O. *Angew. Chem. Int. Ed.* **1983**, 22, 628.

⁴²¹ See Adam, W.; Martinez, G.; Thompson, J.; Yany, F. *J. Org. Chem.* **1981**, 46, 3359.

⁴²² Mulzer, J.; Zippel, M.; Brüntrup, G. *Angew. Chem. Int. Ed.* **1980**, 19, 465; Mulzer, J.; Zippel, M. *Tetrahedron Lett.* **1980**, 21, 751. See also, Moyano, A.; Pericàs, M.A.; Valentí, E. *J. Org. Chem.* **1989**, 573.

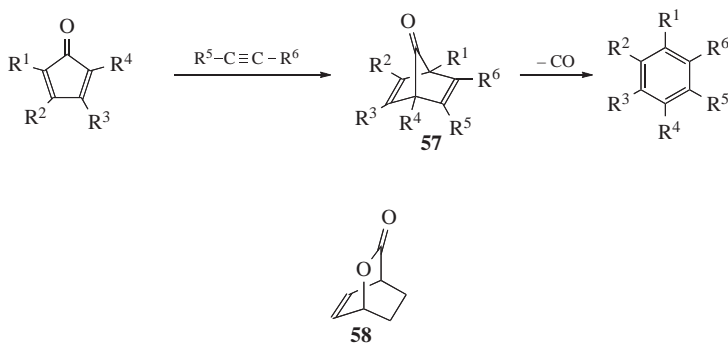
⁴²³ See MacAlpine, G.A.; Warkentin, J. *Can. J. Chem.* **1978**, 56, 308, and references cited therein.

⁴²⁴ Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, 50, 708; Tanabe, M.; Crowe, D.F.; Dehn, R.L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739; Tanabe, M.; Crowe, D.F.; Dehn, R.L. *Tetrahedron Lett.* **1967**, 3943.

⁴²⁵ Corey, E.J.; Sachdev, H.S. *J. Org. Chem.* **1975**, 40, 579.

⁴²⁶ Felix, D.; Müller, R.K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, 55, 1276.

On heating, bicyclo[2.2.1]hept-2,3-en-17-ones (**56**) usually lose CO to give cyclohexadienes,⁴²⁷ in a type of *reverse Diels–Alder reaction*. Bicyclo[2.2.1]heptadienones (**57**) undergo the reaction so readily (because of the stability of the benzene ring produced) that



they cannot generally be isolated. The parent (**57**) has been obtained at 10–15 K in an Ar matrix, where its spectrum could be studied.⁴²⁸ Both **56** and **57** can be prepared by a *Diels–Alder reactions* between a cyclopentadienone and an alkyne or alkene, so that this reaction is a useful method for the preparation of specifically substituted benzene rings and cyclohexadienes.⁴²⁹ Unsaturated bicyclic lactones of the type **58** can also undergo the reaction, losing CO₂ (see also, **17-35**).

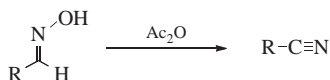
OS **III**, 807; **V**, 604, 1037.

Reversal of the *Diels–Alder reaction* may be considered a fragmentation (see **15-50**).

17.F.iii. Reactions in which C≡N or C=N Bonds Are Formed

17-29 Dehydration of Oximes and Similar Compounds

C- Hydro- N- hydroxy-elimination; C- Acyl- N- hydroxy-elimination



Aldoximes can be dehydrated to nitriles⁴³⁰ by many dehydrating agents, of which acetic anhydride is the most common. Among reagents that are effective under mild conditions⁴³¹

⁴²⁷ See Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, **1967**, pp. 16–46.

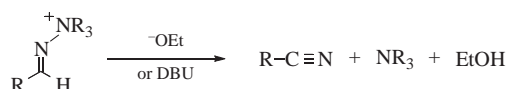
⁴²⁸ Birney, D.M.; Wiberg, K.B.; Berson, J.A. *J. Am. Chem. Soc.* **1988**, *110*, 6631.

⁴²⁹ See Ogliaruso, M.A.; Romanelli, M.G.; Becker, E.I. *Chem. Rev.* **1965**, *65*, 261, pp. 300–348. For references to this and related reactions, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 207–213.

⁴³⁰ Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, **1978**, pp. 1345–1390; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 92–96; Fatiadi, K. in Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, **1978**, pp. 1057–1303.

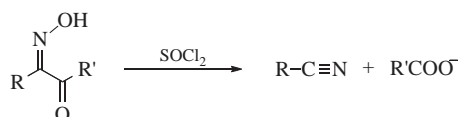
⁴³¹ Attanasi, O.; Palma, P.; Serra-Zanetti, F. *Synthesis* **1983**, 741; Jursic, B. *Synth. Commun.* **1989**, *19*, 689.

(room temperature) are $\text{Ph}_3\text{P}-\text{CCl}_4$,⁴³² PPh_3-I_2 ,⁴³³ $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ in refluxing CH_3CN ,⁴³⁴ ferric sulfate,⁴³⁵ $\text{Cu}(\text{II})$ with ultrasound,⁴³⁶ and $\text{ZnO}/\text{CH}_3\text{COCl}$ under solvent-free conditions.⁴³⁷ N,N -Dimethylformamide catalyzes the thermal dehydration of aldoximes.⁴³⁸ Heating an oxime with a Ru catalyst gives the nitrile.⁴³⁹ Heating with the *Burgess reagent* $[\text{Et}_3\text{N}^+-\text{SO}_2\text{N}-\text{CO}_2\text{Me}]$ in PEG is effective for this transformation.⁴⁴⁰ Sulfuric acid impregnated silica gel⁴⁴¹ gives the nitrile, as does microwave irradiation of an oxime with tetrachloropyridine on alumina.⁴⁴² Aldehydes can be converted to oximes *in situ* and microwave irradiation on alumina⁴⁴³ or with ammonium acetate⁴⁴⁴ gives the nitrile. Solvent-free reactions are known.⁴⁴⁵ The reaction is most successful when the H and OH are anti. Various alkyl and acyl derivatives of aldoximes ($\text{RCH}=\text{NOR}$,⁴⁴⁶ $\text{RCH}=\text{NO}-\text{COR}$, $\text{RCH}=\text{NOSO}_2\text{Ar}$, etc.), also give nitriles, as do chlorimines ($\text{RCH}=\text{NCl}$; the latter with base treatment).⁴⁴⁷ N,N -Dichloro derivatives of primary amines give nitriles upon pyrolysis: $\text{RCH}_2\text{NCl}_2 \rightarrow \text{RCN}$.⁴⁴⁸



Quaternary hydrazonium salts (derived from aldehydes) give nitriles when treated with $-\text{OEt}$ ⁴⁴⁹ or DBU (see Reaction 17-13):⁴⁵⁰ as do dimethylhydrazones ($\text{RCH}=\text{NNMe}_2$), when treated with Et_2NLi and HMPA.⁴⁵¹ All these are methods of converting aldehyde derivatives to nitriles. For the conversion of aldehydes directly to nitriles, without isolation of intermediates (see Reaction 16-16).

Hydroxylamines that have an α -proton are converted to nitrones when treated with a Mn-salen complex.⁴⁵²



⁴³² Kim, J.N.; Chung, K.H.; Ryu, E.K. *Synth. Commun.* **1990**, 20, 2785.

⁴³³ Narsaiah, A.V.; Sreenu, D.; Nagaiah, K. *Synth. Commun.* **2006**, 36, 137.

⁴³⁴ Kim, H.S.; Kim, S.H.; Kim, J.N. *Tetrahedron Lett.* **2009**, 50, 1717.

⁴³⁵ Desai, D.G.; Swami, S.S.; Mahale, G.D. *Synth. Commun.* **2000**, 30, 1623.

⁴³⁶ Jiang, N.; Ragauskas, A.J. *Tetrahedron Lett.* **2010**, 51, 4479.

⁴³⁷ Hosseini Sarvari, M. *Synthesis* **2005**, 787.

⁴³⁸ Supsana, P.; Liaskopoulos, T.; Tsoungas, P.G.; Varvounis, G. *Synlett* **2007**, 267.

⁴³⁹ Yang, S.H.; Chang, S. *Org. Lett.* **2001**, 3, 4209.

⁴⁴⁰ Miller, C.P.; Kaufman, D.H. *Synlett* **2000**, 1169.

⁴⁴¹ Sarvari, M.H. *Synthesis* **2005**, 787.

⁴⁴² Lingaiah, N.; Narender, R. *Synth. Commun.* **2002**, 32, 2391.

⁴⁴³ Bose, D.S.; Narsaiah, A.V. *Tetrahedron Lett.* **1998**, 39, 6533.

⁴⁴⁴ Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* **2000**, 1599.

⁴⁴⁵ See Sharghi, H.; Sarvari, M.H. *Synthesis* **2003**, 243.

⁴⁴⁶ Anand, N.; Owston, N.A.; Parker, A.J.; Slatford, P.A.; Willia, J.M.J. *Tetrahedron Lett.* **2007**, 48, 7761.

⁴⁴⁷ Hauser, C.R.; Le Maistre, J.W.; Rainsford, A.E. *J. Am. Chem. Soc.* **1935**, 57, 1056; Pyun, S.Y.; Lee, D.C.;

Seung, Y.J.; Cho, B.R. *J. Org. Chem.* **2005**, 70, 5327.

⁴⁴⁸ Roberts, J.T.; Rittberg, B.R.; Kovacic, P. *J. Org. Chem.* **1981**, 46, 4111.

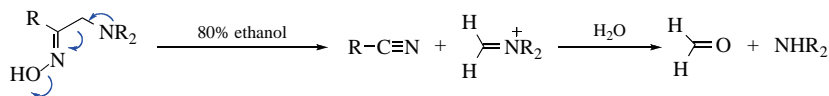
⁴⁴⁹ See Ioffe, B.V.; Zelenina, N.L. *J. Org. Chem. USSR*, **1968**, 4, 1496.

⁴⁵⁰ Moore, J.S.; Stupp, S.I. *J. Org. Chem.* **1990**, 55, 3374.

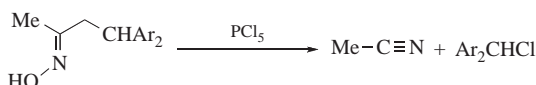
⁴⁵¹ Cuvigny, T.; Le Borgne, J.F.; Larchevêque, M.; Normant, H. *Synthesis* **1976**, 237.

⁴⁵² Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. *Tetrahedron Lett.* **1999**, 40, 1989.

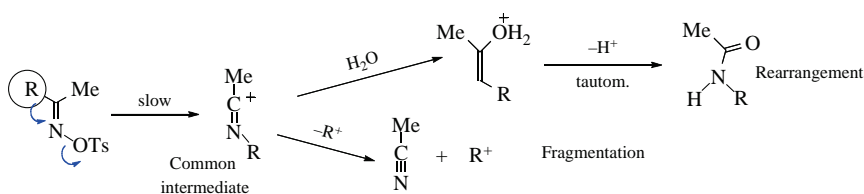
Certain ketoximes can be converted to nitriles by the action of proton or Lewis acids.⁴⁵³ Among these are oximes of α -diketones (illustrated above), α -keto acids, α -dialkylamino ketones, α -hydroxy ketones, β -keto ethers, and similar compounds.⁴⁵⁴ These are fragmentation reactions, analogous to **17-25**. For example, α -dialkylamino ketoximes also give amines and aldehydes or ketones besides nitriles:⁴⁵⁵



The reaction that normally occurs on treatment of a ketoxime with a Lewis or proton acid is the *Beckmann rearrangement* (**18-17**); fragmentations are considered side reactions, often called “abnormal” or “second-order” *Beckmann rearrangements*.⁴⁵⁶ Obviously, the substrates mentioned are much more susceptible to fragmentation than are ordinary ketoximes, since in each case an unshared pair is available to assist in removal of the group cleaving from the carbon. However, fragmentation is a side reaction even with ordinary ketoximes⁴⁵⁷ and, in cases where a particularly stable carbocation can be cleaved, may be the main reaction:⁴⁵⁸



There are indications that the mechanism at least in some cases first involves a rearrangement and then cleavage. The ratio of fragmentation to *Beckmann rearrangement* of a series of oxime tosylates [$\text{RC}(=\text{NOTs})\text{Me}$] was not related to the solvolysis rate but *was* related to the stability of R^+ (as determined by the solvolysis rate of the corresponding RCl), which showed that fragmentation did not take place in the rate-determining step.⁴⁵⁹ It may be postulated then that the first step in the fragmentation and in the rearrangement is the same and that this is the rate-determining step. The product is determined in the second step:



⁴⁵³ Gawley, R.E. *Org. React.* **1988**, 35, 1; McCarty, C.G. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 416-439; Casanova, J. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 915-932.

⁴⁵⁴ See Olah, G.A.; Vankar, Y.D.; Berrier, A.L. *Synthesis* **1980**, 45; Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* **1971**, 4, 197.

⁴⁵⁵ Fischer, H.P.; Grob, C.A. *Helv. Chim. Acta* **1963**, 46, 936.

⁴⁵⁶ See Ferris, A.F. *J. Org. Chem.* **1960**, 25, 12.

⁴⁵⁷ See Hill, R.K.; Conley, R.T. *J. Am. Chem. Soc.* **1960**, 82, 645.

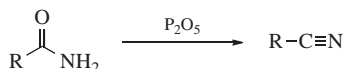
⁴⁵⁸ Hassner, A.; Nash, E.G. *Tetrahedron Lett.* **1965**, 525.

⁴⁵⁹ Grob, C.A.; Fischer, H.P.; Raudenbusch, W.; Zergenyi, J. *Helv. Chim. Acta* **1964**, 47, 1003.

However, in other cases the simple E1 or E2 mechanisms operate.⁴⁶⁰
OS V, 266; IX, 281; OS II, 622; III, 690.

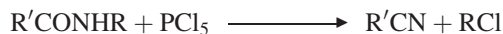
17-30 Dehydration of Unsubstituted Amides

N,N-Dihydro- *C*-oxo-bielimination



Unsubstituted amides can be dehydrated to nitriles.⁴⁶¹ Phosphorous pentoxide is the most common dehydrating agent for this reaction, but many others, including POCl₃, PCl₅, CCl₄—Ph₃P,⁴⁶² HMPA,⁴⁶³ LiCl with a Zr catalyst,⁴⁶⁴ MeOOCNSO₂NEt₃ (the *Burgess reagent*),⁴⁶⁵ Me₂N=CHCl⁺ Cl[−],⁴⁶⁶ AlCl₃/KI/H₂O,⁴⁶⁷ PPh₃/NCS,⁴⁶⁸ oxalyl chloride/DMSO/−78 °C⁴⁶⁹ (*Swern* conditions, see Reaction 19-3), *o*-iodoxybenzoic acid/Et₄NBr,⁴⁷⁰ PdCl₂ in aq media,⁴⁷¹ TBAF and hydrosilanes,⁴⁷² Fe complexes,⁴⁷³ and SOCl₂ have also been used.⁴⁷⁴ Heating an amide with paraformaldehyde and formic acid gives the nitrile.⁴⁷⁵ It is possible to convert an acid to the nitrile, without isolation of the amide, by heating its ammonium salt with the dehydrating agent,⁴⁷⁶ or by other methods.⁴⁷⁷ *N,N*-Disubstituted ureas give cyanamides (R₂N—CO—NH₂ → R₂N—CN) when dehydrated with CHCl₃—NaOH under phase-transfer conditions.⁴⁷⁸ Treatment of an amide with aq NaOH and ultrasound leads to the nitrile.⁴⁷⁹

N-Alkyl-substituted amides can be converted to nitriles and alkyl chlorides by treatment with PCl₅. This is called the *von Braun reaction* (not to be confused with the other von Braun reaction, 10-54).



OS I, 428; II, 379; III, 493, 535, 584, 646, 768; IV, 62, 144, 166, 172, 436, 486, 706; VI, 304, 465.

⁴⁶⁰ Grob, C.A.; Sieber, A. *Helv. Chim. Acta* **1967**, 50, 2520; Green, M.; Pearson, S.C. *J. Chem. Soc. B* **1969**, 593.

⁴⁶¹ Bieron J.F.; Dinan, F.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 274–283; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 96–103; Friedrich, K. in Patai, S.; Rapoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, **1978**, p. 1345.

⁴⁶² Harrison, C.R.; Hodge, P.; Rogers, W.J. *Synthesis* **1977**, 41.

⁴⁶³ Monson, R.S.; Priest, D.N. *Can. J. Chem.* **1971**, 49, 2897.

⁴⁶⁴ Ruck, R.T.; Bergman, R.G. *Angew. Chem. Int. Ed.* **2004**, 43, 5375.

⁴⁶⁵ Claremon, D.A.; Phillips, B.T. *Tetrahedron Lett.* **1988**, 29, 2155.

⁴⁶⁶ Barger, T.M.; Riley, C.M. *Synth. Commun.* **1980**, 10, 479.

⁴⁶⁷ Boruah, M.; Konwar, D. *J. Org. Chem.* **2002**, 67, 7138.

⁴⁶⁸ Iranpoor, N.; Firouzabadi, H.; Aghapoor, G. *Synth. Commun.* **2002**, 32, 2535.

⁴⁶⁹ Nakajima, N.; Ubukata, M. *Tetrahedron Lett.* **1997**, 38, 2099.

⁴⁷⁰ Bhalerao, D.S.; Mahajan, U.S.; Chaudhari, K.H.; Akamanchi, K.G. *J. Org. Chem.* **2007**, 72, 662.

⁴⁷¹ Maffioli, S.I.; Marzorati, E.; Marazzi, A. *Org. Lett.* **2005**, 7, 5237.

⁴⁷² Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Org. Lett.* **2009**, 11, 2461.

⁴⁷³ Zhou, S.; Addis, D.; Das, S.; Junge, K.; Beller, M. *Chem. Commun.* **2009**, 4883.

⁴⁷⁴ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1983–1985.

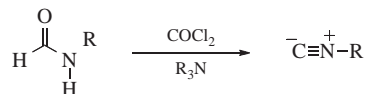
⁴⁷⁵ Heck, M.-P.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1996**, 61, 6486.

⁴⁷⁶ See Imamoto, T.; Takaoka, T.; Yokoyama, M. *Synthesis* **1983**, 142.

⁴⁷⁷ For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1949–1950.

⁴⁷⁸ Schroth, W.; Kluge, H.; Frach, R.; Hodek, W.; Schädler, H.D. *J. Prakt. Chem.* **1983**, 325, 787.

⁴⁷⁹ Sivakumar, M.; Senthilkumar, P.; Pandit, A.B. *Synth. Commun.* **2001**, 31, 2583.

17-31 Conversion of N-Alkylformamides to Isonitriles (Isocyanides)**CN-Dihydro-C-oxo-bielimination**

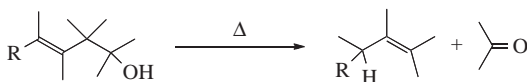
Isonitriles (isonitriles) can be prepared by elimination of water from *N*-alkylformamides⁴⁸⁰ with phosgene and a tertiary amine.⁴⁸¹ Other reagents, among them TsCl in quinoline, POCl₃ and a tertiary amine,⁴⁸² triflic anhydride/*i*Pr₂NEt,⁴⁸³ 2,4,6-Trichloro [1,3,5]triazine (cyanuric chloride, TCT), with microwave irradiation,⁴⁸⁴ and Ph₃P—CCl₄—Et₃N⁴⁸⁵ have also been employed. Formamides react with thionyl chloride (two sequential treatments) to give an intermediate that gives an isonitrile upon electrolysis in DMF with LiClO₄.⁴⁸⁶

A variation of this process uses carbodiimides,⁴⁸⁷ which can be prepared by the dehydration of *N,N'*-disubstituted ureas with various dehydrating agents,⁴⁸⁸ among which are TsCl in pyridine, POCl₃, PCl₅, P₂O₅–pyridine, and TsCl (with phase-transfer catalysis).⁴⁸⁹ Hydrogen sulfide can be removed from the corresponding thioureas by treatment with HgO, NaOCl, or diethyl azodicarboxylate–triphenylphosphine.⁴⁹⁰

OS V, 300, 772; VI, 620, 751, 987. See also, OS VII, 27. For the carbodiimide/thiourea dehydration, see OS V, 555; VI, 951.

17.F.iv. Reactions in which C=O Bonds Are Formed

Many elimination-type reactions in which C=O bonds are formed were considered in Chapter 16, along with their more important reverse reactions (also see, Reactions **12-40** and **12-41**).

17-32 Pyrolysis of β-Hydroxy Alkenes**O- Hydro-C-allyl-elimination**

⁴⁸⁰ See Creedon, S.M.; Crowley, H.K.; McCarthy, D.G. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1015.

⁴⁸¹ Hoffmann, P.; Gokel, G.W.; Marquarding, D.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, **1971**, pp. 10–17; Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem. Int. Ed.* **1965**, *4*, 472; *Newer Methods Prep. Org. Chem.* **1968**, *4*, 37.

⁴⁸² See Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, 400.

⁴⁸³ Baldwin, J.E.; O'Neil, I.A. *Synlett* **1991**, 603.

⁴⁸⁴ Porcheddu, A.; Giacomelli, G.; Salaris, M. *J. Org. Chem.* **2005**, *70*, 2361.

⁴⁸⁵ Appel, R.; Kleinstück, R.; Ziehn, K. *Angew. Chem. Int. Ed.* **1971**, *10*, 132.

⁴⁸⁶ Guirado, A.; Zapata, A.; Gómez, J.L.; Trebalón, L.; Gálvez, J. *Tetrahedron* **1999**, *55*, 9631.

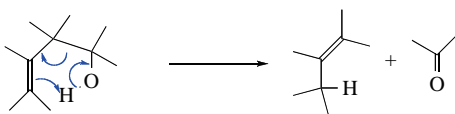
⁴⁸⁷ Bocharov, B.V. *Russ. Chem. Rev.* **1965**, *34*, 212; Williams, A.; Ibrahim, I.T. *Chem. Rev.* **1981**, *81*, 589.

⁴⁸⁸ Also see Kim, S.; Yi, K.Y. *J. Org. Chem.* **1986**, *51*, 2613; *Tetrahedron Lett.* **1986**, *27*, 1925.

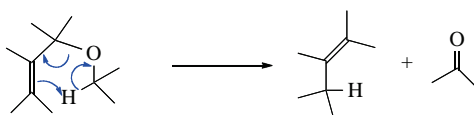
⁴⁸⁹ Jászay, Z.M.; Petneházy, I.; Töke, L.; Szajáni, B. *Synthesis* **1987**, 520.

⁴⁹⁰ Mitsunobu, O.; Kato, K.; Tomari, M. *Tetrahedron* **1970**, *26*, 5731.

When pyrolyzed, β -hydroxy alkenes cleave to give alkenes and aldehydes or ketones.⁴⁹¹ Alkenes produced this way are quite pure, since there are no side reactions. The mechanism has been shown to be pericyclic, primarily by observations that the kinetics are first order⁴⁹² and that, for ROD, the deuterium appeared in the allylic position of the new alkene.⁴⁹³ This mechanism is the reverse of that for the oxygen analogue of the ene synthesis (Reaction 16-54). β -Hydroxyacetylenes react similarly to give the corresponding allenes and carbonyl compounds.⁴⁹⁴ The mechanism is the same despite the linear geometry of the triple bonds.



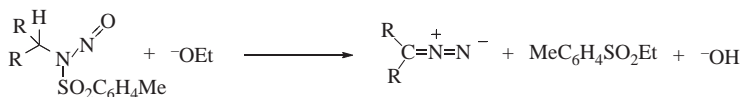
In a related reaction, pyrolysis of allylic ethers that contain at least one α hydrogen gives alkenes and aldehydes or ketones. The mechanism is also pericyclic⁴⁹⁵



17.F.v. Reactions in which N=N Bonds Are Formed

17-33 Eliminations to Give Diazoalkanes

N-Nitrosoamine-diazoalkane transformation



Various *N*-nitroso-*N*-alkyl compounds undergo elimination to give diazoalkanes.⁴⁹⁶ One of the most convenient methods for the preparation of diazomethane involves base treatment of *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide (illustrated above, with R = H).⁴⁹⁷ However, other compounds commonly used are (base treatment is required in all cases):

⁴⁹¹ Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc.* **1959**, *81*, 6643. For a review, see Marvell, E.N.; Whalley, W. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, **1971**, pp. 729–734.

⁴⁹² Voorhees, K.J.; Smith, G.G. *J. Org. Chem.* **1971**, *36*, 1755.

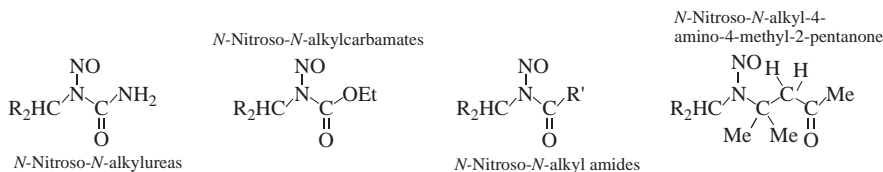
⁴⁹³ Arnold, R.T.; Smolinsky, G. *J. Org. Chem.* **1960**, *25*, 128; Smith, G.G.; Taylor, R. *Chem. Ind. (London)* **1961**, 949.

⁴⁹⁴ Viola, A.; Proverb, R.J.; Yates, B.L.; Larrahondo, J. *J. Am. Chem. Soc.* **1973**, *95*, 3609.

⁴⁹⁵ Kwart, H.; Slutsky, J.; Sarner, S.F. *J. Am. Chem. Soc.* **1973**, *95*, 5242; Egger, K.W.; Vitins, P. *Int. J. Chem. Kinet.* **1974**, *6*, 429.

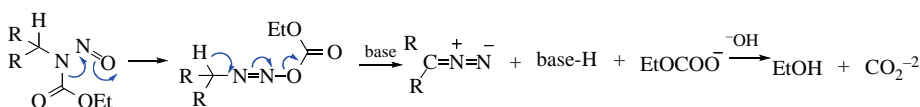
⁴⁹⁶ Regitz, M.; Maas, G. *Diazo Compounds*; Academic Press, NY, **1986**, pp. 296–325; Black, T.H. *Aldrichimica Acta* **1983**, *16*, 3. See Cowell, G.W.; Ledwith, A. *Q. Rev. Chem. Soc.* **1970**, *24*, 119, pp. 126–131; Smith, P.A.S. *Open-chain Nitrogen Compounds*, W. A. Benjamin, NY, **1966**, pp. 257–258, 474–475, in Vol. 2.

⁴⁹⁷ de Boer, T.J.; Backer, H.J. *Org. Synth.* **IV**, 225, 250; Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377.



All of these compounds can be used to prepare diazomethane, although the sulfonamide, which is commercially available, is most satisfactory. *N*-Nitroso-*N*-methylcarbamate and *N*-nitroso-*N*-methylurea give good yields, but are highly irritating and carcinogenic.⁴⁹⁸ For higher diazoalkanes, the preferred substrates are nitrosoalkylcarbamates.

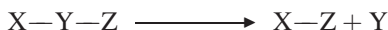
Most of these reactions probably begin with a 1,3 nitrogen-to-oxygen rearrangement, followed by the actual elimination (illustrated for the carbamate):



OS II, 165; III, 119, 244; IV, 225, 250; V, 351; VI, 981.

17.F.vi. Extrusion Reactions

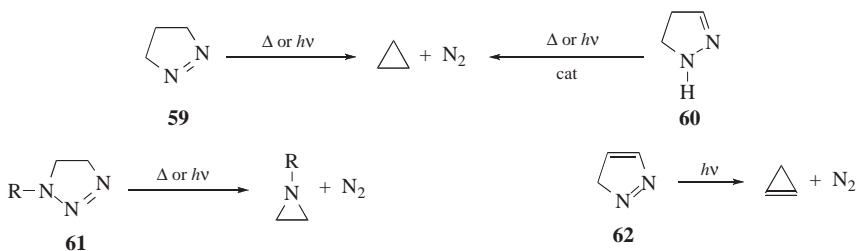
We consider an *extrusion reaction*⁴⁹⁹ to be one in which an atom or group Y connected to two other atoms X and Z is lost from a molecule, leading to a product in which X is bonded directly to Z.



Reactions **14-32** and **17-20** also fit this definition. Reaction **17-28** does not fit the definition, but is often also classified as an extrusion reaction. A scale of extrusion facility has been developed, showing that the ease of extrusion of the common Y groups is in the order: $-\text{N}=\text{N}- > -\text{COO}- > -\text{SO}_2- > -\text{CO}-$.⁵⁰⁰

17-34 Extrusion of N₂ from Pyrazolines, Pyrazoles, and Triazolines

Azo-extrusion

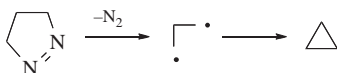


⁴⁹⁸ Searle, C.E. *Chem. Br.* **1970**, 6, 5.

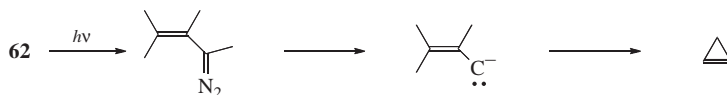
⁴⁹⁹ Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, **1967**. For a review of extrusions that are photochemically induced, see Givens, R.S. *Org. Photochem.* **1981**, 5, 227.

⁵⁰⁰ Paine, A.J.; Warkentin, J. *Can. J. Chem.* **1981**, 59, 491.

1-Pyrazolines (**59**) can be converted to cyclopropane and N_2 on photolysis⁵⁰¹ or pyrolysis.⁵⁰² The tautomeric 2-pyrazolines (**60**), which are more stable than **59**, also give the reaction, but in this case an acidic or basic catalyst is required, the function of which is to convert **60** to **59**.⁵⁰³ In the absence of such catalysts, **60** does not react.⁵⁰⁴ In a similar manner, triazolines (**61**) are converted to aziridines.⁵⁰⁵ Side reactions are frequent with both **59** and **61**, and some substrates do not give the reaction at all. However, the reaction has proved synthetically useful in many cases. In general, photolysis gives better yields and fewer side reactions than pyrolysis with both **59** and **61**. 3*H*-Pyrazoles⁵⁰⁶ (**62**) are stable to heat, but in some cases can be converted to cyclopropenes on photolysis,⁵⁰⁷ although in other cases other types of products are obtained.



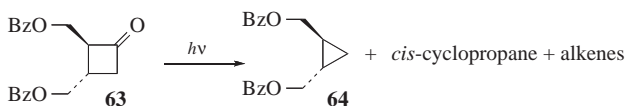
There is much evidence that the mechanism⁵⁰⁸ of the 1-pyrazoline reactions generally involves diradicals, although the mode of formation and detailed structure (e.g., singlet vs triplet) of these radicals may vary with the substrate and reaction conditions. The reactions of the 3*H*-pyrazoles (**62**) have been postulated to proceed through a diazo compound that loses N_2 to give a vinylic carbene.⁵⁰⁹



OS V, 96, 929. See also, OS VIII, 597.

17-35 Extrusion of CO or CO₂

Carbonyl-extrusion



Although the reaction is not general, certain cyclic ketones can be photolyzed to give ring-contracted products.⁵¹⁰ In the example above, the cyclobutanone (**63**) was

⁵⁰¹ Van Auken, T.V.; Rinehart, Jr., K.L. *J. Am. Chem. Soc.* **1962**, 84, 3736.

⁵⁰² Adam, W.; De Lucchi, O. *Angew. Chem. Int. Ed.* **1980**, 19, 762; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, **1967**, pp. 116–151. See Mackenzie, K. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, **1975**, pp. 329–442.

⁵⁰³ See Jones, W.M.; Sanderfer, P.O.; Baarda, D.G. *J. Org. Chem.* **1967**, 32, 1367.

⁵⁰⁴ McGreer, D.E.; Wai, W.; Carmichael, G. *Can. J. Chem.* **1960**, 38, 2410; Kocsis K.; Ferrini, P.G.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1960**, 43, 2178.

⁵⁰⁵ For a review, see Scheiner, P. *Sel. Org. Transform.* **1970**, 1, 327.

⁵⁰⁶ See Sammes, M.P.; Katritzky, A.R. *Adv. Heterocycl. Chem.* **1983**, 34, 2.

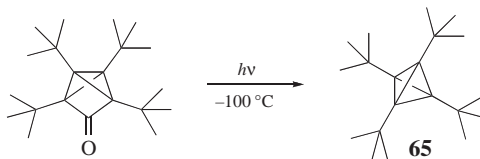
⁵⁰⁷ See Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc.* **1973**, 95, 7536.

⁵⁰⁸ Engel, P.S. *Chem. Rev.* **1980**, 80, 99; Engel, P.S.; Nalepa, C.J. *Pure Appl. Chem.* **1980**, 52, 2621; Reedich, D.E.; Sheridan, R.S. *J. Am. Chem. Soc.* **1988**, 110, 3697.

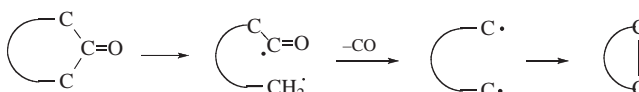
⁵⁰⁹ Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc.* **1973**, 95, 7536.

⁵¹⁰ See Redmore, D.; Gutsche, C.D. *Adv. Alicyclic Chem.* **1971**, 3, 1, see pp. 91–107; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, **1967**, pp. 47–71.

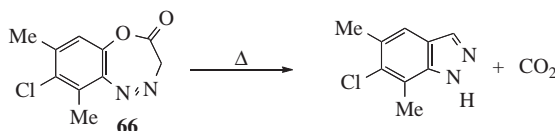
photolyzed to give **64**.⁵¹¹ This reaction was used to synthesize tetra-*tert*-butyltetrahydronaphthalene, (**65**).⁵¹²



The mechanism probably involves a *Norrish-type I cleavage* (Sec. 7.A.vii), loss of CO from the resulting radical, and recombination of the radical fragments.



Certain lactones extrude CO₂ on heating or on irradiation (e.g., the pyrolysis of **66**).⁵¹³

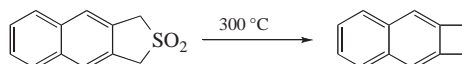


Decarboxylation of β -lactones (see **17-26**) may be regarded as a degenerate example of this reaction. Unsymmetrical diacyl peroxides (RCO—OO—COR') lose two molecules of CO₂ when photolyzed in the solid state to give the product RR'.⁵¹⁴ Electrolysis was also used, but yields were lower. This is an alternative to the *Kolbe reaction* (**11-34**) (see also, **17-28** and **17-38**).

There are no OS references, but see OS VI, 418, for a related reaction.

17-36 Extrusion of SO₂

Sulfonyl-extrusion



In a reaction similar to **17-35**, certain sulfones, both cyclic and acyclic,⁵¹⁵ extrude SO₂ on heating or photolysis to give ring-contracted products.⁵¹⁶ An example is the preparation of naphtho(*b*)cyclobutene shown above.⁵¹⁷ In a different kind of reaction, five-membered

⁵¹¹ Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem.* **1997**, 75, 518. See also, Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem.* **2001**, 79, 114.

⁵¹² Maier, G.; Pfriem, S.; Schäfer, U.; Matusch, R. *Angew. Chem. Int. Ed.* **1978**, 17, 520.

⁵¹³ Ried, W.; Wagner, K. *Liebigs Ann. Chem.* **1965**, 681, 45.

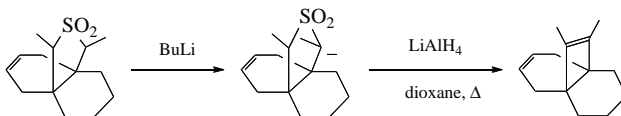
⁵¹⁴ Lomölder, R.; Schäfer, H.J. *Angew. Chem. Int. Ed.* **1987**, 26, 1253.

⁵¹⁵ Gould, I.R.; Tung, C.; Turro, N.J.; Givens, R.S.; Matuszewski, B. *J. Am. Chem. Soc.* **1984**, 106, 1789.

⁵¹⁶ Vögtle, F.; Rossa, L. *Angew. Chem. Int. Ed.* **1979**, 18, 515; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, **1967**, pp. 72–90; Kice, J.L. in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, **1966**, pp. 115–136. For a review of extrusion reactions of S, Se, and Te compounds, see Guzic, Jr., F.S.; SanFilippo, L.J. *Tetrahedron* **1988**, 44, 6241.

⁵¹⁷ Cava, M.P.; Shirley, R.L. *J. Am. Chem. Soc.* **1960**, 82, 654.

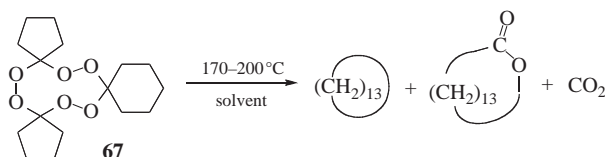
cyclic sulfones can be converted to cyclobutenes by treatment with butyllithium followed by LiAlH_4 ,⁵¹⁸ for example,



This method is most successful when both the α and α' position of the sulfone bear alkyl substituents (see also, Reaction 17-20). Treating four-membered ring sultams with SnCl_2 led to aziridine products via loss of SO_2 .⁵¹⁹

OS VI, 482.

17-37 The Story Synthesis

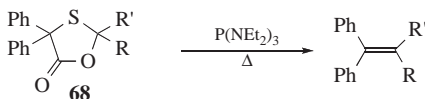


When cycloalkylidene peroxides (e.g., **60**) are heated in an inert solvent (e.g., decane), extrusion of CO_2 takes place; the products are the cycloalkane containing three carbon atoms less than the starting peroxide and the lactone containing two carbon atoms less⁵²⁰ (the *Story synthesis*).⁵²¹ The two products are formed in comparable yields, usually ~ 15 –25% each. Although the yields are low, the reaction is useful because there are not many other ways to prepare large rings. The reaction is versatile, having been used to prepare rings of every size from 8 to 33 members.

Both dimeric and trimeric cycloalkylidene peroxides can be synthesized⁵²² by treatment of the corresponding cyclic ketones with H_2O_2 in acid solution.⁵²³ The trimeric peroxide is formed first and is subsequently converted to the dimeric compound.⁵²⁴

17-38 Alkene synthesis by Twofold Extrusion

Carbon dioxide,thio-extrusion



⁵¹⁸ Photis, J.M.; Paquette, L.A. *J. Am. Chem. Soc.* **1974**, 96, 4715.

⁵¹⁹ Kataoka, T.; Iwama, T. *Tetrahedron Lett.* **1995**, 36, 5559.

⁵²⁰ Sanderson, J.R.; Story, P.R.; Paul, K. *J. Org. Chem.* **1975**, 40, 691; Sanderson, J.R.; Paul, K.; Story, P.R. *Synthesis* **1975**, 275.

⁵²¹ See Story, P.R.; Busch, P. *Adv. Org. Chem.* **1972**, 8, 67, see pp. 79–94.

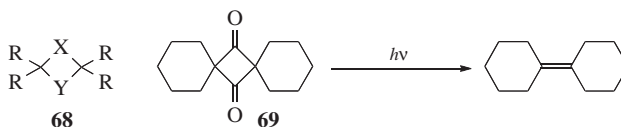
⁵²² See Paul, K.; Story, P.R.; Busch, P.; Sanderson, J.R. *J. Org. Chem.* **1976**, 41, 1283.

⁵²³ Kharasch, M.S.; Sosnovsky, G. *J. Org. Chem.* **1958**, 23, 1322; Ledaal, T. *Acta Chem. Scand.*, **1967**, 21, 1656.

For another method, see Sanderson, J.R.; Zeiler, A.G. *Synthesis* **1975**, 125.

⁵²⁴ Story, P.R.; Lee, B.; Bishop, C.E.; Denson, D.D.; Busch, P. *J. Org. Chem.* **1970**, 35, 3059. See also, Sanderson, J.R.; Wilterdink, R.J.; Zeiler, A.G. *Synthesis* **1976**, 479.

4,4-Diphenyloxathiolan-5-ones (**68**) give good yields of the corresponding alkenes when heated with tris(diethylamino)phosphine.⁵²⁵ This reaction is an example of a general type: alkene synthesis by twofold extrusion of X and Y from a molecule of the type **69**.⁵²⁶ Other examples are photolysis of 1,4-diones⁵²⁷ (e.g., **70**) and treatment of acetoxy sulfones [RCH(OAc)CH₂SO₂Ph] with Mg/EtOH and a catalytic amount of HgCl₂.⁵²⁸ **68** can be prepared by the condensation of thiobenzilic acid [Ph₂C(SH)COOH] with aldehydes or ketones.



OS V, 297.

⁵²⁵ Barton, D.H.R.; Willis, B.J. *J. Chem. Soc. Perkin Trans. 1* **1972**, 305.

⁵²⁶ See Guziec, Jr., F.S.; SanFilippo, L.J. *Tetrahedron* **1988**, *44*, 6241.

⁵²⁷ Turro, N.J.; Leermakers, P.A.; Wilson, H.R.; Neckers, D.C.; Byers, G.W.; Vesley, G.F. *J. Am. Chem. Soc.* **1965**, *87*, 2613.

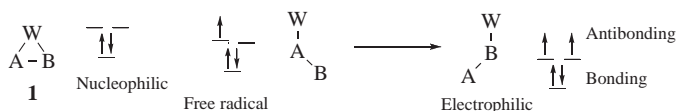
⁵²⁸ Lee, G.H.; Lee, H.K.; Choi, E.B.; Kim, B.T.; Pak, C.S. *Tetrahedron Lett.* **1995**, *36*, 5607.

Rearrangements

In a rearrangement reaction, a group moves from one atom to another in the same molecule.¹ Most are migrations from an atom to an adjacent one (called 1,2-shifts), but some are over longer distances. The group



that migrates (W) may move with its electron pair (these can be called *nucleophilic* or *anionotropic* rearrangements; the migrating group can be regarded as a nucleophile), without its electron pair (*electrophilic* or *cationotropic* rearrangements; in the case of migrating hydrogen, *prototropic* rearrangements), or with just one electron (radical rearrangements). The atom A is called the *migration origin* and B is the *migration terminus*. However, there are some rearrangements that do not lend themselves to neat categorization in this manner. Among these are those with cyclic transition states (Reactions **18-27–18-36**).



As will be seen, nucleophilic 1,2-shifts are much more common than electrophilic or free radical 1,2-shifts. The reason for this can be seen by a consideration of the transition states (or in some cases intermediates) involved. The transition state or intermediate for all three cases can be represented by **1**, in which the two-electron A—W bond overlaps with the orbital on atom B, which contains zero, one, and two electrons, in the case of nucleophilic, free radical, and electrophilic migration, respectively. The overlap of these orbitals gives rise to three new orbitals, which have an energy relationship similar to those in Section 2.K.i (one bonding and two degenerate antibonding orbitals). In a nucleophilic migration, where only two electrons are involved, both can go into the bonding orbital and **1** is a low-energy transition state. In a free radical or electrophilic migration, there are, respectively, three or four electrons that must be accommodated, and antibonding orbitals

¹ de Mayo, P. *Rearrangements in Ground and Excited States*, 3 Vols., Academic Press, NY, **1980**; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, **1973**; Collins, C.J.; Eastham, J.F. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 761–821. See also, the series *Mechanisms of Molecular Migrations*.

must be occupied. It is not surprising therefore that, when 1,2-electrophilic or free radical shifts are found, the migrating group W is usually aryl or some other group that can accommodate the extra one or two electrons and thus effectively remove them from the three-membered transition state or intermediate (see 41).

In any rearrangement two possible modes of reaction can, in principle, be distinguished. In one of these, the group W becomes completely detached from A and may end up on the B atom of a different molecule (*intermolecular* rearrangement). In the other, W goes from A to B in the *same* molecule (*intramolecular* rearrangement), in which case there must be some continuing tie holding W to the A—B system, preventing it from coming completely free. Strictly speaking, only the intramolecular type fits our definition of a rearrangement, but the general practice, which is followed here, is to include under the title “rearrangement” all net rearrangements whether they are inter- or intramolecular. It is usually not difficult to tell whether a given rearrangement is inter- or intramolecular. The most common method involves the use of *cross over* experiments. In this type of experiment, rearrangement is carried out on a mixture of W—A—B and V—A—C, where V is closely related to W (say, methyl vs ethyl) and B to C. In an intramolecular process, only A—B—W and A—C—V are recovered, but if the reaction is intermolecular, then not only will these two be found, but also A—B—V and A—C—W.

18.A. MECHANISMS

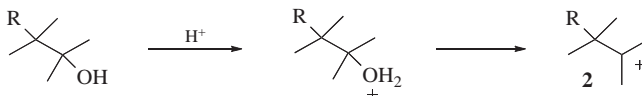
18.A.i. Nucleophilic Rearrangements²

Broadly speaking, such rearrangements consist of three steps, of which the actual migration is the second:



This process has been called the *Whitmore 1,2-shift*.³ Since the migrating group carries the electron pair with it, the migration terminus B must be an atom with only six electrons in its outer shell (an open sextet). The first step therefore is creation of a system with an open sextet. Such a system can arise in various ways, but two of these are the most important:

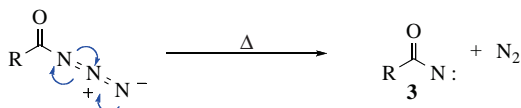
1. *Formation of a Carbocation:* These can be formed in a number of ways (see Sec. 5. A.iii), but one of the most common methods is the acid treatment of an alcohol to give **2** from an intermediate oxonium ion. Such carbocations are subject to rearrangement to a more stable carbocation. These two steps are of course the same as the first two steps of the S_N1cA or the E1 reactions of alcohols.



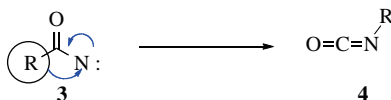
² Vogel, P. *Carbocation Chemistry*; Elsevier, NY, **1985**, pp. 323–372; Shubin, V.G. *Top. Curr. Chem.* **1984**, 116/117, 267; Saunders, M.; Chandrasekhar, J.; Schleyer, P.v.R. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, **1980**, pp. 1–53; Kirmse, W. *Top. Curr. Chem.* **1979**, 80, 89. For reviews of rearrangements in vinylic cations, see Schegolev, A.A.; Kanishchev, M.I. *Russ. Chem. Rev.* **1981**, 50, 553; Lee, C.C. *Isot. Org. Chem.* **1980**, 5, 1.

³ It was first postulated by Whitmore, F.C. *J. Am. Chem. Soc.* **1932**, 54, 3274.

2. *Formation of a Nitrene:* The decomposition of acyl azides is one of several ways in which acyl nitrenes (**3**) are formed (see Sec. 5.E). After the migration has taken place, the atom at the migration origin (A) must necessarily have an open sextet. In the third step, this atom acquires an octet. In the case of carbocations, combinations with a nucleophile (rearrangement with substitution) and loss of H^+ (rearrangement with elimination). Constitute the most common third step.



Although this mechanism is presented as taking place in three steps, and some reactions do take place in this way, in others the transformation is simultaneous. For example, in the nitrene example above, as the R migrates, an electron pair from the nitrogen moves into the C—N bond to give a stable isocyanate, (**4**). In this example, what are shown as the second and third steps are simultaneous. It is also possible for the second and third steps to be simultaneous even when the “third” step involves more than just a simple motion of a pair of electrons. Similarly, there are many reactions in which the first two steps are simultaneous; that is, there is no actual formation of a species (e.g., **2** or **3**). In these instances, it may be said that R assists in the removal of the leaving group, with migration of R and the removal of the leaving group taking place simultaneously. Many investigations have been carried out in attempts to determine, in various reactions, whether such intermediates as (**2**) or (**3**) actually form, or whether the steps are simultaneous (see, e.g., the discussions in Reaction **16-45** and Sec. 18.A.ii), but the difference between the two possibilities is often subtle, and the question is not always easily answered.⁴

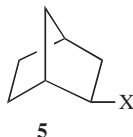


Evidence for this mechanism is that rearrangements of this sort occur under conditions where previously carbocations have been encountered: $\text{S}_{\text{N}}1$ conditions, *Friedel–Crafts alkylation*, and so on. Solvolysis of neopentyl bromide leads to rearrangement products, and the rate increases with increasing ionizing power of the solvent, but is unaffected by concentration of base,⁵ so that the first step is carbocation formation. The same compound under $\text{S}_{\text{N}}2$ conditions gave no rearrangement, but slowly gave only ordinary substitution. Thus with neopentyl bromide, formation of a carbocation leads only to rearrangement. Carbocations usually rearrange to more stable carbocations. Thus the direction of rearrangement is usually primary \rightarrow secondary \rightarrow tertiary. Neopentyl (Me_3CCH_2), neophyl ($\text{PhCMe}_2\text{CH}_2$), and norbornyl (e.g., **5**) type systems are especially prone to carbocation rearrangement

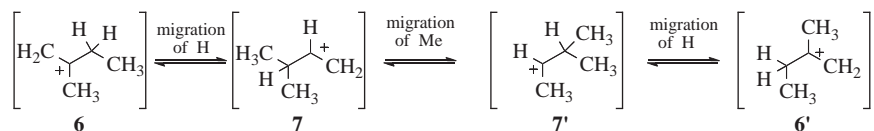
⁴ The IUPAC designations depend on the nature of the steps. For the rules, see Guthrie, R.D. *Pure Appl. Chem.* **1989**, 61, 23, pp. 44–45.

⁵ Dostrovsky, I.; Hughes, E.D. *J. Chem. Soc.* **1946**, 166.

reactions. It has been shown that the rate of migration increases with the degree of electron deficiency at the migration terminus.⁶



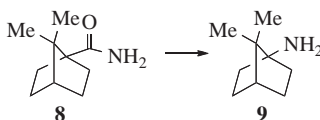
It was previously mentioned (Sec. 5.A.ii) that stable tertiary carbocations could be obtained, in solution, at very low temperatures. The NMR studies have shown that when these solutions are warmed, rapid migrations of hydride and of alkyl groups take place, resulting in an equilibrium mixture of structures.⁷ For example, the *tert*-pentyl cation (**5**)⁸ equilibrates as follows:



Carbocations that rearrange to give products of identical structure ($\mathbf{6} \rightleftharpoons \mathbf{6'}$, $\mathbf{7} \rightleftharpoons \mathbf{7'}$) are called *degenerate carbocations*. Such rearrangements are *degenerate rearrangements* and many examples are known.⁹

18.A.ii. The Actual Nature of the Migration

Most nucleophilic 1,2-shifts are intramolecular. The W group does not become free, but always remains connected in some way to the substrate. Apart from the evidence from cross-over experiments, the strongest evidence is that when the W group is chiral, the configuration is *retained* in the product. For example, (+)-PhCHMeCO₂H was converted to (–)-PhCHMeNH₂ by the *Curtius* (**18-14**), *Hofmann* (**18-13**), *Lossen* (**18-15**), and *Schmidt* (**18-16**) reactions.¹⁰ In these reactions, the extent of retention varied from 95.8 to 99.6%. Retention of configuration in the migrating group has been shown many times since.¹¹ Another experiment demonstrating retention was the easy conversion of **8** to **9**.¹¹ Neither inversion nor racemization could take place at a bridgehead.



⁶ Borodkin, G.I.; Shakirov, M.M.; Shubin, V.G.; Koptuyug, V.A. *J. Org. Chem. USSR* **1978**, *14*, 290, 924.

⁷ Brouwer, D.M.; Hogeveen, H. *Prog. Phys. Org. Chem.* **1972**, *9*, 179, see pp. 203–237; Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, pp. 751–760, 766–778. For a discussion of the rates of these reactions, see Sorensen, T.S. *Acc. Chem. Res.* **1976**, *9*, 257.

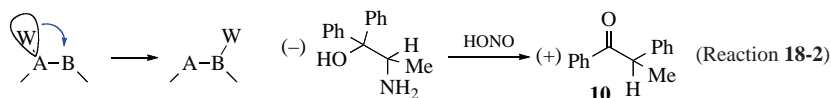
⁸ Brouwer, D.M. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 210; Saunders, M.; Hagen, E.L. *J. Am. Chem. Soc.* **1968**, *90*, 2436.

⁹ Ahlberg, P.; Jonsäll, G.; Engdahl, C. *Adv. Phys. Org. Chem.* **1983**, *19*, 223; Leone, R.E.; Barborak, J.C.; Schleyer, P.v.R. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, **1970**, pp. 1837–1939; Leone, R.E.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* **1970**, *9*, 860.

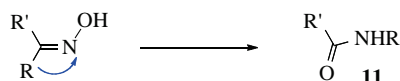
¹⁰ Campbell, A.; Kenyon, J. *J. Chem. Soc.* **1946**, 25, and references cited therein.

¹¹ See Kirmse, W.; Gruber, W.; Knist, J. *Chem. Ber.* **1973**, *106*, 1376; Borodkin, G.I.; Panova, Y.B.; Shakirov, M.M.; Shubin, V.G. *J. Org. Chem. USSR* **1983**, *19*, 103.

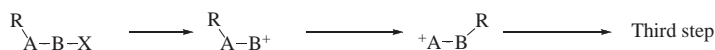
Using the simple example W-A-B, there is much evidence that retention of configuration usually occurs in W, and inversion never occurs.¹² However, this is not the state of affairs at A and B. In many reactions, of course, the structure of W—A—B is such that the product has only one steric possibility at A or B or both, and in most of these cases nothing can be learned. But in cases where the steric nature of A or B can be investigated, the results are mixed. It has been shown that either inversion or racemization can occur at A or B. One example is **10**, where the conversion proceeded with inversion (equivalent to inversion at B).¹³ Inversion at A has been



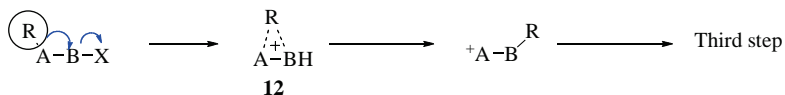
shown in other cases.¹⁴ However, in many other cases, racemization occurs at A or B or both.¹⁵ It is not always necessary for the product to have two steric possibilities in order to investigate the stereochemistry at A or B. Thus, in most *Beckmann rearrangements* (18-17), only the group trans (usually called *anti*) to the hydroxyl group migrates, as illustrated by formation of **11**, which shows inversion at B.



This information tells us about the degree of concertedness of the three steps of the rearrangement. First, consider the migration terminus B in R—A—B—X. If racemization is found at B, it is probable that the first step takes place before the second and that a positively charged carbon (or other sextet atom) is present at B:



With respect to B this is an S_N1 type process. If inversion occurs at B, it is likely that the first two steps are concerted, that a carbocation is *not* an intermediate, and that the process is S_N2 like:



In this case, participation by R assists in removal of X in the same way that neighboring groups do (Sec. 10.C). Indeed, R *is* a neighboring group here. The only difference is that, in the case of the neighboring-group mechanism of nucleophilic substitution, R never becomes detached from A, while in a rearrangement the bond between R and A is broken.

¹² See Cram, D.J. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, **1956**; pp. 251–254; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, **1960**, pp. 597–604.

¹³ Bernstein, H.I.; Whitmore, F.C. *J. Am. Chem. Soc.* **1939**, *61*, 1324. For other examples, see Tsuchihashi, G.; Tomooka, K.; Suzuki, K. *Tetrahedron Lett.* **1984**, *25*, 4253.

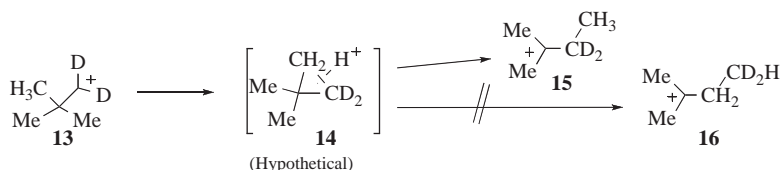
¹⁴ See Meerwein, H.; van Emster, K. *Ber.* **1920**, *53*, 1815; **1922**, *55*, 2500; Meerwein, H.; Gérard, L. *Liebigs Ann. Chem.* **1923**, *435*, 174.

¹⁵ See Winstein, S.; Morse, B.K. *J. Am. Chem. Soc.* **1952**, *74*, 1133.

In either case, the anchimeric assistance results in an increased rate of reaction. Of course, for such a process to take place, R must be in a favorable geometrical position (R and X antiperiplanar). Intermediate **12** may be a true intermediate, or there may only be a transition state, depending on what migrates. In certain cases of the S_N1 type process, it is possible for migration to take place with net retention of configuration at the migrating terminus because of conformational effects in the carbocation.¹⁶

A few conclusions may be summarized:

1. The S_N1 type process occurs mostly when B is a tertiary atom or has one aryl group and at least one other alkyl or aryl group. In other cases, the S_N2 type process is more likely. Inversion of configuration (indicating an S_N2 type process) has been shown for a neopentyl substrate by the use of the chiral neopentyl-1-*d* alcohol.¹⁷ There is other evidence that neopentyl systems undergo rearrangement by a carbocation (S_N1 type) mechanism.¹⁸
2. The question as to whether **12** is an intermediate or a transition state has been much debated. When R is aryl or vinyl, then **12** is probably an intermediate and the migrating group lends anchimeric assistance¹⁹ (see Sec. 10.C.i, category 3-preceding category 4 for resonance stabilization of this intermediate, when R is aryl). When R is alkyl, **12** is a protonated cyclopropane (edge- or corner protonated; see Sec. 15.B.iv). There is much evidence that in simple migrations of a methyl group, the bulk of the products formed do not arise from protonated cyclopropane *intermediates*. Evidence for this statement has already been given (Sec. 10.C.i, category 4c). Further evidence was obtained from experiments involving labeling.



Rearrangement of the neopentyl cation labeled with deuterium in the 1 position (**13**) gave only *tert*-pentyl products with the label in the 3 position (derived from **15**), though if **14** were an intermediate, the cyclopropane ring could just as well cleave the other way to give *tert*-pentyl derivatives labeled in the 4 position (derived from **16**).²⁰ Another experiment that led to the same conclusion was the generation, in several ways, of $\text{Me}_3\text{C}^{13}\text{CH}_2^+$. The only *tert*-pentyl products isolated were labeled in C-3, that is, $\text{Me}_2\text{C}^+-^{13}\text{CH}_2\text{CH}_3$ derivatives; no derivatives of $\text{Me}_2\text{C}^+-\text{CH}_2^{13}\text{CH}_3$ were found.²¹

¹⁶ Collins, C.J.; Benjamin, B.M. *J. Org. Chem.* **1972**, *37*, 4358, and references cited therein.

¹⁷ Mosher, H.S. *Tetrahedron* **1974**, *30*, 1733. See also, Guthrie, R.D. *J. Am. Chem. Soc.* **1967**, *89*, 6718.

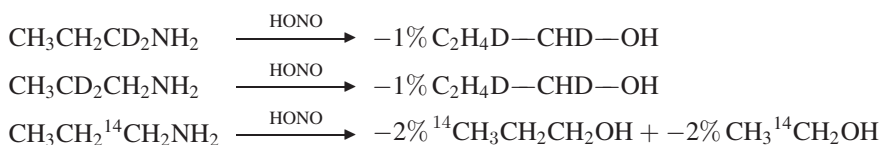
¹⁸ Shiner, Jr., V.J.; Imhoff, M.A. *J. Am. Chem. Soc.* **1985**, *107*, 2121.

¹⁹ Rachoń, J.; Goedken, V.; Walborsky, H.M. *J. Org. Chem.* **1989**, *54*, 1006. An opposing view: Kirmse, W.; Feyen, P. *Chem. Ber.* **1975**, *108*, 71; Kirmse, W.; Plath, P.; Schaffrodt, H. *Chem. Ber.* **1975**, *108*, 79.

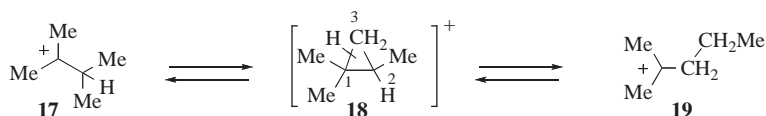
²⁰ Skell, P.S.; Starer, I.; Krapcho, A.P. *J. Am. Chem. Soc.* **1960**, *82*, 5257.

²¹ Karabatsos, G.J.; Orzech, Jr., C.E.; Meyerson, S. *J. Am. Chem. Soc.* **1964**, *86*, 1994.

Although the bulk of the products are not formed from protonated cyclopropane intermediates, there is considerable evidence that at least in 1-propyl systems, a small part of the product can in fact arise from such intermediates.²² Among this evidence is the isolation of 10–15% cyclopropanes (mentioned in Sec. 10.C.i, category 4c). Additional evidence comes from propyl cations generated by diazotization of labeled amines ($\text{CH}_3\text{CH}_2\text{CD}_2^+$, $\text{CH}_3\text{CD}_2\text{CH}_2^+$, $\text{CH}_3\text{CH}_2^{14}\text{CH}_2^+$), where isotopic distribution in the products indicated that a small amount ($\sim 5\%$) of the product had to be formed from protonated cyclopropane intermediates, for example,²³



Even more scrambling was found in trifluoroacetolysis of 1-propyl-1- ^{14}C -mercuric perchlorate.²⁴ However, protonated cyclopropane intermediates accounted for $< 1\%$ of the products from diazotization of labeled isobutylamine²⁵ and from formolysis of labeled 1-propyl tosylate.²⁶



It is likely that protonated cyclopropane transition states or intermediates are also responsible for certain non-1,2 rearrangements. For example, in superacid solution, the ions **17** and **19** are in equilibrium. It is not possible for these to interconvert solely by 1,2-alkyl or hydride shifts unless primary carbocations, which are highly unlikely, are intermediates. However, the reaction can be explained²⁷ by postulating that (in the forward reaction) it is the 1,2-bond of the intermediate or transition state **18** that opens up rather than the 2,3-bond, which is the one that would open if the reaction were a normal 1,2-shift of a methyl group. In this case, opening of the 1,2-bond produces a tertiary cation, while opening of the 2,3-bond would give a secondary cation. (In the reaction **19** \rightarrow **17**, it is of course the 1,3-bond that opens).

3. There has been much discussion of H as the migrating group. There is no conclusive evidence that **10** in this case is or is not a true intermediate, although both positions have been argued (see Sec. 10.C.i, category 4c).

²² Saunders, M.; Vogel, P.; Hagen, E.L.; Rosenfeld, J. *Acc. Chem. Res.* **1973**, 6, 53; Lee, C.C. *Prog. Phys. Org. Chem.* **1970**, 7, 129; Collins, C.J. *Chem. Rev.* **1969**, 69, 543. See also, Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* **1982**, 605.

²³ Karabatsos, G.J.; Orzech, Jr., C.E.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* **1970**, 92, 606.

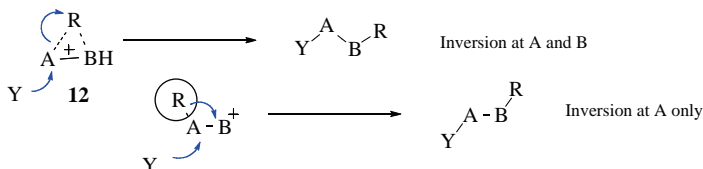
²⁴ Lee, C.C.; Cessna, A.J.; Ko, E.C.F.; Vassie, S. *J. Am. Chem. Soc.* **1973**, 95, 5688. See also, Lee, C.C.; Reichle, R. *J. Org. Chem.* **1977**, 42, 2058 and references cited therein.

²⁵ Karabatsos, G.J.; Hsi, N.; Meyerson, S. *J. Am. Chem. Soc.* **1970**, 92, 621. See also, Karabatsos, G.J.; Anand, M.; Rickter, D.O.; Meyerson, S. *J. Am. Chem. Soc.* **1970**, 92, 1254.

²⁶ Karabatsos, G.J.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* **1970**, 92, 614. See also, Lee, C.C.; Zohdi, H.F. *Can. J. Chem.* **1983**, 61, 2092.

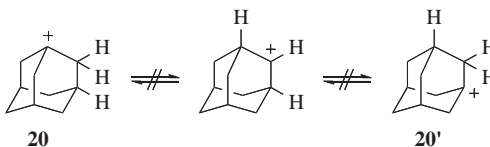
²⁷ Saunders, M.; Jaffe, M.H.; Vogel, P. *J. Am. Chem. Soc.* **1971**, 93, 2558; Saunders, M.; Vogel, P. *J. Am. Chem. Soc.* **1971**, 93, 2559, 2561; Kirmse, W.; Loosen, K.; Prolingheuer, E. *Chem. Ber.* **1980**, 113, 129.

The stereochemistry at the migration origin A is less often involved, since in most cases it does not end up as a tetrahedral atom; but when there is inversion here, there is an S_N2 type process at the beginning of the migration. This may or may not be accompanied by an S_N2 process at the migration terminus B:



In some cases, it has been found that, when H is the migrating species, the configuration at A may be *retained*.²⁸

There is evidence that the configuration of the molecule may be important even where the leaving group is gone long before migration takes place. For example, the 1-adamantyl cation (**20**) does not equilibrate intramolecularly, even at temperatures up to 130 °C,²⁹ though open-chain (e.g., **6-6'**) and cyclic tertiary carbocations undergo such equilibration at 0 °C or below. On the basis of this and other evidence, it has been concluded that for a 1,2-shift of hydrogen or methyl to proceed as smoothly as possible, the vacant *p* orbital of the carbon bearing the positive charge and the *sp*³ orbital carrying the migrating group must be coplanar,²⁹ which is not possible for **20**.



18.A.iii. Migratory Aptitudes³⁰

In many reactions, there is no question about which group migrates. For example, in the *Hofmann*, *Curtius*, and similar reactions there is only one possible migrating group in each molecule, and one can measure migratory aptitudes only by comparing the relative rearrangement rates of different compounds. In other instances, there are two or more potential migrating groups, but which migrates is settled by the geometry of the molecule. The *Beckmann rearrangement* (Reaction **18-17**) provides an example. As seen in the formation of **11**, only the group trans to the OH migrates. In compounds whose geometry is not restricted in this manner, there still may be eclipsing effects (see Sec. 17.C), so that the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule.³¹ However, in some reactions, especially the *Wagner–Meerwein* (**18-1**) and the *pinacol* (**18-2**) rearrangements, the molecule may contain several groups that, geometrically at least, have approximately equal chances

²⁸ Kirmse, W.; Ratajczak, H.; Rauleder, G. *Chem. Ber.* **1977**, *110*, 2290.

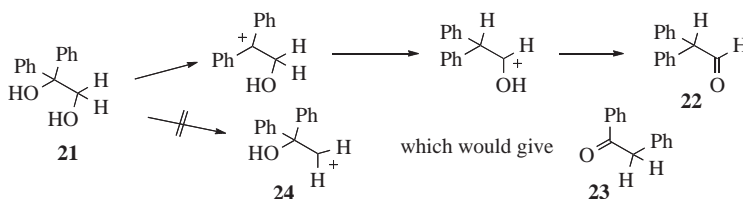
²⁹ Brouwer, D.M.; Hogeveen, H. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 211; Majerski, Z.; Schleyer, P.v.R.; Wolf, A.P. *J. Am. Chem. Soc.* **1970**, *92*, 5731.

³⁰ See Koptug, V.A.; Shubin, V.G. *J. Org. Chem. USSR* **1980**, *16*, 1685; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, **1960**, pp. 573–597.

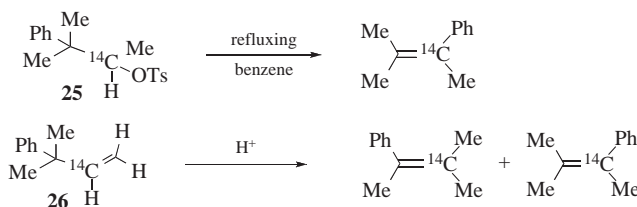
³¹ See Cram, D.J. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, **1956**, pp. 270–276. For an interesting example, see Nickon, A.; Weglein, R.C. *J. Am. Chem. Soc.* **1975**, *97*, 1271.

of migrating, and these reactions have often been used for the direct study of relative migratory aptitudes. In the *pinacol rearrangement*, there is the additional question of which OH group leaves and which does not, since a group can migrate only if the OH group on the *other* carbon is lost.

We deal with the second question first. To study this question, the best type of substrate to use is one of the form $R_2C(OH)-C(OH)R'_2$, since the only thing that determines migratory aptitude is which OH group comes off. Once the OH group is gone, the migrating group is determined. As might be expected, the OH that leaves is the one whose loss gives rise to the more stable carbocation. Thus 1,1-diphenylethanediol (**21**) gives diphenylacetaldehyde (**22**), not phenylacetophenone (**23**). Obviously, it does not matter in this case whether phenyl has a greater inherent migratory aptitude than hydrogen or not. Only the hydrogen can migrate because **24** is not formed. Remember that carbocation stability is enhanced by groups in the order aryl > alkyl > hydrogen, and this normally determines which side loses the OH group. However, exceptions are known, and which group is lost may depend on the reaction conditions (e.g., see the reaction of **59**).



In order to answer the question about inherent migratory aptitudes, the obvious type of substrate to use (in the pinacol rearrangement) is $R'RC(OH)-COH)RR'$, since the same carbocation is formed no matter which OH leaves, and it would seem that a direct comparison of the migratory tendencies of R and R' is possible. On closer inspection, however, it is clear that several factors are operating. Apart from the question of possible conformational effects, already mentioned, there is also the fact that whether the group R or R' migrates is determined not only by the relative inherent migrating abilities of R and R', but also by whether the group that does *not* migrate is better at stabilizing the positive charge that will now be found at the migration origin.³² Thus, migration of R gives rise to the cation $R'C^+(OH)CR_2R'_2$, while migration of R' gives the cation $R^+C(OH)CRR'_2$ and these cations have different stabilities. It is possible that in a given case R might be found to migrate less than R', not because it actually has a lower inherent migrating tendency, but because it is much



better at stabilizing the positive charge. In addition to this factor, the migrating ability of a group is also related to its capacity to render anchimeric assistance to the departure of the

³² See McCall, M.J.; Townsend, J.M.; Bonner, W.A. *J. Am. Chem. Soc.* **1975**, *97*, 2743; Brownbridge, P.; Hodgson, P.K.G.; Shepherd, R.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* **1976**, 2024.

nucleofuge. An example of this effect is the decomposition of tosylate (**25**) where only the phenyl group migrates, while in acid treatment of the corresponding alkene (**26**), there is competitive migration of both methyl and phenyl (in these reactions ^{14}C labeling is necessary to determine which group has migrated).³³ Both **25** and **26** give the same carbocation; the differing results must be caused by the fact that in **25** the phenyl group can assist the leaving group, while no such process is possible for **26**. This example clearly illustrates the difference between migration to a relatively free terminus and one that proceeds with the migrating group lending anchimeric assistance.³⁴

Therefore, it is not surprising that clear-cut answers as to relative migrating tendencies are not available. More often than not migratory aptitudes are in the order aryl > alkyl, but exceptions are known, and the position of hydrogen in this series is often unpredictable. In some cases, migration of hydrogen is preferred to aryl migration; in other cases, migration of alkyl is preferred to that of hydrogen. Mixtures are often found, and the isomer that predominates often depends on conditions. For example, the comparison between methyl and ethyl has been made many times in various systems, and in some cases methyl migration and in others ethyl migration has been found to predominate.³⁵ However, it can be said that among aryl migrating groups, electron-donating substituents in the para and meta positions increase the migratory aptitudes, while the same substituents in the ortho positions decrease them. Electron-withdrawing groups decrease migrating ability in all positions. The following are a few of the relative migratory aptitudes determined for aryl groups:³⁶ *p*-anisyl, 500; *p*-tolyl, 15.7; *m*-tolyl, 1.95; phenyl, 1.00; *p*-chlorophenyl, 0.7; *o*-anisyl, 0.3. For the *o*-anisyl group, the poor migrating ability probably has a steric cause, while for the others there is a fair correlation with activation or deactivation of electrophilic aromatic substitution, which is what the process is with respect to the benzene ring. It has been reported that at least in certain systems acyl groups have a greater migratory aptitude than alkyl groups.³⁷

18.A.iv. Memory Effects³⁸

Solvolysis of the endo bicyclic compound (**27**, X = ONs, see Sec. 10.G.iii, or Br) gave mostly the bicyclic allylic alcohol (**30**), along with a smaller amount of the tricyclic alcohol (**34**), while solvolysis of the exo isomers, (**31**), gave mostly **34**, with smaller amounts of **30**.³⁹ Note that endo and exo here refers to the position of the XCH_2 group over the $\text{C}=\text{C}$ unit or opposite the $\text{C}=\text{C}$ unit, respectively. The two isomers gave entirely different ratios of products, although the carbocation initially formed seems to be the same for each (marked **28** and **32** for convenience). With **28**, a second rearrangement (a shift of the 1,7 bond) follows to give **29**, while with **32**

³³ Grimaud, J.; Laurent, A. *Bull. Soc. Chim. Fr.* **1967**, 3599.

³⁴ See Fischer, A.; Henderson, G.N. *J. Chem. Soc., Chem. Commun.* **1979**, 279, and references cited therein. See also, Marx, J.N.; Hahn, Y.P. *J. Org. Chem.* **1988**, 53, 2866.

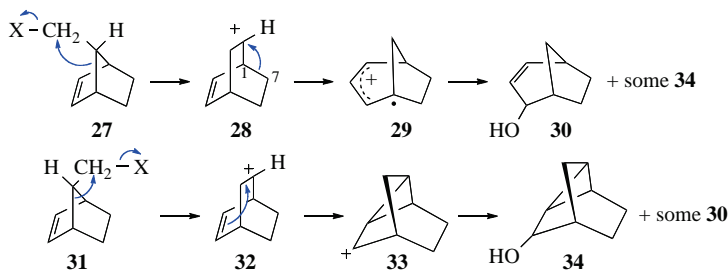
³⁵ See Pilkington, J.W.; Waring, A.J. *J. Chem. Soc. Perkin Trans. 2* **1976**, 1349; Korchagina, D.V.; Derendyaev, B.G.; Shubin, V.G.; Koptuyg, V.A. *J. Org. Chem. USSR* **1976**, 12, 378; Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* **1981**, 22, 4069; Jost, R.; Laali, K.; Sommer, J. *Nouv. J. Chim.* **1983**, 7, 79.

³⁶ Bachmann, W.E.; Ferguson, J.W. *J. Am. Chem. Soc.* **1934**, 56, 2081.

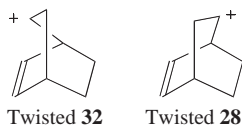
³⁷ Le Drian, C.; Vogel, P. *Helv. Chim. Acta* **1987**, 70, 1703; *Tetrahedron Lett.* **1987**, 28, 1523.

³⁸ For a review, see Berson, J.A. *Angew. Chem. Int. Ed.* **1968**, 7, 779.

³⁹ Berson, J.A.; Poonian, M.S.; Libbey, W.J. *J. Am. Chem. Soc.* **1969**, 91, 5567; Berson, J.A.; Donald, D.S.; Libbey, W.J. *J. Am. Chem. Soc.* **1969**, 91, 5580; Berson, J.A.; Wege, D.; Clarke, G.M.; Bergman, R.G. *J. Am. Chem. Soc.* **1969**, 91, 5594, 5601.



an intramolecular addition of the positive carbon to the double bond gives **33**. It seems as if **28** and **32** “remember” how they were formed before they go on to give the second step. Such effects are called *memory effects* and other such cases are known.⁴⁰ The causes of these effects are not well understood, although there has been much discussion. One possible cause is differential solvation of the apparently identical ions **28** and **32**. Other possibilities are (1) that the ions have geometrical structures that are twisted in opposite senses (e.g., a twisted **32** might have its positive



carbon closer to the double bond than a twisted **28**); (2) that ion pairing is responsible⁴¹; and (3) that nonclassical carbocations are involved.⁴² One possibility that has been ruled out is that steps **27** → **28** → **29** and **31** → **32** → **33** are concerted, so that **28/32** never exist at all. This possibility has been excluded by several kinds of evidence, including the fact that **27** gives not only **30**, but also some **34**; and **31** gives some **30** along with **34**. This means that some of the **28** and **32** ions interconvert, a phenomenon known as *leakage*.

18.B. LONGER NUCLEOPHILIC REARRANGEMENTS

The question as to whether a group can migrate with its electron pair from A to C in W—A—B—C or over longer distances has been much debated. Although claims have been made that alkyl groups can migrate in this way, the evidence is that such migration is extremely rare, if it occurs at all. One experiment that demonstrated this was the generation of the 3,3-dimethyl-1-butyl cation ($\text{Me}_3\text{CCH}_2\text{CH}_2^+$). If 1,3-methyl migrations are possible, this cation would appear to be a favorable substrate, since such a migration would convert a primary cation into the tertiary 2-methyl-2-pentyl cation ($\text{Me}_2\text{C}^+\text{CH}_2\text{CH}_2\text{CH}_3$), while the only possible 1,2 migration (of hydride) would give only a secondary cation. However, no products arising from the 2-methyl-2-pentyl cation were found, the only rearranged products being those formed by the 1,2-hydride migration.⁴³ 1,3-Migration of bromine has been reported.⁴⁴

⁴⁰ See Collins, C.J. *Acc. Chem. Res.* **1971**, *4*, 315; Collins, J.A.; Glover, I.T.; Eckart, M.D.; Raaen, V.F.; Benjamin, B.M.; Benjaminov, B.S. *J. Am. Chem. Soc.* **1972**, *94*, 899; Svensson, T. *Chem. Scr.* **1974**, *6*, 22.

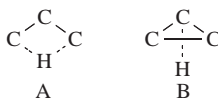
⁴¹ See Collins, C.J. *Chem. Soc. Rev.* **1975**, *4*, 251.

⁴² See Kirmse, W.; Günther, B. *J. Am. Chem. Soc.* **1978**, *100*, 3619.

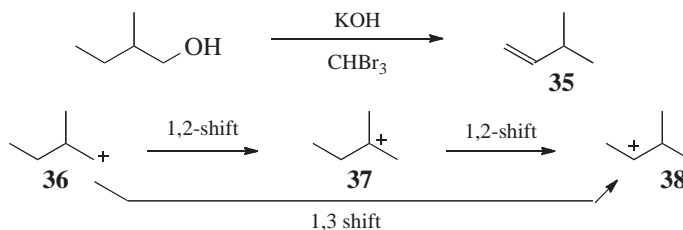
⁴³ Skell, P.S.; Reichenbacher, P.H. *J. Am. Chem. Soc.* **1968**, *90*, 2309.

⁴⁴ Reineke, C.E.; McCarthy, Jr., J.R. *J. Am. Chem. Soc.* **1970**, *92*, 6376; Smolina, T.A.; Gopius, E.D.; Gruzdnova, V.N.; Reutov, O.A. *Doklad. Chem.* **1973**, *209*, 280.

Most of the debate over the possibility of 1,3-migrations has concerned not methyl or bromine but 1,3-hydride shifts.⁴⁵ Many instances have been found of *apparent* 1,3-hydride shifts, but the question is whether they are truly direct hydride shifts or whether they occur by another mechanism. There are at least two ways in



which indirect 1,3-hydride shifts can take place: (1) by successive 1,2-shifts or (2) through the intervention of protonated cyclopropanes (see Sec. 18.A.ii, category 2). A direct 1,3-shift would have transition state **A**, while the transition state for a 1,3-shift involving a protonated cyclopropane intermediate would resemble **B**. The evidence is that most reported 1,3-hydride shifts are actually the result of successive 1,2-migrations,⁴⁶ but in some cases small amounts of products cannot be accounted for in this way. The reaction of 2-methyl-1-butanol with KOH and bromoform gave a mixture of alkenes, nearly all of which could have arisen from simple elimination or 1,2-shifts of hydride or alkyl. However, 1.2% of the product was **35**.⁴⁷ Hypothetically, **35** could have arisen from a 1,3 shift (direct or through a protonated cyclopropane) or from two successive 1,2-shifts:



However, the same reaction applied to 2-methyl-2-butanol gave no **35**, which demonstrated that **38** was not formed from **37**. The conclusion made was that **38** was formed directly from **36**. This experiment does not answer the question as to whether **38** was formed by a direct shift or through a protonated cyclopropane, but from other evidence⁴⁸ it appears that 1,3-hydride shifts that do not result from successive 1,2-migrations usually take place through protonated cyclopropane intermediates, which (as seen in Sec. 18.A.ii, category 2) account for only a small percentage of the product in any case. However, there is evidence that direct 1,3-hydride shifts by way of **A** (see above) may take place in superacid solutions.⁴⁹ Although direct nucleophilic rearrangements over distances $>1,2$ are rare (or perhaps nonexistent) when the migrating atom or group must move along a chain, this is not so for a shift across a ring of 8–11 members. Many such transannular rearrangements are known⁵⁰ (see Sec. 4.Q.ii): the mechanism for the

⁴⁵ See Fry, J.L.; Karabatsos, G.J. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, p. 527.

⁴⁶ See Kirmse, W.; Knist, J.; Ratajczak, H. *Chem. Ber.* **1976**, 109, 2296.

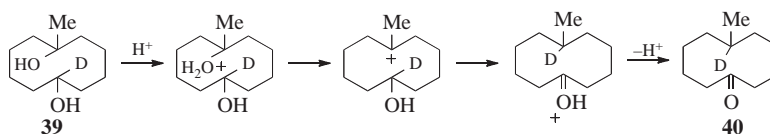
⁴⁷ Skell, P.S.; Maxwell, R.J. *J. Am. Chem. Soc.* **1962**, 84, 3963. See also, Skell, P.S.; Starer, I. *J. Am. Chem. Soc.* **1962**, 84, 3962.

⁴⁸ Hudson, H.R.; Koplick, A.J.; Poulton, D.J. *Tetrahedron Lett.* **1975**, 1449; Fry, J.L.; Karabatsos, G.J. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, p. 527.

⁴⁹ Saunders, M.; Stofko, Jr., J.J. *J. Am. Chem. Soc.* **1973**, 95, 252.

⁵⁰ See Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* **1966**, 20, 119.

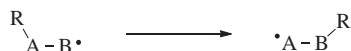
conversion of **39** to **40** is shown.⁵¹



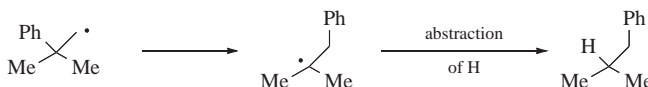
Note that the *methyl* group does not migrate in this system. *It is generally true that alkyl groups do not undergo transannular migration.*⁵² In most cases, it is the hydride that undergoes this type of migration, though a small amount of phenyl migration has also been shown.⁵³

18.C. FREE RADICAL REARRANGEMENTS⁵⁴

1,2-Free radical rearrangements are much less common than the nucleophilic type previously considered, for the reasons mentioned in the introductory Section 18.A. Where they do occur, the general pattern is similar. There must first be generation of a free radical, and then the actual migration in which the migrating group moves with one electron:



Finally, the new free radical will undergo a further reaction to generate a neutral molecule. The order of radical stability leads to a prediction that here too, as with carbocation rearrangements, migrations should be in the order primary \rightarrow secondary \rightarrow tertiary, and that the logical place to look for them should be in neopentyl and neophyl systems. The most common way of generating free radicals for the purpose of detection of rearrangements is by decarbonylation of aldehydes (Reaction **14-32**). In this manner, it was found that neophyl radicals *do* undergo rearrangement.⁵⁵ Thus, $\text{PhCMe}_2\text{CH}_2\text{CHO}$ treated with di-*tert*-butyl peroxide gave about equal amounts of the normal product $\text{PhCMe}_2\text{CH}_3$ and the product arising from migration of phenyl⁵⁶:



⁵¹ Prelog, V.; Küng, W. *Helv. Chim. Acta* **1956**, *39*, 1394.

⁵² For an apparent exception, see Farcasiu, D.; Seppo, E.; Kizirian, M.; Ledlie, D.B.; Sevin, A. *J. Am. Chem. Soc.* **1989**, *111*, 8466.

⁵³ Cope, A.C.; Burton, P.E.; Caspar, M.L. *J. Am. Chem. Soc.* **1962**, *84*, 4855.

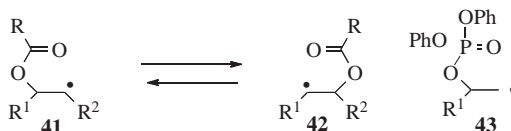
⁵⁴ Beckwith, A.L.J.; Ingold, K.U. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, **1980**, pp. 161–310; Wilt, J.W. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, **1973**, pp. 333–501; Stepukhovich, A.D.; Babayan, V.I. *Russ. Chem. Rev.* **1972**, *41*, 750; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, **1974**, pp. 498–552; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, **1970**, pp. 235–255; Freidlina, R.Kh. *Adv. Free-Radical Chem.* **1965**, *1*, 211–278; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, **1966**, pp. 266–284.

⁵⁵ Antunes, C.S.A.; Bietti, M.; Ercolani, G.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 3884.

⁵⁶ Seubold Jr., F.H. *J. Am. Chem. Soc.* **1953**, *75*, 2532. For the observation of this rearrangement by ESR, see Hamilton, Jr., E.J.; Fischer, H. *Helv. Chim. Acta* **1973**, *56*, 795.

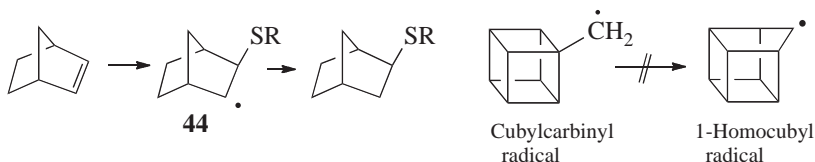
Many other cases of free radical migration of aryl groups have been found.⁵⁷ Intramolecular radical rearrangements are known.⁵⁸ The C-4 radicals of α - and β -thujone undergo two distinct rearrangement reactions, and it has been proposed that these could serve as simultaneous but independent radical clocks.⁵⁹

A 1,2-shift has been observed in radicals bearing an OCOR group at the β -carbon where the oxygen group migrates as shown in the interconversion of **41** and **42**. This has been proven by ^{18}O isotopic labeling experiments⁶⁰ and other mechanistic explorations.⁶¹ A similar rearrangement was observed with phosphatoxy alkyl radicals (e.g., as **43**).⁶² A 1,2-shift of hydrogen atoms has been observed in aryl radicals.⁶³



Note that the extent of migration is much less than with corresponding carbocations: Thus in the example given, there was only $\sim 50\%$ migration, whereas the carbocation would have given much more. Also noteworthy is that there was no migration of the methyl group. In general, it may be said that free radical migration of alkyl groups does not occur at ordinary temperatures. *Many attempts have been made to detect such migration on the traditional neopentyl and bornyl types of substrates. However, alkyl migration is not observed, even in substrates where the corresponding carbocations undergo facile rearrangement.*⁶⁴ Another type of migration that is very common for carbocations, but not observed for free radicals, is 1,2-migration of hydrogen. We confine ourselves to a few examples of the lack of migration of alkyl groups and hydrogen:

1. 3,3-Dimethylpentanal ($\text{EtCMe}_2\text{CH}_2\text{CHO}$) gave no rearranged products on decarbonylation.⁶⁵
2. Addition of RSH to norbornene gave only *exo*-norbornyl sulfides, though **44** is an intermediate, and the corresponding carbocation cannot be formed without rearrangement.⁶⁶



⁵⁷ See Walter, D.W.; McBride, J.M. *J. Am. Chem. Soc.* **1981**, *103*, 7069, 7074. For a review, see Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649.

⁵⁸ Prévost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383.

⁵⁹ He, X.; Ortiz de Montellano, P.R. *J. Org. Chem.* **2004**, *69*, 5684.

⁶⁰ Crich, D.; Filzen, G.F. *J. Org. Chem.* **1995**, *60*, 4834.

⁶¹ Beckwith, A.L.J.; Duggan, P.J. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1777; **1993**, 1673.

⁶² Crich, D.; Yao, Q. *Tetrahedron Lett.* **1993**, *34*, 5677. See Ganapathy, S.; Cambron R.T.; Dockery, K.P.; Wu, Y.-W.; Harris, J.M.; Bentrude, W.G. *Tetrahedron Lett.* **1993**, *34*, 5987.

⁶³ Brooks, M.A.; Scott, L.T. *J. Am. Chem. Soc.* **1999**, *121*, 5444.

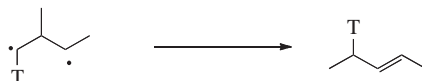
⁶⁴ Several unsuccessful attempts: Slauch, L.H.; Magoon, E.F.; Guinn, V.P. *J. Org. Chem.* **1963**, *28*, 2643.

⁶⁵ Seubold Jr., F.H. *J. Am. Chem. Soc.* **1954**, *76*, 3732.

⁶⁶ Cristol, S.J.; Brindell, G.D. *J. Am. Chem. Soc.* **1954**, *76*, 5699.

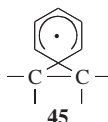
3. The cubylcarbonyl radical did not rearrange to the 1-homocubyl radical, though doing so would result in a considerable decrease in strain.⁶⁷
4. It was shown⁶⁸ that no rearrangement of isobutyl radical to *tert*-butyl radical, which would involve the formation of a more stable radical by a hydrogen shift, took place during the chlorination of isobutane.

However, 1,2-migration of alkyl groups has been shown to occur in certain *diradicals*.⁶⁹ For example, the following rearrangement has been established by tritium labeling.⁷⁰



In this case, the fact that migration of the methyl group leads directly to a compound in which all electrons are paired undoubtedly contributes to the driving force of the reaction.

The fact that aryl groups migrate, but alkyl groups and hydrogen generally do not, leads to the proposition that **45**, in which the odd electron is not found in the three-membered ring, may be an intermediate. There has been much controversy on this point, but the bulk of the evidence indicates that **45** is a transition state, not an intermediate.⁷¹ Among the evidence is the failure to observe **45** either by ESR⁷² or CIDNP.⁷³ Both of these techniques can detect free radicals with extremely short lifetimes (Sec. 5.C.i).⁷⁴



In addition, aryl, vinylic⁷⁵ and acetoxy groups⁷⁶ also migrate. Vinylic groups migrate via a cyclopropylcarbinyl radical intermediate (**46**),⁷⁷ while the migration of acetoxy groups may involve the charge-separated structure shown.⁷⁸ Thermal isomerization of 1-(3-butenyl)cyclopropane at 415 °C leads to bicyclo[2.2.1]heptane.⁷⁹ Migration has been

⁶⁷ Eaton, P.E.; Yip, Y. *J. Am. Chem. Soc.* **1991**, *113*, 7692.

⁶⁸ Brown, H.C.; Russel, G.A. *J. Am. Chem. Soc.* **1952**, *74*, 3995. See also, Desai, V.R.; Nechvatal, A.; Tedder, J.M. *J. Chem. Soc. B* **1970**, 386.

⁶⁹ See Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* **1974**, *43*, 129.

⁷⁰ McKnight, C.; Rowland, F.S. *J. Am. Chem. Soc.* **1966**, *88*, 3179. See Gajewski, J.J.; Burka, L.T. *J. Am. Chem. Soc.* **1972**, *94*, 8857, 8860, 8865; Adam, W.; Aponte, G.S. *J. Am. Chem. Soc.* **1971**, *93*, 4300.

⁷¹ For MO calculations indicating that **45** is an intermediate, see Yamabe, S. *Chem. Lett.* **1989**, 1523.

⁷² Edge, D.J.; Kochi, J.K. *J. Am. Chem. Soc.* **1972**, *94*, 7695.

⁷³ Olah, G.A.; Krishnamurthy, V.V.; Singh, B.P.; Iyer, P.S. *J. Org. Chem.* **1983**, *48*, 955. **45** has been detected as an intermediate in a different reaction: Effio, A.; Griller, D.; Ingold, K.U.; Scaiano, J.C.; Sheng, S.J. *J. Am. Chem. Soc.* **1980**, *102*, 6063; Leardini, R.; Nanni, D.; Pedulli, G.F.; Tundo, A.; Zanardi, G.; Foresti, E.; Palmieri, P. *J. Am. Chem. Soc.* **1989**, *111*, 7723.

⁷⁴ See Martin, M.M. *J. Am. Chem. Soc.* **1962**, *84*, 1986; Rüchardt, C.; Hecht, R. *Chem. Ber.* **1965**, *98*, 2460, 2471; Rüchardt, C.; Trautwein, H. *Chem. Ber.* **1965**, *98*, 2478.

⁷⁵ See Newcomb, M.; Glenn, A.G.; Williams, W.G. *J. Org. Chem.* **1989**, *54*, 2675.

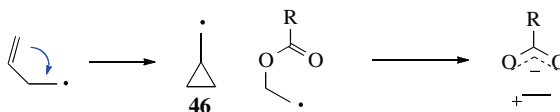
⁷⁶ See Lewis, S.N.; Miller, J.J.; Winstein, S. *J. Org. Chem.* **1972**, *37*, 1478.

⁷⁷ See Montgomery, L.K.; Matt, J.W. *J. Am. Chem. Soc.* **1967**, *89*, 934, 6556; Giese, B.; Heinrich, N.; Horler, H.; Koch, W.; Schwarz, H. *Chem. Ber.* **1986**, *119*, 3528.

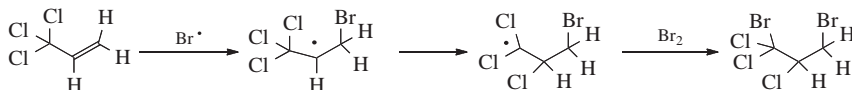
⁷⁸ Barclay, L.R.C.; Luszyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* **1984**, *106*, 1793.

⁷⁹ Baldwin, J.E.; Burrell, R.C.; Shukla, R. *Org. Lett.* **2002**, *4*, 3305.

observed for chloro (and to a much lesser extent bromo) groups.



For example, in the reaction of Cl₃CCH=CH₂ with bromine under the influence of peroxides, the products were 47% Cl₃CCHBrCH₂Br (the normal addition product) and 53% BrCCl₂CHClCH₂Br, which arose by rearrangement:

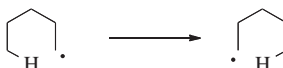


In this particular case, the driving force for the rearrangement is the particular stability of dichloroalkyl free radicals.⁸⁰ It has been shown that the 1,2-migration of Cl readily occurs if the migration origin is tertiary and the migration terminus is primary.⁸¹ Migration of Cl and Br could take place by a transition state in which the odd electron is accommodated in a vacant *d* orbital of the halogen.

Migratory aptitudes have been measured for the phenyl and vinyl groups, and for three other groups, using the system RMe₂CH₂• → Me₂OC•CH₂R. These were found to be in the order R = H₂C=CH₂ > Me₃CC=O > Ph > Me₃CC≡C > CN.⁸²

In summary, 1,2 free radical migrations are much less prevalent than the analogous carbocation processes, and are important only for aryl, vinylic, acetoxy, and halogen migrating groups. The direction of migration is normally toward the more stable radical, but “wrong-way” rearrangements are also known.⁸³

Despite the fact that hydrogen atoms do not migrate 1,2, longer free radical migrations of hydrogen are known.⁸⁴ The most common are 1,5-shifts, but 1,6 and longer shifts have also been found (see Reaction 18-29). The possibility of 1,3-hydrogen shifts has been much investigated, but it is not certain if any actually occur. If they do they are rare, presumably because the most favorable geometry for C••H••C in the transition state is linear and this geometry cannot be achieved in a 1,3-shift. 1,4-Shifts are definitely known, but are still not very common. These long shifts are best regarded as internal abstractions of hydrogen (for Reactions, see 14-6 and 18-40):



Transannular shifts of hydrogen atoms have also been observed.⁸⁵

⁸⁰ See Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* **1979**, *48*, 828; Freidlina, R.Kh. *Adv. Free-Radical Chem.* **1965**, *1*, 211, pp. 231–249.

⁸¹ See Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* **1974**, *96*, 2201.

⁸² Lindsay, D.A.; Luszyk, J.L.; Ingold, K.U. *J. Am. Chem. Soc.* **1984**, *106*, 7087.

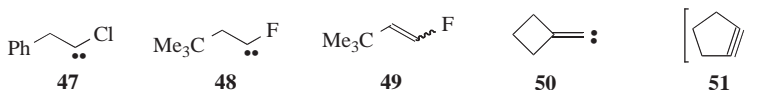
⁸³ See Dannenberg, J.J.; Dill, K. *Tetrahedron Lett.* **1972**, 1571.

⁸⁴ See Freidlina, R.Kh.; Terent'ev, A.B. *Acc. Chem. Res.* **1977**, *10*, 9.

⁸⁵ Traynham, J.G.; Couvillon, T.M. *J. Am. Chem. Soc.* **1967**, *89*, 3205.

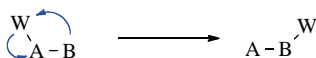
18.D. CARBENE REARRANGEMENTS⁸⁶

Carbenes can rearrange to alkenes in many cases.⁸⁷ A 1,2-hydrogen shift leads to an alkene, and this is often competitive with insertion reactions.⁸⁸ Benzylchlorocarbene (**47**) rearranges via a 1,2-hydrogen shift to give the alkene.⁸⁹ Similarly, carbene **48** rearranges to alkene **49**, and replacement of H on the α -carbon with D showed a deuterium isotope effect of ~ 5 .⁹⁰ Vinylidene carbene ($\text{H}_2\text{C}=\text{C}:$) rearranges to acetylene.⁹¹ Rearrangement of alkylidene carbene (**50**) has been calculated to give the highly unstable cyclopentyne (**51**), which cannot be isolated, but can give a [2 + 2] cycloaddition product (Reaction 15-63) when generated in the presence of a simple alkene.⁹² The spiro carbenes undergo rearrangement reactions.⁹³



18.E. ELECTROPHILIC REARRANGEMENTS⁹⁴

Rearrangements in which a group migrates without its electrons are rarer than the two kinds previously considered, but the general principles are the same. A carbanion (or other negative ion) is created first, and the actual rearrangement step involves migration of a group without its electrons:



The product of the rearrangement may be stable or may react further, depending on its nature (see also, Reaction 18-2). An *ab initio* study predicts that a [1,2]-alkyl shift in alkyne anions should be facile.⁹⁵

18.F. REACTIONS

The reactions in this chapter are classified into three main groups and 1,2-shifts are considered first. Within this group, reactions are classified according to (1) the identity of the substrate atoms A and B and (2) the nature of the migrating group W. The cyclic

⁸⁶ See Baird, M.S. *Chem. Rev.* **2003**, 103, 1271.

⁸⁷ de Meijere, A.; Kozhushkov, S.I.; Faber, D.; Bagutskii, V.; Boese, R.; Haumann, T.; Walsh, R. *Eur. J. Org. Chem.* **2001**, 3607.

⁸⁸ Nickon, A.; Stern, A.G.; Ilao, M.C. *Tetrahedron Lett.* **1993**, 34, 1391.

⁸⁹ Merrer, D.C.; Moss, R.A.; Liu, M.T.H.; Banks, J.-T.; Ingold, K.U. *J. Org. Chem.* **1998**, 63, 3010.

⁹⁰ Moss, R.A.; Ho, C.-J.; Liu, W.; Sierakowski, C. *Tetrahedron Lett.* **1992**, 33, 4287.

⁹¹ Hayes, R.L.; Fattal, E.; Govind, N.; Carter, E.A. *J. Am. Chem. Soc.* **2001**, 123, 641.

⁹² Gilbert, J.C.; Kirschner, S. *Tetrahedron Lett.* **1993**, 34, 599, 603.

⁹³ Moss, R.A.; Zheng, F.; Krough-Jespersen, K. *Org. Lett.* **2001**, 3, 1439.

⁹⁴ See Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, **1980**, pp. 391–470; Grovenstein Jr., E. *Angew. Chem. Int. Ed.* **1978**, 17, 313; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, **1968**, pp. 21–30; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, **1965**, pp. 223–243.

⁹⁵ Borosky, G.L. *J. Org. Chem.* **1998**, 63, 3337.

rearrangements are in the second group. The third group consists of rearrangements that cannot be fitted into either of the first two categories.

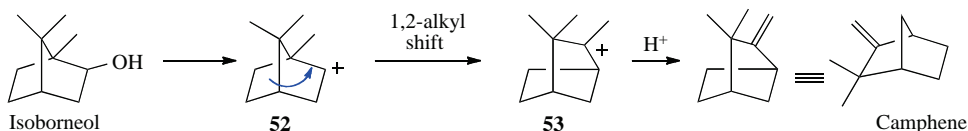
Reactions in which the migration terminus is on an aromatic ring have been treated under aromatic substitution. These are Reactions **11-27–11-32**, **11-36**, **13-30–13-32**, and, partially, **11-33**, **11-38**, and **11-39**. Double-bond shifts have also been treated in other chapters, although they may be considered rearrangements (Sec. 8.A and Reactions **12-4**, and **12-2**). Other reactions that may be regarded as rearrangements are the *Pummerer* (**19-83**) and *Willgerodt* (**19-84**) reactions.

18.F.i. 1,2-Rearrangements

A. Carbon-to-Carbon Migrations of R, H, and Ar

18-1 Wagner–Meerwein and Related Reactions

1/Hydro,1/hydroxy-(2/→1/alkyl)- migro- elimination, and so on



Wagner–Meerwein rearrangements were first discovered in reactions of bicyclic terpenes, and most of the early development of this reaction was with these compounds.⁹⁶ An example is the conversion of isoborneol to camphene. It fundamentally involves a 1,2-alkyl shift of an intermediate carbocation, (e.g., **52** \rightarrow **53**). When alcohols are treated with acids, simple substitution (e.g., Reaction **10-48**) or elimination (Reaction **17-1**) usually accounts for most or all of the products. But in many cases, especially where two or three alkyl or aryl groups are on the β carbon, some or all of the product is rearranged. These rearrangements have been called *Wagner–Meerwein rearrangements*, although this term is nowadays reserved for relatively specific transformations (e.g., isoborneol to camphene and related reactions). As pointed out previously, the carbocation that is a direct product of the rearrangement must stabilize itself, and most often it does this by the loss of a hydrogen β to it, so the rearrangement product is usually an alkene.⁹⁷ If there is a choice of protons, *Zaitsev's rule* (Sec. 17.A.i, category 3) governs the direction, as expected. Sometimes a different positive group is lost instead of a proton. Less often, the new carbocation reacts with a nucleophile instead of losing a proton. The nucleophile may be the water that is the original leaving group, in which case the product is a rearranged alcohol; or it may be some other species present (solvent, added nucleophile, etc.).

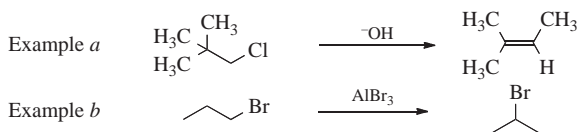
Rearrangement is usually predominant in neopentyl and neophyl types of substrates, and with these types normal nucleophilic substitution is difficult (normal elimination is of course impossible). Under S_N2 conditions, substitution is extremely slow⁹⁸; and under S_N1 conditions, carbocations are formed that rapidly rearrange. However, free radical

⁹⁶ See Hogeveen, H.; van Kruchten, E.M.G.A. *Top. Curr. Chem.* **1979**, 80, 89; Arbuzov, B.A.; Isaeva, Z.G. *Russ. Chem. Rev.* **1976**, 45, 673; Banthorpe, D.V.; Whittaker, D. *Q. Rev. Chem. Soc.* **1966**, 20, 373.

⁹⁷ See Kaupp, G. *Top. Curr. Chem.* **1988**, 146, 57.

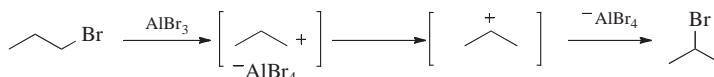
⁹⁸ See, however, Lewis, R.G.; Gustafson, D.H.; Erman, W.F. *Tetrahedron Lett.* **1967**, 401; Paquette, L.A.; Philips, J.C. *Tetrahedron Lett.* **1967**, 4645; Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* **1974**, 96, 3171.

substitution, unaccompanied by rearrangement, can be carried out on neopentyl systems, although, as seen previously (Sec. 18.C), neophyl systems undergo rearrangement as well as substitution.



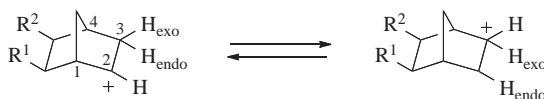
Examples of carbocation rearrangements are found in simpler systems (e.g., neopentyl chloride, example *a*) and even 1-bromopropane (example *b*). These examples illustrate the following points:

1. Hydride ion can migrate. In example *b*, it was hydride that shifted, not bromine:



2. The leaving group does not have to be H₂O, but can be any departing species whose loss creates a carbocation, including N₂ from aliphatic diazonium ions⁹⁹ (see the section on leaving groups in nucleophilic substitution in Sec. 10.A.ii, category 1). Rearrangement may follow when the carbocation is created by addition of a proton or other positive species to a double bond.
3. Example *b* illustrates that the last step can be substitution instead of elimination.
4. Example *a* illustrates that the new double bond is formed in accord with *Zaitsev's rule*.

2-Norbornyl cations (see **52**), besides displaying the 1,2-shifts of a CH₂ group previously illustrated for the isoborneol → camphene conversion, are also prone to rapid hydride shifts from the 3 to the 2 position (known as 3,2-shifts). These 3,2-shifts usually take place from the *exo* side¹⁰⁰; that is, the 3-*exo* hydrogen migrates to the 2-*exo* position.¹⁰¹ This stereoselectivity is analogous to the behavior previously seen for norbornyl systems, namely, that nucleophiles attack norbornyl cations from the *exo* side (Sec. 10.C.i, category 4) and that addition to norbornenes is also usually from the *exo* direction (Sec. 15.B.iii).



For rearrangements of alkyl carbocations, the direction of rearrangement is usually toward the most stable carbocation (or radical), which is tertiary > secondary > primary, but rearrangements in the other direction have also been found,¹⁰² and the product is

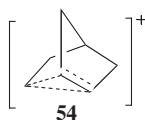
⁹⁹ See, in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, **1968**, the articles by White, E.H.; Woodcock, D.J. pp. 407–497 (473–483) and by Banthorpe, D.V. pp. 585–667 (pp. 586–612).

¹⁰⁰ See Berson, J.A.; Hammons, J.H.; McRowe, A.W.; Bergman, R.G.; Remanick, A.; Houston, D. *J. Am. Chem. Soc.* **1967**, 89, 2590.

¹⁰¹ For an example of a 3,2-endo shift, see Wilder, Jr., P.; Hsieh, W. *J. Org. Chem.* **1971**, 36, 2552.

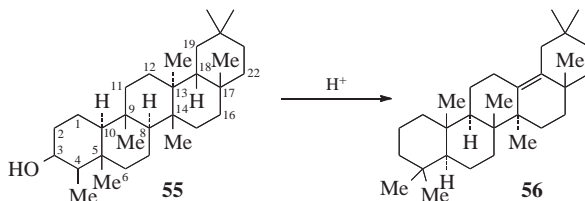
¹⁰² See Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* **1982**, 605.

sometimes a mixture corresponding to an equilibrium mixture of the possible carbocations. The *Wagner–Meerwein rearrangement* has been observed for a secondary to a secondary carbocation rearrangement, leading to some controversy. Winstein¹⁰³ described norbornyl cations in terms of the resonance structures represented by the nonclassical ion **54**.¹⁰⁴ This view was questioned, primarily by Brown,¹⁰⁵ who suggested that the facile rearrangements could be explained by a series of fast *1,3-Wagner–Meerwein shifts*.¹⁰⁶ There is considerable evidence, however, that *the norbornyl cation rearranges with σ participation*,¹⁰⁷ and there is strong NMR evidence for the nonclassical ion in superacids at low temperatures.¹⁰⁸



As alluded to above, the term “*Wagner–Meerwein rearrangement*” is not precise. Some use it to refer to all the rearrangements in this section and in Reaction **18-2**. Others use it only when an alcohol is converted to a rearranged alkene. Many use the term only for rearrangements that involve a nonclassical carbocation intermediate. Terpene chemists call the migration of a methyl group the *Nametkin rearrangement*. The term *retropinacol rearrangement* is often applied to some or all of these. Fortunately, this disparity in nomenclature does not seem to cause much confusion. Catalytic asymmetric *Wagner–Meerwein shifts* have been observed.¹⁰⁹ An asymmetric, Pd catalyzed *Wagner–Meerwein shift* has been reported with allenic alcohols.¹¹⁰

Several of these rearrangements sometimes occur in one molecule, either simultaneously or in rapid succession. A spectacular example is found in the triterpene series. Friedelin is a triterpenoid ketone found in cork. Reduction gives 3 β -friedelanol (**55**). When this compound is treated with acid, 13(18)-oleanene (**56**) is formed.¹¹¹ In this case, *seven* 1,2-shifts take place. Loss of H₂O from position 3 leaves a positive charge, and



¹⁰³ See Winstein, S. *Quart. Rev. Chem. Soc.* **1969**, 23, 141.

¹⁰⁴ Berson, J.A. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Academic Press, NY, **1980**, p. 111; Sargent, G.D. *Quart. Rev. Chem. Soc.* **1966**, 20, 301; Olah, G.A. *Acc. Chem. Res.* **1976**, 9, 41; Scheppele, S.E. *Chem. Rev.* **1972**, 72, 511.

¹⁰⁵ Brown, H.C. *The Non-Classical Ion Problem*, Plenum, New York, **1977**; Brown, H.C. *Tetrahedron* **1976**, 32, 179; Brown, H.C.; Kawakami, J.H. *J. Am. Chem. Soc.* **1970**, 92, 1990. See also, Story, R.R.; Clark, B.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, New York, **1972**, p. 1007.

¹⁰⁶ Brown, H.C.; Ravindranathan, M. *J. Am. Chem. Soc.* **1978**, 100, 1865.

¹⁰⁷ Coates, R.M.; Fretz, E.R. *J. Am. Chem. Soc.* **1977**, 99, 297; Brown, H.C.; Ravindranathan, M. *J. Am. Chem. Soc.* **1977**, 99, 299.

¹⁰⁸ Olah, G.A. *Carbocations and Electrophilic Reactions*, Verlag Chemie/Wiley, New York, **1974**, pp. 80–89; Olah, G.A.; White, A.M.; DeMember, J.R.; Commeyras, A.; Lui, C.Y. *J. Am. Chem. Soc.* **1970**, 92, 4627.

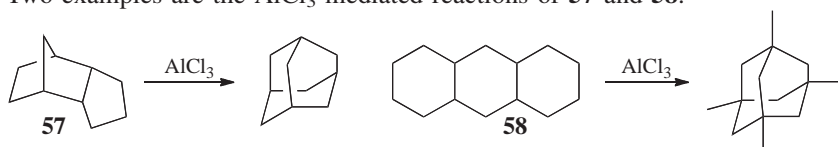
¹⁰⁹ Trost, B.M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, 123, 7162.

¹¹⁰ Trost, B.M.; Xie, J. *J. Am. Chem. Soc.* **2006**, 128, 6044.

¹¹¹ Corey, E.J.; Ursprung, J.J. *J. Am. Chem. Soc.* **1956**, 78, 5041.

the following shifts occur: hydride from 4 to 3; methyl from 5 to 4; hydride from 10 to 5; methyl from 9 to 10; hydride from 8 to 9; methyl from 14 to 8; and methyl from 13 to 14. This leaves a positive charge at position 13, which is stabilized by loss of the proton at the 18 position to give **56**. All these shifts are stereospecific, the group always migrating on the side of the ring system on which it is located; that is, a group above the “plane” of the ring system (indicated by a solid line in **55**) moves above the plane, and a group below the plane (dashed line) moves below it. It is probable that the seven shifts are not all concerted, although some of them may be, for intermediate products can be isolated.¹¹² As an illustration of point 2 (see above), it may be mentioned that friedelene, derived from dehydration of **55**, also gives **56** on treatment with acid.¹¹³

Some alkanes undergo *Wagner–Meerwein rearrangements* if treated with Lewis acids and a small amount of initiator. An interesting application of this reaction is the conversion of tricyclic molecules to adamantane and its derivatives.¹¹⁴ It has been found that *all* tricyclic alkanes containing 10 carbons are converted to adamantane by treatment with a Lewis acid, (e.g., AlCl_3). If the substrate contains > 10 carbons, alkyl-substituted adamantanes are produced. The IUPAC name for these reactions is *Schleyer adamantization*. Two examples are the AlCl_3 -mediated reactions of **57** and **58**.



If 14 or more carbons are present, the product may be diamantane or a substituted diamantane.¹¹⁵ These reactions are successful because of the high thermodynamic stability of adamantane, diamantane, and similar diamond-like molecules. The most stable of a set of C_nH_m isomers (called the *stabilomer*) will be the end product if the reaction reaches equilibrium.¹¹⁶ Best yields are obtained by the use of “sludge” catalysts¹¹⁷ (i.e., a mixture of AlX_3 and *tert*-butyl bromide or *sec*-butyl bromide).¹¹⁸ Though it is certain that these adamantane-forming reactions take place by nucleophilic 1,2 shifts, the exact pathways are not easy to unravel because of their complexity.¹¹⁹ Treatment of adamantane-2- ^{14}C with AlCl_3 results in total carbon scrambling on a statistical basis.¹²⁰

As already indicated, the mechanism of the *Wagner–Meerwein rearrangement* is usually nucleophilic. Free radical rearrangements are also known (see Section 18.A), though virtually only with aryl migration. However, carbanion mechanisms (electrophilic)

¹¹² See Whitlock Jr., H.W.; Olson, A.H. *J. Am. Chem. Soc.* **1970**, 92, 5383.

¹¹³ Dutler, H.; Jeger, O.; Ruzicka, L. *Helv. Chim. Acta* **1955**, 38, 1268; Brownlie, G.; Spring, F.S.; Stevenson, R.; Strachan, W.S. *J. Chem. Soc.* **1956**, 2419; Coates, R.M. *Tetrahedron Lett.* **1967**, 4143.

¹¹⁴ See McKervey, M.A.; Rooney, J.J. in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, **1990**, pp. 39–64; McKervey, M.A. *Tetrahedron* **1980**, 36, 971; *Chem. Soc. Rev.* **1974**, 3, 479; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, **1978**, pp. 178–202; Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* **1971**, 18, 1, pp. 3–23.

¹¹⁵ See Gund, T.M.; Osawa, E.; Williams, Jr., V.Z.; Schleyer, P.v.R. *J. Org. Chem.* **1974**, 39, 2979.

¹¹⁶ See Godleski, S.A.; Schleyer, P.v.R.; Osawa, E.; Wipke, W.T. *Prog. Phys. Org. Chem.* **1981**, 13, 63.

¹¹⁷ Schneider, A.; Warren, R.W.; Janoski, E.J. *J. Org. Chem.* **1966**, 31, 1617; Williams, Jr., V.Z.; Schleyer, P.v.R.; Gleicher, G.J.; Rodewald, L.B. *J. Am. Chem. Soc.* **1966**, 88, 3862; Robinson, M.J.T.; Tarratt, H.J.F. *Tetrahedron Lett.* **1968**, 5.

¹¹⁸ See Olah, G.A.; Wu, A.; Farooq, O.; Prakash, G.K.S. *J. Org. Chem.* **1989**, 54, 1450.

¹¹⁹ See Klester, A.M.; Ganter, C. *Helv. Chim. Acta* **1985**, 68, 734.

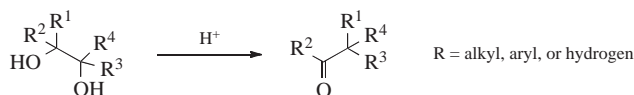
¹²⁰ Majerski, Z.; Ligero, S.H.; Schleyer, P.v.R.; Wolf, A.P. *Chem. Commun.* **1970**, 1596.

have also been found.⁹⁴ Thus $\text{Ph}_3\text{CCH}_2\text{Cl}$ treated with sodium gave $\text{Ph}_2\text{CHCH}_2\text{Ph}$ along with unrearranged products.¹²¹ This is called the *Grovenstein-Zimmerman rearrangement*. The intermediate is $\text{Ph}_3\text{CCH}_2^-$, and the phenyl moves without its electron pair. Only aryl and vinylic,¹²² and not alkyl, groups migrate by the electrophilic mechanism (see the introductory section preceding Sec. 18.A) and transition states or intermediates analogous to **41** and **42** are likely.¹²³

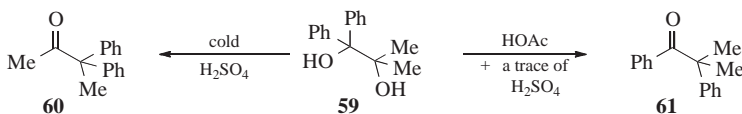
OS V, 16, 194; VI, 378, 845.

18-2 The Pinacol Rearrangement

1/O-Hydro,3/hydroxy-(2/→3/alkyl)-migr-o-elimination



When 1,2-diols (*vic*-diols; glycols) are treated with acids,¹²⁴ they rearrange to give aldehydes or ketones, although elimination without rearrangement can also be accomplished. This reaction is called the *pinacol rearrangement*; the reaction gets its name from a prototype compound pinacol ($\text{Me}_2\text{COHCOHMe}_2$), which is rearranged to pinacolone ($\text{Me}_3\text{C-COCH}_3$).¹²⁵ In this type of reaction, reduction can compete with rearrangement.¹²⁶ The reaction has been accomplished many times, with alkyl, aryl, hydrogen, and even ethoxycarbonyl (CO_2Et)¹²⁷ as migrating groups. In most cases, each carbon has at least one alkyl or aryl group, and the reaction is most often carried out with tri- and tetrasubstituted glycols. As mentioned earlier, glycols in which the four R groups are not identical can give rise to more than one product, depending on which group migrates (see Sec. 18.A.iii for a discussion of migratory aptitudes). A noncatalytic reaction is possible in supercritical water.¹²⁸



Stereodifferentiation is possible in this reaction.¹²⁹ When TMSOTf was used to initiate the reaction, it was shown to be highly regioselective.¹³⁰ Mixtures are often produced, and which group preferentially migrates may depend on the reaction conditions as well as on the nature

¹²¹ Grovenstein, Jr., E.; Williams Jr., L.P. *J. Am. Chem. Soc.* **1961**, 83, 412; Zimmerman, H.E.; Zweig, A. *J. Am. Chem. Soc.* **1961**, 83, 1196. See also, Grovenstein, Jr., E.; Cheng, Y. *J. Am. Chem. Soc.* **1972**, 94, 4971.

¹²² See Grovenstein, Jr., E.; Black, K.W.; Goel, S.C.; Hughes, R.L.; Northrop, J.H.; Streeter, D.L.; VanDerveer, D. *J. Org. Chem.* **1989**, 54, 1671, and references cited therein.

¹²³ Bertrand, J.A.; Grovenstein, Jr., E.; Lu, P.; VanDerveer, D. *J. Am. Chem. Soc.* **1976**, 98, 7835.

¹²⁴ See Lopez, L.; Mele, G.; Mazzeo, C. *J. Chem. Soc. Perkin Trans. 1* **1994**, 779; de Sanabria, J.A.; Carrión, A.E. *Tetrahedron Lett.* **1993**, 34, 7837; Harada, T.; Mukaiyama, T. *Chem. Lett.* **1992**, 81.

¹²⁵ Bartók, M.; Molnár, A. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, **1980**, pp. 722–732; Collins, C.J.; Eastham, J.F. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 762–771.

¹²⁶ Grant, A.A.; Allukian, M.; Fry, A.J. *Tetrahedron Lett.* **2002**, 43, 4391.

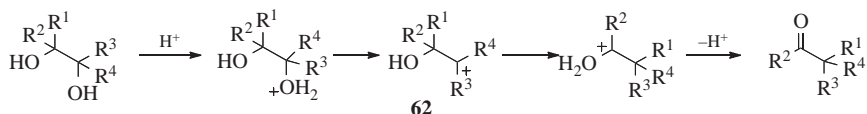
¹²⁷ Kagan, J.; Agdeppa Jr., D.A.; Mayers, D.A.; Singh, S.P.; Walters, M.J.; Wintermute, R.D. *J. Org. Chem.* **1976**, 41, 2355. Also see Berner, D.; Cox, D.P.; Dahn, H. *J. Am. Chem. Soc.* **1982**, 104, 2631.

¹²⁸ Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T.; Arai, M. *J. Am. Chem. Soc.* **2000**, 122, 1908.

¹²⁹ Paquette, L.A.; Lanter, J.C.; Johnston, J.N. *J. Org. Chem.* **1997**, 62, 1702.

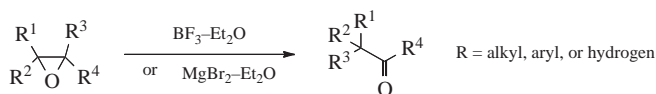
¹³⁰ Kudo, K.; Saigo, K.; Hashimoto, Y.; Saito, K.; Hasegawa, M. *Chem. Lett.* **1992**, 1449.

of the substrate. Thus the action of cold, concentrated sulfuric acid on **59** produces mainly the ketone **60** (methyl migration), while treatment of **59** with acetic acid containing a trace of sulfuric acid gives mostly **61** (phenyl migration).¹³¹ If at least one R is hydrogen, aldehydes can be produced as well as ketones. Generally, aldehyde formation is favored by the use of mild conditions (lower temperatures, weaker acids), because under more drastic conditions the aldehydes may be converted to ketones (Reaction **18-4**). The reaction has been carried out in the solid state, by treating solid substrates with HCl gas or with a solid organic acid.¹³²



The mechanism involves a simple 1,2-shift. The ion **62** (where all four R groups are Me) has been trapped by the addition of tetrahydrothiophene.¹³³ A migration takes place from the tertiary position because carbocations stabilized by an oxygen atom are even more stable than tertiary alkyl cations (Sec. 5.A.ii). In addition, the new carbocation can immediately stabilize itself by losing a proton.

It is obvious that other compounds in which a positive charge can be placed on a carbon α to one bearing an OH group can also give this rearrangement. This is true for β -amino alcohols, which rearrange on treatment with nitrous acid (this is called the *semipinacol rearrangement*), for iodohydrins, for which the reagent is mercuric oxide or silver nitrate, for β -hydroxyalkyl selenides $[\text{R}^1\text{R}^2\text{C}(\text{OH})\text{C}(\text{SeR}^5)\text{R}^3\text{R}^4]$,¹³⁴ and for allylic alcohols,¹³⁵ which can rearrange on treatment with a strong acid that protonates the double bond. A related rearrangement is the Et_2Zn mediated rearrangement of bromohydrins to give ketones.¹³⁶



A similar rearrangement is given by epoxides, when treated with acidic reagents (e.g., BF_3 -etherate or MgBr_2 -etherate), 5M LiClO_4 in ether,¹³⁷ InCl_3 ,¹³⁸ $\text{Bi}(\text{OTf})_3$,¹³⁹ or sometimes by heat alone.¹⁴⁰ Epoxides are converted to aldehydes or ketones on treatment with certain metallic catalysts¹⁴¹ including treatment with iron complexes,¹⁴² IrCl_3 ,¹⁴³ or

¹³¹ Ramart-Lucas, P.; Salmon-Legagneur, F. C. *R. Acad. Sci.* **1928**, 188, 1301.

¹³² Toda, F.; Shigemasa, T. *J. Chem. Soc. Perkin Trans. 1* **1989**, 209.

¹³³ Bosshard, H.; Baumann, M.E.; Schetty, G. *Helv. Chim. Acta* **1970**, 53, 1271.

¹³⁴ For a review, see Krief, A.; Laboureur, J.L.; Dumont, W.; Labar, D. *Bull. Soc. Chim. Fr.* **1990**, 681.

¹³⁵ See Wang, B.M.; Song, Z.L.; Fan, C.A.; Tu, Y.Q.; Chen, W.M. *Synlett* **2003**, 1497; Hurley, P.B.; Dake, G.R. *Synlett* **2003**, 2131.

¹³⁶ Li, L.; Cai, P.; Guo, Q.; Xue, S. *J. Org. Chem.* **2008**, 73, 3516.

¹³⁷ Sankararaman, S.; Nesakumar, J.E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3173.

¹³⁸ Ranu, B.C.; Jana, U. *J. Org. Chem.* **1998**, 63, 8212.

¹³⁹ Bhatia, K.A.; Eash, K.J.; Leonard, N.M.; Oswald, M.C.; Mohan, R.S. *Tetrahedron Lett.* **2001**, 42, 8129.

¹⁴⁰ For a list of reagents with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1277–1280.

¹⁴¹ See Prandi, J.; Namy, J.L.; Menoret, G.; Kagan, H.B. *J. Organomet. Chem.* **1985**, 285, 449; Miyashita, A.; Shimada, T.; Sugawara, A.; Nohira, H. *Chem. Lett.* **1986**, 1323; Maruoka, K.; Nagahara, S.; Ooi, T.; Yamamoto, H. *Tetrahedron Lett.* **1989**, 30, 5607.

¹⁴² Suda, K.; Baba, K.; Nakajima, S.-I.; Takanami, T. *Tetrahedron Lett.* **1999**, 40, 7243.

¹⁴³ Karamé, I.; Tommasino, M.L.; LeMaire, M. *Tetrahedron Lett.* **2003**, 44, 7687.

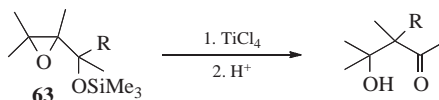
with BiOClO_4 .¹⁴⁴ Base-induced rearrangement is also known, but the products are usually different.¹⁴⁵

The *Meinwald rearrangement* converts epoxides to carbonyl compounds.¹⁴⁶ Several reagents mediate this transformation, including Cu compounds.¹⁴⁷ A closely related reaction of vinyl epoxides gives alkenyl ketones upon treatment with Ga compounds.¹⁴⁸ It has been shown that epoxides are intermediates in the pinacol rearrangements of certain glycols.¹⁴⁹ Among the evidence for the mechanism given is that $\text{Me}_2\text{COHCOHMe}_2$, $\text{Me}_2\text{COHC}(\text{NH}_2)\text{Me}_2$, and $\text{Me}_2\text{COHCClMe}_2$ gave the reaction at different rates (as expected), but yielded the *same mixture* of two products, pinacol and pinacolone, indicating a common intermediate.¹⁵⁰

A good way to prepare β -diketones consists of heating α,β -epoxy ketones at 80–140 °C in toluene with small amounts of $(\text{Ph}_3\text{P})_4\text{Pd}$ and dppe.¹⁵¹ Epoxides are converted to 1,2-diketones with Bi, DMSO, O_2 and a catalytic amounts of $\text{Cu}(\text{OTf})_2$ at 100 °C.¹⁵² α,β -Epoxy ketones are also converted to 1,2-diketones with a Ru catalyst¹⁵³ or an Fe catalyst.¹⁵⁴ Epoxides with an α -hydroxyalkyl substituent give a pinacol rearrangement product in the presence of a ZnBr_2 ¹⁵⁵ or $\text{Tb}(\text{OTf})_3$ ¹⁵⁶ catalyst to give a γ -hydroxy ketone.

Oxaziridines are converted to ring-expanded lactams under photochemical conditions.¹⁵⁷ *N*-Tosyl aziridines with an α -hydroxyalkyl substituent give a pinacol rearrangement product in the presence of Lewis acids (e.g., SmI_2), in this case a keto-*N*-tosyl amide.¹⁵⁸

β -Hydroxy ketones can be prepared by treating the silyl ethers (**63**) of α,β -epoxy alcohols with TiCl_4 .¹⁵⁹



OS **I**, 462; **II**, 73, 408; **III**, 312; **IV**, 375, 957; **V**, 326, 647; **VI**, 39, 320; **VII**, 129. See also, OS **VII**, 456.

¹⁴⁴ Anderson, A.M.; Blazek, J.M.; Garg, P.; Payne, B.J.; Mohan, R.S. *Tetrahedron Lett.* **2000**, 41, 1527.

¹⁴⁵ See Yandovskii, V.N.; Ershov, B.A. *Russ. Chem. Rev.* **1972**, 41, 403, 410. Also see Hodgson, D.M.; Robinson, L.A.; Jones, M.L. *Tetrahedron Lett.* **1999**, 40, 8637.

¹⁴⁶ See Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, 85, 582.

¹⁴⁷ Robinson, M.W.C.; Pillinger, K.S.; Graham, A.E. *Tetrahedron Lett.* **2006**, 47, 5919; Robinson, M.W.C.; Pillinger, K.S.; Mabbett, I.; Timms, D.A.; Graham, A.E. *Tetrahedron* **2010**, 66, 8377.

¹⁴⁸ Deng, X.-M.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2005**, 70, 6537.

¹⁴⁹ See Pocker, Y.; Ronald, B.P. *J. Am. Chem. Soc.* **1970**, 92, 3385; *J. Org. Chem.* **1970**, 35, 3362; Tamura, K.; Moriyoshi, T. *Bull. Chem. Soc. Jpn.* **1974**, 47, 2942.

¹⁵⁰ Pocker, Y. *Chem. Ind. (London)*, **1959**, 332. See also, Herlihy, K.P. *Aust. J. Chem.* **1981**, 34, 107.

¹⁵¹ Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980**, 102, 2095.

¹⁵² Antonietti, S.; Duñach, E. *Chem. Commun.* **2001**, 2566.

¹⁵³ Chang, C.-L.; Kumar, M.P.; Liu, R.-S. *J. Org. Chem.* **2004**, 69, 2793.

¹⁵⁴ Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Chem. Commun.* **2002**, 2570.

¹⁵⁵ Tu, Y.Q.; Fan, C.A.; Ren, S.K.; Chan, A.S.C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3791.

¹⁵⁶ Bickley, J.F.; Hauer, B.; Pena, P.C.A.; Roberts, S.M.; Skidmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1253.

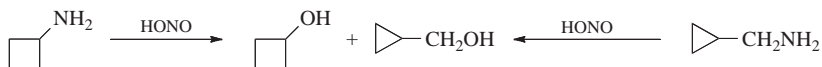
¹⁵⁷ Bourguet, E.; Baneres, J.-L.; Girard, J.-P.; Parello, J.; Vidal, J.-P.; Lusinch, X.; Declercq, J.-P. *Org. Lett.* **2001**, 3, 3067.

¹⁵⁸ Wang, B.M.; Song, Z.L.; Fan, C.A.; Tu, Y.Q.; Shi, Y. *Org. Lett.* **2002**, 4, 363.

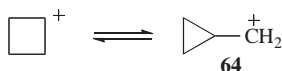
¹⁵⁹ Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, 108, 3827.

18-3 Expansion and Contraction of Rings

Demyanov ring contraction; Demyanov ring expansion



When a positive charge is formed on an alicyclic carbon, migration of an alkyl group can take place to give ring contraction, producing a ring that is one carbon smaller than the original, as in the interconversion of the cyclobutyl cation and the cyclopropylcarbinyl cation (**64**). Note that this change involves conversion of a



secondary to a primary carbocation. In a similar manner, when a positive charge is placed on a carbon α to an alicyclic ring, ring expansion can take place.¹⁶⁰ The new carbocation, and the old one, can then give products by combination with a nucleophile (e.g., the alcohols shown above), or by elimination, so that this reaction is a special case of **18-1**. Often, both rearranged and unrearranged products are formed, so that, for example, cyclobutylamine and cyclopropylmethanamine give similar mixtures of the two alcohols shown above on treatment with nitrous acid (a small amount of 3-buten-1-ol is also produced). When the carbocation is formed by diazotization of an amine, the reaction is called the *Demyanov rearrangement*,¹⁶¹ but of course similar products are formed when the carbocation is generated in other ways. The expansion reaction has been performed on rings of C_3 – C_8 ,¹⁶² but yields are best with the smaller rings, where relief of small-angle strain provides a driving force for the reaction. Strain is apparently much less of a factor in the cyclobutyl–cyclopropylmethyl interconversion (for a discussion of this interconversion, see Sec. 10.C.i). The influence of substituents on this rearrangement has been examined.¹⁶³ Note that a hybrid of a [1,2]-sigmatropic hydrogen shift (also See **18-29**) and a two-electron-electrocyclic ring opening has been discovered for cyclopropylcarbinyl cations that was labeled as a “hiscotropic” rearrangement.”¹⁶⁴ The contraction reaction has been applied to four-membered rings and to rings of C_6 – C_8 , but contraction of a cyclopentyl cation to a cyclobutylmethyl system is generally not feasible because of the additional strain involved.

A related rearrangement involves cyclopropyl propargylic alcohols, which gives an alkylidene cyclobutanone in the presence of Ag and Au catalysts,¹⁶⁵ or Ru and In catalysts.¹⁶⁶ Cyclopropylcarbinyl rearrangements are catalyzed by ionic liquids under

¹⁶⁰ See Hesse, M. *Ring Enlargement in Organic Chemistry*, VCH, NY, **1991**; Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, **1968**; Baldwin, J.E.; Adlington, R.M.; Robertson, J. *Tetrahedron* **1989**, *45*, 909; Salaün, J. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, **1987**, pp. 809–878; Conia, J.M.; Robson, M.J. *Angew. Chem. Int. Ed.* **1975**, *14*, 473. For a list of ring expansions and contractions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1283–1302.

¹⁶¹ See Smith, P.A.S.; Baer, D.R. *Org. React.* **1960**, *11*, 157. See also, Chow, L.; McClure, M.; White, J. *Org. Biomol. Chem.* **2004**, *2*, 648.

¹⁶² See Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165, see pp. 182–186; Breslow, R. in Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, **1963**, pp. 233–294.

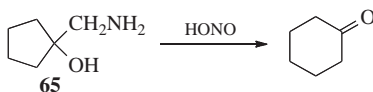
¹⁶³ Wiberg, K.B.; Shobe, D.; Nelson, G.C. *J. Am. Chem. Soc.* **1993**, *115*, 10645.

¹⁶⁴ Nouri, D.H.; Tantillo, D.J. *J. Org. Chem.* **2006**, *71*, 3686.

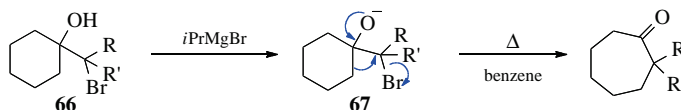
¹⁶⁵ Markham, J.P.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 9708.

¹⁶⁶ Trost, B.M.; Xie, J.; Maulide, N. *J. Am. Chem. Soc.* **2008**, *130*, 17258.

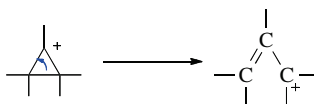
solvent-free conditions.¹⁶⁷ Methylene cyclopropanes rearrange to cyclobutenes in the presence of 1 atm of CO and Pt catalyst¹⁶⁸ or a Pd catalyst, mediated by a Cu catalyst.¹⁶⁹ Arylvinylenecyclopropanes rearrange to bicyclic systems in the presence of a Lewis acid.¹⁷⁰



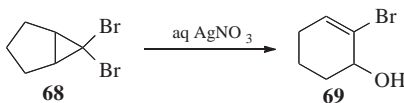
Ring expansions of certain hydroxyamines (e.g., **65**) are analogous to the semipinacol rearrangement (Reaction **18-2**). This reaction is called the *Tiffeneau–Demyanov ring expansion*. These have been performed on rings of C_4 – C_8 and the yields are better than for the simple *Demyanov ring expansion*. A similar reaction has been used to expand rings of from five to eight members.¹⁷¹ In this case, a cyclic bromohydrin of the form **66** is treated with a *Grignard reagent*, which, acting as a base, removes the OH proton to give the alkoxide **67**. When **67** is heated to reflux, ring enlargement occurs. The reaction has been done with **66** in which at least one R group is phenyl or methyl,¹⁷² but fails when both R groups are hydrogen.¹⁷³



A positive charge generated on a three-membered ring gives “contraction” to an allylic cation, as shown.¹⁷⁴



As seen in Section 10.G.i, category 7, this is the reason nucleophilic substitutions are not feasible at a cyclopropyl substrate. The reaction is often used to convert cyclopropyl halides and tosylates to allylic products, especially for the purpose of ring expansion, an example being the conversion of **68** to **69**.¹⁷⁵ The stereochemistry of these cyclopropyl cleavages is governed by the principle of orbital symmetry conservation (for a discussion, see Reaction **18-27**, the *Möbius–Hückel method*).



¹⁶⁷ Ranu, B.C.; Banerjee, S.; Das, A. *Tetrahedron Lett.* **2006**, 47, 881.

¹⁶⁸ Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, 128, 6306.

¹⁶⁹ Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* **2006**, 128, 7430.

¹⁷⁰ Xu, G.-C.; Liu, L.-P.; Lu, J.-M.; Shi, M. *J. Am. Chem. Soc.* **2005**, 127, 14552.

¹⁷¹ Sisti, A.J. *J. Org. Chem.* **1968**, 33, 453. See also, Sisti, A.J.; Vitale, A.C. *J. Org. Chem.* **1972**, 37, 4090.

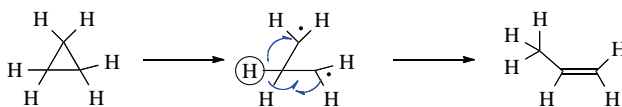
¹⁷² Sisti, A.J.; Rusch, G.M. *J. Org. Chem.* **1974**, 39, 1182.

¹⁷³ Sisti, A.J. *J. Org. Chem.* **1968**, 33, 3953.

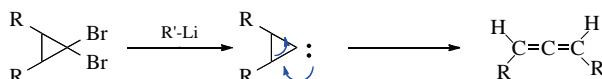
¹⁷⁴ Marvell, E.N. *Thermal Electrocyclic Reactions*, Academic Press, NY, **1980**, pp. 23–53; Sorensen, T.S.; Rauk, A. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, **1977**, pp. 1–78.

¹⁷⁵ Skell, P.S.; Sandler, S.R. *J. Am. Chem. Soc.* **1958**, 80, 2024.

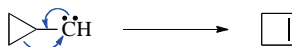
Three-membered rings can also be cleaved to unsaturated products in at least two other ways. (1) Upon pyrolysis, cyclopropanes can undergo “contraction” to propenes.¹⁷⁶ In the simplest case, cyclopropane gives propene when heated to 400–500 °C. The mechanism is generally regarded¹⁷⁷ as involving a diradical



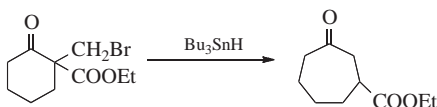
intermediate¹⁷⁸ (recall that free radical 1,2-migration is possible for diradicals, Sec. 18.C). (2) The generation of a carbene or carbenoid carbon in a three-membered ring can lead to allenes, and allenes are often prepared in



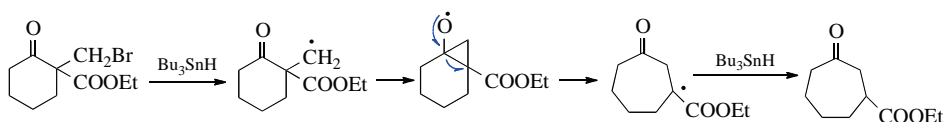
this way.¹⁷⁹ Flash vacuum pyrolysis of 1-chlorocyclopropane thermally rearranges to chloroallene.¹⁸⁰ One way to generate such a species is treatment of a 1,1-dihalocyclopropane with an alkyl lithium compound (Reaction 12-39).¹⁸¹ In contrast, the generation of a carbene or carbenoid at a cyclopropylmethyl carbon gives ring expansion.¹⁸²



Some free radical ring enlargements are also known, an example being¹⁸³:



This reaction has been used to make rings of 6, 7, 8, and 13 members. A possible mechanism is



¹⁷⁶ See Berson, J.A. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, **1980**, pp. 324–352; *Ann. Rev. Phys. Chem.* **1977**, 28, 111; Bergman, R.G. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, **1973**, pp. 191–237; Frey, H.M. *Adv. Phys. Org. Chem.* **1966**, 4, 147, see pp. 148–170. Also see Baldwin, J.E.; Day, L.S.; Singer, S.R. *J. Am. Chem. Soc.* **2005**, 127, 9370.

¹⁷⁷ See Baldwin, J.E.; Grayston, M.W. *J. Am. Chem. Soc.* **1974**, 96, 1629, 1630.

¹⁷⁸ See Bergman, R.G.; Carter, W.L. *J. Am. Chem. Soc.* **1969**, 91, 7411.

¹⁷⁹ See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, **1984**, pp. 20–23; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, **1971**, pp. 462–467.

¹⁸⁰ Billups, W.E.; Bachman, R.E. *Tetrahedron Lett.* **1992**, 33, 1825.

¹⁸¹ See Baird, M.S.; Baxter, A.G.W. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2317, and references cited therein.

¹⁸² See Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, **1968**, pp. 111–117.

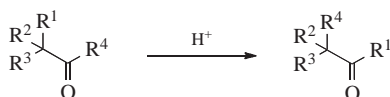
¹⁸³ Dowd, P.; Choi, S. *Tetrahedron* **1991**, 47, 4847. For a related ring expansion, see Baldwin, J.E.; Adlington, R.M.; Robertson, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1404.

This reaction has been extended to the expansion of rings by three or four carbons, by the use of a substrate containing $(\text{CH}_2)_n\text{X}$ ($n = 3$ or 4) instead of CH_2Br .¹⁸⁴ By this means, 5-, 6-, and 7-membered rings were enlarged to 18–11-membered rings. A β -keto ester (e.g., 2-carboxyethyl cyclohexanone) is converted to 3-carboxyethyl cycloheptanone when treated with $\text{CF}_3\text{CO}_2\text{ZnCH}_2\text{I}$.¹⁸⁵

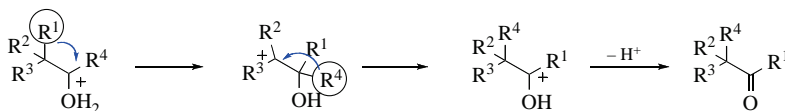
OS **III**, 276; **IV**, 221, 957; **V**, 306, 320; **VI**, 142, 187; **VII**, 12, 114, 117, 129, 135; **VIII**, 179, 467, 556, 578.

18-4 Acid-Catalyzed Rearrangements of Aldehydes and Ketones

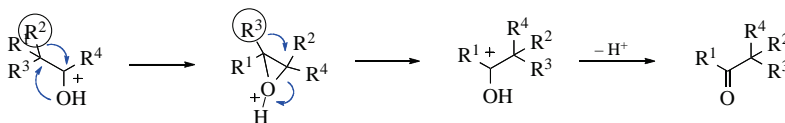
1/Alkyl,2/alkyl-interchange, and so on



Rearrangements of this type, where a group α to a carbonyl “changes places” with a group attached to the carbonyl carbon, occur when migratory aptitudes are favorable.¹⁸⁶ The R^2 , R^3 , and R^4 groups may be alkyl or hydrogen. Certain aldehydes have been converted to ketones, and ketones to other ketones (though more drastic conditions are required for the latter), but no rearrangement of a ketone to an aldehyde ($\text{R}^1 = \text{H}$) has so far been reported. There are two mechanisms,¹⁸⁷ each beginning with protonation of the oxygen and each involving two migrations. In one pathway, the migrations are in opposite directions¹⁸⁸:



In the other pathway, the migrations are in the same direction. The actual mechanism of this pathway is not certain, but an epoxide (protonated) intermediate¹⁸⁹ is one possibility¹⁹⁰:



If the reaction is carried out with ketone labeled in the $\text{C}=\text{O}$ group with ^{14}C , the first pathway predicts that the product will contain all the ^{14}C in the $\text{C}=\text{O}$ carbon, while in the second pathway the label will be in the α carbon (demonstrating migration of oxygen). The results of such experiments¹⁹¹ have shown that in some cases only the $\text{C}=\text{O}$ carbon was

¹⁸⁴ Dowd, P.; Choi, S. *J. Am. Chem. Soc.* **1987**, 109, 6548; *Tetrahedron Lett.* **1991**, 32, 565.

¹⁸⁵ Xue, S.; Liu, Y.-K.; Li, L.-Z.; Guo, Q.-X. *J. Org. Chem.* **2005**, 70, 8245.

¹⁸⁶ See Fry, A. *Mech. Mol. Migr.* **1971**, 4, 113; Collins, C.J.; Eastham, J.F. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 771–790.

¹⁸⁷ Favorskii, A.; Chilingaren, A. *C. R. Acad. Sci.* **1926**, 182, 221.

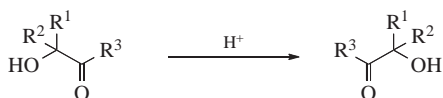
¹⁸⁸ Collins, C.J.; Bowman, N.S. *J. Am. Chem. Soc.* **1959**, 81, 3614.

¹⁸⁹ Zook, H.D.; Smith, W.E.; Greene, J.L. *J. Am. Chem. Soc.* **1957**, 79, 4436.

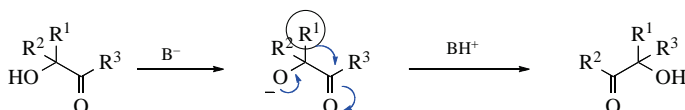
¹⁹⁰ Some such pathway is necessary to account for the migration of oxygen that is found. It may involve a protonated epoxide, a 1,2-diol, or simply a 1,2-shift of an OH group.

¹⁹¹ See Fry, A.; Oka, M. *J. Am. Chem. Soc.* **1979**, 101, 6353.

labeled, in other cases only the α carbon, while in still others both carbons bore the label, indicating that in these cases both pathways were in operation. With α -hydroxy aldehydes and ketones, the process may stop after only one migration (this is called the α -ketol rearrangement).

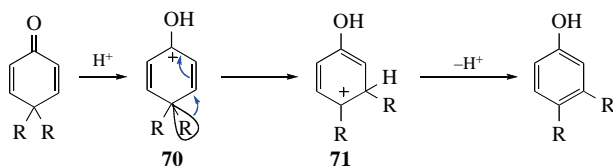


The α -ketol rearrangement can also be brought about by base catalysis, but only if the alcohol is tertiary, since if R^1 or $R^2 = \text{hydrogen}$, enolization of the substrate is more favored than rearrangement.

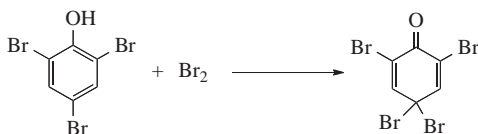


18-5 The Dienone–Phenol Rearrangement

2/C→5/O-Hydro,1/C→2/C-alkyl-bis-migration



Cyclohexadienone derivatives that have two alkyl groups in the 4 position undergo, on acid treatment,¹⁹² 1,2-migration of one of these groups from **70** to give the phenol. Note that a photochemical version of this reaction has been observed.¹⁹³ The driving force in the overall reaction (the *dienone–phenol rearrangement*) is of course creation of an aromatic system.¹⁹⁴ Note that **70** and **71** are arenium ions (Sec. 5.A.ii), the same as those generated by attack of a phenol on an electrophile.¹⁹⁵ Sometimes, in the reaction of a phenol with an electrophile, a kind of reverse rearrangement (called the *phenol–dienone rearrangement*) takes place, though without an actual migration.¹⁹⁶ An example is



¹⁹² See Chalais, S.; Laszlo, P.; Mathy, A. *Tetrahedron Lett.* **1986**, 27, 2627.

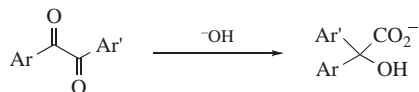
¹⁹³ Guo, Z.; Schultz, A.G. *Org. Lett.* **2001**, 3, 1177.

¹⁹⁴ Perkins, M.J.; Ward, P. *Mech. Mol. Migr.* **1971**, 4, 55, pp. 90–103; Miller, B. *Mech. Mol. Migr.* **1968**, 1, 247; Shine, H.J. *Aromatic Rearrangements*; Elsevier, NY, **1967**, pp. 55–68; Waring, A.J. *Adv. Alicyclic Chem.* **1966**, 1, 129, pp. 207–223. See Miller, B. *Acc. Chem. Res.* **1975**, 8, 245.

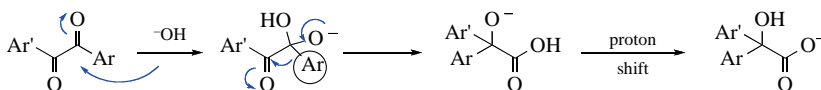
¹⁹⁵ See Vitullo, V.P.; Grossman, N. *J. Am. Chem. Soc.* **1972**, 94, 3844; Planas, A.; Tomás, J.; Bonet, J. *Tetrahedron Lett.* **1987**, 28, 471.

¹⁹⁶ See Ershov, V.V.; Volod'kin, A.A.; Bogdanov, G.N. *Russ. Chem. Rev.* **1963**, 32, 75.

18-6 The Benzil–Benzilic Acid Rearrangement

1/*O*-Hydro,3/oxido-(1/→2/aryl)-*migro*-addition

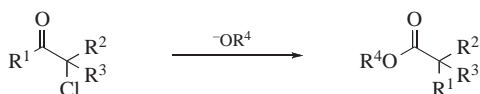
When treated with base, α -diketones rearrange to give the salts of α -hydroxy acids, a reaction known as the *benzil–benzilic acid rearrangement* (benzil is PhCOCOPh ; benzilic acid is $\text{Ph}_2\text{COHCO}_2\text{H}$).¹⁹⁷ A Rh catalyzed version of this reaction has also been reported.¹⁹⁸ Though the reaction is usually illustrated with aryl groups, it can also be applied to aliphatic diketones¹⁹⁹ and to α -keto aldehydes. The use of an alkoxide instead of hydroxide gives the corresponding ester directly,²⁰⁰ although alkoxide ions that are readily oxidized (e.g., OEt^- or OCHMe_2^-) are not useful here, since they reduce the benzil to a benzoin. The mechanism is similar to the rearrangements in Reaction 18-1–18-4, but there is a difference: The migrating group does not move to a carbocation. The first step is attack of the base at the carbonyl group, the same as the first step of the tetrahedral mechanism of nucleophilic substitution (Sec. 16.A.i) and of many additions to the $\text{C}=\text{O}$ bond (Chapter 16):



The mechanism has been intensely studied,¹⁸⁸ and there is much evidence for it.²⁰¹ The reaction is irreversible.

OS I, 89.

18-7 The Favorskii Rearrangement

2/Alkoxy-de-chloro(2/→1/alkyl)-*migro*-substitution

The reaction of α -halo ketones (chloro, bromo, or iodo) with alkoxide ions²⁰² to give rearranged esters is called the *Favorskii rearrangement*.²⁰³ The use of hydroxide ions or amines as bases leads to the free carboxylic acid (salt) or amide, respectively,

¹⁹⁷ See Selman, S.; Eastham, J.F. *Q. Rev. Chem. Soc.* **1960**, 14, 221.

¹⁹⁸ Shimizu, I.; Tekawa, M.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* **1992**, 1365.

¹⁹⁹ For an example, see Schaltegger, A.; Bigler, P. *Helv. Chim. Acta* **1986**, 69, 1666.

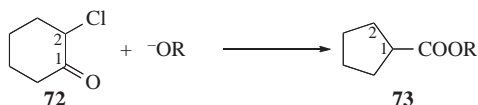
²⁰⁰ Doering, W. von E.; Urban, R.S. *J. Am. Chem. Soc.* **1956**, 78, 5938.

²⁰¹ However, see Screttas, C.G.; Micha-Screttas, M.; Cazianis, C.T. *Tetrahedron Lett.* **1983**, 24, 3287.

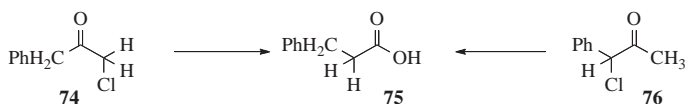
²⁰² See Giordano, C.; Castaldi, G.; Casagrande, F.; Abis, L. *Tetrahedron Lett.* **1982**, 23, 1385.

²⁰³ Boyer, L.E.; Brazzillo, J.; Forman, M.A.; Zannoni, B. *J. Org. Chem.* **1996**, 61, 7611; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, **1980**, pp. 437–461; Rappe, C. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, **1973**, pp. 1084–1101; Redmore, D.; Gutsche, C.D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, **1968**, pp. 46–69; Satoh, T.; Motohashi, S.; Kimura, S.; Tokutake, N.; Yamakawa, K. *Tetrahedron Lett.* **1993**, 34, 4823.

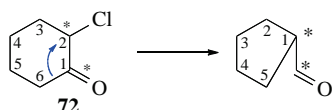
instead of the ester. Cyclic α -halo ketones give ring contraction, as in the conversion of **72** to **73**.



The reaction has also been carried out on α -hydroxy ketones²⁰⁴ and on α,β -epoxy ketones, which give β -hydroxy acids.²⁰⁵ The fact that an epoxide gives a reaction analogous to a halide indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step.



Investigation of the mechanism²⁰⁶ of the *Favorskii rearrangement* has led to proposals for at least five different mechanisms. However, the finding²⁰⁷ that **74** and **75** both give **76** (this behavior is typical) shows that any mechanism where the halogen leaves and R^1 takes its place is invalid, since in such a case **74** would be expected to give **76** (with PhCH_2 migrating), but **75** should give PhCHMeCOOH (with CH_3 migrating). That is, in the case of **75**, it was PhCH that migrated and not methyl. Another important result was determined by radioactive labeling. Chloroketone (**72**), in which C-1 and C-2 were equally labeled with ^{14}C , was converted to **73**. The product was found to contain 50% of the label on the carbonyl carbon, 25% on C-1, and 25% on C-2.²⁰⁸ Now the carbonyl carbon, which originally carried half of the radioactivity, still had this much, so the rearrangement did not directly affect it. However, if the C-6 carbon had migrated to C-2, the other half of the radioactivity would be only on C-1 of the product:



On the other hand, if the migration had gone the other way (if the C-2 carbon had migrated to C-6), then this half of the radioactivity would be found solely on C-2 of the product. The fact that C-1 and C-2 were equally labeled showed that *both migrations occurred*, with equal probability. Since C-2 and C-6 of **72** are not equivalent, this means that there must be a symmetrical intermediate.²⁰⁹ The type of intermediate that best fits the circumstances is a cyclopropanone,²¹⁰ and the mechanism (for the general case) is formulated (replacing R^1

²⁰⁴ Craig, J.C.; Dinner, A.; Mulligan, P.J. *J. Org. Chem.* **1972**, 37, 3539.

²⁰⁵ See Mouk, R.W.; Patel, K.M.; Reusch, W. *Tetrahedron* **1975**, 31, 13.

²⁰⁶ See Baretta, A.; Waegell, B. *React. Intermed. (Plenum)* **1982**, 2, 527. For a theoretical study, see Hamblin, G. D.; Jimenez, R.P.; Sorensen, T.S. *J. Org. Chem.* **2007**, 72, 8033.

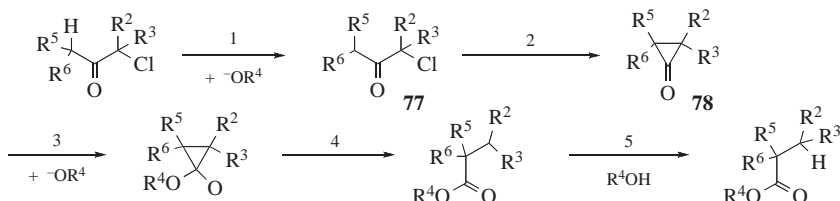
²⁰⁷ Bordwell, F.G.; Scamehorn, R.G.; Springer, W.R. *J. Am. Chem. Soc.* **1969**, 91, 2087.

²⁰⁸ Loftfield, R.B. *J. Am. Chem. Soc.* **1951**, 73, 4707.

²⁰⁹ A preliminary migration of the chlorine from C-2 to C-6 was ruled out by the fact that recovered **72** had the same isotopic distribution as the starting **72**.

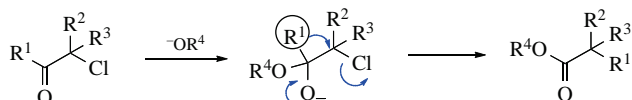
²¹⁰ See Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* **1974**, 47, 73; Turro, N.J. *Acc. Chem. Res.* **1969**, 2, 25.

of our former symbolism with CHR^5R^6 , since it is obvious that for this mechanism an α hydrogen is required on the non-halogenated side of the carbonyl):



The intermediate corresponding to **78**, in the case of **72**, is a symmetrical compound, and the three-membered ring can be opened with equal probability on either side of the carbonyl, accounting for the results with ^{14}C . In the general case, **78** is not symmetrical and should open on the side that gives the more stable carbanion.²¹¹ This accounts for the fact that **74** and **75** give the same product. The intermediate in both cases is **77**, which always opens to give the carbanion stabilized by resonance. The cyclopropanone intermediate (**78**) has been isolated in the case where $\text{R}^2 = \text{R}^5 = t\text{-Bu}$ and $\text{R}^3 = \text{R}^6 = \text{H}$,²¹² and it has also been trapped.²¹³ Also, cyclopropanones synthesized by other methods have been shown to give Favorskii products on treatment with NaOMe or other bases.²¹⁴

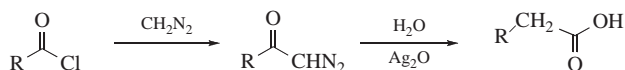
The mechanism discussed is in accord with all the facts when the halo ketone contains an α hydrogen on the other side of the carbonyl group. However, ketones that do not have an α hydrogen also rearrange to give the same type of product in what is usually called the *quasi-Favorskii rearrangement*. The *quasi-Favorskii rearrangement* cannot take place by the cyclopropanone mechanism. The mechanism that is generally accepted (called the *semibenzilic mechanism*²¹⁵) is a base-catalyzed pinacol rearrangement-type mechanism similar to that of **18-6**. This mechanism requires inversion at the migration terminus and this has been found.²¹⁶ It has been shown that even where there is an appropriately situated α hydrogen, the semibenzilic mechanism may still operate.²¹⁷



An interesting analogue of the *Favorskii rearrangement* treats a ketone, (e.g., 4-*tert*-butylcyclohexanone), without an α -halogen with $\text{Ti}(\text{NO}_3)_3$ to give 3-*tert*-butylcyclopentane-1-carboxylic acid.²¹⁸

OS IV, 594; VI, 368, 711.

18-8 The Arndt–Eistert Synthesis



²¹¹ See Rappe, C.; Knutsson, L.; Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* **1970**, 92, 2032.

²¹² Pazos, J.F.; Pacifici, J.G.; Pierson, G.O.; Sclove, D.B.; Greene, F.D. *J. Org. Chem.* **1974**, 39, 1990.

²¹³ See Baldwin, J.E.; Cardellina, J.H.I. *Chem. Commun.* **1968**, 558.

²¹⁴ Wharton, P.S.; Fritzberg, A.R. *J. Org. Chem.* **1972**, 37, 1899.

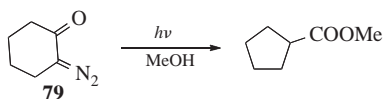
²¹⁵ Tchoubar, B.; Sackur, O. *C. R. Acad. Sci.* **1939**, 208, 1020.

²¹⁶ Baudry, D.; Bégue, J.; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* **1971**, 1416.

²¹⁷ See Salaun, J.R.; Garnier, B.; Conia, J.M. *Tetrahedron* **1973**, 29, 2895.

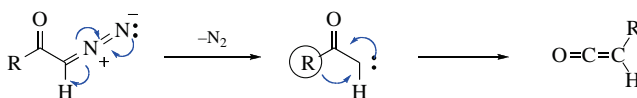
²¹⁸ Ferraz, H.M.; Silva, Jr., J.F. *Tetrahedron Lett.* **1997**, 38, 1899.

In the *Arndt–Eistert synthesis*, an acyl halide is converted to a carboxylic acid with one additional carbon.²¹⁹ The first step of this process is Reaction **16-89**. The actual rearrangement occurs in the second step after treatment of the diazo ketone with water and silver oxide or with silver benzoate and triethylamine. This rearrangement is called the *Wolff rearrangement*.²²⁰ It is the best method of increasing a carbon chain by one from a *carboxylic acid* (see Reaction **10-75** and **16-30**). If an alcohol ($R'OH$) is used instead of water, the ester (RCH_2CO_2R') is isolated.²²¹ Similarly, treatment with ammonia gives the amide. Other catalysts are sometimes used (colloidal Pt, Cu, etc.), but occasionally the diazo ketone is simply heated or photolyzed in the presence of water, an alcohol, or ammonia, with no catalyst at all using ultrasound.²²² The photolysis method²²³ often gives better results than the Ag catalysis method. Of course, diazo ketones prepared in any other way also give the rearrangement.²²⁴ The reaction is of wide scope. The R group may be alkyl or aryl and may contain many functional groups including unsaturation, but not including groups acidic enough to react with CH_2N_2 or diazo ketones (e.g., Reaction **10-5** and **10-19**). Sometimes the reaction is performed with other diazoalkanes (i.e., $R'CHN_2$) to give $RCHR'COOH$. The reaction has been used for ring contraction of cyclic diazo ketones²²⁵ (e.g., **79**).²²⁶



An asymmetric variation converted ketones to esters using an azaferrocene catalyst.²²⁷

The mechanism is generally regarded as involving formation of a carbene.²²⁸ It is the divalent carbon that has the open sextet and to which the migrating group brings its electron pair:



The actual product of the reaction is thus the ketene, which then reacts with water (**15-3**), an alcohol (**15-5**), or ammonia or an amine (**15-8**). Particularly stable ketenes²²⁹

²¹⁹ Meier, H.; Zeller, K. *Angew. Chem. Int. Ed.* **1975**, *14*, 32; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, **1971**, pp. 475–493; Whittaker, D. in Patai, S. *The Chemistry of Diazonium and Diazo Compounds*, pt. 2, Wiley, NY, **1978**, pp. 593–644.

²²⁰ Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193. See Sudrik, S.G.; Sharma, J.; Chavan, V.B.; Chaki, N.K.; Sonawane, H.R.; Vijayamohanam, K.P. *Org. Lett.* **2006**, *8*, 1089.

²²¹ Winum, J.-Y.; Kamal, M.; Leydet, A.; Roque, J.-P.; Montero, J.-L. *Tetrahedron Lett.* **1996**, *37*, 1781.

²²² For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1850–1851.

²²³ See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, **1986**, pp. 185–195; Ando, W. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, 78, pp. 458–475.

²²⁴ See Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4461.

²²⁵ Redmore, D.; Gutsche, C.D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, **1968**, pp. 125–136.

²²⁶ Korobitsyna, I.K.; Rodina, L.L.; Sushko, T.P. *J. Org. Chem. USSR* **1968**, *4*, 165; Jones, Jr., M.; Ando, W. *J. Am. Chem. Soc.* **1968**, *90*, 2200. See Lee, Y.R.; Suk, J.Y.; Kim, B.S. *Tetrahedron Lett.* **1999**, *40*, 8219.

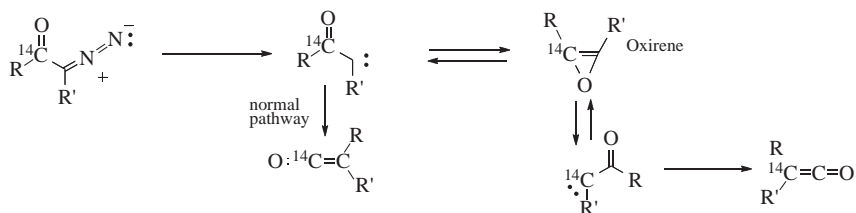
²²⁷ Wiskur, S.L.; Fu, G.C. *J. Am. Chem. Soc.* **2005**, *127*, 6176.

²²⁸ See Scott, A.P.; Platz, M.S.; Radom, L. *J. Am. Chem. Soc.* **2001**, *123*, 6069.

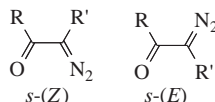
²²⁹ See Farlow, R.A.; Thamattloor, D.A.; Sunoj, R.B.; Hadad, C.M. *J. Org. Chem.* **2002**, *67*, 3257.

(e.g., $\text{Ph}_2\text{C}=\text{C}=\text{O}$) have been isolated and others have been trapped in other ways (e.g., as β -lactams,²³⁰ reaction **16-96**). The purpose of the catalyst is not well understood, though many suggestions have been made. This mechanism is strictly analogous to that of the *Curtius rearrangement* (Reaction **18-14**). Although the mechanism as shown above involves a free carbene and there is much evidence to support this,²³¹ it is also possible that at least in some cases the two steps are concerted and a free carbene is absent.

When the *Wolff rearrangement* is carried out photochemically, the mechanism is basically the same,²²³ but another pathway can intervene. Some of the ketocarbene originally formed can undergo a carbene-carbene rearrangement, through an oxirene intermediate.²³² This was shown by ^{14}C labeling experiments, where



diazoketones labeled in the carbonyl group gave rise to ketenes that bore the label at both $\text{C}=\text{C}$ carbons.²³³ In general, the smallest degree of scrambling (and thus of the oxirene pathway) was found when $\text{R}'=\text{H}$. An intermediate believed to be an oxirene has been detected by laser spectroscopy.²³⁴ The oxirene pathway is not found in the thermal *Wolff rearrangement*. It is likely that an excited singlet state of the carbene is necessary for the oxirene pathway to intervene.²³⁵ In the photochemical process, ketocarbene intermediates, in the triplet state, have been isolated in an Ar matrix at 10–15 K, where they have been identified by UV-visible, IR, and ESR spectra.²³⁶ These intermediates went on to give the rearrangement via the normal pathway, with no evidence for oxirene intermediates.



The diazo ketone can exist in two conformations, called *s*-(*E*) and *s*-(*Z*). Studies have shown that *Wolff rearrangement* takes place preferentially from the *s*-(*Z*) conformation.²³⁷ OS **III**, 356; **VI**, 613, 840.

²³⁰ Kirmse, W.; Horner, L. *Chem. Ber.* **1956**, 89, 2759. Also see, Horner, L.; Spietschka, E. *Chem. Ber.* **1956**, 89, 2765.

²³¹ See Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, **1971**, pp. 476–480. See also, Torres, M.; Ribo, J.; Clement, A.; Strausz, O.P. *Can. J. Chem.* **1983**, 61, 996; Tomoika, H.; Hayashi, N.; Asano, T.; Izawa, Y. *Bull. Chem. Soc. Jpn.* **1983**, 56, 758.

²³² See Lewars, Y. *Chem. Rev.* **1983**, 83, 519.

²³³ Fenwick, J.; Frater, G.; Ogi, K.; Strausz, O.P. *J. Am. Chem. Soc.* **1973**, 95, 124; Zeller, K. *Chem. Ber.* **1978**, 112, 678. See also, Majerski, Z.; Redvanly, C.S. *J. Chem. Soc., Chem. Commun.* **1972**, 694.

²³⁴ Tanigaki, K.; Ebbesen, T.W. *J. Am. Chem. Soc.* **1987**, 109, 5883. See also, Bachmann, C.; N'Guessan, T.Y.; Debü, F.; Monnier, M.; Pourcin, J.; Aycard, J.; Bodot, H. *J. Am. Chem. Soc.* **1990**, 112, 7488.

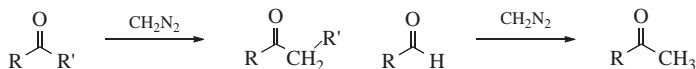
²³⁵ Csizmadia, I.G.; Gunning, H.E.; Gosavi, R.K.; Strausz, O.P. *J. Am. Chem. Soc.* **1973**, 95, 133.

²³⁶ McMahon, R.J.; Chapman, O.L.; Hayes, R.A.; Hess, T.C.; Krimmer, H. *J. Am. Chem. Soc.* **1985**, 107, 7597.

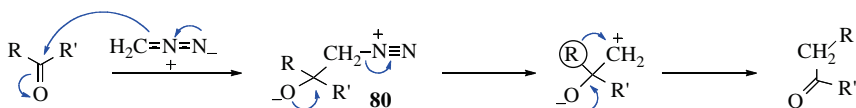
²³⁷ Tomioka, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* **1980**, 45, 5278.

18-9 Homologation of Aldehydes and Ketones

Methylene-insertion



Aldehydes and ketones²³⁸ can be converted to their homologues with diazomethane.²³⁹ Several other reagents²⁴⁰ are also effective, including Me_3SiI , and then silica gel.²⁴¹ With the diazomethane reaction, formation of an epoxide (**16-46**) is a side reaction. Superficially, this reaction appears to be similar to the insertion of carbenes into C—H bonds, (Reaction **12-21**, and IUPAC names it as an insertion), but the mechanism is quite different. However, it is a true rearrangement and no free carbene is involved. The first step is an addition to the C=O bond:



The betaine (**80**) can sometimes be isolated. As shown in Reaction **16-46**, intermediate **80** can also go to the epoxide. The evidence for this mechanism has been summarized in the review by Gutsche.²³⁹ Note that this mechanism is essentially the same as in the apparent “insertions” of oxygen (Reaction **18-19**) and nitrogen (Reaction **18-16**) into ketones.

1,3-Diketones are converted to 1,4-diketones upon treatment with $\text{CF}_3\text{CO}_2\text{ZnCH}_2\text{I}$.²⁴² In a related reaction, alkenes insert into aldehydes in the presence of a Rh catalyst to give the corresponding ketone.²⁴³

Aldehydes give fairly good yields of methyl ketones; that is, hydrogen migrates in preference to alkyl. The most abundant side product is not the homologous aldehyde, but the epoxide. However, the yield of aldehyde at the expense of methyl ketone can be increased by the addition of methanol. If the aldehyde contains electron-withdrawing groups, the yield of epoxides is increased and the ketone is formed in smaller amounts, if at all. Ketones give poorer yields of homologous ketones. Epoxides are usually the predominant product here, especially when one or both R groups contain an electron-withdrawing group. The yield of ketones also decreases with increasing length of the chain. The use of a Lewis acid increases the yield of ketone.²⁴⁴ Cyclic ketones,²⁴⁵ three membered²⁴⁶ and larger, behave particularly well and give good yields of ketones with the ring expanded by one.²⁴⁷ Aliphatic diazo compounds (RCHN_2 and R_2CN_2) are sometimes used instead of

²³⁸ See Yamamoto, M.; Nakazawa, M.; Kishikawa, K.; Kohmoto, S. *Chem. Commun.* **1996**, 2353.

²³⁹ See Gutsche, C.D. *Org. React.* **1954**, 8, 364.

²⁴⁰ See Aoyama, T.; Shioiri, T. *Synthesis* **1988**, 228.

²⁴¹ Lemini, C.; Ordoñez, M.; Pérez-Flores, J.; Cruz-Almanza, R. *Synth. Commun.* **1995**, 25, 2695.

²⁴² Xue, S.; Li, L.-Z.; Liu, Y.-K.; Guo, Q.-X. *J. Org. Chem.* **2006**, 71, 215.

²⁴³ Aïssa, C.; Fürstner, A. *J. Am. Chem. Soc.* **2007**, 129, 14836.

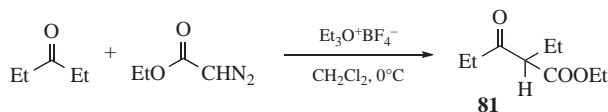
²⁴⁴ See Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* **1966**, 7, 128, see pp. 137–150.

²⁴⁵ See Krief, A.; Laboureur, J.L. *Tetrahedron Lett.* **1987**, 28, 1545; Krief, A.; Laboureur, J.L.; Dumont, W. *Tetrahedron Lett.* **1987**, 28, 1549; Abraham, W.D.; Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* **1987**, 28, 2203; Trost, B.M.; Mikhail, G.K. *J. Am. Chem. Soc.* **1987**, 109, 4124.

²⁴⁶ See Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* **1970**, 92, 2036.

²⁴⁷ See Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, **1968**, pp. 81–98. For a review pertaining to bridged bicyclic ketones, see Krow, G.R. *Tetrahedron* **1987**, 43, 3.

diazomethane, with the expected results.²⁴⁸ Ethyl diazoacetate can be used analogously, in the presence of a Lewis acid or of triethyloxonium fluoroborate,²⁴⁹ to give a β -keto ester, (e.g., **81**).



When unsymmetrical ketones were used in this reaction (with BF_3 as catalyst), the less highly substituted carbon preferentially migrated.²⁵⁰ The reaction can be made regioselective by applying this method to the α -halo ketone, in which case only the other carbon migrates.²⁵¹ The ethyl diazoacetate procedure has also been applied to the acetals or ketals of α,β -unsaturated aldehydes and ketones.²⁵²

Bicyclic ketones can be expanded to form monocyclic ketones in the presence of certain reagents. Treatment of a bicyclo[4.1.0]hexan-4-one derivative with SmI_2 led to a cyclohexanone.²⁵³ The SmI_2 also converts α -halomethyl cyclic ketones to the next larger ring ketone²⁵⁴ and cyclic ketones to the next larger ring ketone in the presence of CH_2I_2 .²⁵⁵

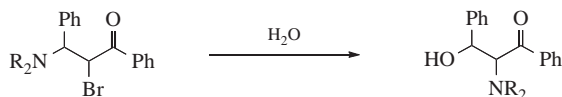
Another homologation reaction converts an aldehyde to its tosyl hydrazone, and subsequent reaction with an aldehyde and NaOEt/EtOH give a ketone.²⁵⁶ The reaction of an aldehyde with vinyl acetate and Ba(OH)_2 gives the homologated conjugated aldehyde.²⁵⁷

OS **IV**, 225, 780. For homologation of carboxylic acid derivatives, see OS **IX**, 426

B. Carbon-to-Carbon Migrations of Other Groups

18-10 Migrations of Halogen, Hydroxyl, Amino, and so on

Hydroxy-de-bromo-*cine*-substitution, and so on



When a nucleophilic substitution is carried out on a substrate that has a neighboring group (Sec. 10.C) on the adjacent carbon, a cyclic intermediate can be generated that is opened on the opposite side, resulting in migration of the neighboring group. In the example shown above (NR_2 = morpholino),²⁵⁸ the reaction took place via an aziridinium salt (**82**) to give an α -amino- β -hydroxy ketone. Sulfonate esters and halides can also

²⁴⁸ See Loeschorn, C.A.; Nakajima, M.; Anselme, J. *Bull. Soc. Chim. Belg.* **1981**, 90, 985.

²⁴⁹ Mock, W.L.; Hartman, M.E. *J. Org. Chem.* **1977**, 42, 459, 466; Baldwin, S.W.; Landmesser, N.G. *Synth. Commun.* **1978**, 8, 413.

²⁵⁰ Liu, H.J.; Majumdar, S.P. *Synth. Commun.* **1975**, 5, 125.

²⁵¹ Dave, V.; Warnhoff, E.W. *J. Org. Chem.* **1983**, 48, 2590.

²⁵² Doyle, M.P.; Trudell, M.L.; Terpstra, J.W. *J. Org. Chem.* **1983**, 48, 5146.

²⁵³ Lee, P.H.; Lee, J. *Tetrahedron Lett.* **1998**, 39, 7889.

²⁵⁴ Hasegawa, E.; Kitazume, T.; Suzuki, K.; Tosaka, E. *Tetrahedron Lett.* **1998**, 39, 4059.

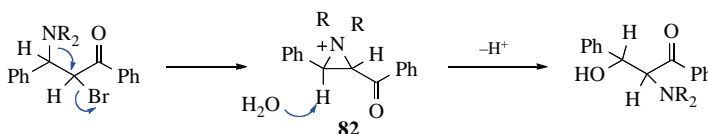
²⁵⁵ Fukuzawa, S.; Tsuchimoto, T. *Tetrahedron Lett.* **1995**, 36, 5937.

²⁵⁶ Angle, S.R.; Neitzel, M.L. *J. Org. Chem.* **2000**, 65, 6458.

²⁵⁷ Mahata, P.K.; Barun, O.; Ila, H.; Junjappa, H. *Synlett* **2000**, 1345.

²⁵⁸ Southwick, P.L.; Walsh, W.L. *J. Am. Chem. Soc.* **1955**, 77, 405. See also, Kiss, L.; Mangelinckx, S.; Fülöp, F.; De Kimpe, N. *Org. Lett.* **2007**, 9, 4399.

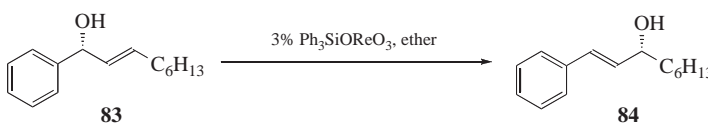
migrate in this reaction.²⁵⁹



α-Halo and α-acyloxy epoxides undergo ready rearrangement to α-halo and α-acyloxy ketones, respectively.²⁶⁰ These substrates are prone to rearrange, and often do so upon standing without a catalyst, although an acid catalyst is necessary in some cases. The reaction is essentially the same as the rearrangement of epoxides shown in **18-2**, except that halogen or acyloxy is the migrating group (as shown above; however, it is also possible for one of the R groups (alkyl, aryl, or hydrogen) to migrate instead, and mixtures are sometimes obtained). In a related reaction, α-bromoaziridines undergo rearrangement to the isomerized α-bromoaziridine in the presence of MgBr₂.²⁶¹

In the presence of a Cu catalyst, alkenyl epoxides (vinyl oxiranes) rearrange to a 2,5-dihydrofuran.²⁶² Alkenyl thiiranes are similarly converted to 2,5-dihydrothiophenes with a Cu catalyst.²⁶³

Allylic alcohols migrate to give a new allylic alcohol in the presence of a Re catalyst. An example is the conversion of **83** to **84**.²⁶⁴ Variations using Rh²⁶⁵ or Ir²⁶⁶ catalysts are known, and methanesulfonic acid catalyzes the isomerization.²⁶⁷ In the presence of a Ru catalyst, an allylic alcohol was isomerized to an aliphatic ketone.²⁶⁸ There is a similar Au catalyzed isomerization of allylic acetates.²⁶⁹



The *Meyer-Schuster Rearrangement* is an acid-catalyzed rearrangement of a propargyl alcohol to a conjugated carbonyl compound.²⁷⁰ Rearrangement was also catalyzed by a cationic Rh-bisphosphane complex.²⁷¹ An Au catalyzed rearrangement of ethoxyalkynyl carbinols gave α,β-unsaturated esters.²⁷² The base-induced isomerization of a propargylic

²⁵⁹ See Peterson, P.E. *Acc. Chem. Res.* **1971**, 4, 407. See also, Brusova, G.P.; Gopius, E.D.; Smolina, T.A.; Reutov, O.A. *Doklad. Chem.* **1980**, 253, 334; Kobrina, L.S.; Kovtonyuk, V.N. *Russ. Chem. Rev.* **1988**, 57, 62; Warren, S. *Acc. Chem. Res.* **1978**, 11, 403. See also, Aggarwal, V.K.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* **1987**, 2579.

²⁶⁰ For a review, see McDonald, R.N. *Mech. Mol. Migr.* **1971**, 3, 67.

²⁶¹ Karikomi, M.; Takayama, T.; Haga, K.; Hiratani, K. *Tetrahedron Lett.* **2005**, 46, 6541.

²⁶² Batory, L.A.; McInnis, C.E.; Njardarson, J.T. *J. Am. Chem. Soc.* **2006**, 128, 16054.

²⁶³ Rogers, E.; Araki, H.; Batory, L.A.; McInnis, C.E.; Njardarson, J.T. *J. Am. Chem. Soc.* **2007**, 129, 2768.

²⁶⁴ Morrill, C.; Grubbs, R.H. *J. Am. Chem. Soc.* **2005**, 127, 2842; Morrill, C.; Beutner, G.L.; Grubbs, R.H. *J. Org. Chem.* **2006**, 71, 7813.

²⁶⁵ Boeda, F.; Mosset, P.; Crévisy, C. *Tetrahedron Lett.* **2006**, 47, 5021.

²⁶⁶ Mantilli, L.; Gérard, D.; Torche, S.; Besnard, C.; Mazet, C. *Pure Appl. Chem.* **2010**, 82, 1461.

²⁶⁷ Leleti, R.R.; Hu, B.; Prashad, M.; Repič, O. *Tetrahedron Lett.* **2007**, 48, 8505.

²⁶⁸ Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* **2005**, 127, 6172.

²⁶⁹ Marion, N.; Gealageas, R.; Nolan, S.P. *Org. Lett.* **2007**, 9, 2653.

²⁷⁰ Meyer, K.H.; Schuster, K. *Ber.* **1922**, 55, 819; Swaminathan, S.; Narayan, K.V. *Chem. Rev.* **1971**, 71, 429.

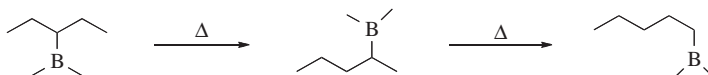
²⁷¹ Tanaka, K.; Shoji, T.; Hirano, M. *Eur. J. Org. Chem.* **2007**, 2687.

²⁷² Lopez, S.S.; Engel, D.A.; Dudley, G.B. *Synlett* **2007**, 949.

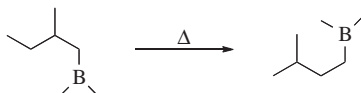
alcohol gave a conjugated ketone,²⁷³ and a combination of Mo—Au led to rapid 1,3-rearrangement of propargyl alcohols.²⁷⁴ An Au—Ag catalyzed reaction with propargyl esters gave a 2-O-pivaloyl conjugated aldehyde.²⁷⁵ A similar reaction with a Pt catalyst converted a 1-ethoxy propargylic ester to a 2-carboethoxy conjugated ketone.²⁷⁶ An Au catalyzed isomerization of allenyl carbinol esters is also known.²⁷⁷

18-11 Migration of Boron

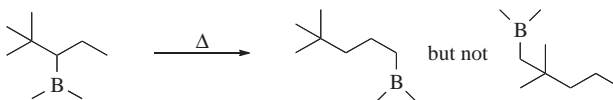
Hydro,dialkylboro-interchange, and so on



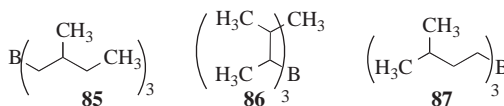
Boranes are prepared by the reaction of BH_3 (B_2H_6) or an alkylborane with an alkene (**15-16**). When a nonterminal borane is heated at temperatures ranging from 100 to 200 °C, the boron moves toward the end of the chain.²⁷⁸ The reaction is catalyzed by small amounts of borane or other species containing B—H bonds. The boron can move past a branch, for example,



but not past a double branch, for example,



The reaction is an equilibrium: **85**, **86**, and **87** each gave a mixture containing ~40% **85**, 1% **86**, and 59% **87**. The migration can go quite a long distance, including a migration of 11 positions.²⁷⁹ If the boron is on a cycloalkyl ring, it can move around the ring; if any alkyl chain is also on the ring, the boron may move from the ring to the chain, ending up at the end of the chain.²⁸⁰ The reaction is useful for the migration of double bonds in a controlled way (see **12-2**). The mechanism may involve a π complex, at least partially.²⁸¹



²⁷³ Sonye, J.P.; Koide, K. *J. Org. Chem.* **2007**, 72, 1846.

²⁷⁴ Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* **2008**, 10, 1867.

²⁷⁵ Witham, C.A.; Mauleón, P.; Shapiro, N.D.; Sherry, B.D.; Toste, F.D. *J. Am. Chem. Soc.* **2007**, 129, 5838.

²⁷⁶ Barluenga, J.; Riesgo, L.; Vicente, R.; López, L.A.; Tomás, M. *J. Am. Chem. Soc.* **2007**, 129, 7772.

²⁷⁷ Buzas, A.K.; Istrate, F.M.; Gagosz, F. *Org. Lett.* **2007**, 9, 985.

²⁷⁸ Brown, H.C. *Hydroboration*, W. A. Benjamin, NY, **1962**, pp. 136–149; Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* **1966**, 88, 1433. See also, Brown, H.C.; Racherla, U.S. *J. Organomet. Chem.* **1982**, 241, C37.

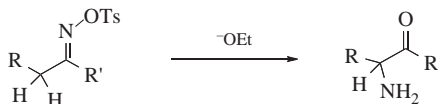
²⁷⁹ Logan, T.J. *J. Org. Chem.* **1961**, 26, 3657.

²⁸⁰ Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* **1967**, 89, 561.

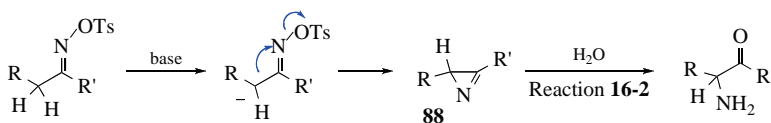
²⁸¹ See Wood, S.E.; Rickborn, B. *J. Org. Chem.* **1983**, 48, 555; Field, L.D.; Gallagher, S.P. *Tetrahedron Lett.* **1985**, 26, 6125.

18-12 The Neber Rearrangement

Neber oxime tosylate-amino ketone rearrangement



α -Amino ketones can be prepared by treatment of ketoxime tosylates with a base (e.g., ethoxide or pyridine).²⁸² This reaction is called the *Neber rearrangement*. The R group is usually aryl, although the reaction has been carried out with R = alkyl or hydrogen. The R' group may be alkyl or aryl, but not hydrogen. The *Beckmann rearrangement* (Reaction 18-17) and the abnormal *Beckmann reaction* (elimination to the nitrile, Reaction 17-30) may be side reactions, although these generally occur in acid media. A similar rearrangement is given by *N,N*-dichloroamines of the type $\text{RCH}_2\text{CH}(\text{NCl}_2)\text{R}'$, where the product is also $\text{RCH}(\text{NH}_2)\text{COR}'$.²⁸³ The mechanism of the Neber rearrangement involves an azirine intermediate (**88**).²⁸⁴ The best evidence for this mechanism is that the azirine intermediate has been isolated.²⁸⁵ In contrast to the *Beckmann rearrangement*, this one is sterically indiscriminate.²⁸⁶ Both a syn and an anti ketoxime give the same product. The mechanism, as shown above, consists of three steps. However, it is possible that the first two steps are concerted, and it is also possible that what is shown as the second step is actually two steps: loss of OTs to give a nitrene, and formation of the azirine. In the case of the dichloroamines, HCl is first lost to give $\text{RCH}_2\text{C}(=\text{NCl})\text{R}'$, which then behaves analogously.²⁸⁷ *N*-Chloroimines prepared in other ways also give the reaction.²⁸⁸ Indoles have been prepared via a *Neber rearrangement*.²⁸⁹



OS V, 909; VII, 149.

C. Carbon-to-Nitrogen Migrations of R and Ar

The reactions in this group are nucleophilic migrations from a carbon to a nitrogen atom. In each case, the nitrogen atom either has six electrons in its outer shell (and thus invites the migration of a group carrying an electron pair) or else loses a nucleofuge concurrently with the migration (Sec. 18.A.i). Reactions 18-13–18-16 are used to prepare amines from acid derivatives. Reactions 18-16 and 18-17 are used to prepare amines from ketones. The mechanisms of Reaction 18-13–18-16 (with carboxylic acids) are very similar and follow

²⁸² For a review, see Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* **1971**, 4, 197, pp. 289–304.

²⁸³ Baumgarten, H.E.; Petersen, H.E. *J. Am. Chem. Soc.* **1960**, 82, 459, and references cited therein.

²⁸⁴ Cram, D.J.; Hatch, M.J. *J. Am. Chem. Soc.* **1953**, 75, 33; Hatch, M.J.; Cram, D.J. *J. Am. Chem. Soc.* **1953**, 75, 38.

²⁸⁵ Neber, P.W.; Burgard, A. *Liebigs Ann. Chem.* **1932**, 493, 281; Parcell, R.F. *Chem. Ind. (London)* **1963**, 1396. Also see Ref. 284.

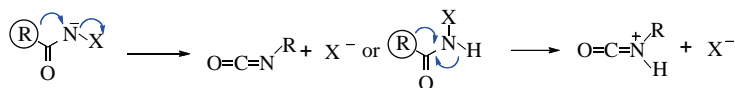
²⁸⁶ House, H.O.; Berkowitz, W.F. *J. Org. Chem.* **1963**, 28, 2271.

²⁸⁷ See Nakai, M.; Furukawa, N.; Oae, S. *Bull. Chem. Soc. Jpn.* **1969**, 42, 2917.

²⁸⁸ Baumgarten, H.E.; Petersen, J.M.; Wolf, D.C. *J. Org. Chem.* **1963**, 28, 2369.

²⁸⁹ Taber, D.F.; Tian, W. *J. Am. Chem. Soc.* **2006**, 128, 1058.

one of two patterns:

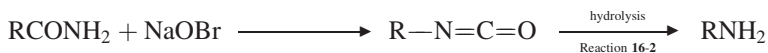


Some of the evidence²⁹⁰ is (1) configuration is retained in R (Sec. 18.A.ii); (2) the kinetics are first order; (3) intramolecular rearrangement is shown by labeling; and (4) no rearrangement occurs *within* the migrating group, for example, a neopentyl group on the carbon of the starting material is still a neopentyl group on the nitrogen of the product.

In many cases, it is not certain whether the nucleofuge X is lost first, creating an intermediate nitrene²⁹¹ or nitrenium ion, or whether migration and loss of the nucleofuge are simultaneous, as shown above.²⁹² It is likely that both possibilities can exist, depending on the substrate and reaction conditions.

18-13 The Hofmann Rearrangement

Bishydrogen-(2/→1/N-alkyl)-migro-detachment (formation of isocyanate)



In the *Hofmann rearrangement*, an unsubstituted amide is treated with sodium hypobromite (or sodium hydroxide and bromine, which is essentially the same thing) to give an isocyanate, but this compound is seldom isolated²⁹³ since it is usually hydrolyzed under the reaction conditions. The final isolated product is a primary amine that has one carbon fewer than the starting amide.²⁹⁴ The R group may be alkyl or aryl, but if it is an alkyl group of more than about six or seven carbons, low yields are obtained unless Br₂ and NaOMe are used instead of Br₂ and NaOH.²⁹⁵ Another modification uses NBS/NaOMe.²⁹⁶ Under these conditions, the product of addition to the isocyanate is the carbamate (RNHCOOMe, Reaction 16-8), which is easily isolated or can be hydrolyzed to the amine.²⁹⁷ A mixture of NBS and DBU (see Reaction 17-13) in methanol gives the carbamate,²⁹⁸ as does electrolysis in methanol.²⁹⁹

Side reactions when NaOH is the base are formation of ureas (RNHCONHR) and acylureas (RCONHCONHR) by addition, respectively, of RNH₂ and RCONH₂ to RNCO (16-20). If acylureas are desired, they can be made the main products by using only one-half of the usual quantities of Br₂ and NaOH. Another side product, but only from primary R, is the nitrile derived from oxidation of RNH₂ (Reaction 19-5).

Imides react to give amino acids, (e.g., phthalimide gives *o*-aminobenzoic acid). α-Hydroxy and α-halo amides give aldehydes and ketones by way of the unstable

²⁹⁰ Smith, P.A.S. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, **1963**, Vol. 1, pp. 258–550.

²⁹¹ See Boyer, J.H. *Mech. Mol. Migr.* **1969**, 2, 267.

²⁹² The question is discussed by Lwowski, W. in Lwowski, W. *Nitrenes*, Wiley, NY, **1970**, pp. 217–221.

²⁹³ See Sy, A.O.; Raksis, J.W. *Tetrahedron Lett.* **1980**, 21, 2223.

²⁹⁴ See Wallis, E.S.; Lane, J.F. *Org. React.* **1946**, 3, 267.

²⁹⁵ See Radlick, P.; Brown, L.R. *Synthesis* **1974**, 290.

²⁹⁶ Huang, X.; Keillor, J.W. *Tetrahedron Lett.* **1997**, 38, 313.

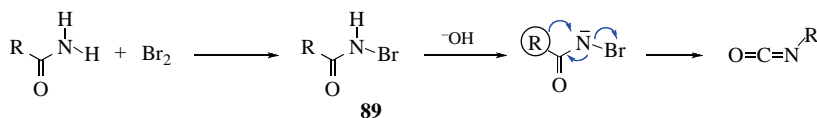
²⁹⁷ See Gogoi, P.; Konwar, D. *Tetrahedron Lett.* **2007**, 48, 531.

²⁹⁸ Huang, X.; Seid, M.; Keillor, J.W. *J. Org. Chem.* **1997**, 62, 7495.

²⁹⁹ Matsumura, Y.; Maki, T.; Satoh, Y. *Tetrahedron Lett.* **1997**, 38, 8879.

α -hydroxy- or α -haloamines. However, a side product with an α -halo amide is a *gem*-dihalide. Ureas analogously give hydrazines.

The mechanism follows the pattern outlined in the discussion preceding Reaction 18-13.



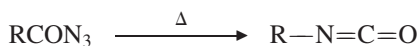
The first step is an example of Reaction 12-52 and intermediate *N*-halo amides (**89**) have been isolated. Compound **89** is acidic because of the presence of two electron-withdrawing groups (acyl and halo) on the nitrogen, and in the second step, **89** loses a proton to the base. It is possible that the third step is actually two steps: loss of bromide to form a nitrene, followed by the actual migration, but most of the available evidence favors the concerted reaction.³⁰⁰ A similar reaction can be effected by the treatment of amides with lead tetraacetate.³⁰¹ Among other reagents that convert RCONH_2 to RNH_2 (R = alkyl, but not aryl) are phenyliodosyl bis(trifluoroacetate) $[\text{PhI}(\text{OCOCF}_3)_2]$ ³⁰² and hydroxy(tosyloxy) iodobenzene $[\text{PhI}(\text{OH})\text{OTs}]$.³⁰³

A variation of the *Hofmann rearrangement* treated a β -hydroxy primary amide with $\text{PhI}(\text{O}_2\text{CCF}_3)_3$ in aq acetonitrile, giving an isocyanate via $-\text{CON}-\text{I}$, which reacts with the hydroxyl group intramolecularly to give a cyclic carbamate.³⁰⁴ Note that carbamates are converted to isocyanates by heating with Montmorillonite K-10.³⁰⁵

OS II, 19, 44, 462; IV, 45; VIII, 26, 132.

18-14 The Curtius Rearrangement

Dinitrogen-(2/→1/*N*-alkyl)-migratio-detachment



The *Curtius rearrangement* involves heating acyl azides to yield isocyanates.³⁰⁶ The reaction gives good yields of isocyanates, since no water is present to hydrolyze them to the amine. Of course, they can be subsequently hydrolyzed, and indeed the reaction *can* be carried out in water or alcohol, in which case the products are amines, carbamates, or acylureas, as in 18-13.³⁰⁷ This is a very general reaction and can be applied to almost any carboxylic acid: aliphatic, aromatic, alicyclic, heterocyclic, unsaturated, and containing many functional groups. Acyl azides can be prepared as in Reaction 10-43 or by treatment

³⁰⁰ Imamoto, T.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1632, 1639, 1644; Imamoto, T.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2776.

³⁰¹ Baumgarten, H.E.; Smith, H.L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554.

³⁰² Loudon, G.M.; Radhakrishna, A.S.; Almond, M.R.; Blodgett, J.K.; Boutin, R.H. *J. Org. Chem.* **1984**, *49*, 4272; Boutin, R.H.; Loudon, G.M. *J. Org. Chem.* **1984**, *49*, 4277; Pavlides, V.H.; Chan, E.D.; Pennington, L.; McParland, M.; Whitehead, M.; Coutts, I.G.C. *Synth. Commun.* **1988**, *18*, 1615.

³⁰³ Vasudevan, A.; Koser, G.F. *J. Org. Chem.* **1988**, *53*, 5158.

³⁰⁴ Yu, C.; Jiang, Y.; Liu, B.; Hu, L. *Tetrahedron Lett.* **2001**, *42*, 1449.

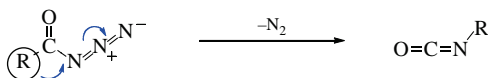
³⁰⁵ Uriz, P.; Serra, M.; Salagre, P.; Castillon, S.; Claver, C.; Fernandez, E. *Tetrahedron Lett.* **2002**, *43*, 1673.

³⁰⁶ See Banthorpe, D.V. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, **1971**, pp. 397–405.

³⁰⁷ See Pfister, J.R.; Wyman, W.E. *Synthesis* **1983**, 38. See also, Lebel, H.; Leogane, O. *Org. Lett.* **2005**, *7*, 4107. See also, Ma, B.; Lee, W.-C. *Tetrahedron Lett.* **2010**, *51*, 385.

of acylhydrazines (hydrazides) with nitrous acid (analogous to Reaction 12-49). The Curtius rearrangement is catalyzed by Lewis acids or protic acids, but these are usually not necessary for good results.

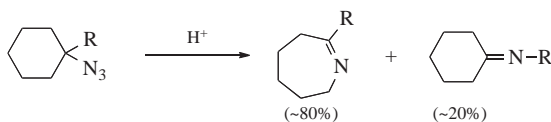
The mechanism is similar to that in Reaction 18-13 to give an isocyanate. Also note the exact analogy between this Reaction and 18-8. However, in this case, there is no evidence for a free nitrene and it is probable that the conversion is concerted.³⁰⁸



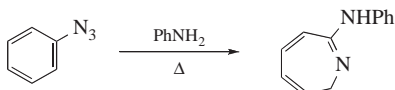
Alkyl azides can be similarly pyrolyzed to give imines, in an analogous reaction³⁰⁹:



The R groups may be alkyl, aryl, or hydrogen, although if hydrogen migrates, the product is the unstable $\text{R}_2\text{C}=\text{NH}$. The mechanism is essentially the same as that of the *Curtius rearrangement*. However, in pyrolysis of tertiary alkyl azides, there is evidence that free alkyl nitrenes are intermediates.³¹⁰ The reaction can also be carried out with acid catalysis, in which case lower temperatures can be used, although the acid may hydrolyze the imine (16-2). Cycloalkyl azides give ring expansion as shown.³¹¹



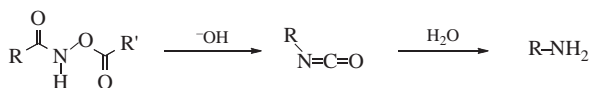
Aryl azides also give ring expansion on heating, for example,³¹²



OS III, 846; IV, 819; V, 273; VI, 95, 910. Also see, OS VI, 210.

18-15 The Lossen Rearrangement

Hydro,acetoxy-(2/→1*N*-alkyl)-migr-o-detachment



³⁰⁸ See, Smalley, R.K.; Bingham, T.E. *J. Chem. Soc. C* **1969**, 2481.

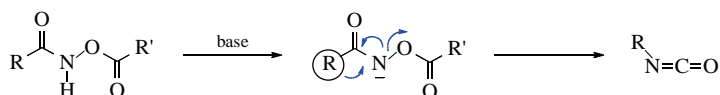
³⁰⁹ See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, **1984**; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, **1973**, pp. 45–52; in Lwowski, W. *Nitrenes*, Wiley, NY, **1970**, the chapters by Lewis, F.D.; Saunders Jr., W.H. pp. 47–97, pp. 47–78 and by Smith, P.A.S. pp. 99–162.

³¹⁰ Montgomery, F.C.; Saunders, Jr., W.H. *J. Org. Chem.* **1976**, *41*, 2368.

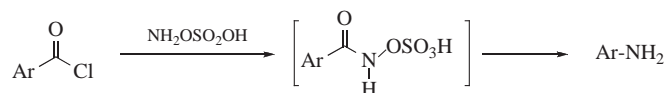
³¹¹ Smith, P.A.S.; Lakritz, J. cited in Smith, P.A.S. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, **1963**, p. 474.

³¹² Huisgen, R.; Vossius, D.; Appl, M. *Chem. Ber.* **1958**, *91*, 1,12.

The *O*-acyl derivatives of hydroxamic acids³¹³ give isocyanates when treated with bases or sometimes even just on heating, in a reaction known as the *Lossen rearrangement*.³¹⁴ The mechanism is similar to that of Reaction 18-13 and 18-14:

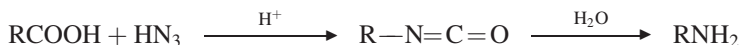


In a similar reaction, aromatic acyl halides are converted to amines in one laboratory step by treatment with hydroxylamine-*O*-sulfonic acid.³¹⁵



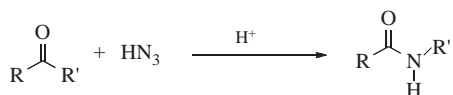
A chiral *Lossen rearrangement* is known.³¹⁶

18-16 The Schmidt Reaction



There are actually three reactions called by the name *Schmidt reaction*, involving the addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and alkenes.³¹⁷ The most common is the reaction with carboxylic acids, illustrated above.³¹⁸ Sulfuric acid is a common catalyst, but Lewis acids have also been used. Good results are obtained for aliphatic R, especially for long chains. When R is aryl, the yields are variable, being best for sterically hindered compounds like mesitoic acid. This method has the advantage over Reaction 18-13 and 18-14 in that there is just one laboratory step from the acid to the amine, but conditions are more drastic.³¹⁹ Under the acid conditions employed, the isocyanate is virtually never isolated.

The reaction between a ketone and hydrazoic acid is a method for “insertion” of NH between the carbonyl group and one R group, converting a ketone into an amide.³²⁰



Either or both of the R groups may be aryl. In general, dialkyl ketones and cyclic ketones react more rapidly than alkyl aryl ketones, and these more rapidly than diaryl ketones. The latter require sulfuric acid and do not react in concentrated HCl, which is strong enough for

³¹³ See Bauer, L.; Exner, O. *Angew. Chem. Int. Ed.* **1974**, 13, 376.

³¹⁴ See Salomon, C.J.; Breuer, E. *J. Org. Chem.* **1997**, 62, 3858.

³¹⁵ Wallace, R.G.; Barker, J.M.; Wood, M.L. *Synthesis* **1990**, 1143.

³¹⁶ Chandrasekhar, S.; Sridhar, M. *Tetrahedron Asymmetry* **2000**, 11, 3467.

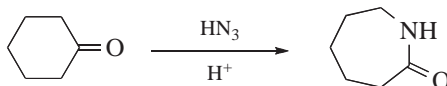
³¹⁷ See Banthorpe, D.V. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, **1971**, pp. 405–434.

³¹⁸ See Koldobskii, G.I.; Ostrovskii, V.A.; Gidasov, B.V. *Russ. Chem. Rev.* **1978**, 47, 1084.

³¹⁹ See Smith, P.A.S. *Org. React.* **1946**, 3, 337, pp. 363–366.

³²⁰ See Koldobskii, G.I.; Tereschenko, G.F.; Gerasimova, E.S.; Bagal, L.I. *Russ. Chem. Rev.* **1971**, 40, 835; Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 137–145.

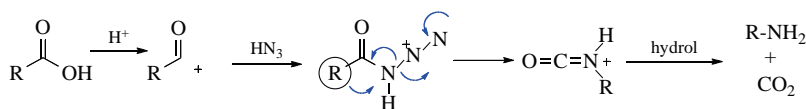
dialkyl ketones. Dialkyl and cyclic ketones react sufficiently faster than diaryl or aryl alkyl ketones or carboxylic acids or alcohols so that these functions may be present in the same molecule without interference. Cyclic ketones give lactams³²¹. With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky.³²²



The reaction has been applied to a few aldehydes, but rarely. With aldehydes the product is usually the nitrile (Reaction **16-16**). Even with ketones, conversion to the nitrile is often a side reaction, especially with the type of ketone that gives **17-30**. A useful variation of the Schmidt reaction treats a cyclic ketone with an alkyl azide (RN₃)³²³ in the presence of TiCl₄, generating a lactam.³²⁴ An intramolecular *Schmidt reaction* gives bicyclic amines.³²⁵ Another variation treats a silyl enol ether of a cyclic ketone with TMSN₃ and photolyzes the product with UV light to give a lactam.³²⁶ An α-azido cyclic ketone rearrangement to lactams under radical conditions (Bu₃SnH/AIBN).³²⁷

Alcohols and alkenes react with HN₃ to give alkyl azides,³²⁸ which in the course of reaction rearrange in the same way as discussed in Reaction **18-14**.³⁰⁹ The *Mitsunobu Reaction* (**10-17**) can be used to convert alcohols to alkyl azides, and an alternative reagent for azides [(PhO)₂PON₃], for use in the *Mitsunobu* is now available.³²⁹ In the presence of an Au catalyst, an acetylenic azide was converted to a pyrrole derivative.³³⁰ An intramolecular *Schmidt reaction* gives bicyclic lactams in the presence of MeAlCl₂.³³¹

There is evidence that the mechanism with carboxylic acids³²⁰ is similar to that of Reaction **18-14**, except that it is the protonated azide that undergoes the rearrangement³³²:



The first step is the same as that of the A_{AC}1 mechanism (Reaction **16-59**, which explains why good results are obtained with hindered substrates. The mechanism with ketones

³²¹ See Krow, G.R. *Tetrahedron* **1981**, 37, 1283.

³²² Exceptions to this statement are found in Bhalerao, U.T.; Thyagarajan, G. *Can. J. Chem.* **1968**, 46, 3367; Tomita, M.; Minami, S.; Uyeo, S. *J. Chem. Soc. C* **1969**, 183.

³²³ See Furness, K.; Aubé, J. *Org. Lett.* **1999**, 1, 495.

³²⁴ Sahasrabudhe, K.; Gracías, V.; Furness, K.; Smith, B.T.; Katz, C.E.; Reddy, D.S.; Aubé, J. *J. Am. Chem. Soc.* **2003**, 125, 7914. See Mossman, C.J.; Aubé, J. *Tetrahedron*, **1996**, 52, 3403.

³²⁵ Pearson, W.H.; Hutta, D.A.; Fang, W.-k. *J. Org. Chem.* **2000**, 65, 8326. See also, Wroblewski, A.; Aubé, J. *J. Org. Chem.* **2001**, 66, 886.

³²⁶ Evans, P.A.; Modi, D.P. *J. Org. Chem.* **1995**, 60, 6662.

³²⁷ Benati, L.; Nanni, D.; Sangiorgi, C.; Spagnolo, P. *J. Org. Chem.* **1999**, 64, 7836.

³²⁸ See Kumar, H.M.S.; Reddy, B.V.S.; Anjaneyulu, S.; Yadav, J.S. *Tetrahedron Lett.* **1998**, 39, 7385. Also see, Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1997**, 38, 3955.

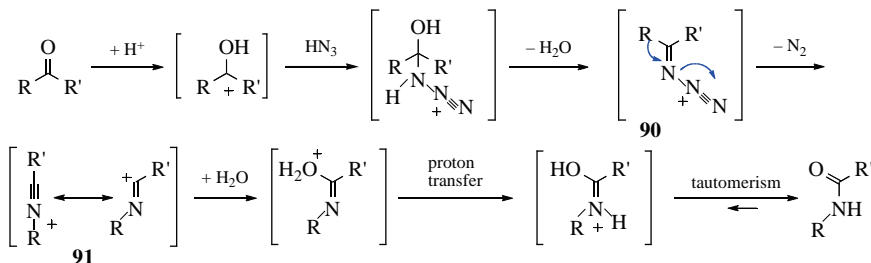
³²⁹ Thompson, A.S.; Humphrey, G.R.; DeMarco, A.M.; Mathre, D.J.; Grabowski, E.J.J. *J. Org. Chem.* **1993**, 58, 5886.

³³⁰ Gorin, D.J.; Davis, N.R.; Toste, F.D. *J. Am. Chem. Soc.* **2005**, 127, 11260.

³³¹ Yao, L.; Aubé, J. *J. Am. Chem. Soc.* **2007**, 129, 2766.

³³² This mechanism has been controversial, see Vogler, E.A.; Hayes, J.M. *J. Org. Chem.* **1979**, 44, 3682.

involves formation of a nitrilium ion (**82**), which reacts with water.

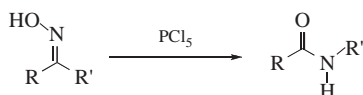


Intermediates (e.g., **90**) have been independently generated in aqueous solution.³³³ Note the similarity of this mechanism to those of “insertion” of CH₂ (Reaction **18-9**) and of O (Reaction **18-19**). The three reactions are essentially analogous, both in products and in mechanism.^{334,320} Also note the similarity of the latter part of this mechanism to that of the *Beckmann rearrangement* (Reaction **18-17**).

OS V, 408; VI, 368; VII, 254; X, 207. See also, OS V, 623.

18-17 The Beckmann Rearrangement

Beckmann oxime–amide rearrangement



When oximes are treated with PCl₅ or a number of other reagents, they rearrange to substituted amides in a reaction called the *Beckmann rearrangement*.³³⁵ Reagents used include concentrated H₂SO₄ acid, formic acid, liquid SO₂, silica gel,³³⁶ RuCl₃,³³⁷ Y(OTf)₃,³³⁸ I₂,³³⁹ HgCl₂,³⁴⁰ triphosphazene,³⁴¹ bromodimethylsulfonium bromide–ZnCl₂,³⁴² neat with FeCl₃,³⁴³ cyanuric acid,³⁴⁴ and polyphosphoric acid.³⁴⁵ Simply heating the oxime of benzophenone neat leads to *N*-phenyl benzamide.³⁴⁶ The reaction has been

³³³ Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* **1991**, 113, 1867.

³³⁴ See Ostrovskii, V.A.; Koshtaleva, T.M.; Shirokova, N.P.; Koldobskii, G.I.; Gidasov, B.V. *J. Org. Chem. USSR* **1974**, 10, 2365 and references cited therein.

³³⁵ Gawley, R.E. *Org. React.* **1988**, 35, 1; McCarty, C.G. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 408–439. Also see, Nguyen, M.T.; Raspoet, G.; Vanquickenborne, L.G. *J. Am. Chem. Soc.* **1997**, 119, 2552.

³³⁶ Costa, A.; Mestres, R.; Riego, J.M. *Synth. Commun.* **1982**, 12, 1003.

³³⁷ De, S.K. *Synth. Commun.* **2004**, 34, 3431.

³³⁸ De, S.K. *Org. Prep. Proceed. Int.* **2004**, 36, 383.

³³⁹ Ganguly, N.C.; Mondal, P. *Synthesis* **2010**, 3705.

³⁴⁰ Ramalingam, C.; Park, Y.-T. *J. Org. Chem.* **2007**, 72, 4536.

³⁴¹ Hashimoto, M.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2008**, 73, 2894.

³⁴² Yadav, L.D.S.; Patel, R.; Srivastava, V.P. *Synthesis* **2010**, 1771. See also Yadav, L.D.S.; Garima, Srivastava, V.P. *Tetrahedron Lett.* **2010**, 51, 739.

³⁴³ Khodaei, M.M.; Meybodi, F.A.; Rezai, N.; Salehi, P. *Synth. Commun.* **2001**, 31, 2047.

³⁴⁴ Furuya, Y.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, 127, 11240. In ionic liquids, see Betti, C.; Landini, D.; Maia, A.; Pasi, M. *Synlett* **2008**, 908.

³⁴⁵ See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 131–137.

³⁴⁶ Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* **2001**, 42, 8123.

done in supercritical water³⁴⁷ and in ionic liquids.³⁴⁸ A polymer-bound Beckman rearrangement has been reported.³⁴⁹ Microwave assisted *Beckmann rearrangements* are known.³⁵⁰ Note that the reaction of an imine with $\text{BF}_3 \cdot \text{OEt}_2$ and *m*-chloroperoxybenzoic acid leads to a formamide.³⁵¹

The oximes of cyclic ketones give ring enlargement and form the lactam,³⁵² as in the formation of caprolactam (see Reaction **18-16**) from the oxime of cyclohexanone. Solvent-free reactions are known.³⁵³ Cyclic ketones can be converted directly to lactams in one laboratory step by treatment with $\text{NH}_2\text{OSO}_2\text{OH}$ and formic acid (Reaction **16-14** takes place first, then the *Beckmann rearrangement*).³⁵⁴

Of the groups attached to the carbon of the $\text{C}=\text{N}$ unit, the one that migrates in the *Beckman rearrangement* is generally the one anti to the hydroxyl, and this is often used as a method of determining the configuration of the oxime. However, it is not unequivocal. It is known that with some oximes the syn group migrates and that with others, especially where R and R' are both alkyl, mixtures of the two possible amides are obtained. However, this behavior does not necessarily mean that the syn group actually undergoes migration. In most cases, the oxime undergoes isomerization under the reaction conditions *before* migration takes place.³⁵⁵ The scope of the reaction is quite broad and R and R' may be alkyl, aryl, or hydrogen. However, hydrogen very seldom migrates, so the reaction is not generally a means of converting aldoximes to unsubstituted amides (RCONH_2). This latter conversion can be accomplished, however, by treatment of the aldoxime with nickel acetate under neutral conditions³⁵⁶ or by heating the aldoxime for 60 h at 100 °C after it has been adsorbed onto silica gel.³⁵⁷ As in the case of the *Schmidt rearrangement* (Reaction **18-16**), when the oxime is derived from an alkyl aryl ketone, it is generally the aryl group that preferentially migrates.³⁵⁸

Not only do oximes undergo the *Beckmann rearrangement*, but so also do esters of oximes with many acids, organic and inorganic. A side reaction with many substrates is the formation of nitriles (the "abnormal" *Beckmann rearrangement*, Reaction **17-30**). The *O*-carbonates of imines (e.g., $\text{Ph}_2\text{C}=\text{N}-\text{OCO}_2\text{Et}$) react with $\text{BF}_3 \cdot \text{OEt}_2$ to give the corresponding amide in this case *N*-phenyl benzamide.³⁵⁹

In the first step of the mechanism, the OH group is converted by the reagent to a better leaving group, for example, proton acids convert it to OH_2^+ . After that, the mechanism³⁶⁰ follows a course analogous to that for the *Schmidt reaction* of ketones (**18-16**) from the

³⁴⁷ Boero, M.; Ikeshoji, T.; Liew, C.C.; Terakura, K.; Parrinello, M. *J. Am. Chem. Soc.* **2004**, *126*, 6280.

³⁴⁸ Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 403; Ren, R.X.; Zueva, L.D.; Ou, X. *Tetrahedron Lett.* **2001**, *42*, 8441.

³⁴⁹ His, S.; Meyer, C.; Cossy, J.; Emeric, G.; Greiner, A. *Tetrahedron Lett.* **2003**, *44*, 8581.

³⁵⁰ Thakur, A.J.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* **2000**, *30*, 2105; On silica with microwave irradiation, see Loupy, A.; Régnier, S. *Tetrahedron Lett.* **1999**, *40*, 6221.

³⁵¹ An, G.-i.; Kim, M.; Kim, J.Y.; Rhee, H. *Tetrahedron Lett.* **2003**, *44*, 2183.

³⁵² Vinnik, M.I.; Zarakhani, N.G. *Russ. Chem. Rev.* **1967**, *36*, 51; Krow, G.R. *Tetrahedron* **1981**, *37*, 1283.

³⁵³ Sharghi, H.; Hosseini, M. *Synthesis* **2002**, 1057; Eshghi, H.; Gordi, Z. *Synth. Commun.* **2003**, *33*, 2971; Moghaddam, F.M.; Rad, A.A.R.; Zali-Boinee, H. *Synth. Commun.* **2004**, *34*, 2071.

³⁵⁴ Olah, G.A.; Fung, A.P. *Synthesis* **1979**, 537. See also, Novoselov, E.F.; Isaev, S.D.; Yurchenko, A.G.; Vodichka, L.; Trshiska, Ya. *J. Org. Chem. USSR* **1981**, *17*, 2284.

³⁵⁵ See Lansbury, P.T.; Mancuso, N.R. *Tetrahedron Lett.* **1965**, 2445.

³⁵⁶ Field, L.; Hughmark, P.B.; Shumaker, S.H.; Marshall, W.S. *J. Am. Chem. Soc.* **1961**, *83*, 1983. See also, Leusink, A.J.; Meerbeek, T.G.; Noltes, J.G. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 123; **1977**, *96*, 142.

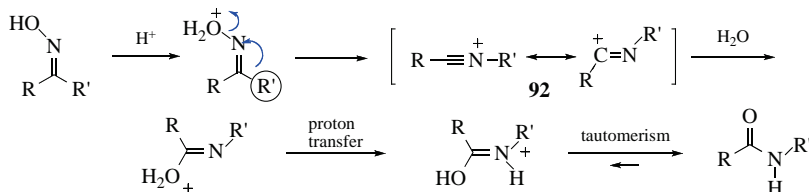
³⁵⁷ Chattopadhyaya, J.B.; Rama Rao, A.V. *Tetrahedron* **1974**, *30*, 2899.

³⁵⁸ See Arisawa, M.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 311.

³⁵⁹ Anilkumar, R.; Chandrasekhar, S. *Tetrahedron Lett.* **2000**, *41*, 5427.

³⁶⁰ See Nguyen, M.T.; Vanquickenborne, L.G. *J. Chem. Soc. Perkin Trans. 2* **1993**, 1969.

formation of nitrilium ion (**92**) on³⁶¹: Alternative modes of reaction are possible. For example, when PCl_5 is used to induce the reaction, a N-O-PCl_4 species is formed, which generates **92**. Intermediates of the form **92** have been detected by NMR and UV spectroscopy.³⁶² The rearrangement has also been found to take place by a different mechanism, involving formation of a nitrile by fragmentation, and then addition by a *Ritter Reaction* (**16-91**).³⁶³ *Beckmann rearrangements* have also been carried out photochemically.³⁶⁴ A computational study compared concerted versus stepwise mechanisms for the *Beckmann rearrangement*, and found that proton relay between the substrate and the solvent molecules controls the reaction, and migration and N-O bond scission occur simultaneously.³⁶⁵



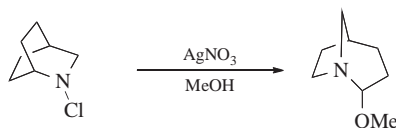
If the rearrangement of oxime sulfonates is induced by organoaluminum reagents,³⁶⁶ the nitrilium ion intermediate (**92**) is captured by the nucleophile originally attached to the Al. By this means an oxime can be converted to an imine, an imino thioether (R-N=C-SR), or an imino nitrile (R-N=C-CN).³⁶⁷ In the last case, the nucleophile comes from added trimethylsilyl cyanide. In the presence of LiI , 2-benzoyloxypyridine is converted to *N*-benzyl-2-pyridone.³⁶⁸

In a related reaction, treatment of spirocyclic oxaziridines with $\text{MnCl}(\text{tpp})$ (tpp = triphenylphosphine, ligand)³⁶⁹ or photolysis³⁷⁰ leads to a lactam.

OS II, 76, 371; VIII, 568.

18-18 Stieglitz and Related Rearrangements

Methoxy-de-*N*-chloro-(2/→1/*N*-alkyl)-migno-substitution, and so on



In addition to the reactions discussed at **18-13–18-17**, other rearrangements are known in which an alkyl group migrates from C to N. Certain bicyclic *N*-haloamines (e.g.,

³⁶¹ Donaruma, L.G.; Heldt, W.Z. *Org. React.* **1960**, *11*, 1, pp. 5–14; Smith, P.A.S. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, **1963**, 483–507, pp. 488–493.

³⁶² Gregory, B.J.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* **1970**, 338.

³⁶³ Palmere, R.M.; Conley, R.T.; Rabinowitz, J.L. *J. Org. Chem.* **1972**, *37*, 4095.

³⁶⁴ See, Sugimoto, H.; Yagihashi, F. *J. Chem. Soc. Perkin Trans. 1* **1977**, 2488.

³⁶⁵ Yamabe, S.; Tsuchida, N.; Yamazaki, S. *J. Org. Chem.* **2005**, *70*, 10638.

³⁶⁶ For a review, see Maruoka, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* **1985**, *24*, 668.

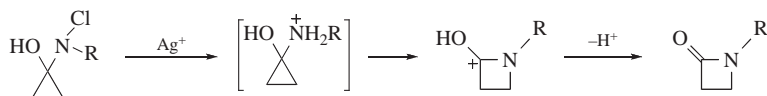
³⁶⁷ Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831; Maruoka, K.; Nakai, S.; Yamamoto, H. *Org. Synth.* **66**, 185.

³⁶⁸ Lanni, E.L.; Bosscher, M.A.; Ooms, B.; Shandro, C.A.; Ellsworth, B.A.; Anderson, C.E. *J. Org. Chem.* **2008**, *73*, 6425.

³⁶⁹ Suda, K.; Sashima, M.; Izutsu, M.; Hino, F. *J. Chem. Soc., Chem. Commun.* **1994**, 949.

³⁷⁰ Post, A.J.; Nwaukwa, S.; Morrison, H. *J. Am. Chem. Soc.* **1994**, *116*, 6439.

N-chloro-2-azabicyclo[2.2.2]octane, above), undergo rearrangement when solvolyzed in the presence of silver nitrate.³⁷¹ This reaction is similar to the *Wagner–Meerwein rearrangement* (**18-1**) and is initiated by the silver-catalyzed departure of the chloride ion.³⁷² Similar reactions have been used for ring expansions and contractions, analogous to those discussed for Reaction **18-3**.³⁷³ An example is the conversion of 1-(*N*-chloroamino)cyclopropanols to β -lactams.³⁷⁴ Methyl prolinate was converted to the 2-piperidone upon treatment with SmI_2 and pivalic acid–THF.³⁷⁵



The name *Stieglitz rearrangement* is generally applied to the rearrangements of trityl *N*-haloamines and

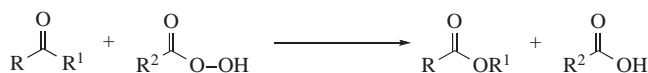


hydroxylamines. These reactions are similar to the rearrangements of alkyl azides (**18-14**), and the name *Stieglitz rearrangement* is also given to the rearrangement of trityl azides. Another similar reaction is the rearrangement undergone by tritylamines when treated with lead tetraacetate ($\text{Ar}_3\text{CNH}_2 \rightarrow \text{Ar}_2\text{C}=\text{NAr}$).³⁷⁶

D. Carbon-to-Oxygen Migrations of R and Ar

18-19 The Baeyer–Villiger Rearrangement³⁷⁷

Oxy-insertion



The treatment of ketones with peroxyacids (e.g., peroxybenzoic or peroxyacetic acid or with other peroxy compounds in the presence of acid catalysts, gives carboxylic esters by migration of an alkyl group oxygen³⁷⁸ and the carboxylic acid parent of the peroxyacid as a byproduct. In other words, there is a $\text{C} \rightarrow \text{O}$ rearrangement, and the reaction is called the *Baeyer–Villiger rearrangement*.³⁷⁹ A particularly good reagent is peroxytrifluoroacetic

³⁷¹ Gassman, P.G.; Fox, B.L. *J. Am. Chem. Soc.* **1967**, 89, 338. See also, Davies, J.W.; Malpass, J.R.; Walker, M.P. *J. Chem. Soc., Chem. Commun.* **1985**, 686; Hoffman, R.V.; Kumar, A.; Buntain, G.A. *J. Am. Chem. Soc.* **1985**, 107, 4731.

³⁷² See Kovacic, P.; Lowery, M.K.; Roskos, P.D. *Tetrahedron* **1970**, 26, 529.

³⁷³ Hoffman, R.V.; Buntain, G.A. *J. Org. Chem.* **1988**, 53, 3316.

³⁷⁴ Wasserman, H.H.; Glazer, E.A.; Hearn, M.J. *Tetrahedron Lett.* **1973**, 4855.

³⁷⁵ Honda, T.; Ishikawa, F. *Chem. Commun.* **1999**, 1065.

³⁷⁶ Sisti, A.J.; Milstein, S.R. *J. Org. Chem.* **1974**, 39, 3932.

³⁷⁷ For a review, see Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737. For a review of green procedures, see ten Brink, G.-J.; Arends, I.W.C.E.; Sheldon, R.A. *Chem. Rev.* **2004**, 104, 4105.

³⁷⁸ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1665–1667.

³⁷⁹ Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, **1990**, pp. 186–195; Plesnicar, B. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, **1978**, pp. 254–267; House, H.O. *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin, NY, **1972**, pp. 321–329; Lewis, S.N. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, **1969**, pp. 237–244. Also see, Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* **2001**, 66, 1193.

acid. Reactions with this reagent are rapid and clean, giving high yields of product, although it is often necessary to add a buffer (e.g., Na_2HPO_4), to prevent transesterification of the product with trifluoroacetic acid that is also formed during the reaction. The reaction is often applied to cyclic ketones to give lactones.³⁸⁰ Hydrogen peroxide has been used to convert cyclic ketones to lactones using a catalytic amount of MeReO_3 ³⁸¹ or a diselenide catalyst.³⁸² Heterogeneous catalysts are used for the *Baeyer–Villiger reaction*.³⁸³ Transition metal catalysts have been used with peroxyacids to facilitate the oxidation.³⁸⁴ Polymer-supported peroxy acids have been used,³⁸⁵ and solvent-free *Bayer–Villiger reactions* are known.³⁸⁶ Potassium peroxomonosulfate supported on acidic silica gel has been used.³⁸⁷

Enantioselective synthesis³⁸⁸ of chiral lactones from achiral ketones has been achieved by the use of enzymes³⁸⁹ and other asymmetric reactions are known.³⁹⁰ Chiral Pd complexes give chiral lactones from cyclic ketones with high enantioselectivity.³⁹¹ Other chiral catalysts include those based on Al.³⁹² *Baeyer–Villiger oxidation* of chiral substrates with *m*-chloroperoxybenzoic acid (mcpba) also leads to chiral lactones.³⁹³

For acyclic compounds, R' must usually be secondary, tertiary, or vinylic, although primary R' has been rearranged with peroxytrifluoroacetic acid,³⁹⁴ with $\text{I}_2\text{—H}_2\text{O}_2$,³⁹⁵ $\text{BF}_3\text{—H}_2\text{O}_2$,³⁹⁶ and with $\text{K}_2\text{S}_2\text{O}_8\text{—H}_2\text{SO}_4$.³⁹⁷ For unsymmetrical ketones, the approximate order of migration is tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl. Since the methyl group has a low migrating ability, the reaction provides a means of cleaving a methyl ketone ($\text{R}'\text{COMe}$) to produce an alcohol or phenol ($\text{R}'\text{OH}$, by hydrolysis of the ester $\text{R}'\text{OCOMe}$). The migrating ability of aryl groups is increased by electron-donating and decreased by electron-withdrawing substituents.³⁹⁸ There is a preference of *anti*- over *gauche* migration.³⁹⁹

³⁸⁰ See Krow, G.R. *Tetrahedron* **1981**, 37, 2697.

³⁸¹ Phillips, A.M.F.; Romão, C. *Eur. J. Org. Chem.* **1999**, 1767. In an ionic liquid, see Bernini, R.; Coratti, A.; Fabrizi, G.; Goggiamani, A. *Tetrahedron Lett.* **2003**, 44, 8991.

³⁸² ten Brink, G.-J.; Vis, J.-M.; Arends, I.W.C.E.; Sheldon, R.A. *J. Org. Chem.* **2001**, 66, 2429.

³⁸³ For a review, see Jiménez-Sanchidrián, C.; Ruiz, J.R. *Tetrahedron* **2008**, 64, 2011.

³⁸⁴ Alam, M.M.; Varala, R.; Adapa, S.R. *Synth. Commun.* **2003**, 33, 3035.

³⁸⁵ Lambert, A.; Elings, J.A.; Macquarrie, D.J.; Carr, G.; Clark, J.H. *Synlett* **2000**, 1052. See Hagiwara, H.; Nagatomo, H.; Yoshii, F.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2645.

³⁸⁶ Yakura, T.; Kitano, T.; Ikeda, M.; Uenishi, J. *Tetrahedron Lett.* **2002**, 43, 6925.

³⁸⁷ González-Núñez, M.E.; Mello, R.; Olmos, A.; Asensio, G. *J. Org. Chem.* **2005**, 70, 10879. In supercritical CO_2 , see González-Núñez, M.E.; Mello, R.; Olmos, A.; Asensio, G. *J. Org. Chem.* **2006**, 71, 6432.

³⁸⁸ See Bolm, C.; Frison, J.-C.; Zhang, Y.; Wulff, W.D. *Synlett* **2004**, 1619.

³⁸⁹ See Mihovilovic, M.D.; Müller, B.; Kayser, M.M.; Stewart, J.D.; Stanetty, P. *Synlett* **2002**, 703. See Clouthier, C.M.; Kayser, M.M.; Reetz, M.T. *J. Org. Chem.* **2006**, 71, 8431; Pazmiño, D.E.T.; Snajdrova, R.; Baas, B.-J.; Ghobrial, M.; Mihovilovic, M.D.; Fraaije, M.W. *Angew. Chem. Int. Ed.* **2008**, 47, 2275.

³⁹⁰ See Watanabe, A.; Uchida, T.; Ito, K.; Katsuki, T. *Tetrahedron Lett.* **2002**, 43, 4481; Murhashi, S.-I.; Ono, S.; Imada, Y. *Angew. Chem. Int. Ed.* **2002**, 41, 2366.

³⁹¹ Malkov, A.V.; Friscourt, F.; Bell, M.; Swarbrick, M.E.; Koovský, P. *J. Org. Chem.* **2008**, 73, 3996.

³⁹² Frison, J.-C.; Palazzi, C.; Bolm, C. *Tetrahedron* **2006**, 62, 6700.

³⁹³ Hunt, K.W.; Grieco, P.A. *Org. Lett.* **2000**, 2, 1717.

³⁹⁴ Emmons, W.D.; Lucas, G.B. *J. Am. Chem. Soc.* **1955**, 77, 2287.

³⁹⁵ Gaikwad, D.D.; Dake, S.A.; Kulkarni, R.S.; Jadhav, W.N.; Kakde, S.B.; Pawar, R.P. *Synth. Commun.* **2007**, 37, 4093.

³⁹⁶ McClure, J.D.; Williams, P.H. *J. Org. Chem.* **1962**, 27, 24.

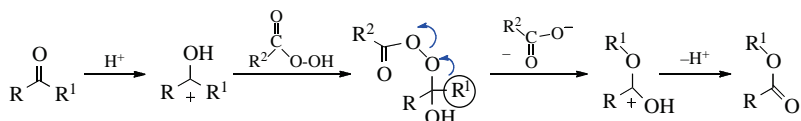
³⁹⁷ Deno, N.C.; Billups, W.E.; Kramer, K.E.; Lastomirsky, R.R. *J. Org. Chem.* **1970**, 35, 3080. See Chrobok, A. *Tetrahedron* **2010**, 66, 6212.

³⁹⁸ See Noyori, R.; Sato, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1983**, 56, 2661.

³⁹⁹ Snowden, M.; Bermudez, A.; Kelly, D.R.; Radkiewicz-Poutsma, J.L. *J. Org. Chem.* **2004**, 69, 7148.

Enolizable β -diketones do not react. α -Diketones can be converted to anhydrides.⁴⁰⁰ With aldehydes, migration of hydrogen gives the carboxylic acid, and this is a way of accomplishing Reaction **19-23**. Migration of the other group would give formates, but this seldom happens, though aryl aldehydes have been converted to formates with H_2O_2 and a selenium compound⁴⁰¹ (see also, the *Dakin Reaction* in **19-11**).

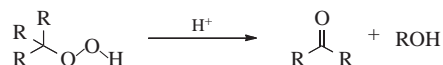
The mechanism⁴⁰² is similar to those of the analogous reactions with hydrazoic acid (**18-16** with ketones) and diazomethane (**18-8**):



One important piece of evidence for this mechanism was that benzophenone- ^{18}O gave ester entirely labeled in the carbonyl oxygen, with none in the alkoxy oxygen.⁴⁰³ Carbon-14 isotope-effect studies on acetophenones have shown that migration of aryl groups takes place in the rate-determining step,⁴⁰⁴ demonstrating that migration of Ar is concerted with departure of OCOR^2 .⁴⁰⁵ It is hardly likely that migration would be the slow step if the leaving group departed first to give an ion with a positive charge on an oxygen atom, which would be a highly unstable species.

18-20 Rearrangement of Hydroperoxides

C-Alkyl-O-hydroxy-elimination



Hydroperoxides (R = alkyl, aryl, or hydrogen) can be cleaved by proton or Lewis acids in a reaction whose principal step is a rearrangement.⁴⁰⁶ The reaction has also been applied to peroxy esters ($\text{R}_3\text{COOCOR}'$), but less often. When aryl and alkyl groups are both present, migration of aryl dominates. It is not necessary actually to prepare and isolate hydroperoxides. The reaction takes place when the alcohols are treated with H_2O_2 and acids. Migration of an alkyl group of a primary hydroperoxide provides a means for converting an alcohol to its next lower homolo ($\text{RCH}_2\text{OOH} \rightarrow \text{CH}_2=\text{O} + \text{ROH}$).

⁴⁰⁰ See Cullis, P.M.; Arnold, J.R.P.; Clarke, M.; Howell, R.; DeMira, M.; Naylor, M.; Nicholls, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1088.

⁴⁰¹ Syper, L. *Synthesis* **1989**, 167. See also, Godfrey, I.M.; Sargent, M.V.; Elix, J.A. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1353.

⁴⁰² Proposed by Criegee, R. *Liebigs Ann. Chem.* **1948**, 560, 127.

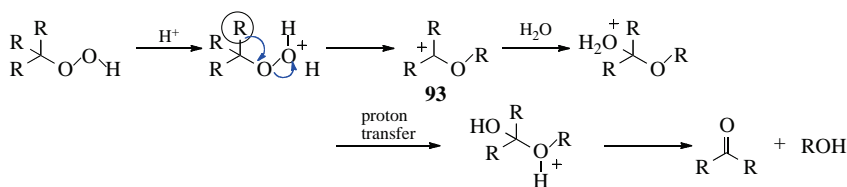
⁴⁰³ Doering, W. von E.; Dorfman, E. *J. Am. Chem. Soc.* **1953**, 75, 5595. Also see Smith, P.A.S. in de Mayo, P. *Molecular Rearrangements* Vol. 1, Wiley, NY, **1963**, pp. 578–584.

⁴⁰⁴ Palmer, B.W.; Fry, A. *J. Am. Chem. Soc.* **1970**, 92, 2580. See Mitsuhashi, T.; Miyadera, H.; Simamura, O. *Chem. Commun.* **1970**, 1301; Winnik, M.A.; Stoute, V.; Fitzgerald, P. *J. Am. Chem. Soc.* **1974**, 96, 1977.

⁴⁰⁵ Also see Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1972**, 37, 2953.

⁴⁰⁶ Yablokov, V.A. *Russ. Chem. Rev.* **1980**, 49, 833; Lee, J.B.; Uff, B.C. *Q. Rev. Chem. Soc.* **1967**, 21, 429, 445–449.

The mechanism is as follows⁴⁰⁷:



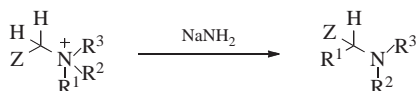
The last step is hydrolysis of the unstable hemiacetal. Alkoxy carbocation intermediates (**93**, R = alkyl) have been isolated in superacid solution⁴⁰⁸ at low temperatures, and their structures proved by NMR.⁴⁰⁹ The protonated hydroperoxides could not be observed in these solutions, evidently reacting immediately on formation.

OS V, 818.

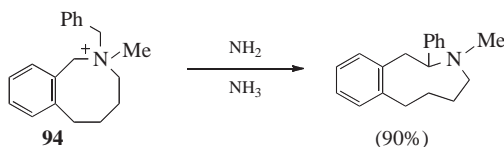
E. Nitrogen-to-Carbon, Oxygen-to-Carbon, and Sulfur-to-Carbon Migration

18-21 The Stevens Rearrangement

Hydron-(2/N→1/alkyl)-migrato-detachment



In the *Stevens rearrangement*,⁴¹⁰ a quaternary ammonium salt containing an electron-withdrawing group Z on one of the carbons attached to the nitrogen is treated with a strong base (e.g., NaOR or NaNH₂) to give a rearranged tertiary amine. The Z group may be RCO, ROOC, or phenyl.⁴¹¹ The most common migrating groups are allylic, benzylic, benzhydryl, 3-phenylpropargyl, and phenacyl, though even methyl migrates to a sufficiently negative center. Migration of aryl is rare, but has been reported.⁴¹² When an allylic group migrates, it may or may not involve an allylic rearrangement within the migrating group (see Reaction **18-35**), depending on the substrate and reaction conditions. The reaction has been used for ring enlargement,⁴¹³ illustrated by the rearrangement of **94**.



⁴⁰⁷ See Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* **1981**, 22, 3389.

⁴⁰⁸ See Olah, G.A.; Parker, D.G.; Yoneda, N. *Angew. Chem. Int. Ed.* **1978**, 17, 909.

⁴⁰⁹ Sheldon, R.A.; van Doorn, J.A. *Tetrahedron Lett.* **1973**, 1021.

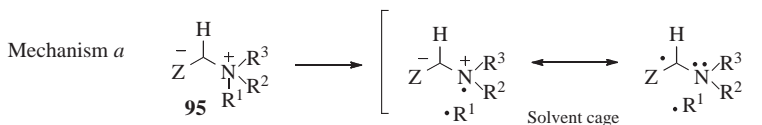
⁴¹⁰ For syntheses, see Vanecko, J.A.; Wan, H.; West, F.G. *Tetrahedron* **2006**, 62, 1043.

⁴¹¹ Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* **1971**, 3, 297; Pine, S.H. *Org. React.* **1970**, 18, 403; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, **1973**, pp. 81–116; Wilt, J.W. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, **1973**, pp. 448–458; Iwai, I. *Mech. Mol. Migr.* **1969**, 2, 73, see pp. 105–113; Stevens, T.S. *Prog. Org. Chem.* **1968**, 7, 48.

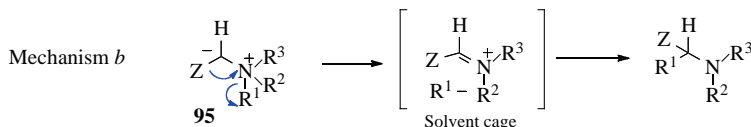
⁴¹² Heaney, H.; Ward, T.J. *Chem. Commun.* **1969**, 810; Truce, W.E.; Heuring, D.L. *Chem. Commun.* **1969**, 1499.

⁴¹³ Elmasmodi, A.; Cotellet, P.; Barbry, D.; Hasiak, B.; Couturier, D. *Synthesis* **1989**, 327.

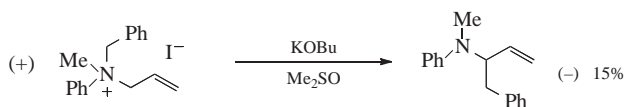
The mechanism has been the subject of much study.⁴¹⁴ The rearrangement is intramolecular, as shown by cross-over experiments, by ¹⁴C labeling,⁴¹⁵ and by the fact that retention of configuration is found at R¹.⁴¹⁶ The first step is loss of the acidic proton to give the ylid (**95**), which has been isolated.⁴¹⁷ The finding⁴¹⁸ that CIDNP is observed⁴¹⁹ in many instances shows that in these cases the product is formed directly from a free-radical precursor. The following radical pair mechanism was proposed⁴²⁰:



The radicals do not drift apart because the solvent cage holds them together. According to this mechanism, the radicals must recombine rapidly in order to account for the fact that R¹ does not racemize. Other evidence in favor of mechanism *a* is that in some cases small amounts of coupling products (R¹–R¹) have been isolated,⁴²¹ which would be expected if some •R¹ leaked from the solvent cage. However, not all the evidence is easily compatible with mechanism *a*.⁴²² It is possible that another mechanism (*b*), similar to mechanism *a*, but



involving ion pairs in a solvent cage instead of radical pairs, operates in some cases. A third possible mechanism would be a concerted 1,2-shift,⁴²³ but the orbital symmetry principle requires that this take place with inversion at R¹.⁴²⁴ (see Reaction **18-30** and [1,5]-migration). *Since the actual migration takes place with retention, it cannot, according to this argument, proceed by a concerted mechanism.* However, in the case where the migrating group is allylic, a concerted mechanism can also operate (Reaction **18-35**). An interesting finding compatible with all three mechanisms is that optically active allylbenzylmethylphenylammonium iodide (asymmetric nitrogen, see Sec. 4.C, category 3) gave an optically active product⁴²⁵:



⁴¹⁴ See Heard, G.L.; Yates, B.F. *Aust. J. Chem.* **1994**, *47*, 1685.

⁴¹⁵ Stevens, T.S. *J. Chem. Soc.* **1930**, 2107; Johnstone, R.A.W.; Stevens, T.S. *J. Chem. Soc.* **1955**, 4487.

⁴¹⁶ Brewster, J.H.; Kline, M.W. *J. Am. Chem. Soc.* **1952**, *74*, 5179; Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* **1969**, 3415.

⁴¹⁷ Jemison, R.W.; Mageswaran, S.; Ollis, W.D.; Potter, S.E.; Pretty, A.J.; Sutherland, I.O.; Thebtaranonth, Y. *Chem. Commun.* **1970**, 1201.

⁴¹⁸ See Lepley, A.R.; Becker, R.H.; Giumanini, A.G. *J. Org. Chem.* **1971**, *36*, 1222.

⁴¹⁹ For a review of the application of CIDNP to rearrangement reactions, see Lepley, A.R. in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, **1973**, pp. 323–384.

⁴²⁰ Ollis, W.D.; Rey, M.; Sutherland, I.O. *J. Chem. Soc. Perkin Trans. 1* **1983**, 1009, 1049.

⁴²¹ Hennion, G.F.; Shoemaker, M.J. *J. Am. Chem. Soc.* **1970**, *92*, 1769.

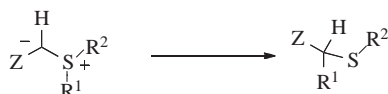
⁴²² See, for example, Pine, S.H.; Catto, B.A.; Yamagishi, F.G. *J. Org. Chem.* **1970**, *35*, 3663.

⁴²³ For evidence against this mechanism, see Jenny, E.F.; Druey, J. *Angew. Chem. Int. Ed.* **1962**, *1*, 155.

⁴²⁴ Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, **1970**, p. 131.

⁴²⁵ Hill, R.K.; Chan, T. *J. Am. Chem. Soc.* **1966**, *88*, 866.

The *Sommelet–Hauser rearrangement* competes when Z is an aryl group (see Reaction 13-31). *Hofmann elimination* competes when one of the R groups contains a β hydrogen atom (Reaction 17-7 and 17-8).



Sulfur ylids containing a Z group give an analogous rearrangement (see the reaction), sometimes referred to as a *Stevens rearrangement*.⁴²⁶ In this case too, there is much evidence (including CIDNP) that a radical-pair cage mechanism is operating,⁴²⁷ except that when the migrating group is allylic, the mechanism may be different (see Reaction 18-35).



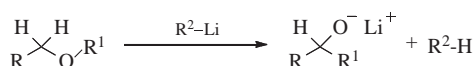
Another reaction with a similar mechanism⁴²⁸ is the *Meisenheimer rearrangement*,⁴²⁹ in which certain tertiary amine oxides rearrange on heating to give substituted hydroxylamines (see reaction).⁴³⁰ The migrating group R¹ is almost always allylic or benzylic.⁴³¹ Both R² and R³ may be alkyl or aryl, but if one of the R groups contains a β hydrogen, *Cope elimination* (Reaction 17-9) often competes. In a related reaction, when 2-methylpyridine N-oxides are treated with trifluoroacetic anhydride, the *Boekelheide reaction* occurs to give 2-hydroxymethylpyridines.⁴³²

Certain tertiary benzylic amines, when treated with BuLi, undergo a rearrangement analogous to the *Wittig rearrangement* (Reaction 18-22, e.g., PhCH₂NPh₂ → Ph₂CHNPh).⁴³³ Only aryl groups migrate in this reaction.

Isocyanides, when heated in the gas phase or in nonpolar solvents, undergo a 1,2-intramolecular rearrangement to nitriles (RNC → RCN).⁴³⁴ In polar solvents, the mechanism is different.⁴³⁵

18-22 The Wittig Rearrangement⁴³⁶

Hydron-(2/O → 1/alkyl)-migro-detachment



⁴²⁶ Olsen, R.K.; Currie, Jr., J.O. in Patai, S. *The Chemistry of The Thiol Group*, pt. 2, Wiley, NY, **1974**, pp. 561–566. See Okazaki, Y.; Asai, T.; Ando, F.; Koketsu, J. *Chem. Lett.* **2006**, 35, 98.

⁴²⁷ See Iwamura, H.I.; Iwamura, M.; Nishida, T.; Yoshida, M.; Nakayama, T. *Tetrahedron Lett.* **1971**, 63.

⁴²⁸ See Ostermann, G.; Schölkopf, U. *Liebigs Ann. Chem.* **1970**, 737, 170; Lorand, J.P.; Grant, R.W.; Samuel, P.A.; O'Connell, E.; Zaro, J. *Tetrahedron Lett.* **1969**, 4087.

⁴²⁹ Johnstone, R.A.W. *Mech. Mol. Migr.* **1969**, 2, 249. See Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2327.

⁴³⁰ See Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *Tetrahedron Asymmetry*, **1998**, 9, 1995.

⁴³¹ See Khuthier, A.; Al-Mallah, K.Y.; Hanna, S.Y.; Abdulla, N.I. *J. Org. Chem.* **1987**, 52, 1710, and references cited therein.

⁴³² Fontenas, C.; Bejan, E.; Haddon, H.A.; Balavoine, G.G.A. *Synth. Commun.* **1995**, 25, 629.

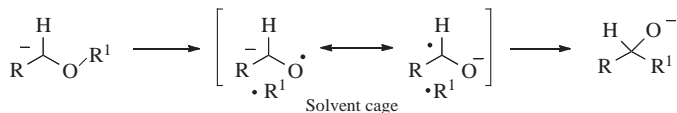
⁴³³ Eisch, J.J.; Kovacs, C.A.; Chobe, P. *J. Org. Chem.* **1989**, 54, 1275.

⁴³⁴ See Pakusch, J.; Rüchardt, C. *Chem. Ber.* **1991**, 124, 971 and references cited therein.

⁴³⁵ Meier, M.; Rüchardt, C. *Chimia* **1986**, 40, 238.

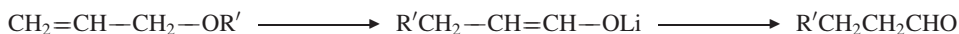
⁴³⁶ See Hiersemann, M.; Abraham, L.; Pollex, A. *Synlett* **2003**, 1088.

The rearrangement of ethers upon treatment with alkyllithium reagents is called the *Wittig rearrangement* (not to be confused with the *Wittig Reaction*, **16-44**) and is similar to **18-21**.⁴⁴¹ However, a stronger base is required (e.g., phenyllithium or sodium amide). The R and R' groups may be alkyl,⁴³⁷ aryl, or vinylic.⁴³⁸ Also, one of the hydrogen atoms may be replaced by an alkyl or aryl group, in which case the product is the salt of a tertiary alcohol. Migratory aptitudes here are allylic, benzylic > ethyl > methyl > phenyl.⁴³⁹ The stereospecificity of the *1,2-Wittig rearrangement* has been discussed.⁴⁴⁰ The following radical-pair mechanism⁴⁴¹ (similar to mechanism *a* of Reaction **18-21**) is likely, after removal of the proton by the base. One of the



the radical pair is a ketyl. Evidence for this mechanism includes (1) the rearrangement is largely intramolecular; (2) migratory aptitudes are in the order of free-radical stabilities, not of carbanion stabilities⁴⁴² (which rules out an ion-pair mechanism similar to mechanism *b* of Reaction **18-21**); (3) aldehydes are obtained as side products⁴⁴³; (4) partial racemization of R' has been observed⁴⁴⁴ (the remainder of the product retained its configuration); (5) cross-over products have been detected⁴⁴⁵; and (6) when ketyl radicals and R• radicals from different precursors were brought together, similar products resulted.⁴⁴⁶ However, there is evidence that at least in some cases the radical-pair mechanism accounts for only a portion of the product, and some kind of concerted mechanism can also take place.⁴⁴⁷ Most of the above investigations were carried out with systems where R' is alkyl, but a radical-pair mechanism has also been suggested for the case where R' is aryl.⁴⁴⁸ When R' is allylic a concerted mechanism can operate (Reaction **18-35**).

When R is vinylic it is possible, by using a combination of an alkyllithium and *t*-BuOK, to get migration to the γ carbon (as well as to the α carbon), producing an enolate that, on hydrolysis, gives an aldehyde⁴⁴⁹:



⁴³⁷ See Bailey, W.F.; England, M.D.; Mealy, M.J.; Thongsornkleeb, C.; Teng, L. *Org. Lett.* **2000**, 2, 489.

⁴³⁸ For migration of vinyl, see Rautenstrauch, V.; Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* **1974**, 96, 2576. For rearrangement of an α -trimethylsilyl allyl ether see Maleczka, Jr., R.E.; Geng, F. *Org. Lett.* **1999**, 1, 1115.

⁴³⁹ Wittig, G. *Angew. Chem.* **1954**, 66, 10; Solov'yanov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Chem. Soc., Chem. Commun.* **1987**, 23, 1232.

⁴⁴⁰ Maleczka Jr., R.E.; Geng, F. *J. Am. Chem. Soc.* **1998**, 120, 8551.

⁴⁴¹ See Schöllkopf, U. *Angew. Chem. Int. Ed.* **1970**, 9, 763.

⁴⁴² See Schäfer, H.; Schöllkopf, U.; Walter, D. *Tetrahedron Lett.* **1968**, 2809.

⁴⁴³ See Cast, J.; Stevens, T.S.; Holmes, J. *J. Chem. Soc.* **1960**, 3521.

⁴⁴⁴ Hebert, E.; Welvert, Z. *J. Chem. Soc., Chem. Commun.* **1980**, 1035; *Nouv. J. Chim.* **1981**, 5, 327.

⁴⁴⁵ Lansbury, P.T.; Pattison, V.A. *J. Org. Chem.* **1962**, 27, 1933; *J. Am. Chem. Soc.* **1962**, 84, 4295.

⁴⁴⁶ Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* **1973**, 95, 6870.

⁴⁴⁷ Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* **1976**, 98, 1526. For evidence against this, see Hebert, E.; Welvert, Z.; Ghelfenstein, M.; Szwarc, H. *Tetrahedron Lett.* **1983**, 24, 1381.

⁴⁴⁸ Eisch, J.J.; Kovacs, C.A.; Rhee, S. *J. Organomet. Chem.* **1974**, 65, 289.

⁴⁴⁹ Schlosser, M.; Strunk, S. *Tetrahedron* **1989**, 45, 2649.

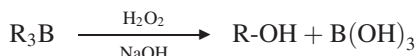
An *aza-Wittig rearrangement* is also known.⁴⁵⁰ Other [2,3]-rearrangements are discussed in Reaction 18-35.

There are no OS references, but see OS VIII, 501, for a related reaction.

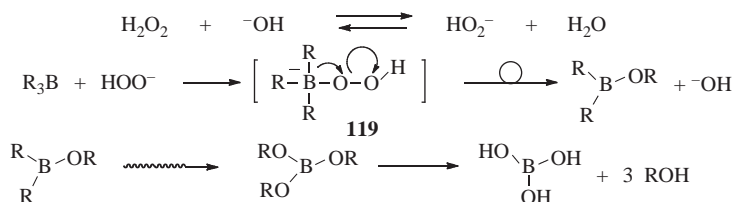
F. Boron-to-Carbon Migrations⁴⁵¹

For another reaction involving boron-to-carbon migration, see 10-73.

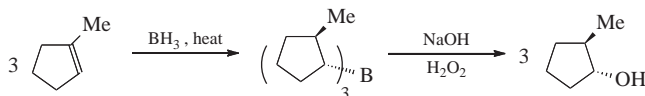
18-23 Conversion of Boranes to Alcohols



Oxidation of trialkylboranes (see Reaction 15-16) uses NaOH and H₂O₂, which react to give the hydroperoxide anion, (HOO[−]). Reaction of the organoborane with basic H₂O₂ (via HOO[−]) leads to an ate-complex, and subsequent B → O rearrangement of an alkyl group on boron to a peroxy oxygen, with expulsion of hydroxide, leads to a borate, and then an alcohol after hydrolysis. The proposed mechanism⁴⁵² is shown in which a trialkylborane is converted to 3 molar equivalents of the alcohol, along with boric acid.



Using the hydroboration reaction in 15-16, this procedure converts alkenes to an *anti-Markovnikov* borane, and oxidation leads to the *anti-Markovnikov alcohol*. An example is the conversion of methylcyclopentene to *trans*-2-methylcyclopentanol.⁴⁵³ Formation of the organoborane proceeds via a cis-addition of B—H, placing the boron trans to the methyl group, and stereoselective oxidation and B → O rearrangement leads to retention of configuration in the alcohol, as shown.



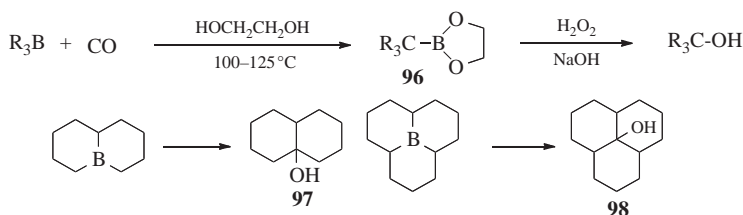
⁴⁵⁰ Anderson, J.C.; Siddons, D.C.; Smith, S.C.; Swarbrick, M.E. *J. Chem. Soc., Chem. Commun.* **1995**, 1835; Ahman, J.; Somfai, P. *J. Am. Chem. Soc.* **1994**, 116, 9781.

⁴⁵¹ Matteson, D.S. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, **1984**, pp. 307–409, pp. 346–387; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, pp. 256–301; Negishi, E.; Idacavage, M.J. *Org. React.* **1985**, 33, 1; Suzuki, A. *Top. Curr. Chem.* **1983**, 112, 67; Pelter, A. *Chem. Soc. Rev.* **1982**, 11, 191; Cragg, G.M.L.; Koch, K.R. *Chem. Soc. Rev.* **1977**, 6, 393; Weill-Raynal, J. *Synthesis* **1976**, 633; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, **1973**, pp. 249–300; Paetzold, P.I.; Grundke, H. *Synthesis* **1973**, 635.

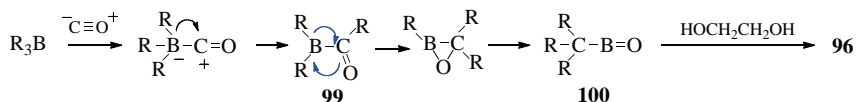
⁴⁵² Brown, H.C. *Hydroboration*, W.A. Benjamin, New York, **1962**. See Kuivila, H.G. *J. Am. Chem. Soc.* **1954**, 76, 870; **1955**, 77, 4014; Kuivila, H.G.; Wiles, R.A. *J. Am. Chem. Soc.* **1955**, 77, 4830; Kuivila, H.G.; Armour, A.G. *J. Am. Chem. Soc.* **1957**, 79, 5659; Wechter, W.J. *Chem. & Ind. (London)* **1959**, 294.

⁴⁵³ Zweifel, G.; Brown, H.C. *Org. React.* **1964**, 13, 1.

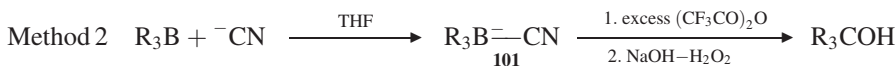
Trialkylboranes can be prepared from alkenes by Reaction **15-16**, and they react with carbon monoxide⁴⁵⁴ at 100–125 °C in the presence of ethylene glycol to give the 2-bora-1,3-dioxolanes (**96**), which are easily oxidized (Reaction **12-27**) to tertiary alcohols.⁴⁵⁵ The R groups may be primary, secondary, or tertiary, and may be the same or different.⁴⁵⁶ Yields are high and the reaction is quite useful, especially for the preparation of sterically hindered alcohols (e.g., tricyclohexylcarbinol, **97** and tri-2-norbornylcarbinol, **98**), which are difficult to prepare by Reaction **16-24**. Heterocycles in which boron is a ring atom react similarly (except that high CO pressures are required), and cyclic alcohols can be obtained from these substrates.⁴⁵⁷ The preparation of such heterocyclic boranes was discussed at Reaction **15-16**. The overall conversion of a diene or triene to a cyclic alcohol has been described by H.C. Brown as “stitching” with boron and “riveting” with carbon.



The mechanism has been shown to be intramolecular by the failure to find cross-over products when mixtures of boranes are used.⁴⁵⁸ The following scheme, involving three boron-to-carbon migrations, to **99** and then to **100** has been suggested.



The purpose of the ethylene glycol is to intercept the boronic anhydride (**100**), which otherwise forms polymers that are difficult to oxidize. As will be seen in Reaction **18-23** and **18-24**, it is possible to stop the reaction after only one or two migrations have taken place.



There are two other methods for achieving the conversion $\text{R}_3\text{B} \rightarrow \text{R}_3\text{COH}$, which often give better results: (1) treatment with α,α -dichloromethyl methyl ether and the base lithium triethylcarboxide⁴⁵⁹ (2) treatment with a suspension of sodium cyanide in THF

⁴⁵⁴ See Negishi, E. *Intra-Sci. Chem. Rep.* **1973**, 7(1), 81; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, **1972**, pp. 343–371; *Acc. Chem. Res.* **1969**, 2, 65.

⁴⁵⁵ See Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* **1986**, 51, 4925.

⁴⁵⁶ Negishi, E.; Brown, H.C. *Synthesis* **1972**, 197.

⁴⁵⁷ Brown, H.C.; Negishi, E.; Dickason, W.C. *J. Org. Chem.* **1985**, 50, 520, and references cited therein.

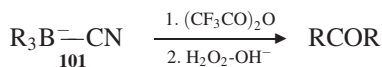
⁴⁵⁸ Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* **1967**, 89, 4528.

⁴⁵⁹ Brown, H.C.; Carlson, B.A. *J. Org. Chem.* **1973**, 38, 2422; Brown, H.C.; Katz, J.; Carlson, B.A. *J. Org. Chem.* **1973**, 38, 3968.

followed by reaction of the resulting trialkylcyanoborate (**101**) with an excess (>2 equiv) of trifluoroacetic anhydride.⁴⁶⁰ All the above migrations take place with retention of configuration at the migrating carbon.⁴⁶¹

Several other methods for the conversion of boranes to tertiary alcohols are also known.⁴⁶²

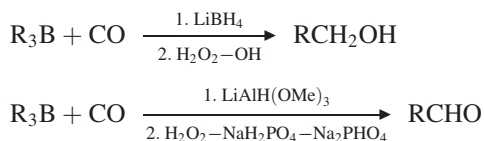
If the reaction between trialkylboranes and carbon monoxide (**18-23**) is carried out in the presence of water followed by addition of NaOH, the product is a secondary alcohol. If H₂O₂ is added along with the NaOH, the corresponding ketone is obtained instead.⁴⁶³ Various functional groups (e.g., OAc, COOR, CN) may be present in R without being affected,⁴⁶⁴ although if they are in the α or β position relative to the boron atom, difficulties



may be encountered. The use of an equimolar amount of trifluoroacetic anhydride leads to the ketone rather than the tertiary alcohol.⁴⁶⁵ By this procedure the xylboranes (RR'R²B, where R² = hexyl) can be converted to unsymmetrical ketones (RCOR').⁴⁶⁶ Variations of this methodology have been used to prepare optically active alcohols.⁴⁶⁷ For another conversion of trialkylboranes to ketones see Reaction **18-26**.⁴⁶⁸

OS VII, 427. Also see, OS VI, 137.

18-24 Conversion of Boranes to Primary Alcohols, Aldehydes, or Carboxylic Acids



When the reaction between a trialkylborane and carbon monoxide (**18-23**) is carried out in the presence of a reducing agent (e.g., lithium borohydride or potassium triisopropoxyborohydride), the reduction agent intercepts the intermediate (**99**), so that only one boron→carbon migration takes place, and the product is hydrolyzed to a primary alcohol or oxidized to an aldehyde.⁴⁶⁹ This procedure wastes two of the three R groups, but this problem can be avoided by the use of B-alkyl-9-BBN derivatives (see Reaction **15-16**).

⁴⁶⁰ Pelter, A.; Hutchings, M.G.; Smith, K.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* **1975**, 145, and references cited therein.

⁴⁶¹ See, however, Pelter, A.; Maddocks, P.J.; Smith, K. *J. Chem. Soc., Chem. Commun.* **1978**, 805.

⁴⁶² See Pelter, A.; Rao, J.M. *J. Organomet. Chem.* **1985**, 285, 65; Junchai, B.; Hongxun, D. *J. Chem. Soc., Chem. Commun.* **1990**, 323.

⁴⁶³ Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* **1967**, 89, 2738.

⁴⁶⁴ Brown, H.C.; Kabalka, G.W.; Rathke, M.W. *J. Am. Chem. Soc.* **1967**, 89, 4530.

⁴⁶⁵ Pelter, A.; Smith, K.; Hutchings, M.G.; Rowe, K. *J. Chem. Soc. Perkin Trans. 1* **1975**, 129; See also, Mallison, P.R.; White, D.N.J.; Pelter, A.; Rowe, K.; Smith, K. *J. Chem. Res. (S)*, **1978**, 234. See also, Ref. 460.

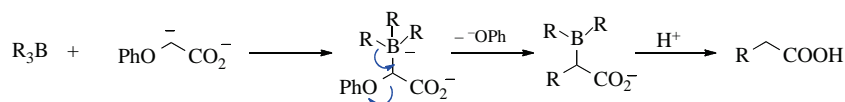
⁴⁶⁶ See Brown, H.C.; Bakshi, R.K.; Singaram, B. *J. Am. Chem. Soc.* **1988**, 110, 1529.

⁴⁶⁷ See Matteson, D.S. *Mol. Struct. Energ.* **1988**, 5, 343; *Acc. Chem. Res.* **1988**, 21, 294; *Synthesis* **1986**, 973, pp. 980–983.

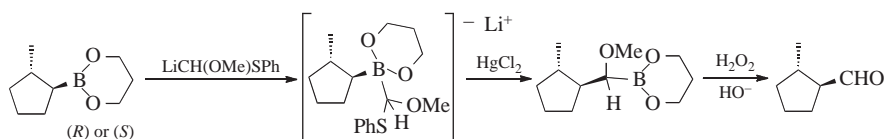
⁴⁶⁸ See Pelter, A.; Rao, J.M. *J. Organomet. Chem.* **1985**, 285, 65; Brown, H.C.; Bhat, N.G.; Basavaiah, D. *Synthesis* **1983**, 885; Narayana, C.; Periasamy, M. *Tetrahedron Lett.* **1985**, 26, 6361.

⁴⁶⁹ Brown, H.C.; Hubbard, J.L.; Smith, K. *Synthesis* **1979**, 701, and references cited therein. See Hubbard, J.L.; Smith, K. *J. Organomet. Chem.* **1984**, 276, C41.

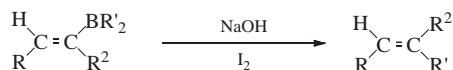
Since only the 9-alkyl group migrates, this method permits the conversion in high yield of an alkene to a primary alcohol or aldehyde containing one more carbon.⁴⁷⁰ When B-alkyl-9-BBN derivatives are treated with CO and lithium tri-*tert*-butoxyaluminum hydride,⁴⁷¹ other functional groups (e.g., CN and ester) can be present in the alkyl group without being reduced.⁴⁷² Boranes can be directly converted to carboxylic acids by reaction with the dianion of phenoxyacetic acid.⁴⁷³



Boronic esters $[\text{RB}(\text{OR}')_2]$ react with methoxy(phenylthio)methyl lithium $[\text{LiCH}(\text{OMe})\text{SPh}]$ to give salts, which, after treatment with HgCl_2 , and then H_2O_2 , yield aldehydes.⁴⁷⁴ This synthesis has been made enantioselective, with high ee values ($>99\%$), by the use of an optically pure boronic ester,⁴⁷⁵ for example:



18-25 Conversion of Vinylic Boranes to Alkenes



The reaction between trialkylboranes and iodine to give alkyl iodides was mentioned at **12-31**. When the substrate contains a vinylic group, the reaction takes a different course,⁴⁷⁶ with one of the R' groups migrating to the carbon, to give alkenes.⁴⁷⁷ The reaction is stereospecific in two senses: (1) if the groups R and R'' are cis in the starting compound, they will be trans in the product; (2) there is retention of configuration within the migrating group R' .⁴⁷⁸ Since vinylic boranes can be prepared from alkynes (Reaction **15-16**), this is a method for the addition of R' and H to a triple bond. If $\text{R}^2 = \text{H}$, the product is a (*Z*)-alkene. The mechanism is believed to involve an iodonium intermediate, (e.g., **102**) and attack by iodide on boron. When R' is vinylic, the product is a conjugated diene.⁴⁷⁹

⁴⁷⁰ Brown, H.C.; Knights, E.F.; Coleman, R.A. *J. Am. Chem. Soc.* **1969**, *91*, 2144.

⁴⁷¹ Brown, H.C.; Coleman, R.A. *J. Am. Chem. Soc.* **1969**, *91*, 4606.

⁴⁷² See Negishi, E.; Yoshida, T.; Silveira, Jr., A.; Chiou, B.L. *J. Org. Chem.* **1975**, *40*, 814.

⁴⁷³ Hara, S.; Kishimura, K.; Suzuki, A.; Dhillon, R.S. *J. Org. Chem.* **1990**, *55*, 6356. See also, Brown, H.C.; Imai, T. *J. Org. Chem.* **1984**, *49*, 892.

⁴⁷⁴ Brown, H.C.; Imai, T. *J. Am. Chem. Soc.* **1983**, *105*, 6285. For a related method that produces primary alcohols, see Brown, H.C.; Imai, T.; Perumal, P.T.; Singaram, B. *J. Org. Chem.* **1985**, *50*, 4032.

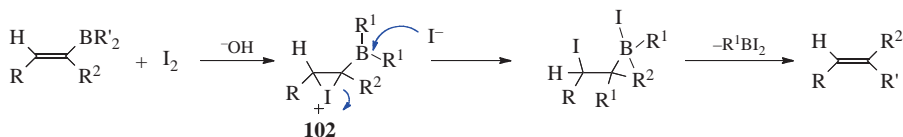
⁴⁷⁵ Brown, H.C.; Imai, T.; Desai, M.C.; Singaram, B. *J. Am. Chem. Soc.* **1985**, *107*, 4980.

⁴⁷⁶ Basavaiah, D.; Kulkarni, S.U.; Bhat, N.G.; Vara Prasad, J.V.N. *J. Org. Chem.* **1988**, *53*, 239.

⁴⁷⁷ For a list of methods of preparing alkenes using boron reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley-VCH, NY, **1999**, pp. 421–427.

⁴⁷⁸ Zweifel, G.; Fisher, R.P.; Snow, J.T.; Whitney, C.C. *J. Am. Chem. Soc.* **1971**, *93*, 6309.

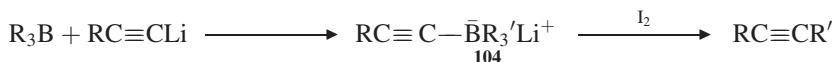
⁴⁷⁹ Hyuga, S.; Takinami, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 977.



In another procedure, the addition of a dialkylborane to a 1-haloalkyne produces an α -halo vinylic borane (**103**).⁴⁸⁰ Treatment of **103** with NaOMe gives the rearrangement shown, and protonolysis of the product produces the (*E*)-alkene.⁴⁷⁸ If R is a vinylic group, the product is a 1,3-diene.⁴⁸¹ If one of the groups is thexyl, the other migrates.⁴⁸² A combination of both of the procedures described above results in the preparation of trisubstituted alkenes.⁴⁸³



18-26 Formation of Alkynes, Alkenes, and Ketones from Boranes and Acetylides



A hydrogen directly attached to a triple-bond carbon can be replaced in high yield by an alkyl or an aryl group, by treatment of the lithium acetylide with a trialkyl- or triarylborane, followed by reaction of the lithium alkynyltrialkylborate (**104**) with iodine.⁴⁸⁴ The R' group may be primary or secondary alkyl as well as aryl, so the reaction has a broader scope than the older Reaction 10-74.⁴⁸⁵ The R group may be alkyl, aryl, or hydrogen, although in the last-mentioned case satisfactory yields are obtained only if lithium acetylide-ethylenediamine is used as the starting compound.⁴⁸⁶ Optically active alkynes can be prepared by using optically active thexylborinates ($\text{RR}^2\text{BOR}'$, $\text{R}^2 = \text{thexyl}$, where R is chiral) and $\text{LiC}\equiv\text{CSiMe}_3$.⁴⁸⁷ The reaction can be adapted to the preparation of alkenes⁴⁸⁸ by treatment of **104** with an electrophile (e.g., propanoic acid⁴⁸⁹ or tributyltin chloride).⁴⁹⁰ The reaction with Bu_3SnCl produces the (*Z*)-alkene stereoselectively.

⁴⁸⁰ For improvements in this method, see Brown, H.C.; Basavaiah, D.; Kulkarni, S.U.; Lee, H.D.; Negishi, E.; Katz, J. *J. Org. Chem.* **1986**, 51, 5270.

⁴⁸¹ Negishi, E.; Yoshida, T. *J. Chem. Soc. Chem. Commun.* **1973**, 606; See also, Negishi, E.; Yoshida, T.; Abramovitch, A.; Lew, G.; Williams, R.H. *Tetrahedron* **1991**, 47, 343.

⁴⁸² Corey, E.J.; Ravindranathan, T. *J. Am. Chem. Soc.* **1972**, 94, 4013; Negishi, E.; Katz, J.; Brown, H.C. *Synthesis* **1972**, 555.

⁴⁸³ Zweifel, G.; Fisher, R.P. *Synthesis* **1972**, 557.

⁴⁸⁴ Suzuki, A.; Miyauchi, N.; Abiko, S.; Itoh, M.; Brown, H.C.; Sinclair, J.A.; Midland, M.M. *J. Org. Chem.* **1986**, 51, 4507; Sikorski, J.A.; Bhat, N.G.; Cole, T.E.; Wang, K.K.; Brown, H.C. *J. Org. Chem.* **1986**, 51, 4521. For a review of reactions of organoborates, see Suzuki, A. *Acc. Chem. Res.* **1982**, 15, 178.

⁴⁸⁵ For a study of the relative migratory aptitudes of R' , see Slayden, S.W. *J. Org. Chem.* **1981**, 46, 2311.

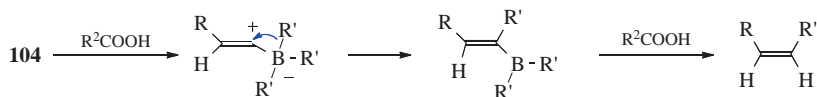
⁴⁸⁶ Midland, M.M.; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* **1974**, 39, 731.

⁴⁸⁷ Brown, H.C.; Mahindroo, V.K.; Bhat, N.G.; Singaram, B. *J. Org. Chem.* **1991**, 56, 1500.

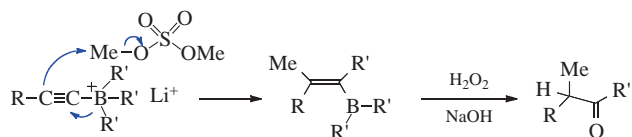
⁴⁸⁸ See Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley-VCH, NY, **1999**, pp. 218–222.

⁴⁸⁹ Pelter, A.; Gould, K.J.; Harrison, C.R. *Tetrahedron Lett.* **1975**, 3327.

⁴⁹⁰ Wang, K.K.; Chu, K. *J. Org. Chem.* **1984**, 49, 5175.



Treatment of **104** with electrophiles (e.g., methyl sulfate, allyl bromide, or triethyloxonium borofluoride), followed by oxidation of the resulting vinylic borane, gives a ketone (illustrated for methyl sulfate)⁴⁹¹:



Note that there are reactions that involve $N \rightarrow O$ rearrangements, including those mediated by silicon.⁴⁹²

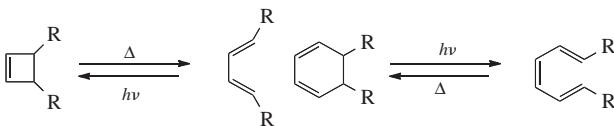
18.F.ii. Non-1,2 Rearrangements

A. Electrocyclic Rearrangements

18-27 Electrocyclic Rearrangements of Cyclobutenes and 1,3-Cyclohexadienes

(4) *seco*-1/4/Detachment; (4) *cyclo*-1/4/Attachment

(6) *seco*-1,6/Detachment; (6) *cyclo*-1/6/Attachment



Cyclobutenes and 1,3-dienes can be interconverted by treatment with UV light or with heat.⁴⁹³ These are 4π -electrocyclizations. The thermal reaction is generally not reversible (although exceptions⁴⁹⁴ are known), and many cyclobutenes have been converted to 1,3-dienes by heating at temperatures between 100 and 200 °C.⁴⁹⁵ Benzocyclobutenes also undergo electrocyclic ring opening,⁴⁹⁶ as do benzocyclobutanones.⁴⁹⁷ The photochemical conversion can in principle be carried out in either direction, but most often 1,3-dienes are converted to cyclobutenes rather than the reverse, because the dienes are stronger absorbers of light at the wavelengths used.⁴⁹⁸ In a similar reaction, 1,3-cyclohexadienes interconvert with 1,3,5-trienes, but in this case the ring-closing process is generally favored thermally and the ring-opening process photochemically, but exceptions are known in both

⁴⁹¹ Pelter, A.; Drake, R.A. *Tetrahedron Lett.* **1988**, 29, 4181.

⁴⁹² Talami, S.; Stirling, C.J.M. *Can. J. Chem.* **1999**, 77, 1105.

⁴⁹³ See Dolbier, Jr., W.R.; Koroniak, H.; Houk, K.N.; Sheu, C. *Acc. Chem. Res.* **1996**, 29, 471; Niwayama, S.; Kallel, E.A.; Spellmeyer, D.C.; Sheu, C.; Houk, K.N. *J. Org. Chem.* **1996**, 61, 2813. The effect of pressure on this reaction has been discussed, see Jenner, G. *Tetrahedron* **1998**, 54, 2771.

⁴⁹⁴ See Steiner, R.P.; Michl, J. *J. Am. Chem. Soc.* **1978**, 100, 6413 and references cited therein.

⁴⁹⁵ See Um, J.M.; Xu, H.; Houk, K.N.; Tang, W. *J. Am. Chem. Soc.* **2009**, 131, 6664.

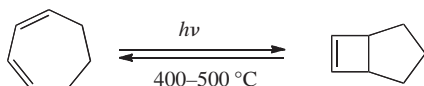
⁴⁹⁶ Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* **2006**, 128, 412.

⁴⁹⁷ Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* **2006**, 128, 13072.

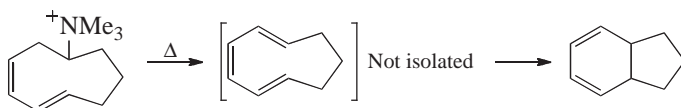
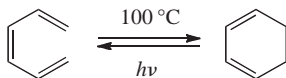
⁴⁹⁸ See Dauben, W.G.; Haubrich, J.E. *J. Org. Chem.* **1988**, 53, 600.

directions.⁴⁹⁹ Substituent effects can lead to acceleration of the electrocyclization process.⁵⁰⁰ *Torquoselectivity* in cyclobutene ring-opening reaction has been examined.⁵⁰¹

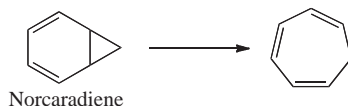
Examples of these types of reactions include:



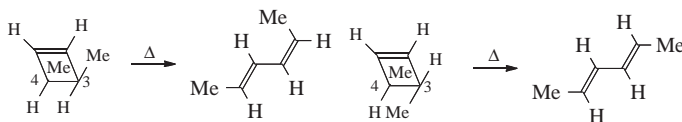
Ref. 502



An interesting example of 1,3-cyclohexadiene→1,3,5-triene interconversion is the reaction of norcaradienes to give cycloheptatrienes.⁵⁰³ This is a 6 π -electrocyclization, and it has been catalyzed by Lewis acids.⁵⁰⁴ Norcaradienes give this reaction so readily (because they are *cis*-1,2-divinylcyclopropanes, see Reaction 18-32) that they cannot generally be isolated, though some exceptions are known⁵⁰⁵ (see also, 15-64).



These reactions, called *electrocyclic rearrangements*,⁵⁰⁶ take place by pericyclic mechanisms. The evidence comes from stereochemical studies, which show a remarkable stereospecificity whose direction depends on whether the reaction is induced by heat or light. For example, it was found for the thermal reaction that *cis*-3,4-dimethylcyclobutene gave only *cis,trans*-2,4-hexadiene, while the *trans* isomer gave only the *trans-trans*-diene⁵⁰⁷:



⁴⁹⁹ See Dauben, W.G.; McInnis, E.L.; Michno, D.M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, **1980**, pp. 91–129. For an *ab initio* study see Rodríguez-Otero, J. *J. Org. Chem.* **1999**, *64*, 6842.

⁵⁰⁰ Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099. See Beaudry, C.M.; Malerich, J.P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

⁵⁰¹ Yasui, M.; Naruse, Y.; Inagaki, S. *J. Org. Chem.* **2004**, *69*, 7246.

⁵⁰² Chapman, O.L.; Pasto, D.J.; Borden, G.W.; Griswold, A.A. *J. Am. Chem. Soc.* **1962**, *84*, 1220.

⁵⁰³ See Maier, G. *Angew. Chem. Int. Ed.* **1967**, *6*, 402; Vogel, E. *Pure Appl. Chem.* **1969**, *20*, 237.

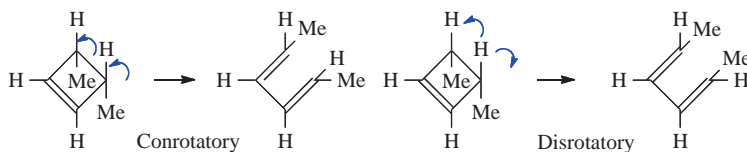
⁵⁰⁴ Bishop, L.M.; Barbarow, J.E.; Bergman, R.G.; Trauner, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8100.

⁵⁰⁵ See Ciganek, E. *J. Am. Chem. Soc.* **1967**, *89*, 1454.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* **1987**, *26*, 559.

⁵⁰⁶ See Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, **1981**; Marvell, E.N. *Thermal Electrocyclic Reactions*, Academic Press, NY, **1980**; Laarhoven, W.H. *Org. Photochem.* **1987**, *9*, 129; George, M. V.; Mitra, A.; Sukumaran, K.B. *Angew. Chem. Int. Ed.* **1980**, *19*, 973; Jutz, J.C. *Top. Curr. Chem.* **1978**, *73*, 125; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, Cambridge University Press, Cambridge, **1972**, pp. 48–72; Criegee, R. *Angew. Chem. Int. Ed.* **1968**, *7*, 559. See Schultz, A.G.; Motyka, L. *Org. Photochem.* **1983**, *6*, 1.

⁵⁰⁷ Winter, R.E.K. *Tetrahedron Lett.* **1965**, 1207; Criegee, R.; Noll, K. *Liebigs Ann. Chem.* **1959**, 627, 1.

This is evidence for a four-membered cyclic transition state and arises from conrotatory motion about the C-3–C-4 bond.⁵⁰⁸ It is called conrotatory because both movements are clockwise (or both counterclockwise). Because both rotate in the same direction, the *cis* isomer gives the *cis*–*trans*-diene.⁵⁰⁹ The other possibility (*disrotatory* motion) would have one moving clockwise while the other moves counterclockwise; the *cis* isomer would have given the *cis*–*cis*-diene (shown) or the *trans*–*trans*-diene. If the motion had been disrotatory, this would still have been evidence for a cyclic mechanism. If the mechanism were a diradical or some other kind of noncyclic process, it is likely that no stereospecificity of either kind would have been observed. The reverse



reaction is also conrotatory. In contrast, the photochemical cyclobutene: 1,3-diene interconversion is *disrotatory* in either direction.⁵¹⁰ On the other hand, the cyclohexadiene: 1,3,5-triene interconversion shows precisely the opposite behavior. The thermal process is *disrotatory*, while the photochemical process is *conrotatory* (in either direction). These startling results are a consequence of the symmetry rules mentioned in Section 15-60, the FOM.⁵¹¹ As in the case of cycloaddition reactions, we will use the FOM and *Möbius–Hückel* approaches.⁵¹²

The Frontier Orbital Method (FOM)⁵¹³

As applied to these reactions, the FOM may be expressed: *A σ bond will open in such a way that the resulting p orbitals will have the symmetry of the highest occupied π orbital of the product.* In the case of cyclobutenes, the HOMO of the product in the thermal reaction is the χ_2 orbital (Fig. 18.1). Therefore, in a thermal process, the cyclobutene must open so that on one side the positive lobe lies above the plane, and on the other side below it. Thus the substituents are forced into conrotatory motion (Fig. 18.2). On the other hand, in the photochemical process, the HOMO of the product is now the χ_3 orbital (Fig. 18.1), and in order for the p orbitals to achieve this symmetry (the two plus lobes on the same side of the plane), the substituents are forced into disrotatory motion.

This reaction may be considered from the opposite direction (ring closing). For this direction, the rule is that *those lobes of orbitals that overlap (in the HOMO) must be of the same sign.* For thermal cyclization of butadienes, this requires conrotatory motion

⁵⁰⁸ Baldwin, J.E.; Gallagher, S.S.; Leber, P.A.; Raghavan, A.S.; Shukla, R. *J. Org. Chem.* **2004**, 69, 7212.

⁵⁰⁹ See Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, 87, 395.

⁵¹⁰ See Leigh, W.J.; Zheng, K. *J. Am. Chem. Soc.* **1991**, 113, 4019; Leigh, W.J.; Zheng, K.; Nguyen, N.; Werstiuk, N.H.; Ma, J. *J. Am. Chem. Soc.* **1991**, 113, 4993, and references cited therein.

⁵¹¹ Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, 87, 395. Also see, Longuet-Higgins, H.C.; Abrahamson, E.W. *J. Am. Chem. Soc.* **1965**, 87, 2045; Fukui, K. *Tetrahedron Lett.* **1965**, 2009.

⁵¹² See Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, **1984**, pp. 352–359; Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, **1978**, pp. 250–263. Also see, Zimmerman, H.E. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, **1977**, pp. 53–107; *Acc. Chem. Res.* **1971**, 4, 272; Dewar, M.J.S. *Angew. Chem. Int. Ed.* **1971**, 10, 761; Jefford, C. W.; Burger, U. *Chimia* **1971**, 25, 297; Herndon, W.C. *J. Chem. Educ.* **1981**, 58, 371.

⁵¹³ Fukui, K. *Fortschr. Acc. Chem. Res.* **1971**, 4, 57; Houk, K.N. *Acc. Chem. Res.* **1975**, 8, 361. See also, Chu, S. *Tetrahedron* **1978**, 34, 645; Fleming, I. *Pericyclic Reactions*, Oxford Univ. Press, Oxford, **1999**; Fukui, K. *Angew. Chem. Int. Ed.* **1982**, 21, 801; Houk, K.N., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, **1977**, pp. 181–271.

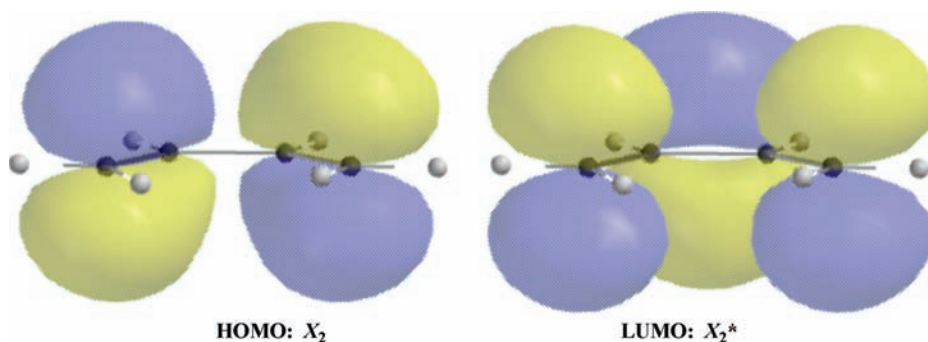


FIG. 18.1. Symmetries of the X_2 and X_3^* orbitals of a conjugated diene

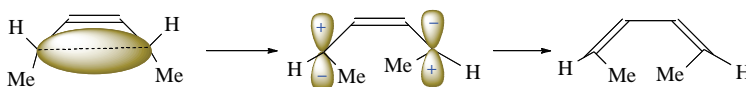


FIG. 18.2. Thermal opening of 1,2-diethylcyclobutene. The two hydrogens and two methyls are forced into conrotatory motion so that the resulting p -orbitals have the symmetry of the HOMO of the diene.

(Fig. 18.3). In the photochemical process, the HOMO is the χ_3 orbital, so that disrotatory motion is required for lobes of the same sign to overlap.

The Möbius–Hückel Method

As seen in Reaction 15-60, the *Möbius–Hückel Method*, a basis set of p orbitals is chosen and inspected for sign inversions in the transition state. Figure 18.4 shows a basis set for a 1,3-diene. It is seen that disrotatory ring closing (Fig. 18.4a) results in overlap of plus lobes only, while in conrotatory closing (Fig. 18.4b) there is one overlap of a plus with a minus lobe. In the first case, there are zero sign inversions, while in the second there is one sign inversion. With zero (or an even number of) sign inversions, the disrotatory transition state is a *Hückel system*, and so is allowed thermally only if the total number of electrons is $4n + 2$ (Sec. 15-60, the *Möbius–Hückel Method*). Since the total here is 4, the disrotatory process is not allowed. On the other hand, the conrotatory process, with one sign inversion, is a *Möbius*

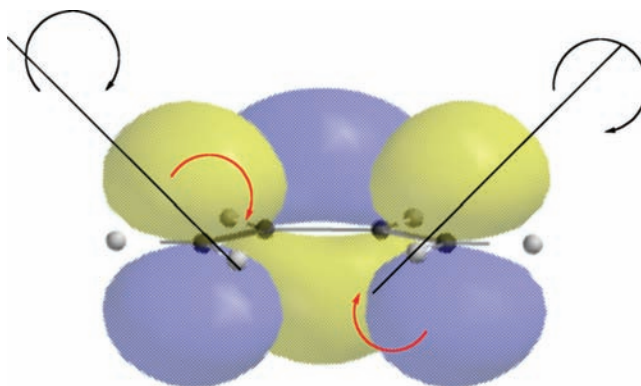


FIG. 18.3. Thermal ring closing of a 1,3-diene. Conrotatory motion is required for two + lobes to overlap.

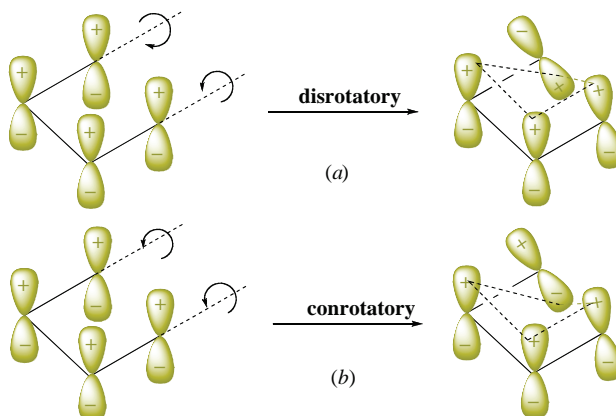
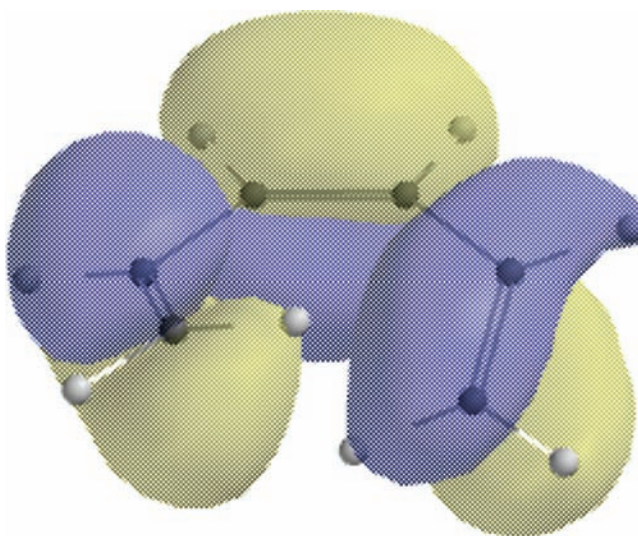


FIG. 18.4. The 1,3-diene–cyclobutene interconversion. The orbitals shown are *not* molecular orbitals, but a basis set of *p* atomic orbitals. (a) Disrotatory ring closure gives zero sign inversion. (b) Conrotatory ring closure gives one sign inversion. We could have chosen to show any other basis set (another basis set would have two plus lobes above the plane and two below, etc.). This would change the number of sign inversion, but the disrotatory mode would still have an even number of sign inversions, and the conrotatory mode an odd number, whichever basis set was chosen.

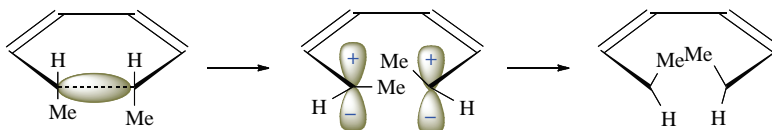
system, which is thermally allowed if the total number is $4n$. The conrotatory process is therefore allowed thermally. For the photochemical reactions, the rules are reversed: A reaction with $4n$ electrons requires a *Hückel* system, so only the disrotatory process is allowed.

Both the FOM and the *Möbius–Hückel* methods can also be applied to the cyclohexadiene: 1,3,5-triene reaction⁵¹⁴; in either case the predicted result is that for the thermal process, only the disrotatory pathway is allowed, and for the photochemical process, only the conrotatory. For example, for 1,3,5-hexatriene, the symmetry of the HOMO is

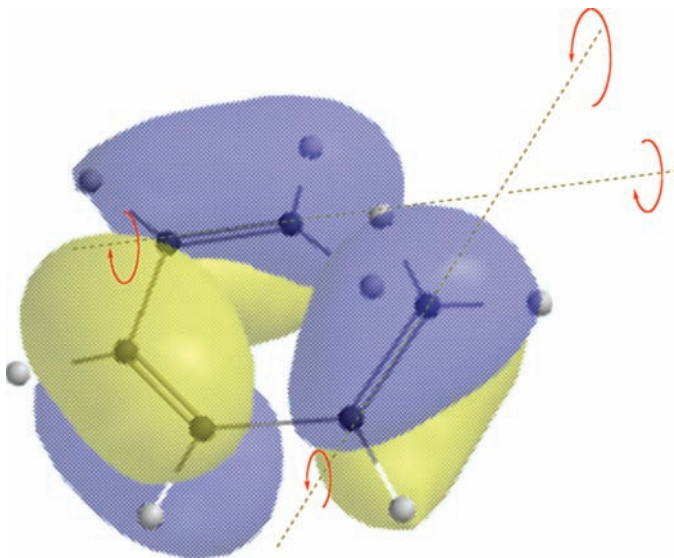


⁵¹⁴ For a discussion of the transition structures and energy, see Zora, M. *J. Org. Chem.* **2004**, 69, 1940.

In the thermal cleavage of cyclohexadienes, then, the positive lobes must lie on the same side of the plane, requiring disrotatory motion:



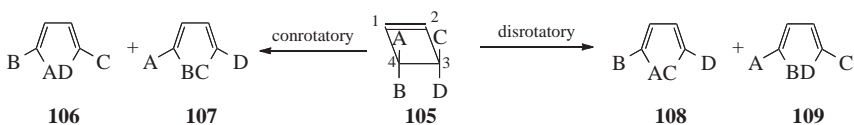
Disrotatory motion is also necessary for the reverse reaction, in order that the orbitals that overlap may be of the same sign:



All these directions are reversed for photochemical processes, because in each case a higher orbital, with inverted symmetry, is occupied.

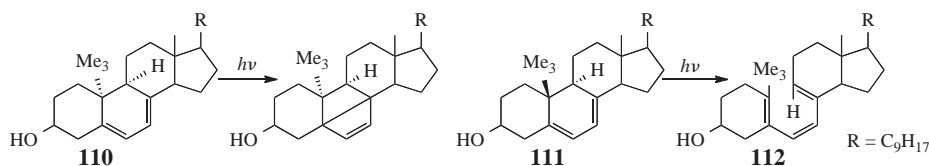
In the *Möbius–Hückel* approach, diagrams similar to Fig. 18.4 can be drawn for this case. Here too, the disrotatory pathway is a *Hückel* system and the conrotatory pathway a *Möbius* system, but since six electrons are now involved, the thermal reaction follows the *Hückel* pathway and the photochemical reaction the *Möbius* pathway.

In the most general case, four possible products can arise from a given cyclobutene or cyclohexadiene: two from the conrotatory and two from the disrotatory pathway. For example, conrotatory ring opening of **105** gives either **106** or **107**, while disrotatory opening gives either **108** or **109**. The orbital-symmetry rules indicate when a given reaction will operate by the conrotatory and when by the disrotatory mode, but not which of the two possible conrotatory or disrotatory pathways will be followed. Often, however, it is possible to make such



predictions on steric grounds. For example, in the opening of **105** by the disrotatory pathway, **108** arises when groups A and C swing in toward each other (clockwise motion around C-4,

counterclockwise around C-3), while **109** is formed when groups B and D swing in and A and C swing out (clockwise motion around C-3, counterclockwise around C-4). This observation leads to a prediction that when A and C are larger than B and D, the predominant or exclusive product will be **109** rather than **108**. Predictions of this kind have largely been borne out.⁵¹⁵ There is evidence, however, that steric effects⁵¹⁶ are not the only factor, and that electronic effects also play a role, and their role may be even greater.⁵¹⁷ An electron-donating group stabilizes the transition state when it rotates *outward*, because it mixes with the LUMO; if it rotates *inward*, it mixes with the HOMO, destabilizing the transition state.⁵¹⁸ The compound 3-formylcyclobutene provided a test. Steric factors would cause the CHO (an electron-withdrawing group) to rotate outward; electronic effects would cause it to rotate inward. The experiment showed inward rotation.⁵¹⁹



Cyclohexadienes are of course 1,3-dienes, and in certain cases it is possible to convert them to cyclobutenes instead of to 1,3,5-trienes.⁵²⁰ An interesting example is found in the pyrocalciferols. Photolysis of the syn isomer (**110**) (or of the other syn isomer, not shown) leads to the corresponding cyclobutene,⁵²¹ while photolysis of the anti isomers (one of them is **111**) gives the ring-opened 1,3,5-triene (**112**). This difference in behavior is at first sight remarkable, but is easily explained by the orbital-symmetry rules. Photochemical ring opening to a 1,3,5-triene must be conrotatory. If **110** were to react by this pathway, the product would be the triene **112**, but this compound would have to contain a *trans*-cyclohexene ring (either the methyl group or the hydrogen would have to be directed inside the ring). On the other hand, photochemical conversion to a cyclobutene must be disrotatory, but if **111** were to give this reaction, the product would have to have a *trans*-fused ring junction. Compounds with such ring junctions are known (Sec. 4.K.iii), but are very strained. Stable *trans*-cyclohexenes are unknown (Sec. 4.Q.iii). Thus, **110** and **111** give the products they do owing to a combination of orbital-symmetry rules and steric influences.

A related process is the *Bergmann cyclization*,⁵²² where an ene-diyne cyclizes to a biradical (**103**) and then aromatizes as shown. Simply heating the en-diyne will usually lead to aromatization via this pathway.⁵²³ Quinones can be formed via *Bergman*

⁵¹⁵ See Gesche, P.; Klinger, F.; Riesen, A.; Tschamber, T.; Zehnder, M.; Streith, J. *Helv. Chim. Acta* **1987**, 70, 2087.

⁵¹⁶ Leigh, W.J.; Postigo, J.A. *J. Am. Chem. Soc.* **1995**, 117, 1688.

⁵¹⁷ Dolbier Jr., W.R.; Gray, T.A.; Keaffaber, J.J.; Celewicz, L.; Koroniak, H. *J. Am. Chem. Soc.* **1990**, 112, 363; Hayes, R.; Ingham, S.; Saengchantara, S.T.; Wallace, T.W. *Tetrahedron Lett.* **1991**, 32, 2953.

⁵¹⁸ See Kallel, E.A.; Wang, Y.; Spellmeyer, D.C.; Houk, K.N. *J. Am. Chem. Soc.* **1990**, 112, 6759.

⁵¹⁹ Piers, E.; Lu, Y.-F. *J. Org. Chem.* **1989**, 54, 2267.

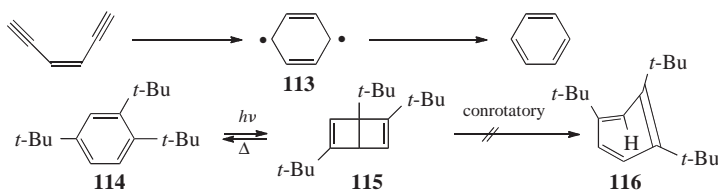
⁵²⁰ See Dauben, W.G.; Kellogg, M.S.; Seeman, J.I.; Vietmeyer, N.D.; Wendschuh, P.H. *Pure Appl. Chem.* **1973**, 33, 197.

⁵²¹ Dauben, W.G.; Fonken, G.J. *J. Am. Chem. Soc.* **1959**, 81, 4060.

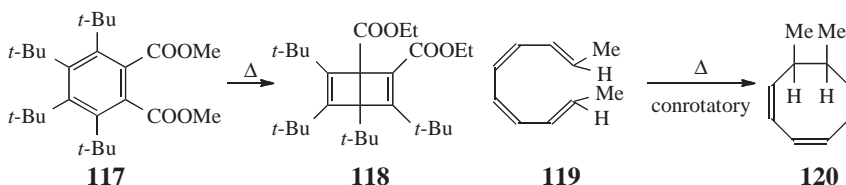
⁵²² Bergman, R.G. *Accs. Chem. Res.* **1973**, 6, 25; Adam, W.; Krebs, O. *Chem. Rev.* **2003**, 103, 4131. See Lewis, K.D.; Matzger, A.J. *J. Am. Chem. Soc.* **2005**, 127, 9968; Zeidan, T.A.; Manoharan, M.; Alabugin, I.V. *J. Org. Chem.* **2006**, 71, 954; Zeidan, T.A.; Kovalenko, S.V.; Manoharan, M.; Alabugin, I.V. *J. Org. Chem.* **2006**, 71, 962.

⁵²³ See Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* **1997**, 381.

cyclization⁵²⁴ and there are other synthetic applications.⁵²⁵ The role of vinyl substitution has been examined.⁵²⁶ An *aza-Bergman cyclization* is known.⁵²⁷



The 1,3-diene-cyclobutene interconversion can even be applied to benzene rings. For example,⁵²⁸ photolysis of 1,2,4-tri-*tert*-butylbenzene (**114**) gives 1,2,5-tri-*tert*-butyl [2.2.0]hexadiene (**115**, a *Dewar benzene*).⁵²⁹ The reaction owes its success to the fact that once **115** is formed, it cannot, under the conditions used, revert to **114** by either a thermal or a photochemical route. The orbital-symmetry rules prohibit thermal conversion of **115** to **114** by a pericyclic mechanism, because thermal conversion of a cyclobutene to a 1,3-diene must be conrotatory, and conrotatory reaction of **115** would result in a 1,3,5-cyclohexatriene containing one trans double bond (**116**), which is of course too strained to exist. Compound **115** cannot revert to **114** by a photochemical pathway either, because light of the frequency used to excite **114** would not be absorbed by **115**. This is another example of a molecule that owes its stability to the orbital-symmetry rules (see Reaction 15-63). Pyrolysis of **115** does give **114**, probably by a diradical mechanism.⁵³⁰ In the case of **117** and **118**, the *Dewar benzene* is actually more stable than the benzene. Compound **117** rearranges to **118** in 90% yield at 120 °C.⁵³¹ In this case, thermolysis of the benzene gives the *Dewar benzene* (rather than the reverse), because of the strain of four adjacent *tert*-butyl groups on the ring.



A number of electrocyclic reactions have been carried out with systems of other sizes, [(e.g., conversion of the 1,3,5,7-octatetraene (**119**) to the cyclooctatriene (**120**)].⁵³² The

⁵²⁴ Jones, G.B.; Warner, P.M. *J. Org. Chem.* **2001**, 66, 8669.

⁵²⁵ Bowles, D.M.; Palmer, G.J.; Landis, C.A.; Scott, J.L.; Anthony, J.E. *Tetrahedron* **2001**, 57, 3753.

⁵²⁶ Jones, G.B.; Warner, P.M. *J. Am. Chem. Soc.* **2001**, 123, 2134.

⁵²⁷ Feng, L.; Kumar, D.; Kerwin, S.M. *J. Org. Chem.* **2003**, 68, 2234.

⁵²⁸ See Ward, H.R.; Wishnok, J.S. *J. Am. Chem. Soc.* **1968**, 90, 1085; Bryce-Smith, D.; Gilbert, A.; Robinson, D.A. *Angew. Chem. Int. Ed.* **1971**, 10, 745. Also see Barlow, M.G.; Haszeldine, R.N.; Hubbard, R. *Chem. Commun.* **1969**, 202; Lemal, D.M.; Staros, J.V.; Austel, V. *J. Am. Chem. Soc.* **1969**, 91, 3373.

⁵²⁹ van Tamelen, E.E. *Acc. Chem. Res.* **1972**, 5, 186. See Schäfer, W.; Criegee, R.; Askani, R.; Grüner, H. *Angew. Chem. Int. Ed.* **1967**, 6, 78). *Dewar benzenes* can be photolyzed further to give prismanes.

⁵³⁰ See Wingert, H.; Irngartinger, H.; Kallfass, D.; Regitz, M. *Chem. Ber.* **1987**, 120, 825.

⁵³¹ Maier, G.; Schneider, K. *Angew. Chem. Int. Ed.* **1980**, 19, 1022. See also, Wingert, H.; Maas, G.; Regitz, M. *Tetrahedron* **1986**, 42, 5341.

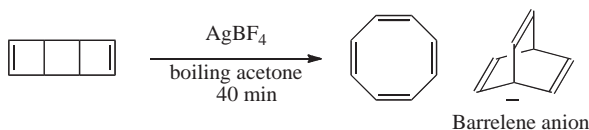
⁵³² Marvell, E.N.; Seubert, J. *J. Am. Chem. Soc.* **1967**, 89, 3377; Huisgen, R.; Dahmen, A.; Huber, H. *Tetrahedron Lett.* **1969**, 1461; Dahmen, A.; Huber, H. *Tetrahedron Lett.* **1969**, 1465.

stereochemistry of these reactions can be predicted in a similar manner. The results of such predictions can be summarized according to whether the number of electrons involved in the cyclic process is of the form $4n$ or $4n + 2$ (where n is any integer including zero).

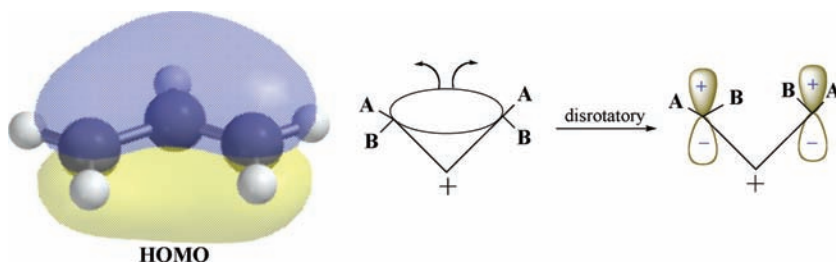
	Thermal Reaction	Photochemical Reaction
$4n$	Conrotatory	Disrotatory
$4n + 2$	Disrotatory	Conrotatory

Although the orbital-symmetry rules predict the stereochemical results in almost all cases, it is necessary to recall (Reaction **15-60**, the *Möbius–Hückel* Method) that they only say what is allowed and what is forbidden, but *the fact that a reaction is allowed does not necessarily mean that the reaction takes place*, and if an allowed reaction does take place, it does not *necessarily* follow that a concerted pathway is involved, since other pathways of lower energy may be available.⁵³³ Furthermore, a “forbidden” reaction might still be made to go, if a method of achieving its high activation energy can be found. This was, in fact, done for the cyclobutene–butadiene interconversion (*cis*-3,4-dichlorocyclobutene gave the forbidden *cis,cis*- and *trans,trans*-1,4-dichloro-1,3-butadienes, as well as the allowed *cis*, *trans* isomer) by the use of IR laser light.⁵³⁴ This is a thermal reaction. The laser light excites the molecule to a higher vibrational level (Sec. 7.A.i), but not to a higher electronic state.

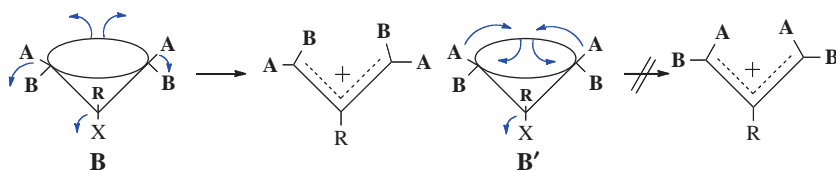
As is the case for $[2 + 2]$ -cycloaddition reactions (**15-63**), certain forbidden electrocyclic reactions can be made to take place by the use of metallic catalysts.⁵³⁵ An example is the silver ion-catalyzed conversion of tricyclo[4.2.0.0^{2,5}]octa-3,7-diene to cyclooctatetraene⁵³⁶:



rule is invoked that the σ bond opens in such a way that the resulting p orbitals have the symmetry of the highest occupied orbital of the product, in this case,



an allylic cation. Recall that an allylic system has three molecular orbitals (Sec. 2.C, category 3). For the cation, with only two electrons, the highest occupied orbital is the one of lowest energy (**HOMO**). Thus, the cyclopropyl cation must undergo a disrotatory ring opening in order to maintain the symmetry. Note that, in contrast, ring opening of the cyclopropyl *anion* must be conrotatory,⁵⁴⁰ since in this case it is the next orbital of the allylic system that is the highest occupied, and this has the opposite symmetry.⁵⁴¹ However, it is difficult to generate a free cyclopropyl cation (Sec. 10.G.i, category 7), and it is likely that in most cases, cleavage of the σ bond is concerted with departure of the leaving group in the original cyclopropyl substrate. This, of course, means that the σ bond provides anchimeric assistance to the removal of the leaving group (an S_N2 type process), and we would expect that such assistance should come from the back side. This has an important effect on the direction of ring opening. The orbital-symmetry rules require that the ring opening is disrotatory, but as seen above, there are two disrotatory pathways and the rules do not indicate which is preferred. But the fact that the σ orbital provides assistance from the backside means that the two substituents that are trans to the leaving group must move *outward*, not inward.⁵⁴² Thus, the disrotatory pathway that is followed is the one shown in **B**, not the one shown in **B'**, because the former puts the electrons of the σ bond on the side opposite



that of the leaving group.⁵⁴³ Strong confirmation of this picture⁵⁴⁴ comes from acetolysis of *endo*- (**121**) and *exo*-bicyclo[3,1,0]hexyl-6-tosylate (**112**). The groups trans to the tosylate must move outward. For **121**, this means that the two hydrogen atoms can go outside the

⁵⁴⁰ See Boche, G. *Top. Curr. Chem.* **1988**, 146, 1.

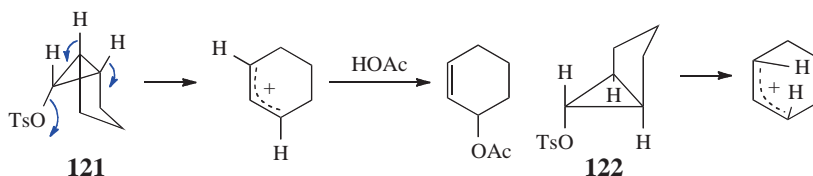
⁵⁴¹ See Coates, R.M.; Last, L.A. *J. Am. Chem. Soc.* **1983**, 105, 7322. For a review of the analogous ring opening of epoxides, see Huisgen, R. *Angew. Chem. Int. Ed.* **1977**, 16, 572.

⁵⁴² DePuy, C.H.; Schnack, L.G.; Hausser, J.W.; Wiedemann, W. *J. Am. Chem. Soc.* **1965**, 87, 4006.

⁵⁴³ It has been suggested that the pathway shown in **C** is possible in certain cases: Hausser, J.W.; Grubber, M.J. *J. Org. Chem.* **1972**, 37, 2648; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* **1972**, 37, 4087.

⁵⁴⁴ Also see Reese, C.B.; Shaw, A. *J. Am. Chem. Soc.* **1970**, 92, 2566; Dolbier, Jr., W.R.; Phanstiel, O. *Tetrahedron Lett.* **1988**, 29, 53, and references cited therein.

framework of the six-membered ring, but for **122** they

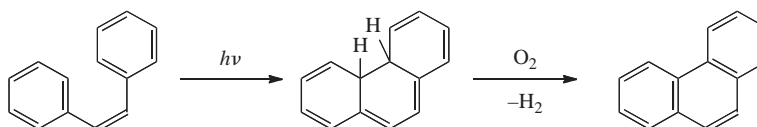


are forced to go inside. Consequently, it is not surprising that the rate ratio for solvolysis of **121/122** was found to be $>2.5 \times 10^6$ and that at 150°C , **122** did not solvolyze at all.⁵⁴⁵ This evidence is kinetic. Unlike the cases of the cyclobutene (1,3-diene and cyclohexadiene) 1,3,5-triene interconversions, the direct product here is a cation, which is not stable but reacts with a nucleophile and loses some of its steric integrity in the process, so that much of the evidence has been of the kinetic type rather than from studies of product stereochemistry. However, it has been shown by investigations in superacids (Sec. 5.A.ii), where it is possible to keep the cations intact and to study their structures by NMR, that in all cases studied the cation that is predicted by these rules is in fact formed.⁵⁴⁶

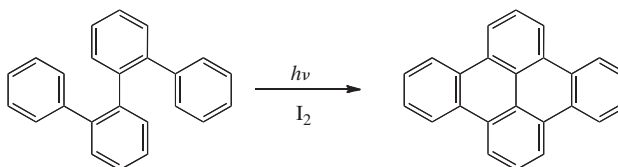
OS V, 235, 277, 467; VI, 39, 145, 196, 422, 427, 862; IX, 180.

18-28 Conversion of One Aromatic Compound to Another

(6) *cyclo-de-hydrogen-coupling* (Overall transformation)



Stilbenes can be converted to phenanthrenes by irradiation with UV light⁵⁴⁷ in the presence of an oxidizing agent, (e.g., dissolved molecular oxygen, FeCl_3 , or iodine).⁵⁴⁸ The reaction is a photochemically allowed conrotatory⁵⁴⁹ conversion of a 1,3,5-hexatriene to a cyclohexadiene, followed by removal of two hydrogen atoms by the oxidizing agent. The intermediate dihydrophenanthrene has been isolated.⁵⁵⁰ The actual reacting species must be the *cis*-stilbene, but *trans*-stilbenes can often be used, because they are isomerized to the *cis* isomers under the reaction conditions. The reaction can be extended to the preparation of many fused aromatic systems, for example⁵⁵¹:



⁵⁴⁵ Schöllkopf, U.; Fellenberger, K.; Patsch, M.; Schleyer, P.v.R.; Su, T.M.; Van Dine, G.W. *Tetrahedron Lett.* **1967**, 3639.

⁵⁴⁶ Schleyer, P.v.R.; Su, T.M.; Saunders, M.; Rosenfeld, J.C. *J. Am. Chem. Soc.* **1969**, 91, 5174.

⁵⁴⁷ Mallory, F.B.; Mallory, C.W. *Org. React.* **1984**, 30, 1; Blackburn, E.V.; Timmons, C.J. *Q. Rev. Chem. Soc.* **1969**, 23, 482. See Laarhoven, W.H. *Org. Photochem.* **1989**, 10, 163.

⁵⁴⁸ See Liu, L.; Yang, B.; Katz, T.J.; Poindexter, M.K. *J. Org. Chem.* **1991**, 56, 3769.

⁵⁴⁹ Cuppen, T.J.H.M.; Laarhoven, W.H. *J. Am. Chem. Soc.* **1972**, 94, 5914.

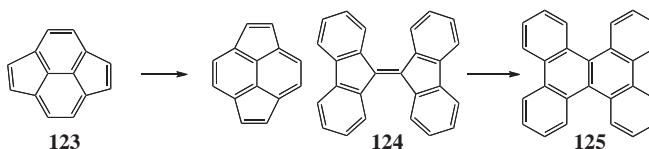
⁵⁵⁰ Doyle, T.D.; Benson, W.R.; Filipescu, N. *J. Am. Chem. Soc.* **1976**, 98, 3262.

⁵⁵¹ Sato, T.; Shimada, S.; Hata, K. *Bull. Chem. Soc. Jpn.* **1971**, 44, 2484.

though not all such systems give a reaction.⁵⁵² The use of substrates containing heteroatoms (e.g., PhN=NPh) allows the formation of heterocyclic ring systems.

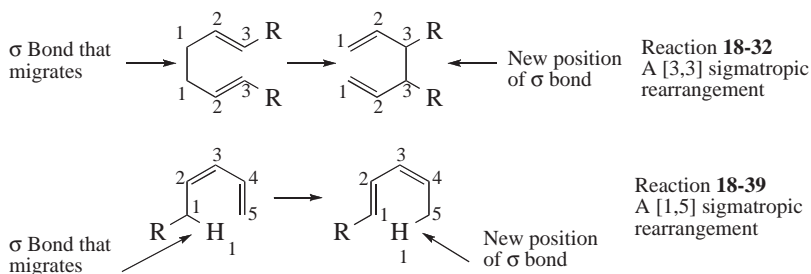
Isomerization of biphenylene to benzo[*a*]pentalene⁵⁵³ is a well-known benzene ring contraction rearrangement,⁵⁵⁴ driven by relief of strain in the four-membered ring. Related to this process is the flash vacuum pyrolysis (FVP) of the alternant polycyclic aromatic hydrocarbon benzo[*b*]biphenylene at 1100 °C, which gives fluoranthene, a nonalternant polycyclic aromatic hydrocarbon, as the major product at 1100 °C in the gas phase.⁵⁵⁵ The mechanism used explain that this isomerization involves equilibrating diradicals of 2-phenyl-naphthalene, which rearrange by the net migration of a phenyl group to give equilibrating diradicals of 1-phenylnaphthalene, one isomer of which then cyclizes to fluoranthene.

Another transformation of one aromatic compound to another is the *Stone–Wales rearrangement* of pyracyclene (**123**),⁵⁵⁶ which is a bond-switching reaction. The rearrangement of bifluorenylidene (**124**) to dibenzo[*g,p*]chrysene (**125**) occurs at temperatures as low as 400 °C and is accelerated in the presence of decomposing iodomethane, a convenient source of methyl radicals.⁵⁵⁷ This result suggested a radical rearrangement. This rearrangement is believed to occur by a radical-promoted mechanism consisting of a sequence of homoallyl-cyclopropylcarbinyl rearrangement steps.⁵⁵⁸



B. Sigmatropic Rearrangements

A sigmatropic rearrangement is defined⁵⁵⁹ as migration, in an uncatalyzed intramolecular process, of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π systems becoming reorganized in the process. Examples are



The *order* of a sigmatropic rearrangement is expressed by two numbers set in brackets: [*i,j*]. These numbers can be determined by counting the atoms over which each end of the

⁵⁵² See Laarhoven, W.H. *Recl. Trav. Chim. Pays-Bas* **1983**, 102, 185, pp. 185–204.

⁵⁵³ Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* **1993**, 34, 6615; Brown, R.F.C.; Choi, N.; Coulston, K.J.; Eastwood, F.W.; Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* **1994**, 35, 4405.

⁵⁵⁴ See Brown, R.F.C.; Eastwood, F.W.; Wong, N.R. *Tetrahedron Lett.* **1993**, 34, 3607.

⁵⁵⁵ Preda, D.V.; Scott, L.T. *Org. Lett.* **2000**, 2, 1489.

⁵⁵⁶ Stone, A.J.; Wales, D.J. *Chem. Phys. Lett.* **1986**, 128, 501.

⁵⁵⁷ Alder, R.W.; Whittaker, G. *J. Chem. Soc., Perkin Trans. 2* **1975**, 712.

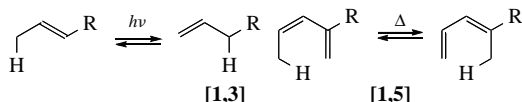
⁵⁵⁸ Alder, R. W.; Harvey, J. N. *J. Am. Chem. Soc.* **2004**, 126, 2490.

⁵⁵⁹ Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, **1970**, p. 114.

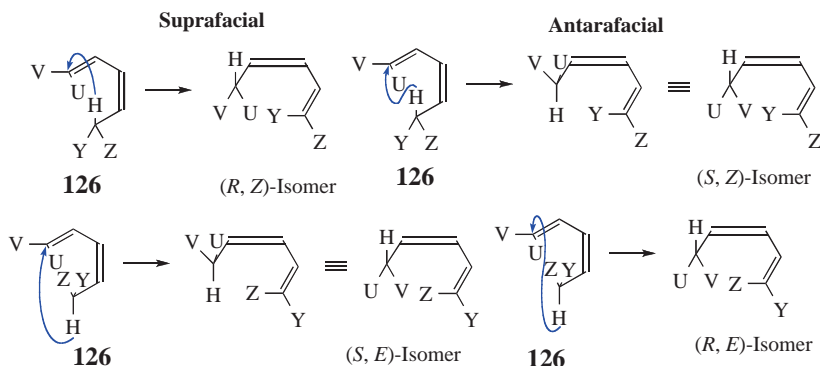
σ bond has moved. Each of the original termini is given the number 1. Thus in the first example above, each terminus of the σ bond has migrated from C-1 to C-3, so the order is [3,3]. In the second example, the carbon terminus has moved from C-1 to C-5, but the hydrogen terminus has not moved at all, so the order is [1,5].

18-29 [1,j]-Sigmatropic Migrations of Hydrogen

1/ \rightarrow 3/Hydrogen-migration; 1/ \rightarrow 5/Hydrogen-migration



Many examples of thermal or photochemical rearrangements in which a hydrogen atom migrates from one end of a system of π bonds to the other have been reported,⁵⁶⁰ although the reaction is subject to geometrical constraints. Isotope effects play a role in sigmatropic rearrangements, and there is evidence for a kinetic silicon isotope effect.⁵⁶¹ Pericyclic mechanisms are involved,⁵⁶² and the hydrogen must, in the transition state, be in contact with both ends of the chain at the same time. This means that for [1,5] and longer rearrangements, the molecule must be able to adopt the cisoid conformation. Furthermore, there are two geometrical pathways by which any sigmatropic rearrangement can take place, illustrated for the case of a [1,5]-sigmatropic rearrangement,⁵⁶³ starting with a substrate of the form **126**, where the migration origin is an asymmetric carbon atom and $U \neq V$. In one of the two pathways, the hydrogen moves along the top or bottom face of the π system. This is called *suprafacial migration*. In the other pathway, the hydrogen moves *across* the π system, from top to bottom, or vice versa. This is *antarafacial migration*. Altogether, a single isomer like **126** (different rotamers) can give four products. In a suprafacial migration, H can move across the top of the π system (as drawn above) to give the (*R,Z*)-isomer, or it can rotate 180° and move across the bottom of the π system to give the (*S,E*)-isomer.⁵⁶⁴ The antarafacial migration can similarly lead to two diastereomers, in this case the (*S,Z*)- and (*R,E*)-isomers.



⁵⁶⁰ Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, **1981**; Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* **1981**, 50, 666; Spangler, C.W. *Chem. Rev.* **1976**, 76, 187.

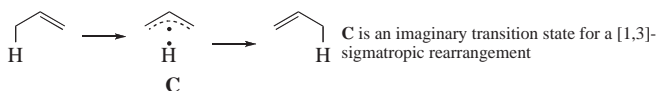
⁵⁶¹ Lin, Y.-L.; Turos, E. *J. Am. Chem. Soc.* **1999**, 121, 856.

⁵⁶² Moss, S.; King, B.T.; de Meijere, A.; Kozhushkov, S.I.; Eaton, P.E.; Michl, J. *Org. Lett.* **2001**, 3, 2375.

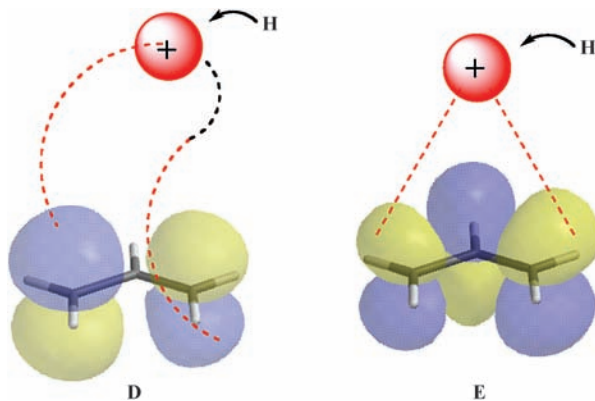
⁵⁶³ Note that a [1,5]-sigmatropic rearrangement of hydrogen is also an internal ene synthesis (Reaction **15-20**).

⁵⁶⁴ The designations U, V, Y, and Z are arbitrary, so which isomer is (*R,Z*) and which is (*S,E*) is arbitrary.

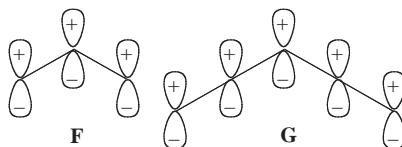
In any given sigmatropic rearrangement, only one of the two pathways is allowed by the orbital-symmetry rules; the other is forbidden. To analyze this situation, first use a modified frontier orbital approach.⁵⁶⁵ Imagine that in the transition state **C**, the migrating H atom breaks away from the rest of the system, which is treated as if it were a free radical.



Note that this is not what actually takes place; it is *imagined* in order to analyze the process. In a [1,3]-sigmatropic rearrangement, the imaginary transition state consists of a hydrogen atom and an allyl radical. The latter species (Sec. 2.C, category 3) has three π orbitals, but the only one that is of concern, the HOMO, which, in a thermal rearrangement is **D**. The electron of the hydrogen atom is of course in a $1s$ orbital, which has only one lobe. The rule governing sigmatropic migration of hydrogen is *the H must move from a plus to a plus or from a minus to a minus lobe, of the HOMO*; it cannot move to a lobe of opposite sign.⁵⁶⁶ The only way this can happen in a thermal [1,3]-sigmatropic rearrangement is by an antarafacial migration. Consequently, the rule predicts that antarafacial thermal [1,3]-sigmatropic rearrangements are allowed, but the suprafacial pathway is forbidden. However, in a photochemical reaction, promotion of an electron means that **E** is now the HOMO; the suprafacial pathway is now allowed and the antarafacial pathway is forbidden.



A similar analysis of [1,5]-sigmatropic rearrangements shows that in this case the thermal reaction must be suprafacial and the photochemical process antarafacial. For the general case, with odd-numbered j , [1, j]-suprafacial migrations are allowed thermally when j is of the form $4n + 1$, and photochemically when j has the form $4n - 1$; the opposite is true for antarafacial migrations.

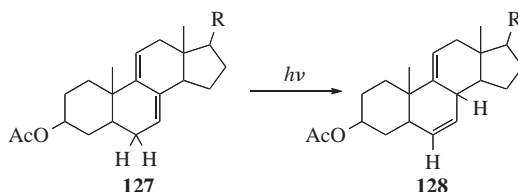


⁵⁶⁵ See Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, **1970**, pp. 114–140.

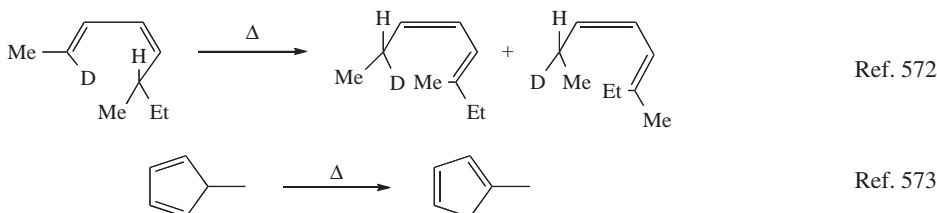
⁵⁶⁶ This follows from the principle that bonds are formed only by overlap of orbitals of the same sign. Since this is a concerted reaction, the hydrogen orbital in the transition state must overlap simultaneously with one lobe from the migration origin and one from the terminus. It is obvious that both of these lobes must have the same sign.

As expected, the *Möbius–Hückel* method leads to the same predictions. Here, examine the basis set of orbitals shown in **F** and **G** for [1,3]- and [1,5]-rearrangements, respectively. A [1,3]-shift involves four electrons, so an allowed thermal pericyclic reaction must be a *Möbius* system (**15-60**, the *Möbius–Hückel* Method) with one or an odd number of sign inversions. As can be seen in **F**, only an antarafacial migration can achieve this. A [1,5]-shift, with six electrons, is allowed thermally only when it is a *Hückel* system with zero or an even number of sign inversions; hence it requires a suprafacial migration.⁵⁶⁷

The actual reported results bear out this analysis. Thus a thermal [1,3]-migration is allowed to take place only antarafacially, but such a transition state would be extremely strained, and thermal [1,3]-sigmatropic migrations of hydrogen are unknown.⁵⁶⁸ On the other hand, the photochemical pathway allows suprafacial [1,3]-shifts, and a few such reactions are known, an example being the photochemical rearrangement of **127** to **128**.⁵⁶⁹ Substituents influence the efficacy of the [1,3]-hydrogen shift.⁵⁷⁰



The situation is reversed for [1,5]-hydrogen shifts. In this case, the thermal rearrangements, being suprafacial, are quite common, while photochemical rearrangements are rare.⁵⁷¹ Two examples of the thermal reaction are



Note that the first example bears out the stereochemical prediction made earlier. Only the two isomers shown were formed. In the second example, migration can continue around the ring. Migrations of this kind are called *circumambulatory rearrangements*,⁵⁷⁴ and such migrations

⁵⁶⁷ See Kless, A.; Nendel, M.; Wilsey, S.; Houk, K.N. *J. Am. Chem. Soc.* **1999**, *121*, 4524.

⁵⁶⁸ See, however, Yeh, M.; Linder, L.; Hoffman, D.K.; Barton, T.J. *J. Am. Chem. Soc.* **1986**, *108*, 7849. See also, Pasto, D.J.; Brophy, J.E. *J. Org. Chem.* **1991**, *56*, 4554.

⁵⁶⁹ Dauben, W.G.; Wipke, W.T. *Pure Appl. Chem.* **1964**, *9*, 539, p. 546. See Kropp, P.J.; Fravel, Jr., H.G.; Fields, T.R. *J. Am. Chem. Soc.* **1976**, *98*, 840.

⁵⁷⁰ Hudson, C.E.; McAdoo, D.J. *J. Org. Chem.* **2003**, *68*, 2735.

⁵⁷¹ See Kiefer, E.F.; Tanna, C.H. *J. Am. Chem. Soc.* **1969**, *91*, 4478; Dauben, W.G.; Poulter, C.D.; Suter, C. *J. Am. Chem. Soc.* **1970**, *92*, 7408.

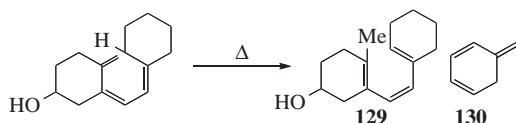
⁵⁷² Roth, W.R.; König, J.; Stein, K. *Chem. Ber.* **1970**, *103*, 426.

⁵⁷³ See Klärner, F. *Top. Stereochem.* **1984**, *15*, 1; Hess, Jr., B.A.; Baldwin, J.E. *J. Org. Chem.* **2002**, *67*, 6025.

⁵⁷⁴ Childs, R.F. *Tetrahedron* **1982**, *38*, 567. See also, Minkin, V.I.; Mikhailov, I.E.; Dushenko, G.A.; Yudilevich, J.A.; Minyaev, R.M.; Zschunke, A.; Mügge, K. *J. Phys. Org. Chem.* **1991**, *4*, 31. For a study of [1,5]-sigmatropic shiftamers, see Tantillo, D.J.; Hoffmann, R. *Acc. Chem. Res.* **2006**, *39*, 477.

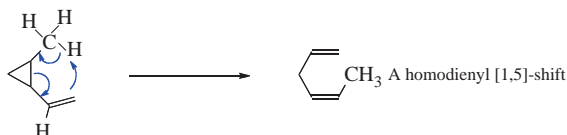
are known for cyclopentadiene,⁵⁷⁵ pyrrole, and phosphole derivatives.⁵⁷⁶ Geminal bond participation has been observed in pentadienes,⁵⁷⁷ the effects of phenyl substituents have been studied,⁵⁷⁸ and the kinetics and activation parameters of [1,5]-hydrogen shifts have been examined.⁵⁷⁹ The [1,5]-hydrogen shifts are also known with vinyl aziridines.⁵⁸⁰ A Ru catalyzed cycloisomerization of en-1-yne leads to cyclic dienes.⁵⁸¹

The rare [1,4]-hydrogen transfer has been observed in radical cyclizations.⁵⁸² With respect to [1,7]-hydrogen shifts, the rules predict the thermal reaction to be antarafacial.⁵⁸³ Unlike the case of [1,3]-shifts, the transition state is not too greatly strained, and an example of such rearrangements is the formation of **129** and **130**.⁵⁸⁴ Photochemical [1,7]-shifts are suprafacial and, not surprisingly, many of these have been observed.⁵⁸⁵



The orbital symmetry rules also help to explain the unexpected stability of certain compounds (see Reaction **15-63**, preceding Reaction **15-64** and **18-27**, the *Möbius-Hückel* Method). Thus, **130** could, by a thermal [1,3]-sigmatropic rearrangement, easily convert to toluene, which of course is far more stable because it has an aromatic sextet. Yet **130** has been prepared and is stable at dry ice temperature and in dilute solutions.⁵⁸⁶

Analogues of sigmatropic rearrangements in which a cyclopropane ring replaces one of the double bonds are also known, for example,⁵⁸⁷



The reverse reaction has also been reported.⁵⁸⁸ 2-Vinylcycloalkanols⁵⁸⁹ undergo an analogous reaction, as do cyclopropyl ketones (see **18-33**, preceding **18-34** for this reaction).

⁵⁷⁵ Shelton, G.R.; Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* **2007**, 129, 164.

⁵⁷⁶ Bachrach, S.M. *J. Org. Chem.* **1993**, 58, 5414.

⁵⁷⁷ Ikeda, H.; Ushioda, N.; Inagaki, S. *Chem. Lett.* **2001**, 166.

⁵⁷⁸ Hayase, S.; Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* **2004**, 126, 10028.

⁵⁷⁹ Baldwin, J.E.; Raghavan, A.S.; Hess, Jr., B.A.; Smentek, L. *J. Am. Chem. Soc.* **2006**, 128, 14854; Baldwin, J.E.; Chapman, B.R. *J. Org. Chem.* **2005**, 70, 377. See also von E. Doering, W.; Keliher, E.J. *J. Am. Chem. Soc.* **2007**, 129, 2488; Peles, D.N.; Thoburn, J.D. *J. Org. Chem.* **2008**, 73, 3135.

⁵⁸⁰ Somfai, P.; Åhman, J. *Tetrahedron Lett.* **1995**, 36, 1953.

⁵⁸¹ Datta, S.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, 127, 11606.

⁵⁸² Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, 33, 1893.

⁵⁸³ See Hess Jr., B.A. *J. Org. Chem.* **2001**, 66, 5897.

⁵⁸⁴ Gurskii, M.E.; Gridnev, I.D.; Il'ichev, Y.V.; Ignatenko, A.V.; Bubnov, Y.N. *Angew. Chem. Int. Ed.* **1992**, 31, 781; Baldwin, J.E.; Reddy, V.P. *J. Am. Chem. Soc.* **1988**, 110, 8223.

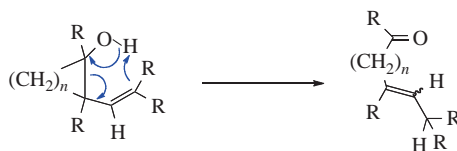
⁵⁸⁵ See ter Borg, A.P.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* **1969**, 88, 266; Tezuka, T.; Kimura, M.; Sato, A.; Mukai, T. *Bull. Chem. Soc. Jpn.* **1970**, 43, 1120.

⁵⁸⁶ Bailey, W.J.; Baylouny, R.A. *J. Org. Chem.* **1962**, 27, 3476.

⁵⁸⁷ See Parziale, P.A.; Berson, J.A. *J. Am. Chem. Soc.* **1990**, 112, 1650; Pegg, G.G.; Meehan, G.V. *Aust. J. Chem.* **1990**, 43, 1009, 1071.

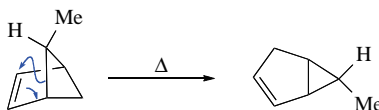
⁵⁸⁸ Roth, W.R.; König, J. *Liebigs Ann. Chem.* **1965**, 688, 28. See, Grimme, W. *Chem. Ber.* **1965**, 98, 756.

⁵⁸⁹ Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc.* **1960**, 82, 4918; Leriverend, P.; Conia, J.M. *Tetrahedron Lett.* **1969**, 2681; Conia, J.M.; Barnier, J.P. *Tetrahedron Lett.* **1969**, 2679.



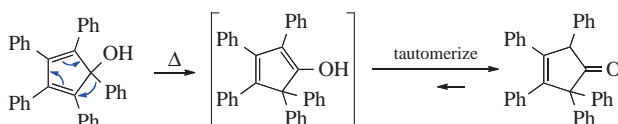
18-30 [1,j]-Sigmatropic Migrations of Carbon

[1,3] migration of alkyl



Ref. 590

[1,5] migration of phenyl



Ref. 591

Sigmatropic migrations of alkyl or aryl groups⁵⁹² are less common than the corresponding hydrogen migrations.⁵⁹³ When they do take place, there is an important difference. Unlike a hydrogen atom, whose electron is in a $1s$ orbital with only one lobe, a carbon free radical has its odd electron in a p orbital that has *two lobes of opposite sign*. Therefore, if the imaginary transition states for this case are drawn (see above), a thermal suprafacial [1,5]-process (Fig. 18.5) is observed, and symmetry can be conserved only if the migrating carbon moves in such a way that the lobe that was originally attached to the π system remains attached to the π system.

This can happen only if configuration is *retained within the migrating group*. On the other hand, thermal suprafacial [1,3]-migration (Fig. 18.6) *can* take place if the migrating carbon switches lobes. If the migrating carbon was originally bonded by its minus lobe, it must now use its plus lobe to form the new C—C bond. Thus, configuration in the migrating group will be *inverted*. From these considerations, suprafacial [1, j]-sigmatropic rearrangements in which carbon is the migrating group should always be allowed, both thermally and photochemically, but thermal [1,3]-migrations⁵⁹⁴ will proceed with inversion and thermal [1,5]-migrations with retention of configuration within the migrating group. More generally, suprafacial [1, j]-migrations of carbon in systems where $j = 4n - 1$ proceed with inversion thermally and retention photochemically, while systems where $j = 4n + 1$ show the opposite behavior. Where antarafacial migrations take place, all these predictions are of course reversed.

⁵⁹⁰ Roth, W.R.; Friedrich, A. *Tetrahedron Lett.* **1969**, 2607.

⁵⁹¹ Youssef, A.K.; Ogliaruso, M.A. *J. Org. Chem.* **1972**, 37, 2601.

⁵⁹² See Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* **1981**, 50, 666; Spangler, C.W. *Chem. Rev.* **1976**, 76, 187.

⁵⁹³ See Shen, K.; McEwen, W.E.; Wolf, A.P. *Tetrahedron Lett.* **1969**, 827; Miller, L.L.; Greisinger, R.; Boyer, R.F. *J. Am. Chem. Soc.* **1969**, 91, 1578.

⁵⁹⁴ See Baldwin, J.E.; Leber, P.A. *Org. Biomol. Chem.* **2008**, 6, 35.

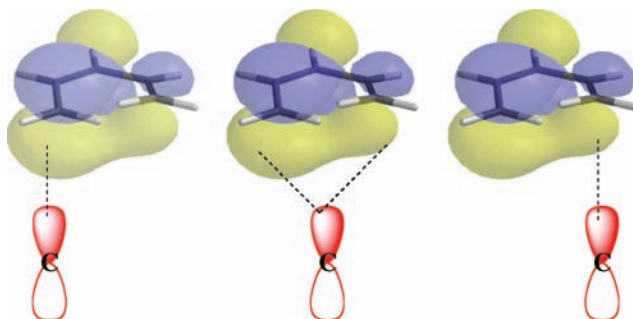


FIG. 18.5. Hypothetical orbital movement for a thermal [1,5]-sigmatropic migration of carbon. To move from one negative lobe, the migrating carbon uses only its own negative lobe, retaining its configuration.

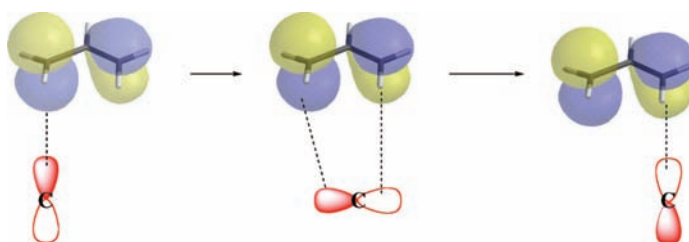


FIG. 18.6. Hypothetical orbital movement for a thermal [1,3]-sigmatropic migration of carbon. The migrating carbon moves a negative to a positive lobe, requiring it to switch its own bonding lobe from negative to positive, inverting its configuration.

The first laboratory test of these predictions was the pyrolysis of deuterated *endo*-bicyclo[3.2.0]hept-2-en-6-yl acetate (**131**), which gave the *exo*-deuterio-*exo*-norbornyl acetate (**132**).⁵⁹⁵ Thus, as predicted by the orbital symmetry rules, this thermal suprafacial [1,3]-sigmatropic reaction took place with complete inversion at C-7. Similar results have been obtained in a number of other cases.⁵⁹⁶ However, similar studies of the pyrolysis of the parent hydrocarbon of **131**, labeled with D at C-6 and C-7, showed that while most of the product was formed with inversion at C-7, a significant fraction (11–29%) was formed with retention.⁵⁹⁷ Other cases of lack of complete inversion are also known.⁵⁹⁸ A diradical mechanism has been invoked to explain such cases.⁵⁹⁹ There is strong evidence for a radical mechanism for some [1,3]-sigmatropic rearrangements.⁶⁰⁰

⁵⁹⁵ Berson, J.A. *Acc. Chem. Res.* **1968**, *1*, 152.

⁵⁹⁶ See Berson, J.A. *Acc. Chem. Res.* **1972**, *5*, 406; Klärner, F.; Adamsky, F. *Angew. Chem. Int. Ed.* **1979**, *18*, 674.

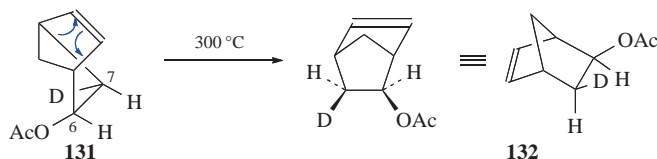
⁵⁹⁷ Baldwin, J.E.; Belfield, K.D. *J. Am. Chem. Soc.* **1988**, *110*, 296; Klärner, F.; Drewes, R.; Hasselmann, D. *J. Am. Chem. Soc.* **1988**, *110*, 297.

⁵⁹⁸ See Pikulin, S.; Berson, J.A. *J. Am. Chem. Soc.* **1988**, *110*, 8500.

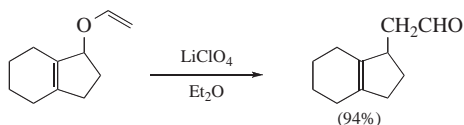
⁵⁹⁹ See Pikulin, S.; Berson, J.A. *J. Am. Chem. Soc.* **1988**, *110*, 8500. See also, Berson, J.A. *Chemtracts: Org. Chem.* **1989**, *2*, 213.

⁶⁰⁰ See Dolbier, W.B.; Phanstiel IV, O. *J. Am. Chem. Soc.* **1989**, *111*, 4907.

Photochemical suprafacial [1,3]-migrations of carbon have been shown to proceed with retention, as predicted.⁶⁰¹



Although allylic vinylic ethers generally undergo [3,3]-sigmatropic rearrangements (Reaction 18-33), they can be made to give the [1,3] kind, to give aldehydes, for example,

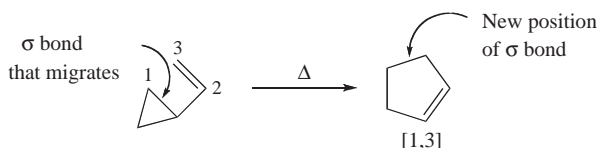


by treatment with LiClO_4 in diethyl ether.⁶⁰² In this case, the C—O bond undergoes a 1,3-migration from the O to the end vinylic carbon. When the vinylic ether is of the type $\text{ROCR}'=\text{CH}_2$, ketones ($\text{RCH}_2\text{COR}'$) are formed. There is evidence that this [1,3]-sigmatropic rearrangement is not concerted, but involves dissociation of the substrate into ions.⁶⁰²

Thermal suprafacial [1,5]-migrations of carbon have been found to take place with retention,⁶⁰³ but also with inversion.⁶⁰⁴ A diradical mechanism has been suggested for the latter case.⁶⁰⁴

Simple nucleophilic, electrophilic, and free radical 1,2-shifts can also be regarded as sigmatropic rearrangements (in this case, [1,2]-rearrangements). As previously discussed (see discussion in introductory section preceding 18.A) similar principles applied to such rearrangements show that nucleophilic 1,2-shifts are allowed, but the other two types are forbidden unless the migrating group has some means of delocalizing the extra electron or electron pair. The mechanism of the forbidden [3s,5s]-sigmatropic shift has been examined.⁶⁰⁵

18-31 Conversion of Vinylcyclopropanes to Cyclopentenenes



The thermal expansion of a vinylcyclopropane to a cyclopentene ring⁶⁰⁶ is a special case of a [1,3]-sigmatropic migration of carbon, although it can also be considered an internal

⁶⁰¹ Cookson, R.C.; Hudec, J.; Sharma, M. *Chem. Commun.* **1971**, 107, 108.

⁶⁰² Grieco, P.A.; Clark, J.D.; Jagoe, C.T. *J. Am. Chem. Soc.* **1991**, *113*, 5488; Palani, N.; Balasubramanian, K.K. *Tetrahedron Lett.* **1995**, *36*, 9527.

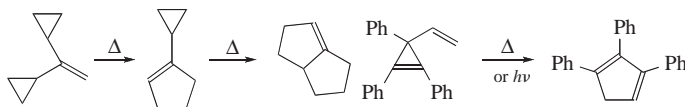
⁶⁰³ Boersma, M.A.M.; de Haan, J.W.; Kloosterziel, H.; van de Ven, L.J.M. *Chem. Commun.* **1970**, 1168.

⁶⁰⁴ See Gajewski, J.J.; Gortva, A.M.; Borden, J.E. *J. Am. Chem. Soc.* **1986**, *108*, 1083; Baldwin, J.E.; Broline, B.M. *J. Am. Chem. Soc.* **1982**, *104*, 2857.

⁶⁰⁵ Leach, A.G.; Catak, S.; Houk, K.N. *Chem. Eur. J.* **2002**, *8*, 1290.

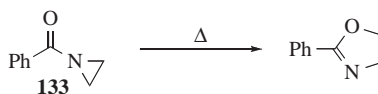
⁶⁰⁶ See Baldwin, J.E. *Chem. Rev.* **2003**, *103*, 1197; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165, pp. 169–172; Hudlicky, T.; Kutchan, T.M.; Naqvi, S.M. *Org. React.* **1985**, *33*, 247; Hudlicky, T.; Reed, J.W. *Angew. Chem. Int. Ed.* **2010**, *49*, 4864. See Tanko, J.M.; Li, X.; Chahma, M.; Jackson, W.F.; Spencer, J.N. *J. Am. Chem. Soc.* **2007**, *129*, 4181.

[$\pi 2 + \sigma 2$]-cycloaddition reaction (see **15-63**). It is known as a *vinylcyclopropane rearrangement*.⁶⁰⁷ The reaction has been carried out on many vinylcyclopropanes bearing various substituents in the ring⁶⁰⁸ or on the vinyl group and has been extended to 1,1-dicyclopropylethene⁶⁰⁹ and (both thermally⁶¹⁰ and photochemically⁶¹¹) to vinylcyclopropenes. This



rearrangement can be catalyzed by Rh and Ag compounds, and has been used to form rings.⁶¹² Two competing reactions are the homodienyl [1,5]-shift (if a suitable H is available, see **18-29**), and simple cleavage of the cyclopropane ring, leading in this case to a diene (see **18-3**).

Flash vacuum pyrolysis of the trimethylsilyl ether of cyclopropylcarbinyl alcohols gives ring expanded ketones.⁶¹³ Various heterocyclic analogues⁶¹⁴ are also known, as in the rearrangement of aziridinyl amides (**133**).⁶¹⁵ Cyclopropyl ketones can be treated with tosylamine and a Zr catalyst, which converts the imine formed *in situ* to a pyrroline.⁶¹⁶ *N*-Cyclopropylimines undergo rearrangement to cyclic imines (pyrrolines) under photochemical conditions.⁶¹⁷ *P*-Vinyl phosphiranes (the P analogue of cyclopropanes with P in the ring) under a similar rearrangement, and the mechanism has been studied.⁶¹⁸



Vinylcyclobutanes can be converted to cyclohexenes,⁶¹⁹ but larger ring compounds do not generally give the reaction.⁶²⁰ Tricyclo[4.1.0.0^{2,5}]heptanes rearrange to give nonconjugated cycloheptadienes.⁶²¹ The bicyclo[2.1.0]pentane derivatives undergo this reaction.

⁶⁰⁷ See Armesto, D.; Ramos, A.; Mayoral, E.P.; Ortiz, M.J.; Agarrabeitia, A.R. *Org. Lett.* **2000**, 2, 183.

⁶⁰⁸ For a study of substituent effects, see McGaffin, G.; Grimm, B.; Heinecke, U.; Michaelsen, H.; de Meijere, A.; Walsh, R. *Eur. J. Org. Chem.* **2001**, 3559.

⁶⁰⁹ Ketley, A.D. *Tetrahedron Lett.* **1964**, 1687; Branton, G.R.; Frey, H.M. *J. Chem. Soc. A* **1966**, 1342.

⁶¹⁰ Small, A.; Breslow, R. cited in Breslow, R. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, **1963**, p. 236.

⁶¹¹ Zimmerman, H.E.; Kreil, D.J. *J. Org. Chem.* **1982**, 47, 2060.

⁶¹² Wender, P.A.; Husfeld, C.O.; Langkopf, E.; Love, J.A. *J. Am. Chem. Soc.* **1998**, 120, 1940.

⁶¹³ Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* **2004**, 6, 2989.

⁶¹⁴ See Boeckman Jr., R.K.; Walters, M.A. *Adv. Heterocycl. Nat. Prod. Synth.* **1990**, 1, 1.

⁶¹⁵ Heine, H.W. *Mech. Mol. Migr.* **1971**, 3, 145; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, **1969**, pp. 282–290. See also, Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, 89, 165, pp. 190–192.

⁶¹⁶ Shi, M.; Yang, Y.-H.; Xu, B. *Synlett* **2004**, 1622.

⁶¹⁷ Campos, P.J.; Soldevilla, A.; Sampedro, D.; Rodriguez, M.A. *Org. Lett.* **2001**, 3, 4087.

⁶¹⁸ Mátrai, J.; Dransfeld, A.; Veszprém, T.; Nguyen, M.T. *J. Org. Chem.* **2001**, 66, 5671.

⁶¹⁹ See Baldwin, J.E.; Fedé, J.-M. *J. Am. Chem. Soc.* **2006**, 128, 5608; Northrop, B.H.; Houk, K.N. *J. Org. Chem.* **2006**, 71, 3; Leber, P.A.; Baldwin, J.E. *Acc. Chem. Res.* **2002**, 35, 279.

⁶²⁰ See Thies, R.W. *J. Am. Chem. Soc.* **1972**, 94, 7074.

⁶²¹ Deak, H.L.; Stokes, S.S.; Snapper, M.L. *J. Am. Chem. Soc.* **2001**, 123, 5152.

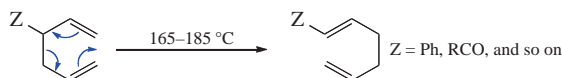
The reaction rate has also been greatly increased by the addition of a one-electron oxidant tris-(4-bromophenyl)aminium hexafluoroantimonate ($\text{Ar}_3\text{N}^+\text{SbF}_6^-$, $\text{Ar} = p\text{-bromophenyl}$).⁶²² This reagent converts the substrate to a cation radical, which undergoes ring expansion much faster.⁶²³

The mechanisms of these ring expansions are not certain. Both concerted⁶²⁴ and diradical⁶²⁵ pathways have been proposed,⁶²⁶ and it is possible that both pathways operate, in different systems.

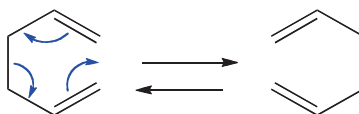
For the conversion of a vinylcyclopropane to a cyclopentene in a different way, see OS 68, 220.

18-32 The Cope Rearrangement

(3/4)→(1/6)-sigma-Migration



When 1,5-dienes are heated, a [3,3]-sigmatropic rearrangement known as the *Cope rearrangement* (not to be confused with the *Cope elimination* Reaction, 17-9) occurs to generate an isomeric 1,5-diene.⁶²⁷ When the diene is symmetrical about the 3,4-bond, the reaction gives a product identical with the starting material⁶²⁸:



Therefore, a *Cope rearrangement* can be detected only when the diene is not symmetrical about this bond. Any 1,5-diene gives the rearrangement; for example, 3-methyl-1,5-hexadiene heated to 300 °C gives 1,5-heptadiene.⁶²⁹ However, the reaction takes place more easily (lower temperature required) when there is a group on the C-3 or C-4 which leads to the new double bond being substituted. The reaction is reversible⁶³⁰ and produces an equilibrium mixture of the two 1,5-dienes, which is *richer in the thermodynamically*

⁶²² Dinnocenzo, J.P.; Conlan, D.A. *J. Am. Chem. Soc.* **1988**, *110*, 2324.

⁶²³ See Bauld, N.L. *Tetrahedron* **1989**, *45*, 5307. For a rearrangement of a housane cation radical, see Gerken, J.B.; Wang, S.C.; Preciado, A.B.; Park, Y.S.; Nishiguchi, G.; Tantillo, D.J.; Little, R.D. *J. Org. Chem.* **2005**, *70*, 4598.

⁶²⁴ See Gajewski, J.J.; Olson, L.P. *J. Am. Chem. Soc.* **1991**, *113*, 7432.

⁶²⁵ See Zimmerman, H.E.; Fleming, S.A. *J. Am. Chem. Soc.* **1983**, *105*, 622; Klumpp, G.W.; Schakel, M. *Tetrahedron Lett.* **1983**, *24*, 4595; McGaffin, G.; de Meijere, A.; Walsh, R. *Chem. Ber.* **1991**, *124*, 939. See Roth, W.R.; Lennartz, H.; Doering, W. von E.; Birladeanu, L.; Guyton, C.A.; Kitagawa, T. *J. Am. Chem. Soc.* **1990**, *112*, 1722 and references cited therein.

⁶²⁶ See Gajewski, J.J.; Olson, L.P.; Willcott III, M.R. *J. Am. Chem. Soc.* **1996**, *118*, 299. For a discussion of the mechanism of this reaction, see Su, M.-D. *Tetrahedron* **1995**, *51*, 5871.

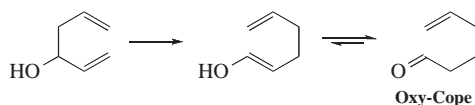
⁶²⁷ Bartlett, P.A. *Tetrahedron* **1980**, *36*, 2, pp. 28–39; Rhoads, S.J.; Raulins, N.R. *Org. React.* **1975**, *22*, 1; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* **1971**, *8*, 75, pp. 153–201; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, pp. 455–461.

⁶²⁸ Note that the same holds true for [1,7]-sigmatropic reactions of symmetrical substrates (18-28 and 18-29).

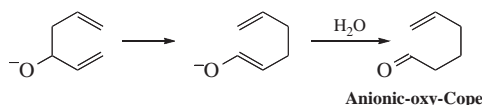
⁶²⁹ Levy, H.; Cope, A.C. *J. Am. Chem. Soc.* **1944**, *66*, 1684.

⁶³⁰ See Cooper, N.J.; Knight, D.W. *Tetrahedron* **2004**, *60*, 243.

more stable isomer. However, the equilibrium can be shifted to the right for 3-hydroxy-1,5-dienes,⁶³¹ because the product tautomerizes to the ketone or aldehyde:



This reaction of 3-hydroxy-1,5-dienes is called the *oxy-Cope rearrangement*,⁶³² and has proved highly useful in synthesis.⁶³³ The *oxy-Cope rearrangement* is greatly accelerated (by factors of 10^{10} – 10^{17}) if the alkoxide is used rather than the alcohol (the *anionic oxy-Cope rearrangement*),⁶³⁴ where the direct product is the enolate ion, which is hydrolyzed to the ketone. A metal-free reaction using a phosphazene base has been reported.⁶³⁵ The silyloxy-*Cope rearrangement* has proven to be quite useful.⁶³⁶ An antibody-catalyzed *oxy-Cope reaction* is known,⁶³⁷ and the mechanism and origins of catalysis for this reaction have been studied.⁶³⁸ Sulfur substituents also lead to rate enhancement of the *oxy-Cope rearrangement*.⁶³⁹ Note that 2-*oxonia Cope rearrangements* have been implicated in *Prins cyclization* reactions (16-54).⁶⁴⁰ A highly diastereoselective *oxonia-Cope rearrangement* proceeded using a chiral aldehyde with a chiral conjugated ester.⁶⁴¹



aza-Cope rearrangements are also known.⁶⁴² There is an enantioselective *aza-Cope rearrangement*.⁶⁴³ There is also a 1,2-*oxaza-Cope rearrangement*. Involving esters and alkyl nitrites.⁶⁴⁴ In *amino-Cope rearrangements*, the solvent plays a role in the regioselectivity of the reaction.⁶⁴⁵ It has been suggested that this latter reaction does not proceed solely by a concerted [3.3]-sigmatropic rearrangement.⁶⁴⁶

⁶³¹ See Elmore, S.W.; Paquette, L.A. *Tetrahedron Lett.* **1991**, 32, 319.

⁶³² Paquette, L.A. *Angew. Chem. Int. Ed.* **1990**, 29, 609; Marvel, E.N.; Whalley, W. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, **1971**, pp. 738–743; Warrington, J.M.; Yap, G.P.A.; Barriault, L. *Org. Lett.* **2000**, 2, 663; Ovaska, T.V.; Roses, J.B. *Org. Lett.* **2000**, 2, 2361; Jung, M.E.; Nishimura, N.; Novack, A.R. *J. Am. Chem. Soc.* **2005**, 127, 11206.

⁶³³ For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley-VCH, NY, **1999**, pp. 1306–1307.

⁶³⁴ See Gajewski, J.J.; Gee, K.R. *J. Am. Chem. Soc.* **1991**, 113, 967. See also, Wender, P.A.; Ternansky, R.J.; Sieburth, S.M. *Tetrahedron Lett.* **1985**, 26, 4319. Also see Schulze, S.M.; Santella, N.; Grabowski, J.J.; Lee, J.K. *J. Org. Chem.* **2001**, 66, 7247.

⁶³⁵ Mamdani, H.T.; Hartley, R.C. *Tetrahedron Lett.* **2000**, 41, 747.

⁶³⁶ For a review, see Schneider, C. *Synlett* **2001**, 1079.

⁶³⁷ Braisted, A.C.; Schultz, P.G. *J. Am. Chem. Soc.* **1994**, 116, 2211.

⁶³⁸ Black, K.A.; Leach, A.G.; Kalani, Y.S.; Houk, K.N. *J. Am. Chem. Soc.* **2004**, 126, 9695.

⁶³⁹ Paquette, L.A.; Reddy, Y.R.; Vayner, G.; Houk, K.N. *J. Am. Chem. Soc.* **2000**, 122, 10788.

⁶⁴⁰ See Jasti, R.; Anderson, C.D.; Rychnovsky, S.D. *J. Am. Chem. Soc.* **2005**, 127, 9939.

⁶⁴¹ Chen, Y.-H.; McDonald, F.E. *J. Am. Chem. Soc.* **2006**, 128, 4568.

⁶⁴² Beholz, L.G.; Stille, J.R. *J. Org. Chem.* **1993**, 58, 5095; Sprules, T.J.; Galpin, J.D.; Macdonald, D. *Tetrahedron Lett.* **1993**, 34, 247; Yadav, J.S.; Reddy, B.V.S.; Rasheed, M.A.; Kumar, H.M.S. *Synlett* **2000**, 487.

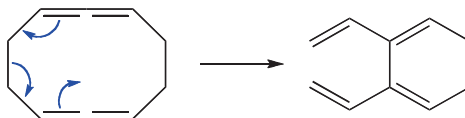
⁶⁴³ Rueping, M.; Antonchick, A.P. *Angew. Chem. Int. Ed.* **2008**, 47, 10090.

⁶⁴⁴ Zakarian, A.; Lu, C.-D. *J. Am. Chem. Soc.* **2006**, 128, 5356.

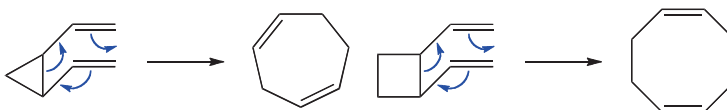
⁶⁴⁵ Dobson, H.K.; LeBlanc, R.; Perrier, H.; Stephenson, C.; Welch, T.R.; Macdonald, D. *Tetrahedron Lett.* **1999**, 40, 3119.

⁶⁴⁶ Allin, S.M.; Button, M.A.C. *Tetrahedron Lett.* **1999**, 40, 3801.

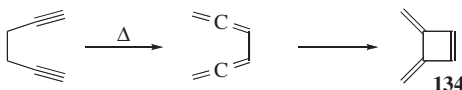
The 1,5-diene system may be inside a ring or part of an allenic system⁶⁴⁷ (the example shown illustrates both of these situations).⁶⁴⁸ However, the reaction does not take place when one of the double bonds is part of



an aromatic system (e.g., 4-phenyl-1-butene).⁶⁴⁹ When the two double bonds are in vinylic groups attached to adjacent ring positions, the product is a ring four carbons larger. This has been applied to divinylcyclopropanes and divinylcyclobutanes, as shown.⁶⁵⁰ Indeed, *cis*-1,2-divinylcyclopropanes give this rearrangement so rapidly



that they generally cannot be isolated at room temperature,⁶⁵¹ but exceptions are known.⁶⁵² Note that divinylloxiranes, divinylphosphiranes, and divinylthiiranes undergo similar rearrangements.⁶⁵³ When heated, 1,5-diynes are converted to 3,4-dimethylenecyclobutenes (**134**).⁶⁵⁴ A rate-determining *Cope rearrangement* is followed by a very rapid electrocyclic (**18-27**) reaction.



The interconversion of 1,3,5-trienes and cyclohexadienes (in Reaction **18-27**) is very similar to the *Cope rearrangement*, but in **18-27**, the 3,4-bond goes from a double to a single bond rather than from a single bond to no bond. Like [2 + 2]-cycloadditions (Reaction **15-63**), *Cope rearrangements* of simple 1,5-dienes can be catalyzed by certain transition metal compounds. For example, the addition of a Pd catalyst causes the reaction to take place at room temperature.⁶⁵⁵

⁶⁴⁷ Duncan, J.A.; Azar, J.K.; Beatle, J.C.; Kennedy, S.R.; Wulf, C.M. *J. Am. Chem. Soc.* **1999**, *121*, 12029.

⁶⁴⁸ Harris, Jr., J.F. *Tetrahedron Lett.* **1965**, 1359.

⁶⁴⁹ See Newcomb, M.; Vieta, R.S. *J. Org. Chem.* **1980**, *45*, 4793. Also see Jung, M.E.; Hudspeth, J.P. *J. Am. Chem. Soc.* **1978**, *100*, 4309; Yasuda, M.; Harano, K.; Kanematsu, K. *J. Org. Chem.* **1980**, *45*, 2368.

⁶⁵⁰ Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165, see pp. 172–174; Mil'vitskaya, E.M.; Tarakanova, A.V.; Plate, A.F. *Russ. Chem. Rev.* **1976**, *45*, 469, see pp. 475–476.

⁶⁵¹ See Schneider, M.P.; Rebell, J. *J. Chem. Soc., Chem. Commun.* **1975**, 283.

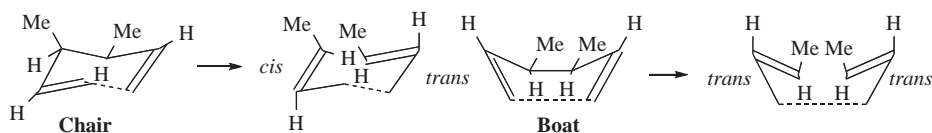
⁶⁵² See Schneider, M.P.; Rau, A. *J. Am. Chem. Soc.* **1979**, *101*, 4426.

⁶⁵³ Zora, M. *J. Org. Chem.* **2005**, *70*, 6018.

⁶⁵⁴ Viola, A.; Collins, J.J.; Filipp, N. *Tetrahedron* **1981**, *37*, 3765; Théron F.; Verny, M.; Vessière, R. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, **1978**, pp. 381–445, pp. 428–430; Huntsman, W.D. *Intra-Sci. Chem. Rep.*, **1972**, *6*, 151.

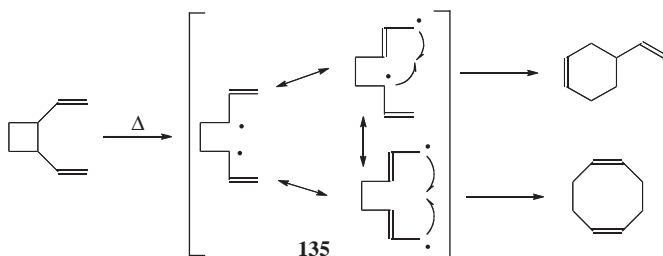
⁶⁵⁵ Siebert, M.R.; Tantillo, D.J. *J. Am. Chem. Soc.* **2007**, *129*, 8686. Overman, L.E. *Angew. Chem. Int. Ed.* **1984**, *23*, 579; Lutz, R.P. *Chem. Rev.* **1984**, *84*, 205. See Overman, L.E.; Renaldo, A.F. *J. Am. Chem. Soc.* **1990**, *112*, 3945.

As indicated with the arrows, the mechanism of the uncatalyzed *Cope rearrangement* is a simple six-centered pericyclic process.⁶⁵⁶ Since the mechanism is so simple, it has been possible to study some rather subtle points, among them the question of whether the six-membered transition state is in the boat or the chair form.⁶⁵⁷ For the case of 3,4-dimethyl-1,5-hexadiene, it was demonstrated conclusively that the transition state is in the chair form. This was shown by the stereospecific nature of the reaction: The meso isomer gave the *cis*–*trans* product, while the (\pm) diastereomer gave the *trans*–*trans*-diene.⁶⁵⁸ If the transition state is in the chair form (taking the meso isomer, e.g.), one methyl must be “axial” and the other “equatorial” and the product must be the



cis–*trans*-alkene. There are two possible boat forms for the transition state of the meso isomer. One leads to a *trans*–*trans* product; the other to a *cis*–*cis*-alkene. For the (\pm) pair, the predictions are just the opposite: There is just one boat form, and it leads to the *cis*–*trans*-alkene, while one chair form (“diaxial” methyls) leads to the *cis*–*cis* product and the other (“diequatorial” methyls) predicts the *trans*–*trans* product. Thus the nature of the products obtained demonstrates that the transition state is a chair and not a boat.⁶⁵⁹ While 3,4-dimethyl-1,5-hexadiene is free to assume either the chair or boat (it prefers the chair), other compounds are not so free. Thus 1,2-divinylcyclopropane (see above) can react *only* in the boat form, demonstrating that such reactions are possible.⁶⁶⁰

Because of the nature of the transition state⁶⁶¹ in the pericyclic mechanism, optically active substrates with a stereogenic carbon at C-3 or C-4 transfer the chirality to the product (see Reaction 18-33 for an example in the mechanistically similar *Claisen rearrangement*).⁶⁶² There are many examples of asymmetric [3,3]-sigmatropic rearrangements.⁶⁶³



⁶⁵⁶ See Poupko, R.; Zimmermann, H.; Müller, K.; Luz, Z. *J. Am. Chem. Soc.* **1996**, *118*, 7995.

⁶⁵⁷ See Shea, K.J.; Stoddard, G.J.; England, W.P.; Haffner, C.D. *J. Am. Chem. Soc.* **1992**, *114*, 2635. See also, Tantillo, D.J.; Hoffmann, R. *J. Org. Chem.* **2002**, *67*, 1419.

⁶⁵⁸ Doering, W. von E.; Roth, W.R. *Tetrahedron* **1962**, *18*, 67. See also, Gajewski, J.J.; Benner, C.W.; Hawkins, C. M. *J. Org. Chem.* **1987**, *52*, 5198; Paquette, L.A.; DeRussy, D.T.; Cottrell, C.E. *J. Am. Chem. Soc.* **1988**, *110*, 890.

⁶⁵⁹ See Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* **1965**, *87*, 4389; Fukui, K.; Fujimoto, H. *Tetrahedron Lett.* **1966**, 251.

⁶⁶⁰ See Gajewski, J.J.; Jimenez, J.L. *J. Am. Chem. Soc.* **1986**, *108*, 468.

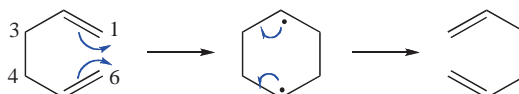
⁶⁶¹ See Özkan, I.; Zora, M. *J. Org. Chem.* **2003**, *68*, 9635.

⁶⁶² See Hill, R.K. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, **1984**, pp. 503–572, 503–545.

⁶⁶³ For a review, see Nubbemeyer, U. *Synthesis* **2003**, 961.

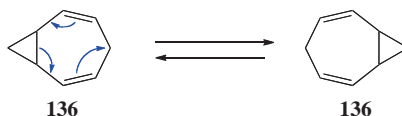
Not all *Cope rearrangements* proceed by the cyclic six-centered mechanism.⁶⁶⁴ Thus *cis*-1,2-divinylcyclobutane (see above) rearranges smoothly to 1,5-cyclooctadiene, since the geometry is favorable. The *trans* isomer also gives this product, but the main product is 4-vinylcyclohexene (resulting from Reaction **18-31**). This reaction can be rationalized as proceeding by a diradical mechanism (see **135**),⁶⁶⁵ although it is possible that at least part of the cyclooctadiene produced comes from a prior epimerization of the *trans*- to the *cis*-divinylcyclobutane followed by *Cope rearrangement* of the latter.⁶⁶⁶

It has been suggested that another type of diradical two-step mechanism may be preferred by some substrates.⁶⁶⁷ Indeed, a nonconcerted *Cope rearrangement* has been reported.⁶⁶⁸ In this pathway,⁶⁶⁹ the 1,6-bond is formed before the 3,4-bond breaks:



This is related to the *Bergman cyclization* that was introduced in Reaction **18-27**.

It was pointed out earlier that a *Cope rearrangement* of the symmetrical 1,5-hexadiene gives 1,5-hexadiene. This is a *degenerate Cope rearrangement* (Sec. 18.A.ii). Bicyclo[5.1.0]octadiene (**136**) undergoes a similar rearrangement.⁶⁷⁰ At room temperature, the NMR spectrum of this compound is in accord with the structure shown on the left. At 180 °C, it is converted by a *Cope reaction* to a compound equivalent to itself. The interesting thing is that at 180 °C the NMR spectrum shows that what exists is an equilibrium mixture of the two



structures. That is, at this temperature the molecule rapidly (faster than 10^3 times per second) changes back and forth between the two structures. This is called *valence tautomerism* and is quite distinct from resonance, even though only electrons shift⁶⁷¹ (see Sec. 2.N for other types of tautomerism). The positions of the nuclei are not the same in the two structures. Molecules like **136** that exhibit valence tautomerism (in this case, at

⁶⁶⁴ See Navarro-Vázquez, A.; Prall, M.; Schreiner, P.R. *Org. Lett.* **2004**, 6, 2981.

⁶⁶⁵ Hammond, G.S.; De Boer, C.D. *J. Am. Chem. Soc.* **1964**, 86, 899; Trecker, D.J.; Henry, J.P. *J. Am. Chem. Soc.* **1964**, 86, 902. Also see, Kessler, H.; Ott, W. *J. Am. Chem. Soc.* **1976**, 98, 5014. Also see Berson, J.A. in de Mayo, P. *Rearrangements in Ground and Excited States*, Academic Press, NY, **1980**, pp. 358–372.

⁶⁶⁶ See Baldwin, J.E.; Gilbert, K.E. *J. Am. Chem. Soc.* **1976**, 98, 8283. For a similar result in the 1,2-divinylcyclopropane series, see Baldwin, J.E.; Ullenius, C. *J. Am. Chem. Soc.* **1984**, 96, 1542.

⁶⁶⁷ Kaufmann, D.; de Meijere, A. *Chem. Ber.* **1984**, 117, 1128; Dewar, M.J.S.; Jie, C. *J. Am. Chem. Soc.* **1987**, 109, 5893; *J. Chem. Soc., Chem. Commun.* **1989**, 98. For evidence against this view, see Halevi, E.A.; Rom, R. *Isr. J. Chem.* **1989**, 29, 311; Owens, K.A.; Berson, J.A. *J. Am. Chem. Soc.* **1990**, 112, 5973.

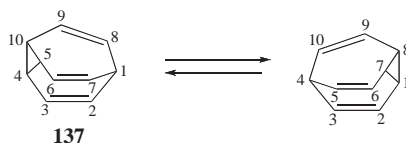
⁶⁶⁸ Roth, W.R.; Gleiter, R.; Paschmann, V.; Hackler, U.E.; Fritzsche, G.; Lange, H. *Eur. J. Org. Chem.* **1998**, 961; Roth, W.R.; Schaffers, T.; Heiber, M. *Chem. Ber.* **1992**, 125, 739.

⁶⁶⁹ For a report of still another mechanism, see Gompper, R.; Ulrich, W. *Angew. Chem. Int. Ed.* **1976**, 15, 299. See McGuire, M.J.; Piecuch, P. *J. Am. Chem. Soc.* **2005**, 127, 2608.

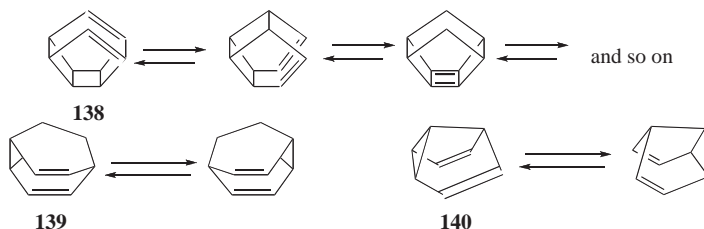
⁶⁷⁰ Doering, W. von E.; Roth, W.R. *Tetrahedron* **1963**, 19, 715.

⁶⁷¹ See Decock-Le Révérend, B.; Goudmand, P. *Bull. Soc. Chim. Fr.* **1973**, 389; Gajewski, J.J. *Mech. Mol. Migr.* **1971**, 4, 1, see pp. 32–49; Paquette, L.A. *Angew. Chem. Int. Ed.* **1971**, 10, 11; Schröder, G.; Oth, J.F.M.; Merényi, R. *Angew. Chem. Int. Ed.* **1965**, 4, 752.

180 °C) are said to have *fluxional* structures. It may be recalled that *cis*-1,2-divinylcyclopropane does not exist at room temperature because it rapidly rearranges to 1,4-cycloheptadiene (see above), but in **136** the *cis*-divinylcyclopropane structure is frozen into the molecule in both structures. Several other compounds with this structural feature are also known. Of these, *bullvalene* (**137**) is especially interesting. The *Cope rearrangement* shown for **137** changes the position of the cyclopropane ring from 4,5,10 to 1,7,8. But the molecule could also have undergone rearrangements to put this ring at 1,2,8 or 1,2,7. Any of these could then undergo several *Cope*



rearrangements. In all, there are $\frac{10!}{3}$ or >1.2 million tautomeric forms, and the cyclopropane ring can be at any three carbons that are adjacent. Since each of these tautomers is equivalent to all the others, this has been called an infinitely degenerate *Cope rearrangement*. Bullvalene has been synthesized and its ^1H NMR spectrum was determined.⁶⁷² At –25 °C, there are two peaks with an area ratio of 6 : 4. This is in accord with a single nontautomeric structure. The six protons are the vinylic protons and the four protons are the allylic ones. But at 100 °C, the compound shows only one NMR peak, indicating that the compound rapidly interchanges its structure among 1.2 million equivalent forms.⁶⁷³ The ^{13}C NMR spectrum of bullvalene also shows only one peak at 100 °C.⁶⁷⁴



Another compound for which degenerate *Cope rearrangements* result in equivalence for all the carbons is *hypostrophene* (**138**).⁶⁷⁵ In the case of the compound *barbaralane* (**139**)⁶⁷⁶ (bullvalene in which one $\text{CH}=\text{CH}$ has been replaced by a CH_2), there are only 2 equiv tautomers.⁶⁷⁷ However, NMR spectra indicate that even at room temperature a rapid interchange of both tautomers is present, although by about –100 °C this has slowed

⁶⁷² Schröder, G. *Chem. Ber.* **1964**, 97, 3140; Merényi, R.; Oth, J.F.M.; Schröder, G. *Chem. Ber.* **1964**, 97, 3150. For a review of bullvalenes, see Schröder, G.; Oth, J.F.M. *Angew. Chem. Int. Ed.* **1967**, 6, 414.

⁶⁷³ See Paquette, L.A.; Malpass, J.R.; Krow, G.R.; Barton, T.J. *J. Am. Chem. Soc.* **1969**, 91, 5296.

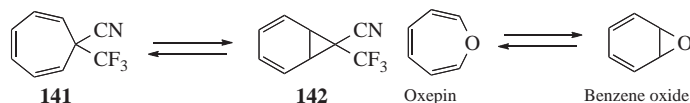
⁶⁷⁴ Oth, J.F.M.; Müllen, K.; Gilles, J.; Schröder, G. *Helv. Chim. Acta* **1974**, 57, 1415; Nakanishi, H.; Yamamoto, O. *Tetrahedron Lett.* **1974**, 1803; Günther, H.; Ulmen, J. *Tetrahedron* **1974**, 30, 3781. See Luger, P.; Buschmann, J.; McMullan, R.K.; Ruble, J.R.; Matias, P.; Jeffrey, G.A. *J. Am. Chem. Soc.* **1986**, 108, 7825.

⁶⁷⁵ McKennis, J.S.; Brener, L.; Ward, J.S.; Pettit, R. *J. Am. Chem. Soc.* **1971**, 93, 4957; Paquette, L.A.; Davis, R.F.; James, D.R. *Tetrahedron Lett.* **1974**, 1615.

⁶⁷⁶ For a study of sigmatropic shiftamers in extended barbaralanes, see Tantillo, D.J.; Hoffmann, R.; Houk, K.N.; Warner, P.M.; Brown, E.C.; Henze, D.K. *J. Am. Chem. Soc.* **2004**, 126, 4256.

⁶⁷⁷ Biethan, U.; Klusacek, H.; Musso, H. *Angew. Chem. Int. Ed.* **1967**, 6, 176; Doering, W. von E.; Ferrier, B.M.; Fossel, E.T.; Hartenstein, J.H.; Jones, Jr., M.; Klumpp, G.W.; Rubin, R.M.; Saunders, M. *Tetrahedron* **1967**, 23, 3943; Henkel, J.G.; Hane, J.T. *J. Org. Chem.* **1983**, 48, 3858.

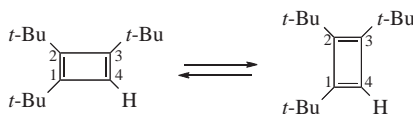
to the point where the spectrum is in accord with a single structure. In the case of *semibullvalene* (**140**) (barbaralane in which the CH₂ has been removed), not only is there a rapid interchange at room temperature, but even at -110°C .⁶⁷⁸ Compound **140** has the lowest energy barrier of any known compound capable of undergoing the *Cope rearrangement*.⁶⁷⁹



The molecules taking part in a valence tautomerization need not be equivalent. Thus, NMR spectra indicate that a true valence tautomerization exists at room temperature between the cycloheptatriene (**141**) and the norcaradiene (**142**).⁶⁸⁰ In this case, one isomer (**142**) has the *cis*-1,2-divinylcyclopropane structure, while the other does not. In an analogous interconversion, benzene oxide⁶⁸¹ and oxepin exist in a tautomeric equilibrium at room temperature.⁶⁸²

Bullvalene and hypostrophene are members of a group of compounds all of whose formulas can be expressed by the symbol $(\text{CH})_{10}$.⁶⁸³ Many other members of this group are known. Similar groups of $(\text{CH})_n$ compounds exist for other even-numbered values of "*n*".⁶⁸⁵ For example, there are 20 possible $(\text{CH})_8$ ⁶⁸⁴ compounds,⁶⁸⁵ and five possible $(\text{CH})_6$ compounds,⁶⁸⁶ all of which are known: benzene, prismane (Sec. 4.Q.i), Dewar benzene (see Reaction 18-27, the *Möbius–Hückel Method*), bicyclopentenyl,⁶⁸⁷ and benzvalene.⁶⁸⁸

An interesting example of valence tautomerism is the case of 1,2,3-*tert*-butylcyclobutadiene (Sec. 2.K.ii). There are two isomers, both rectangular, and ¹³C NMR spectra show that they exist in a dynamic equilibrium, even at -185°C .⁶⁸⁹



⁶⁷⁸ Meinwald, J.; Schmidt, D. *J. Am. Chem. Soc.* **1969**, *91*, 5877; Zimmerman, H.E.; Binkley, R.W.; Givens, R.S.; Grunewald, G.L.; Sherwin, M.A. *J. Am. Chem. Soc.* **1969**, *91*, 3316. See Seefelder, M.; Heubes, M.; Quast, H.; Edwards, W.D.; Armantrout, J.R.; Williams, R.V.; Cramer, C.J.; Goren, A.C.; Hrovat, D.A.; Borden, W.T. *J. Org. Chem.* **2005**, *70*, 3437.

⁶⁷⁹ Moskau, D.; Aydin, R.; Leber, W.; Günther, H.; Quast, H.; Martin, H.-D.; Hassenrück, K.; Miller, L.S.; Grohmann, K. *Chem. Ber.* **1989**, *122*, 925. Are semibullvalenes homoaromatic? See Williams, R.V.; Gadgil, V.R.; Chauhan, K.; Jackman, L.M.; Fernandes, E. *J. Org. Chem.* **1998**, *63*, 3302.

⁶⁸⁰ Ciganek, E. *J. Am. Chem. Soc.* **1965**, *87*, 1149. See Neidlein, R.; Radke, C.M. *Helv. Chim. Acta* **1983**, *66*, 2626; Takeuchi, K.; Kitagawa, T.; Ueda, A.; Senzaki, Y.; Okamoto, K. *Tetrahedron* **1985**, *41*, 5455.

⁶⁸¹ See Shirwaiker, G.S.; Bhatt, M.V. *Adv. Heterocycl. Chem.* **1984**, *37*, 67.

⁶⁸² Vogel, E. *Pure Appl. Chem.* **1969**, *20*, 237. See also, Boyd, D.R.; Stubbs, M.E. *J. Am. Chem. Soc.* **1983**, *105*, 2554.

⁶⁸³ See Balaban, A.T.; Banciu, M. *J. Chem. Educ.* **1984**, *61*, 766; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, **1978**, pp. 203–215; Scott, L.T.; Jones, Jr., M. *Chem. Rev.* **1972**, *72*, 181. See also, Maier, G.; Wiegand, N.H.; Baum, S.; Wüllner, R. *Chem. Ber.* **1989**, *122*, 781.

⁶⁸⁴ See Hassenrück, K.; Martin, H.; Walsh, R. *Chem. Rev.* **1989**, *89*, 1125.

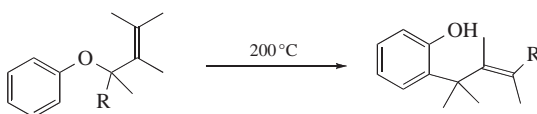
⁶⁸⁵ See Balaban, A.T.; Banciu, M. *J. Chem. Educ.* **1984**, *61*, 766; Banciu, M.; Popa, C.; Balaban, A.T. *Chem. Scr.*, **1984**, *24*, 28.

⁶⁸⁶ Kobayashi, Y.; Kumadaki, I. *Top. Curr. Chem.* **1984**, *123*, 103; Bickelhaupt, F.; de Wolf, W.H. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 459.

⁶⁸⁷ See Davis, J.H.; Shea, K.J.; Bergman, R.G. *J. Am. Chem. Soc.* **1977**, *99*, 1499.

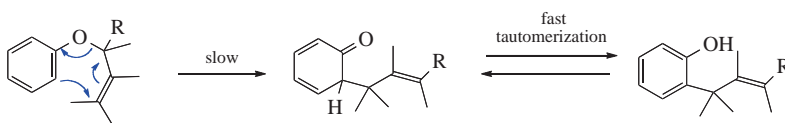
⁶⁸⁸ See Christl, M. *Angew. Chem. Int. Ed.* **1981**, *20*, 529; Burger, U. *Chimia*, **1979**, 147.

⁶⁸⁹ Maier, G.; Kalinowski, H.; Euler, K. *Angew. Chem. Int. Ed.* **1982**, *21*, 693.

18-33 The Claisen Rearrangement⁶⁹⁰

Allylic aryl ethers, when heated, rearrange to *o*-allylphenols in a reaction called the *Claisen rearrangement*.⁶⁹¹ If both ortho positions are filled, the allylic group migrates to the para position (this is often called the *para*-Claisen rearrangement).⁶⁹² There is no reaction when the para and both ortho positions are filled. Migration to the meta position has not been observed. In the ortho migration, the allylic group always undergoes an allylic shift. That is, as shown above, a substituent α to the oxygen is now γ to the ring (and vice versa). On the other hand, in the para migration there is never an allylic shift: The allylic group is found exactly as it was in the original ether. Compounds with propargylic groups (i.e., groups with a triple bond in the appropriate position) do not generally give the corresponding products.

The mechanism is a concerted pericyclic [3,3]-sigmatropic rearrangement⁶⁹³ and accounts for all these facts. For the ortho rearrangement,



Evidence is the lack of a catalyst, the fact that the reaction is first order in the ether, the absence of cross-over products when mixtures are heated, and the presence of the allylic shift, which is required by this mechanism. The allylic shift for the ortho rearrangement (and the absence of one for the para) has been demonstrated by ¹⁴C labeling, even when no substituents are present. Studies of the transition state geometry have shown that, like the *Cope rearrangement*, the *Claisen rearrangement* usually prefers a chair-like transition state.⁶⁹⁴ A *retro*-Claisen rearrangement is known and its mechanism has been examined.⁶⁹⁵

⁶⁹⁰ Castro, A.M.M. *Chem. Rev.* **2004**, 104, 2939; Hiersemann, M.; Nubbemeyer, U *The Claisen Rearrangement: Methods and Applications*. Wiley-VCH, **2007**.

⁶⁹¹ Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, **1999**, pp. 71–83; Moody, C.J. *Adv. Heterocycl. Chem.* **1987**, 42, 203; Bartlett, P.A. *Tetrahedron* **1980**, 36, 2, see pp. 28–39; Ziegler, F.E. *Acc. Chem. Res.* **1977**, 10, 227; Bennett, G.B. *Synthesis* **1977**, 589; Rhoads, S.J.; Raulins, N.R. *Org. React.* **1975**, 22, 1; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1969**, pp. 89–120; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* **1971**, 8, 75, pp. 153–201; Hansen, H.; Schmid, H. *Chimia*, **1970**, 24, 89; Jefferson, A.; Scheinmann, F. *Q. Rev. Chem. Soc.* **1968**, 22, 391.

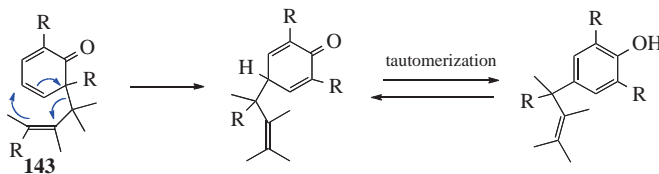
⁶⁹² See Gozzo, F.C.; Fernandes, S.A.; Rodrigues, D.C.; Eberlin, M.N.; Marsaioli, A.J. *J. Org. Chem.* **2003**, 68, 5493.

⁶⁹³ See Kupczyk-Subotkowska, L.; Saunders, Jr., W.H.; Shine, H.J. *J. Am. Chem. Soc.* **1988**, 110, 7153.

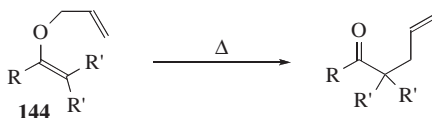
⁶⁹⁴ Copley, S.D.; Knowles, J.R. *J. Am. Chem. Soc.* **1985**, 107, 5306. Also see, Yoo, H.Y.; Houk, K.N. *J. Am. Chem. Soc.* **1994**, 116, 12047.

⁶⁹⁵ Boeckman, Jr., R.K.; Shair, M.D.; Vargas, J.R.; Stolz, L.A. *J. Org. Chem.* **1993**, 58, 1295.

When the ortho positions have no hydrogen, a second [3,3]-sigmatropic migration (a *Cope reaction*) follows:



and the migrating group is restored to its original structure. Intermediates of structure **143** have been trapped by means of a *Diels–Alder reaction* (**15–60**).⁶⁹⁶ The rearrangement of aryl allyl ethers is facilitated by Ag–KI in hot acetic acid,⁶⁹⁷ and by AlMe₃ in water.⁶⁹⁸ A solid-phase reaction of polymer-bound substrate undergoes the *Claisen rearrangement* with microwave irradiation.⁶⁹⁹



Allylic ethers of enols (allylic vinylic ethers, **144**) also undergo the *Claisen rearrangement*⁷⁰⁰; in fact, it was discovered with these compounds first.⁷⁰¹ In these cases of course, the final tautomerization does not take place even when R' = H, since there is no aromaticity to restore, and ketones are more stable than enols.⁷⁰² Catalytic *Claisen rearrangements* of allyl vinyl ethers are well known.⁷⁰³ The use of water as solvent accelerates the reaction.⁷⁰⁴ Microwave induced reactions on silica gel⁷⁰⁵ and in ionic liquids⁷⁰⁶ are known. The mechanism is similar to that with allylic aryl ethers.⁷⁰⁷ In the presence of a chiral Cu complex, *Claisen rearrangements* proceed with good enantioselectivity.⁷⁰⁸ *N*-Heterocyclic carbenes catalyzed an enantioselective *Claisen rearrangement*.⁷⁰⁹ A chiral hydrogen-bond donor has been used for enantioselective *Claisen rearrangements*.⁷¹⁰ A chiral allylic ether gave an enantioselective *Claisen rearrangement* with an Ir catalyst.⁷¹¹

⁶⁹⁶ Conroy, H.; Firestone, R.A. *J. Am. Chem. Soc.* **1956**, *78*, 2290.

⁶⁹⁷ Sharghi, H.; Aghapour, G. *J. Org. Chem.* **2000**, *65*, 2813.

⁶⁹⁸ Wipf, P.; Ribe, S. *Org. Lett.* **2001**, *3*, 1503.

⁶⁹⁹ Kumar, H.M.S.; Anjaneyulu, S.; Reddy, B.V.S.; Yadav, J.C. *Synlett* **2000**, 1129.

⁷⁰⁰ See Ziegler, F.E. *Chem. Rev.* **1988**, *88*, 1423.

⁷⁰¹ Claisen, L. *Ber.* **1912**, *45*, 3157.

⁷⁰² See Boeckman, Jr., R.K.; Flann, C.J.; Poss, K.M. *J. Am. Chem. Soc.* **1985**, *107*, 4359.

⁷⁰³ For reviews, see Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461; Majumdar, K.C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597.

⁷⁰⁴ Grieco, P.A.; Brandes, E.B.; McCann, S.; Clark, J.D. *J. Org. Chem.* **1989**, *54*, 5849. See Guest, J.M.; Craw, J. S.; Vincent, M.A.; Hillier, I.H. *J. Chem. Soc. Perkin Trans. 2* **1997**, 71; Sehgal, A.; Shao, L.; Gao, J. *J. Am. Chem. Soc.* **1995**, *117*, 11337.

⁷⁰⁵ Kotha, S.; Mandal, K.; Deb, A.C.; Banerjee, S. *Tetrahedron Lett.* **2004**, *45*, 9603.

⁷⁰⁶ Lin, Y.-L.; Cheng, J.-Y.; Chu, Y.-H. *Tetrahedron* **2007**, *63*, 10949.

⁷⁰⁷ See Dewar, M.J.S.; Jie, C. *J. Am. Chem. Soc.* **1989**, *111*, 511.

⁷⁰⁸ Balta, B.; Öztürk, C.; Aviyente, V.; Vincent, M.A.; Hillier, I.H. *J. Org. Chem.* **2008**, *73*, 4800.

⁷⁰⁹ Kaebamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J.W. *J. Am. Chem. Soc.* **2010**, *132*, 8810.

⁷¹⁰ Uyeda, C.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2008**, *130*, 9228.

⁷¹¹ Nelson, S.G.; Kan Wang, K. *J. Am. Chem. Soc.* **2006**, *128*, 4232.

Since the *Claisen rearrangement* mechanism does not involve ions, it should not be greatly dependent on the presence or absence of substituent groups on the ring.⁷¹² This is the case. Electron-donating groups increase the rate and electron-withdrawing groups decrease it, but the effect is small, with the *p*-amino compound reacting only ~10–20 times faster than the *p*-nitro compound.⁷¹³ However, solvent effects⁷¹⁴ are greater: Rates varied over a 300-fold range when the reaction was run in 17 different solvents.⁷¹⁵ An especially good solvent is trifluoroacetic acid, in which the reaction can be carried out at room temperature.⁷¹⁶ Most *Claisen rearrangements* are performed without a catalyst, but AlCl₃ or BF₃ are sometimes used.⁷¹⁷ In this case, it may become a *Friedel–Crafts reaction*, with the mechanism no longer cyclic,⁷¹⁸ and ortho, meta, and para products may be obtained.

Allyl allene ethers undergo a *Claisen rearrangement* when heated in DMF to give the expected diene with a conjugated aldehyde unit.⁷¹⁹ Butenolides with a β-allylic ether unit undergo *Claisen rearrangement–Conia reaction*⁷²⁰ cascade to give an oxaspiroheptane with β-keto lactone comprising the five-membered ring.⁷²¹ Allylic esters of β-keto acids undergo a *Claisen rearrangement* in what is known as the *Carroll rearrangement*⁷²² (also called the *Kimel–Cope rearrangement*⁷²³), and the reaction can be catalyzed by a Ru complex.⁷²⁴ An asymmetric *Carroll rearrangement* was catalyzed by a chiral Pd complex.⁷²⁵

Heating an allylic alcohol with *N,N*-dimethylacetamide dimethyl acetal yields a transient intermediate, and subsequent *Claisen rearrangement* gives an amide in a sequence that is known as the *Eschenmoser variant* or the *Eschenmoser–Claisen rearrangement*.⁷²⁶ This reaction has also been called the *Meerwein–Eschenmoser Claisen rearrangement*.⁷²⁷ An enantioselective version has been reported using a chiral Pd complex.⁷²⁸

The enolate anions (**145**) of allylic esters (formed by treatment of the esters with LICA) rearrange to γ,δ-unsaturated acids.⁷²⁹ Alternatively, the silylketene acetal [R³R²C=C(OSiR₃)OCH₂CH=CHR¹] may be used instead of **145**.⁷³⁰ This rearrangement also proceeds at room temperature. By either procedure, the reaction is called the *Ireland–*

⁷¹² There are substituent effects, see Aviyente, V.; Yoo, H.Y.; Houk, K.N. *J. Org. Chem.* **1997**, 62, 6121.

⁷¹³ White, W.N.; Slater, C.D. *J. Org. Chem.* **1962**, 27, 2908; Zahl, G.; Kosbahr, W.; Kresze, G. *Liebigs Ann. Chem.* **1975**, 1733. See also, Desimoni, G.; Fatta, G.; Gamba, A.; Righetti, P.P.; Tacconi, G.; Toma, L. *Tetrahedron* **1990**, 46, 2165; Gajewski, J.J.; Gee, K.R.; Jurayj, J. *J. Org. Chem.* **1990**, 55, 1813.

⁷¹⁴ See Gajewski, J.J. *Accs. Chem. Res.* **1997**, 30, 219.

⁷¹⁵ White, W.N.; Wolfarth, E.F. *J. Org. Chem.* **1970**, 35, 2196. See also, Brandes, E.; Greico, P.A.; Gajewski, J.J. *J. Org. Chem.* **1989**, 54, 515.

⁷¹⁶ Svanholm, U.; Parker, V.D. *J. Chem. Soc. Perkin Trans. 2* **1974**, 169.

⁷¹⁷ See Lutz, R.P. *Chem. Rev.* **1984**, 84, 205.

⁷¹⁸ See Yagodin, V.G.; Bunina-Krivorukova, L.I.; Bal'yan, Kh.V. *J. Org. Chem. USSR* **1971**, 7, 1491.

⁷¹⁹ Parsons, P.J.; Thomson, P.; Taylor, A.; Sparks, T. *Org. Lett.* **2000**, 2, 571.

⁷²⁰ For a review of the *Conia-ene reaction*, see Conia, J.M.; Le Perche, P. *Synthesis* **1975**, 1.

⁷²¹ Schobert, R.; Siegfried, S.; Gordon, G.; Nieuwenhuyzen, M.; Allenmark, S. *Eur. J. Org. Chem.* **2001**, 1951.

⁷²² Carroll, M.F. *J. Chem. Soc.* **1941**, 507; Ziegler, F.E. *Chem. Rev.* **1988**, 88, 1423.

⁷²³ Kimel, W.; Cope, A.C. *J. Am. Chem. Soc.* **1943**, 65, 1992.

⁷²⁴ Burger, E.C.; Tunge, J.A. *Org. Lett.* **2004**, 6, 2603.

⁷²⁵ Kuwano, R.; Ishida, N.; Murakami, M. *Chem. Commun.* **2005**, 3951.

⁷²⁶ Felix, D.; Gschwend-Steen, K.; Wick, A.E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, 52, 1030.

⁷²⁷ Grädl, S. N.; Trauner, D. in *The Meerwein–Eschenmoser–Claisen Rearrangement. In The Claisen Rearrangement*, Hiersemann, M.; Nubbemeyer, U., Eds., Wiley–VCH, Weinheim, **2007**, pp 367–396.

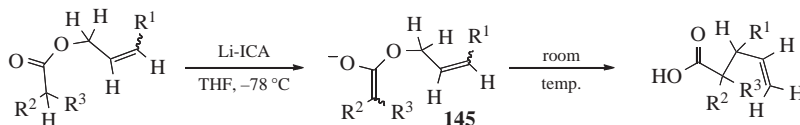
⁷²⁸ Linton, E.C.; Kozłowski, M.C. *J. Am. Chem. Soc.* **2008**, 130, 16162.

⁷²⁹ Gajewski, J.J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, 106, 5733; Cameron, A.G.; Knight, D.W. *J. Chem. Soc. Perkin Trans. 1* **1986**, 161. See Wilcox, C.S.; Babston, R.E. *J. Am. Chem. Soc.* **1986**, 108, 6636.

⁷³⁰ Ireland, R.E.; Wipf, P.; Armstrong, III, J.D. *J. Org. Chem.* **1991**, 56, 650. See also Ref. 714.

Claisen rearrangement.⁷³¹ Note the presence of the negative charge in **145**. As with the *oxy-Cope rearrangement* (in Reaction **18-34**), negative charges generally accelerate the *Claisen reaction*,⁷³² although the extent of the acceleration can depend on the identity of the positive counterion.⁷³³ The reaction proceeds with good syn selectivity in many cases.⁷³⁴ The *Ireland-Claisen rearrangement* has been made enantioselective by converting **145** to an enol borinate in which the boron is attached to a chiral group.⁷³⁵ The *Ireland-Claisen rearrangement* can be done with amide derivatives also.⁷³⁶

As just mentioned, asymmetric *Claisen rearrangement* reactions are well known.⁷³⁷ Chiral Lewis acids have been designed for this purpose.⁷³⁸ In general, asymmetric [3,3]-sigmatropic rearrangements are well known.⁷³⁹



A number of analogues of the *Claisen rearrangement* are known, for example, rearrangement of $\text{ArNHCH}_2\text{CH}=\text{CH}_2$,⁷⁴⁰ of *N*-allylic enamines ($\text{R}_2\text{C}=\text{CRNRCR}_2\text{CR}=\text{CR}_2$)⁷⁴¹ of allylic imino esters $[\text{RC}(\text{OCH}_2\text{CH}=\text{CH}_2)=\text{NR}]$ ⁷⁴² (these have often been rearranged with transition metal catalysts⁷⁴³), and of $\text{RCH}=\text{NRCHRCH}_2\text{CH}=\text{CH}_2$. These rearrangements of nitrogen-containing compounds can be called *aza-Claisen rearrangements*,⁷⁴⁴ but are sometimes called *aza-Cope rearrangements*,⁷⁴⁵ as described in Reaction **18-32**. A Pd catalyzed *aza-Claisen* has been reported.⁷⁴⁶ An important contribution to this variation is the rearrangement of

⁷³¹ See Chai, Y.; Hong, S.-p.; Lindsay, H.A.; McFarland, C.; McIntosh, M.C. *Tetrahedron* **2002**, 58, 2905.

⁷³² See Denmark, S.E.; Harmata, M.A.; White, K.S. *J. Am. Chem. Soc.* **1989**, 111, 8878.

⁷³³ Koreeda, M.; Luengo, J.I. *J. Am. Chem. Soc.* **1985**, 107, 5572; Kirchner, J.J.; Pratt, D.V.; Hopkins, P.B. *Tetrahedron Lett.* **1988**, 29, 4229.

⁷³⁴ Mohamed, M.; Brook, M.A. *Tetrahedron Lett.* **2001**, 42, 191. See Khaledy, M.M.; Kalani, M.Y.S.; Khuong, K.S.; Houk, K.N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. *J. Org. Chem.* **2003**, 68, 572.

⁷³⁵ Corey, E.J.; Lee, D. *J. Am. Chem. Soc.* **1991**, 113, 4026.

⁷³⁶ Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M.; Itô, S. *Tetrahedron Lett.* **1993**, 34, 3297; Walters, M.A.; Hoem, A.B.; Arcand, H.R.; Hegeman, A.D.; McDonough, C.S. *Tetrahedron Lett.* **1993**, 34, 1453.

⁷³⁷ See Zumpe, F.L.; Kazmaier, U. *Synlett* **1998**, 434; Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* **1997**, 38, 4815; Kazmaier, U.; Krebs, A. *Angew. Chem. Int. Ed.* **1995**, 34, 2012. For asymmetric induction in the thio-Claisen rearrangement, see Reddy, K.V.; Rajappa, S. *Tetrahedron Lett.* **1992**, 33, 7957.

⁷³⁸ Maruoka, K.; Saito, S.; Yamamoto, J. *J. Am. Chem. Soc.* **1995**, 117, 1165. See Hiersemann, M.; Abraham, L. *Org. Lett.* **2001**, 3, 49; Miller, S.P.; Morken, J.P. *Org. Lett.* **2002**, 4, 2743.

⁷³⁹ For a review, see Enders, D.; Knopp, M.; Schiffrs, R. *Tetrahedron Asymmetry*, **1996**, 7, 1847.

⁷⁴⁰ Jolidon, S.; Hansen, H. *Helv. Chim. Acta* **1977**, 60, 978.

⁷⁴¹ Anderson, J.C.; Flaherty, A.; Swarbrick, M.E. *J. Org. Chem.* **2000**, 65, 9152. See Wu, P.; Fowler, F.W. *J. Org. Chem.* **1988**, 53, 5998.

⁷⁴² See Metz, P.; Mues, C. *Tetrahedron* **1988**, 44, 6841. Also see Gradl, S.N.; Kennedy-Smith, J.J.; Kim, J.; Trauner, D. *Synlett* **2002**, 411.

⁷⁴³ See Schenck, T.G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, 107, 2058, and references cited therein; Anderson, C.E.; Overman, L.E. *J. Am. Chem. Soc.* **2003**, 125, 12412.

⁷⁴⁴ See Kirsch, S.F.; Overman, L.F.; Watson, M.P. *J. Org. Chem.* **2004**, 69, 8101. For a review, see Majumdar, K.C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* **2009**, 2117. See also, Forte, L.; Lafortune, M.C.; Bierzynski, I.R.; Duncan, J.A. *J. Am. Chem. Soc.* **2010**, 132, 2196.

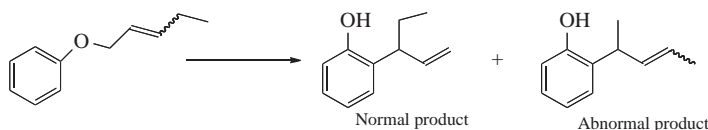
⁷⁴⁵ Blechert, S. *Synthesis* **1989**, 71; Heimgartner, H.; Hansen, H.; Schmid, H. *Adv. Org. Chem.* **1979**, 9, pt. 2, 655.

⁷⁴⁶ Uozumi, Y.; Kato, K.; Hayashi, T. *Tetrahedron Asymmetry*, **1998**, 9, 1065. See Gilbert, J.C.; Cousins, K.R. *Tetrahedron* **1994**, 50, 10671.

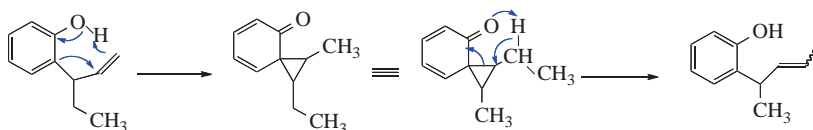
trichloroacetimidate derivatives of prochiral (Z)-2-alken-1-ols, usually with a Pd catalyst, to give chiral allylic esters.⁷⁴⁷ There is a catalytic enantioselective *aza-Cope rearrangement*.⁷⁴⁸ A so-called *amine-Claisen rearrangement* was reported for *N*-allyl indoles, when heated in the presence of $\text{BF}_3 \cdot \text{OEt}_2$.⁷⁴⁹ An *azo-Cope* rearrangement, $\text{CH}_2=\text{CHCR}_2'\text{CR}_2'\text{N}=\text{NAr} \rightarrow \text{R}_2'\text{C}=\text{CHCH}_2\text{NArN}=\text{CR}_2'^2$, has been reported.⁷⁵⁰ In a related reaction, allylic phosphorimidates undergo [3,3]-sigmatropic rearrangement.⁷⁵¹

The conversion of allylic aryl thioethers, ($\text{ArSCH}_2\text{CH}=\text{CH}_2$) to *o*-allylic thiophenols is not feasible, because the latter are not stable,⁷⁵² but react to give bicyclic compounds.⁷⁵³ However, many allylic vinylic sulfides do give the rearrangement (the *thio-Claisen rearrangement*).⁷⁵⁴ Allylic vinylic sulfones (e.g., $\text{H}_2\text{C}=\text{CRCH}_2-\text{SO}_2-\text{CH}=\text{CH}_2$) rearrange, when heated in the presence of ethanol and pyridine, to unsaturated sulfonate salts ($\text{CH}_2=\text{CRCH}_2\text{CH}_2\text{CH}_2\text{SO}_3^-$), produced by reaction of the reagents with the unstable sulfene intermediates $\text{CH}_2=\text{CRCH}_2\text{CH}_2\text{CH}=\text{SO}_2$.⁷⁵⁵ Allylic vinylic sulfoxides rapidly rearrange at room temperature or below.⁷⁵⁶ Chiral vinyl sulfoxides undergo *Claisen rearrangement* with good enantioselectivity.⁷⁵⁷

Ethers with an alkyl group in the γ position ($\text{ArO}-\text{C}-\text{C}=\text{C}-\text{R}$ systems) sometimes give abnormal products, with the β carbon becoming attached to the ring⁷⁵⁸:



It has been established that these abnormal products do not arise directly from the starting ether, but are formed by a further rearrangement of the normal product⁷⁵⁹:



⁷⁴⁷ Kirsch, S.F.; Overman, L.E. *J. Am. Chem. Soc.* **2005**, 127, 2866; Watson, M.P.; Overman, L.E.; Bergman, R.G. *J. Am. Chem. Soc.* **2007**, 129, 5031.

⁷⁴⁸ Rueping, M.; Antonchick, A.P. *Angew. Chem. Int. Ed.* **2008**, 47, 10090.

⁷⁴⁹ Anderson, W.K.; Lai, G. *Synthesis* **1995**, 1287.

⁷⁵⁰ Mitsuhashi, T. *J. Am. Chem. Soc.* **1986**, 108, 2400.

⁷⁵¹ Chen, B.; Mapp, A.K. *J. Am. Chem. Soc.* **2005**, 127, 6712.

⁷⁵² They have been trapped: See, for example, Mortensen, J.Z.; Hedegaard, B.; Lawesson, S. *Tetrahedron* **1971**, 27, 3831; Kwart, H.; Schwartz, J.L. *J. Org. Chem.* **1974**, 39, 1575.

⁷⁵³ Kwart, H.; Cohen, M.H. *J. Org. Chem.* **1967**, 32, 3135; *Chem. Commun.* **1968**, 319; Makisumi, Y.; Murabayashi, A. *Tetrahedron Lett.* **1969**, 1971, 2449.

⁷⁵⁴ For a review, see Majumdar, K.C.; Ghosh, S.; Ghosh, M. *Tetrahedron* **2003**, 59, 7251.

⁷⁵⁵ King, J.F.; Harding, D.R.K. *J. Am. Chem. Soc.* **1976**, 98, 3312.

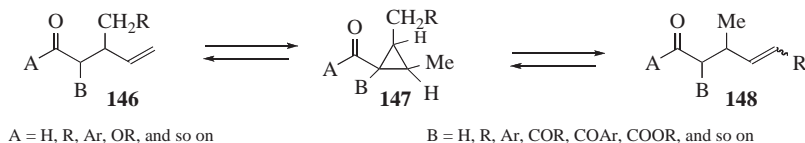
⁷⁵⁶ Block, E.; Ahmad, S. *J. Am. Chem. Soc.* **1985**, 107, 6731.

⁷⁵⁷ de la Pradilla, R.F.; Montero, C.; Tortosa, M.; Viso, A. *Chemistry: Eur. J.* **2009**, 15, 697.

⁷⁵⁸ For abnormal *Claisen rearrangements*, see Hansen, H. *Mech. Mol. Migr.* **1971**, 3, 177; Marvell, E.N.; Whalley, W. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, **1971**, pp. 743–750.

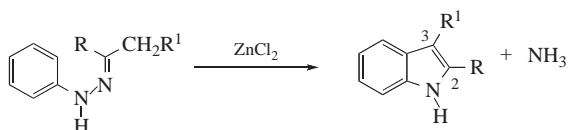
⁷⁵⁹ Lauer, W.M.; Johnson, T.A. *J. Org. Chem.* **1963**, 28, 2913; Fráter, G.; Schmid, H. *Helv. Chim. Acta* **1966**, 49, 1957; Marvell, E.N.; Schatz, B. *Tetrahedron Lett.* **1967**, 67.

This rearrangement, which has been called an *enolene rearrangement*, a *homodienyl* [1,5]-*sigmatropic hydrogen shift* (see Reaction **18-29**), and a [1,5]-*homosigmatropic rearrangement*, involves a shift of three electron pairs over seven atoms. It has been found that this “abnormal” *Claisen rearrangement* is general and can interconvert the enol forms of systems of the types **146** and **147** through the cyclopropane intermediate (**148**).⁷⁶⁰



OS **III**, 418; **V**, 25; **VI**, 298, 491, 507, 584, 606; **VII**, 177; **VIII**, 251, 536.

18-34 The Fischer Indole Synthesis



When arylhydrazones of aldehydes or ketones are treated with a catalyst, elimination of ammonia takes place and an indole is formed, in the *Fischer indole synthesis*.⁷⁶¹ Zinc chloride is a commonly used catalyst, but dozens of others, including other metal halides, proton and Lewis acids, and certain transition metals have also been used. Microwave irradiation has been used to facilitate this reaction.⁷⁶² The reaction has been done using an AlCl_3 complex as an ionic liquid,⁷⁶³ and solid-phase *Fischer indole syntheses* are known.⁷⁶⁴ Aniline derivatives react with α -diazoketones, in the presence of a Rh catalyst, to give indoles as well.⁷⁶⁵ Arylhya zones are easily prepared by the treatment of aldehydes or ketones with phenylhydrazine (Reaction **16-2**) or by aliphatic diazonium coupling (Reaction **12-7**). However, it is not necessary to isolate the arylhydrazone. The aldehyde or ketone can be treated with a mixture of phenylhydrazine and the catalyst; this is now common practice. In order to obtain an indole, the aldehyde or ketone must be of the form $\text{RCOCH}_2\text{R}'$ (R = alkyl, aryl, or hydrogen). Vinyl ethers (e.g., dihydrofuran) serve as an aldehyde surrogate when treated with phenylhydrazine and a catalytic amount of aq H_2SO_4 to give an 3-substituted indole.⁷⁶⁶

⁷⁶⁰ Watson, J.M.; Irvine, J.L.; Roberts, R.M. *J. Am. Chem. Soc.* **1973**, 95, 3348.

⁷⁶¹ Robinson, B. *The Fischer Indole Synthesis*, Wiley, NY, **1983**; Grandberg, I.I.; Sorokin, V.I. *Russ. Chem. Rev.* **1974**, 43, 115; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1969**, pp. 190–207; Sundberg, R.J. *The Chemistry of Indoles*, Academic Press, NY, **1970**, pp. 142–163; Robinson, B. *Chem. Rev.* **1969**, 69, 227. For reviews of so-called abnormal *Fischer indole syntheses*, see Ishii, H. *Acc. Chem. Res.* **1981**, 14, 275; Fusco, R.; Sannicolo, F. *Tetrahedron* **1980**, 36, 161.

⁷⁶² Lipinska, T.; Guibé-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* **1999**, 29, 1349.

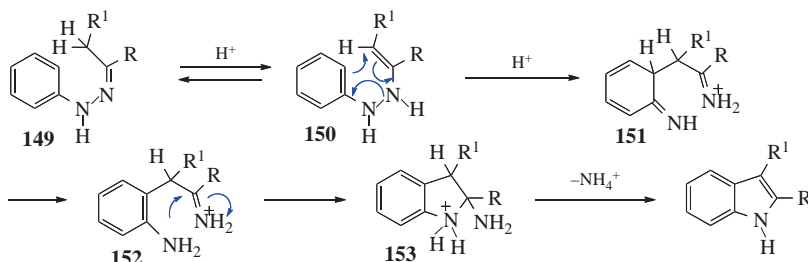
⁷⁶³ Rebeiro, G.L.O.; Khadilkar, B.M. *Synthesis* **2001**, 370.

⁷⁶⁴ Rosenbaum, C.; Katzka, C.; Marzinzik, A.; Waldmann, H. *Chem. Commun.* **2003**, 1822.

⁷⁶⁵ Moody, C.J.; Swann, E. *Synlett* **1998**, 135.

⁷⁶⁶ Campos, K.R.; Woo, J.C.S.; Lee, S.; Tillyer, R.D. *Org. Lett.* **2004**, 6, 79.

At first glance, the reaction does not seem to be a rearrangement. However, the key step of the mechanism⁷⁶⁷ is a [3,3]-sigmatropic rearrangement⁷⁶⁸:

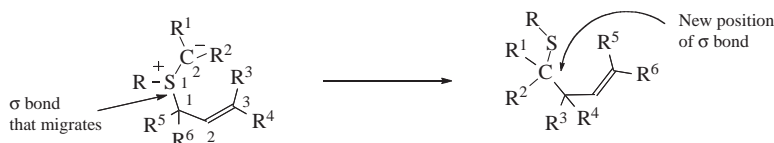


There is much evidence for this mechanism, for example, (1) the isolation of **153**,⁷⁶⁹ (2) the detection of **152** by ^{13}C and ^{15}N NMR,⁷⁷⁰ (3) the isolation of side products that could only have come from **151**,⁷⁷¹ and (4) ^{15}N -labeling experiments showing that it was the nitrogen farther from the ring that is eliminated as ammonia.⁷⁷² The main function of the catalyst seems to be to speed the conversion of **149** to **150**. The reaction can be performed without a catalyst.

OS **III**, 725; **IV**, 884. Also see, OS **IV**, 657.

18-35 [2,3]-Sigmatropic Rearrangements

(2/*S*-3/) \rightarrow (1/*5*/)-*sigma*-Migration



Sulfur ylids bearing an allylic group are converted to unsaturated sulfides on heating.⁷⁷³ This is a concerted [2,3]-sigmatropic rearrangement⁷⁷⁴ and has also been demonstrated for the analogous cases of nitrogen ylids⁷⁷⁵ and the conjugate bases of allylic ethers (in the last case it is called a [2,3]-Wittig rearrangement).⁷⁷⁶ It has been argued that the [2,3]-Wittig rearrangement demands severe deformation of the molecule in order to proceed.⁷⁷⁷ It has been shown that SmI_2 induces a [2,3]-Wittig rearrangement.⁷⁷⁸ The reaction has been

⁷⁶⁷ For a mechanistic study, see Hughes, D.L.; Zhao, D. *J. Org. Chem.* **1993**, 58, 228.

⁷⁶⁸ This mechanism was proposed by Robinson, G.M.; Robinson, R. *J. Chem. Soc.* **1918**, 113, 639.

⁷⁶⁹ See Forrest, T.P.; Chen, F.M.F. *J. Chem. Soc., Chem. Commun.* **1972**, 1067.

⁷⁷⁰ Douglas, A.W. *J. Am. Chem. Soc.* **1978**, 100, 6463; **1979**, 101, 5676.

⁷⁷¹ Bajwa, G.S.; Brown, R.K. *Can. J. Chem.* **1969**, 47, 785; **1970**, 48, 2293 and references cited therein.

⁷⁷² Clausius, K.; Weisser, H.R. *Helv. Chim. Acta* **1952**, 35, 400.

⁷⁷³ See Ma, M.; Peng, L.; Li, C.; Zhang, X.; Wang, J. *J. Am. Chem. Soc.* **2005**, 127, 15106. For a review as applied to ring expansions, see Vedejs, E. *Acc. Chem. Res.* **1984**, 17, 358.

⁷⁷⁴ See Hoffmann, R.W. *Angew. Chem. Int. Ed.* **1979**, 18, 563.

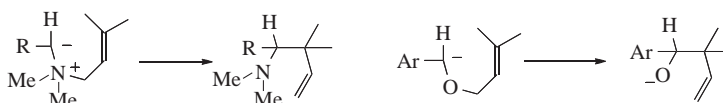
⁷⁷⁵ See Mander, L.N.; Turner, J.V. *J. Org. Chem.* **1973**, 38, 2915; Honda, K.; Inoue, S.; Sato, K. *J. Am. Chem. Soc.* **1990**, 112, 1999.

⁷⁷⁶ Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, 86, 885. See Schöllkopf, U.; Fellenberger, K.; Rizk, M. *Liebigs Ann. Chem.* **1970**, 734, 106; Rautenstrauch, V. *Chem. Commun.* **1970**, 4. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1063–1067.

⁷⁷⁷ You, Z.; Koreeda, M. *Tetrahedron Lett.* **1993**, 34, 2597.

⁷⁷⁸ Kunishima, M.; Hioki, K.; Kono, K.; Kato, A.; Tani, S. *J. Org. Chem.* **1997**, 62, 7542. Also see, Hioki, K.; Kono, K.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* **1998**, 39, 5229. For an enantioselective [2,3]-Wittig rearrangement, see Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* **1994**, 35, 5019.

extended to certain other systems,⁷⁷⁹ even to an all-carbon system.⁷⁸⁰



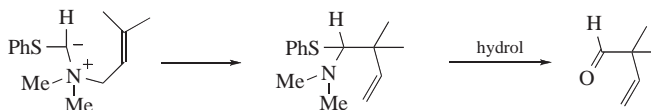
Treatment of an α -(*N*-allylic amino) ketone with NaH led to 2-allylic α -amino ketones via a [2,3]-rearrangement.⁷⁸¹ In the presence of a chiral ligand on nitrogen,⁷⁸¹ or with a chiral additive,⁷⁸² good asymmetric induction is possible. Vinylaziridines undergo [2,3]-sigmatropic rearrangement.⁷⁸³

Since the reactions involve migration of an allylic group from a sulfur, nitrogen, or oxygen atom to an adjacent negatively charged carbon atom, they are special cases of the *Stevens or Wittig rearrangements* (**18-21** and **18-22**). However, in this case the migrating group *must* be allylic (in **18-21** and **18-22** other groups can also migrate). Thus, when the migrating group is allylic, there are two possible pathways: (1) the radical-ion or ion-pair mechanisms (**18-21** and **18-22**) and (2) the concerted pericyclic [2,3]-sigmatropic rearrangement. These are easily distinguished since the latter always involves an allylic shift (as in the *Claisen rearrangement*), while the former pathway does not.



Of these reactions, the [2,3]-*Wittig rearrangement* in particular has often been used as a means of transferring chirality. The product of this reaction has potential stereogenic centers at C-3 and C-4 (if $R^5 \neq R^6$), and if the starting ether is optically active because of a stereogenic center at C-1, the product may be optically active as well. Many examples are known in which optically active ethers were converted to a product that was optically active because of chirality at C-3, C-4, or both.⁷⁸⁴ If a suitable stereogenic center is present in R^1 (or if a functional group in R^1 can be so converted), then stereocontrol over three contiguous stereogenic centers can be achieved. Stereocontrol of the new double bond (*E* or *Z*) has also been accomplished.

If an OR or SR group is attached to the negative carbon, the reaction becomes a method for the preparation of β,γ -unsaturated aldehydes, because the product is easily hydrolyzed.⁷⁸⁵



⁷⁷⁹ See Murata, Y.; Nakai, T. *Chem. Lett.* **1990**, 2069. Also see Reich, H.J. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, **1987**, pp. 365–393; Reich, H.J. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, **1978**, pp. 102–111.

⁷⁸⁰ Baldwin, J.E.; Urban, F.J. *Chem. Commun.* **1970**, 165.

⁷⁸¹ Workman, J.A.; Garrido, N.P.; Sançón, J.; Roberts, E.; Wessel, H.P.; Sweeney, J.B. *J. Am. Chem. Soc.* **2005**, 127, 1066.

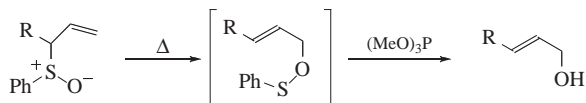
⁷⁸² Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, 127, 9352.

⁷⁸³ Somfai, P.; Panknin, O. *Synlett* **2007**, 1190.

⁷⁸⁴ Mikami, K.; Nakai, T. *Synthesis* **1991**, 594; Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, 86, 885, pp. 888–895. See also, Scheuplein, S.W.; Kusche, A.; Brückner, R.; Harms, K. *Chem. Ber.* **1990**, 123, 917; Wu, Y.; Houk, K.N.; Marshall, J.A. *J. Org. Chem.* **1990**, 55, 1421; Marshall, J.A.; Wang, X. *J. Org. Chem.* **1990**, 55, 2995.

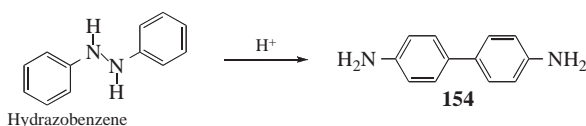
⁷⁸⁵ Huynh, C.; Julia, S.; Lorne, R.; Michelot, D. *Bull. Soc. Chim. Fr.* **1972**, 4057.

Another [2,3]-sigmatropic rearrangement converts allylic sulfoxides to rearranged allylic alcohols by treatment with a thiophilic reagent (e.g., trimethyl phosphite).⁷⁸⁶ This is the *Mislow–Evans rearrangement*. In this case, the migration is from sulfur to oxygen. [2,3]-Oxygen-to-sulfur migrations are also known.⁷⁸⁷ The *Sommelet–Hauser rearrangement* discussed in Reaction 13-31 is also a [2,3]-sigmatropic rearrangement.



OS VIII, 427.

18-36 The Benzidine Rearrangement



When hydrazobenzene is treated with acids, it rearranges to give ~70% 4,4'-diaminobiphenyl (**154**, benzidine) and ~30% 2,4'-diaminobiphenyl. This reaction is called the *benzidine rearrangement* and is general for *N,N'*-diarylhydrazines.⁷⁸⁸ Usually, the major product is the 4,4'-diaminobiaryl, but four other products may also be produced: the 2,4'-diaminobiaryl, already referred to, the 2,2'-diaminobiaryl, and the *o*- and *p*-arylaminoanilines (called *semidines*). The 2,2'- and *p*-arylaminoaniline compounds are formed less often and in smaller amounts than the other two side products. Usually, the 4,4'-diaminobiaryl predominates, except when one or both para positions of the diarylhydrazine are occupied. However, the 4,4'-diamine may still be produced even if the para positions are occupied. If SO_3H , CO_2H , or Cl (but not R , Ar , or NR_2) is present in the para position, it may be ejected. With dinaphthylhydrazines, the major products are not the 4,4'-diaminobinaphthyls, but the 2,2' isomers. Another side reaction is disproportionation to ArNH_2 and $\text{ArN}=\text{NAr}$. For example, *p,p'*- $\text{PhC}_6\text{H}_4\text{NHNHC}_6\text{H}_4\text{Ph}$ gives 88% disproportionation products at 25 °C.⁷⁸⁹

The mechanism has been exhaustively studied and several mechanisms have been proposed.⁷⁹⁰ At one time, it was believed that NHAr broke away from ArNHNHAr and became attached to the para position to give the semidine, which then went on to product. The fact that semidines could be isolated lent this argument support, as did the fact that this would be analogous to the rearrangements considered in Chapter 11 (Reaction 11-28–11-32). However, this theory was proved incorrect when it was discovered that semidines could not be converted to benzidines under the reaction conditions. Cleavage into two

⁷⁸⁶ Evans, D.A.; Andrews, G.C. *Acc. Chem. Res.* **1974**, 7, 147; Hoffmann, R.W. *Angew. Chemie. Int. Ed., Engl.*, **1979**, 18, 563; Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1989**, 54, 2779.

⁷⁸⁷ See Tamaru, Y.; Nagao, K.; Bando, T.; Yoshida, Z. *J. Org. Chem.* **1990**, 55, 1823.

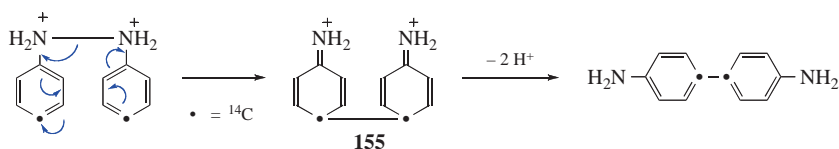
⁷⁸⁸ Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, **1975**, the reviews by Cox, R.A.; Buncel, E. pp. 775–807; Koga, G.; Koga, N.; Anselme, J. pp. 914–921; Williams, D.L.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, **1973**, Vol. 13, 1972, pp. 437–448; Shine, H.J. *Mech. Mol. Migr.* **1969**, 2, 191; Banthorpe, D.V. *Top. Carbocyclic Chem.* **1969**, 1, 1.

⁷⁸⁹ Shine, H.J.; Stanley, J.P. *J. Org. Chem.* **1967**, 32, 905. For investigations of the mechanism of the disproportionation reactions, see Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* **1986**, 108, 1000; **1987**, 109, 5052.

⁷⁹⁰ For a history, see Shine, H.J. *J. Phys. Org. Chem.* **1989**, 2, 491.

independent pieces (either ions or radicals) has been ruled out by many types of cross-over experiments, which always showed that the two rings of the starting material are in the product; that is, $\text{ArNHNHAr}'$ gives no molecules (of any of the five products) containing two Ar groups or two Ar' groups, and mixtures of ArNHNHAr and $\text{Ar}'\text{NHNHAr}'$ give no molecules containing both Ar and Ar' . An important discovery was the fact that, although the reaction is always first order in substrate, it can be either first⁷⁹¹ or second⁷⁹² order in $[\text{H}^+]$. With some substrates the reaction is entirely first order in $[\text{H}^+]$, while with others it is entirely second order in $[\text{H}^+]$, regardless of the acidity. With still other substrates, the reaction is first order in $[\text{H}^+]$ at low acidities and second order at higher acidities. With the latter substrates fractional orders can often be observed,⁷⁹³ because at intermediate acidities, both processes take place simultaneously. These kinetic results seem to indicate that the actual reacting species can be either the monoprotonated substrate ArNHNH_2Ar or the diprotonated $\text{ArNH}_2\text{NH}_2\text{Ar}$.

Most of the proposed mechanisms⁷⁹⁴ attempted to show how all five products could be produced by variations of a single process. An important breakthrough was the discovery that the two main products are formed in entirely different ways, as shown by isotope-effect studies.⁷⁹⁵ When the reaction was run with hydrazobenzene labeled with ^{15}N at both nitrogen atoms, the isotope effect was 1.022 for formation of **154**, but 1.063 for formation of 2,4'-diaminobiphenyl. This showed that the N—N bond is broken in the rate-determining step in both cases, but the steps themselves are obviously different. When the reaction was run with hydrazobenzene labeled with ^{14}C at a para position, there was an isotope effect of 1.028 for formation of **154**, but essentially no isotope effect (1.001) for formation of 2,4'-diaminobiphenyl. This can only mean that for **154** formation of the new C—C bond *and* breaking of the N—N bond both take place in the rate-determining step; in other words, the mechanism is concerted. The following [5,5]-sigmatropic rearrangement accounts for this⁷⁹⁶:



The diion **155** was obtained as a stable species in superacid solution at -78°C by treatment of hydrazobenzene with $\text{FSO}_3\text{H}\text{---}\text{SO}_2$ (SO_2ClF).⁷⁹⁷ Although the results just given were obtained with hydrazobenzene, which reacts by the diprotonated pathway, monoprotonated substrates have been found to react by the same [5,5]-sigmatropic mechanism.⁷⁹⁸

⁷⁹¹ Shine, H.J.; Chamness, J.T. *J. Org. Chem.* **1963**, 28, 1232; Banthorpe, D.V.; O'Sullivan, M. *J. Chem. Soc. B* **1968**, 627.

⁷⁹² Banthorpe, D.V.; Cooper, A.; O'Sullivan, M. *J. Chem. Soc. B* **1971**, 2054.

⁷⁹³ Banthorpe, D.V.; Ingold, C.K.; Roy, J. *J. Chem. Soc. B* **1968**, 64; Banthorpe, D.V.; Ingold, C.K.; O'Sullivan, M. *J. Chem. Soc. B* **1968**, 624.

⁷⁹⁴ Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* **1964**, 2864; Dewar, M.J.S. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, **1963**, pp. 323–344.

⁷⁹⁵ Shine, H.J.; Zmuda, H.; Park, K.H.; Kwart, H.; Horgan, A.J.; Brechbiel, M. *J. Am. Chem. Soc.* **1982**, 104, 2501.

⁷⁹⁶ This step was also part of the "polar-transition-state mechanism". See also Ref. 793.

⁷⁹⁷ Olah, G.A.; Dunne, K.; Kelly, D.P.; Mo, Y.K. *J. Am. Chem. Soc.* **1972**, 94, 7438.

⁷⁹⁸ Shine, H.J.; Park, K.H.; Brownawell, M.L.; San Filippo, Jr., J. *J. Am. Chem. Soc.* **1984**, 106, 7077.

Some of the other rearrangements in this section are also sigmatropic. Thus, formation of the *p*-semidine takes place by a [1,5]-sigmatropic rearrangement,⁷⁹⁹ and the conversion of 2,2'-hydrazonaphthalene to 2,2'-diamino-1,1'-binaphthyl by a [3,3] sigmatropic rearrangement.⁸⁰⁰

2,4'-Diaminobiphenyl is formed by a completely different mechanism, though the details are not known. There is rate-determining breaking of the N—N bond, but the C—C bond is not formed during this step.⁸⁰¹ The formation of the *o*-semidine also takes place by a nonconcerted pathway.⁸⁰² Under certain conditions, benzidine rearrangements have been found to go through radical cations.⁸⁰³

C. Other Cyclic Rearrangements

18-37 Metathesis of Alkenes (Alkene or Olefin Metathesis)⁸⁰⁴

Alkene metathesis



When alkenes are treated with certain catalysts they are converted to other alkenes in a reaction in which one set of alkylidene groups ($\text{R}^1\text{R}^2\text{C}=\text{}$) have become interchanged with other alkylidene groups ($\text{R}^3\text{R}^4\text{C}=\text{}$) by a process schematically illustrated by the equilibrium reaction shown below. In an early example shown above, 2-pentene (either *cis*, *trans*, or a *cis*–*trans* mixture) is converted to a mixture of ~50% 2-pentene, 25% 2-butene, and 25% 3-hexene. Nowadays, superior catalysts and experimental procedures have made this reaction synthetically useful (see below). The reaction is reversible⁸⁰⁵ and the alkene starting material and products exist in equilibrium, so the same mixture can be obtained by starting with equimolar quantities of 2-butene and 3-hexene.⁸⁰⁶ The reaction is called *metathesis* of alkenes or *alkene metathesis* (*olefin metathesis*).⁸⁰⁷ In general, the reaction can be applied to a single unsymmetrical alkene, giving a mixture of itself and two other

⁷⁹⁹ See Shine, H.J.; Zmuda, H.; Kwart, H.; Horgan, A.G.; Brechbiel, M. *J. Am. Chem. Soc.* **1982**, *104*, 5181.

⁸⁰⁰ Shine, H.J.; Gruszecka, E.; Subotkowski, W.; Brownawell, M.; San Filippo, Jr., J. *J. Am. Chem. Soc.* **1985**, *107*, 3218.

⁸⁰¹ See Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* **1986**, *108*, 1000; **1987**, *109*, 5052.

⁸⁰² Rhee, E.S.; Shine, H.J. *J. Org. Chem.* **1987**, *52*, 5633.

⁸⁰³ See Nojima, M.; Ando, T.; Tokura, N. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1504.

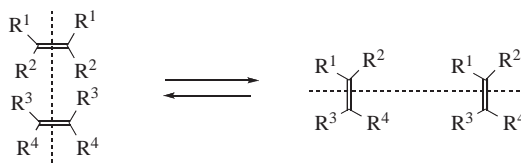
⁸⁰⁴ Grubbs, R.H. *Tetrahedron* **2004**, *60*, 7117; Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2403; Schrock, R.R.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592. See Astruc, D. *New J. Chem.* **2005**, 29, 42; Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3740; Schrock, R.R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748; Grubbs, R.H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760.

⁸⁰⁵ Smith, III, A.B.; Adams, C.M.; Kozmin, S.A. *J. Am. Chem. Soc.* **2001**, *123*, 990.

⁸⁰⁶ See Wang, J.; Menapace, H.R. *J. Org. Chem.* **1968**, *33*, 3794; Hughes, W.B. *J. Am. Chem. Soc.* **1970**, *92*, 532.

⁸⁰⁷ Dragutn, V.; Balaban, A.T.; Dimonie, M. *Olefin Metathesis and Ring-Opening Polymerization of Cyclo-Olefins*, Wiley, NY, **1985**; Ivin, K.J. *Olefin Metathesis*, Academic Press, NY, **1983**; Feast, W.J.; Gibson, V.C. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 5, Wiley, NY, 1989, pp. 199–228; Schrock, R.R. *J. Organomet. Chem.* **1986**, *300*, 249; Grubbs, R.H. in Wilkinson, G. *Comprehensive Organometallic Chemistry*, Vol. 8, Pergamon, Elmsford, NY, **1982**, pp. 499–551; Basset, J.M.; Leconte, M. *CHEMTECH* **1980**, 762; Banks, R.L. *Fortschr. Chem. Forsch.* **1972**, *25*, 39; Calderon N.; Lawrence, J.P.; Ofstead, E.A. *Adv. Organomet. Chem.* **1979**, *17*, 449; Grubbs, R.H. *Prog. Inorg. Chem.* **1978**, *24*, 1; Calderon N. in Patai, S. *The Chemistry of Functional Groups: Supplement A* pt. 2, Wiley, NY, **1977**, pp. 913–964; Acc. Chem. Res. **1972**, *5*, 127; Katz, T.J. *Adv. Organomet. Chem.* **1977**, *16*, 283; Haines, R.J.; Leigh, G.J. *Chem. Soc. Rev.* **1975**, *4*, 155.

alkenes, or to a mixture of two alkenes, in which case the number of different molecules in the product depends on the symmetry of the reactants. In the example, a mixture of $R^1R^2C=CR^1R^2$ and $R^3R^4C=CR^3R^4$ gives rise to only one new alkene ($R^1R^2C=CR^3R^4$), while in the most general case, the reaction of two alkenes ($R^1R^2C=CR^3R^4$ and $R^5R^6C=CR^7R^8$) can give a mixture of 10 alkenes: the original 2 + 8 new ones. In early work, W, Mo,⁸⁰⁸ or Re complexes were used, and with simple alkenes the proportions of products are generally statistical,⁸⁰⁹ which limited the synthetic utility of the reaction since the yield of any one product is low. In some cases, one alkene may be more or less thermodynamically stable than the rest, so that the proportions are not statistical in all cases.



It is possible to shift the equilibrium to favor certain products. For example, 2-methyl-1-butene gives rise to ethylene and 3,4-dimethyl-3-hexene. By allowing the gaseous ethylene to escape, the yield of 3,4-dimethyl-3-hexene can be raised to 95%.⁸¹⁰ This example shows that it is possible to tailor the substrate to include two terminal alkenes that lead to ethylene as a product, whose escape from the reaction drives the equilibrium to product.

The development of better catalysts has revolutionized this reaction,⁸¹¹ making it one of the most important methods available for modern synthesis. Both homogeneous⁸¹² and heterogeneous⁸¹³ catalysts have been used for this reaction. Of the many homogeneous catalysts, Ru complexes are the most important,⁸¹⁴ and important heterogeneous catalysts include oxides of Mo, W, and Re deposited on alumina or silica gel.⁸¹⁵ The major breakthrough in these catalysts was the development of catalysts that are relatively air stable. Three important catalysts are metal carbene complexes **156**⁸¹⁶ and **157**⁸¹⁷ (*Grubbs catalyst I and II*; Mes = mesityl, respectively), and **158** (the *Shrock catalyst*).⁸¹⁸

⁸⁰⁸ See Crowe, W.E.; Zhang, Z.J. *J. Am. Chem. Soc.* **1993**, *115*, 10998.; Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* **1993**, *115*, 3800.

⁸⁰⁹ Calderon N.; Ofstead, E.A.; Ward, J.P.; Judy, W.A.; Scott, K.W. *J. Am. Chem. Soc.* **1968**, *90*, 4133.

⁸¹⁰ Knoche, H. Ger. Pat.(Offen.) 2024835, 1970 [*Chem. Abstr.*, **1971**, *74*, 44118b]. See also, Ichikawa, K.; Fukuzumi, K. *J. Org. Chem.* **1976**, *41*, 2633; Baker, R.; Crimmin, M.J. *Tetrahedron Lett.* **1977**, 441.

⁸¹¹ See Conrad, J.C.; Parnas, H.H.; Snelgrove, J.L.; Fogg, D.E. *J. Am. Chem. Soc.* **2005**, *127*, 11882.

⁸¹² Calderon N.; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* **1967**, 3327. See Hughes, W.B. *Organomet. Chem. Synth.* **1972**, *1*, 341, see pp. 362–368.; Toreki, R.; Schrock, R.R. *J. Am. Chem. Soc.* **1990**, *112*, 2448.

⁸¹³ Banks, R.L.; Bailey, G.C. *Ind. Eng. Chem. Prod. Res. Dev.*, **1964**, *3*, 170. See also, Banks, R.L. *CHEMTECH* **1986**, 112.

⁸¹⁴ Gilbertson, S.R.; Hoge, G.S.; Genov, D.G. *J. Org. Chem.* **1998**, *63*, 10077; Maier, M.E.; Bugl, M. *Synlett* **1998**, 1390; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808.

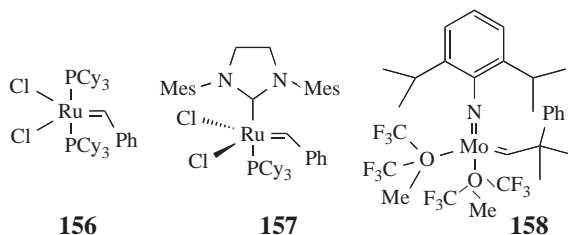
⁸¹⁵ See Banks, R.L. *Fortschr. Chem. Forsch.* **1972**, *25*, 39, pp. 41–46.

⁸¹⁶ Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

⁸¹⁷ Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H. *Org. Lett.* **1999**, *1*, 953.

⁸¹⁸ Bazan, G.C.; Oskam, J.H.; Cho, H.-N.; Park, L.Y.; Schrock, R.R. *J. Am. Chem. Soc.* **1991**, *113*, 6899, and references cited therein.

Catalyst **157** can be generated *in situ* from air stable precursors.⁸¹⁹



The synthetic importance⁸²⁰ of ring-closing and ring-opening metathesis reactions has, in part, led to the ongoing development of new catalysts.⁸²¹ Catalysts have been developed that are compatible with both water and methanol.⁸²² The reaction is compatible with the presence of other functional groups⁸²³ (e.g., other alkene units,⁸²⁴ carbonyl units,⁸²⁵ the alkene unit of conjugated esters,⁸²⁶ butenolides⁸²⁷ and other lactones,⁸²⁸ amines,⁸²⁹ amides,⁸³⁰ sulfones,⁸³¹ phosphine oxides,⁸³² sulfonate esters,⁸³³ and sulfonamides,⁸³⁴ see **149**).⁸³⁵ Ether groups,⁸³⁶ including vinyl ethers,⁸³⁷ vinyl halides,⁸³⁸ vinyl silanes,⁸³⁹ vinyl sulfones,⁸⁴⁰ allylic ethers,⁸⁴¹ and thioethers⁸⁴² are also compatible.

⁸¹⁹ Louie, J.; Grubbs, R.H. *Angew. Chem. Int. Ed.* **2001**, *40*, 247.

⁸²⁰ See Nicolaou, K.C.; Bulger, P.G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; Donohoe, T.J.; Fishlock, L.P.; Procopiou, P.A. *Chemistry: European J.* **2008**, *14*, 5716; Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086.

⁸²¹ Schrock, R.R.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592; Grela, K.; Kim, M. *Eur. J. Org. Chem.* **2003**, 963; Zhang, W.; Kraft, S.; Moore, J.S. *J. Am. Chem. Soc.* **2004**, *126*, 329; Iyer, K.; Rainier, J.D. *J. Am. Chem. Soc.* **2007**, *129*, 12604; Vougioukalakis, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* **2008**, *130*, 2234; Matsugi, M.; Curran, D.P. *J. Org. Chem.* **2005**, *70*, 1636; Rix, D.; Caijo, F.; Laurent, I.; Boeda, F.; Clavier, H.; Nolan, S.P.; Mauduit, M. *J. Org. Chem.* **2008**, *73*, 4225; Katz, T.J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3010.

⁸²² Kirkland, T.A.; Lynn, D.M.; Grubbs, R.H. *J. Org. Chem.* **1998**, *63*, 9904.

⁸²³ See Deiter, S.A.; Martin, S.F. *Chem. Rev.* **2004**, *104*, 2199.

⁸²⁴ Takahashi, T.; Kotori, M.; Kasai, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2693.

⁸²⁵ Schneider, M.F.; Junga, H.; Blechert, S. *Tetrahedron* **1995**, *51*, 13003.

⁸²⁶ Lee, C.W.; Grubbs, R.H. *J. Org. Chem.* **2001**, *66*, 7155.

⁸²⁷ Paquette, L.A.; Méndez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301.

⁸²⁸ Brimble, M.A.; Trzoss, M. *Tetrahedron* **2004**, *60*, 5613.

⁸²⁹ See Dolman, S.J.; Sattely, E.S.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* **2002**, *124*, 6991.

⁸³⁰ See Ma, S.; Ni, B.; Liang, Z. *J. Org. Chem.* **2004**, *69*, 6305.

⁸³¹ Yao, Q. *Org. Lett.* **2002**, *4*, 427.

⁸³² Demchuk, O.M.; Pietrusiewicz, K.M.; Michrowska, A.; Grela, K. *Org. Lett.* **2003**, *5*, 3217.

⁸³³ LeFlohic, A.; Meyer, C.; Cossy, J.; Desmurs, J.-R.; Galland, J.-C. *Synlett* **2003**, 667.

⁸³⁴ See Kinderman, S.S.; Van Maarseveen, J.H.; Schoemaker, H.E.; Hiemstra, H.; Rutjes, F.P.J.T. *Org. Lett.* **2001**, *3*, 2045.

⁸³⁵ Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P.H. *Chem. Commun.* **1998**, 1315; Maier, M.E.; Lapeva, T. *Synlett* **1998**, 891; Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082; O'Mahony, D.J.R.; Belanger, D.B.; Livinghouse, T. *Synlett* **1998**, 443.

⁸³⁶ Edwards, S.D.; Lewis, T.; Taylor, R.J.K. *Tetrahedron Lett.* **1999**, *40*, 4267.

⁸³⁷ See Rainier, J.D.; Cox, J.M.; Allwein, S.P. *Tetrahedron Lett.* **2001**, *42*, 179.

⁸³⁸ Chao, W.; Weinreb, S.M. *Org. Lett.* **2003**, *5*, 2505.

⁸³⁹ Schuman, M.; Gouverneur, V. *Tetrahedron Lett.* **2002**, *43*, 3513.

⁸⁴⁰ Kim, S.; Lim, C.J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3265.

⁸⁴¹ Delgado, M.; Martín, J.D. *Tetrahedron Lett.* **1997**, *38*, 6299; Miller, S.J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R.H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.

⁸⁴² Leconte, M.; Pagano, S.; Mutch, A.; Lefebvre, F.; Basset, J.M. *Bull. Soc. Chim. Fr.* **1995**, *132*, 1069.

Asymmetric ring-closing metathesis reactions have been reported,⁸⁴³ and chiral metathesis catalysts are continually being developed.⁸⁴⁴ The enantioselective synthesis of bicyclic lactams from dienyl lactams used a chiral Mo catalyst.⁸⁴⁵ Asymmetric ring-opening metathesis has also been reported.⁸⁴⁶

Recyclable catalysts have been developed,⁸⁴⁷ and the reaction has been done in ionic liquids,⁸⁴⁸ supercritical CO₂⁸⁴⁹ (Sec. 9.D.ii), and in aqueous media.⁸⁵⁰ Microwave-induced ring-closing metathesis⁸⁵¹ and also cross-metathesis reactions⁸⁵² are known. Polymer-bound Ru⁸⁵³ and Mo catalysts⁸⁵⁴ have been used, and catalyst **157** has been immobilized on PEG.⁸⁵⁵ Efficient methods have been developed for the removal of Ru byproducts from metathesis reactions that include the use of a scavenger resin,⁸⁵⁶ and removal by aqueous extraction.⁸⁵⁷

By choice of the proper catalyst, the reaction has been applied to terminal and internal alkenes, straight chain or branched. The effect of substitution on the ease of reaction is $\text{CH}_2 = >\text{RCH}_2\text{CH} = >\text{R}_2\text{CHCH} = >\text{R}_2\text{C} =$.⁸⁵⁸ Note that isomerization of the C=C unit can occur after metathesis,⁸⁵⁹ but methods have been developed to prevent this, including addition of 2,6-dichlorobenzoquinone.⁸⁶⁰ Cross-metathesis⁸⁶¹ (or symmetrical homo-metathesis⁸⁶²) of alkenes to give new alkenes can be accomplished. Monosubstituted alkenes react faster than disubstituted alkenes.⁸⁶³ A double metathesis reaction of a diene (also called *domino*⁸⁶⁴ or *tandem metathesis*⁸⁶⁵) with conjugated aldehydes has been

⁸⁴³ Cefalo, D.R.; Kiely, A.F.; Wuchrer, M.; Jamieson, J.Y.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2001**, *123*, 3139.

⁸⁴⁴ See Funk, T.W.; Berlin, J.M.; Grubbs, R.H. *J. Am. Chem. Soc.* **2006**, *128*, 1840.

⁸⁴⁵ Sattely, E.S.; Cortez, G.A.; Moebius, D.C.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2005**, *127*, 8526.

⁸⁴⁶ Gillingham, D.G.; Kataoka, O.; Garber, S.B.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2004**, *126*, 12288.

⁸⁴⁷ Kingsbury, J.S.; Harrity, J.P.A.; Bonitatebus, Jr., P.J.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

⁸⁴⁸ Buijsman, R.C.; van Vuuren, E.; Sterrenburg, J.G. *Org. Lett.* **2001**, *3*, 3785. See Clavier, H.; Audic, N.; Mauduit, M.; Guillemin, J.-C. *Chem. Commun.* **2004**, 2282.

⁸⁴⁹ Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, *123*, 9000.

⁸⁵⁰ Binder, J.B.; Blank, J.J.; Raines, R.T. *Org. Lett.* **2007**, *9*, 4885; Zaman, S.; Curnow, O.J.; Abell, A.D. *Austr. J. Chem.* **2009**, *62*, 91; Burtcher, D.; Grela, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 442.

⁸⁵¹ See Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125. For a solvent-free microwave-induced reaction, see Thanh, G.V.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 9091.

⁸⁵² Bargiggia, F.C.; Murray, W.V. *J. Org. Chem.* **2005**, *70*, 9636.

⁸⁵³ Yao, Q. *Angew. Chem. Int. Ed.* **2000**, *39*, 3896; Schürer, S.C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 3898.

⁸⁵⁴ Hultsch, K.C.; Jernelius, J.A.; Hoveyda, A.H.; Schrock, R.R. *Angew. Chem. Int. Ed.* **2002**, *41*, 589.

⁸⁵⁵ A recyclable catalyst, see Yao, Q.; Motta, A.R. *Tetrahedron Lett.* **2004**, *45*, 2447.

⁸⁵⁶ Ahn, Y.M.; Yang, K.; Georg, G.I. *Org. Lett.* **2001**, *3*, 1411; Cho, J.H.; Kim, B.M. *Org. Lett.* **2003**, *5*, 531. See Westhus, M.; Gonthier, E.; Brohm, D.; Breinbauer, R. *Tetrahedron Lett.* **2004**, *45*, 3141.

⁸⁵⁷ Hong, S.H.; Grubbs, R.H. *Org. Lett.* **2007**, *9*, 1955.

⁸⁵⁸ See Chatterjee, A.K.; Choi, T.-L.; Sanders, D.P.; Grubbs, R.H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

⁸⁵⁹ See Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672; Sutton, A.E.; Seigal, B.A.; Finnegan, D.F.; Snapper, M.L. *J. Am. Chem. Soc.* **2002**, *124*, 13390.

⁸⁶⁰ Hong, S.H.; Sanders, D.P.; Lee, C.W.; Grubbs, R.H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

⁸⁶¹ See Stewart, I.C.; Douglas, C.J.; Grubbs, R.H. *Org. Lett.* **2008**, *10*, 441; Lipshutz, B.H.; Aguinado, G.T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* **2008**, *10*, 1325.

⁸⁶² Blanco, O.M.; Castedo, L. *Synlett* **1999**, 557.

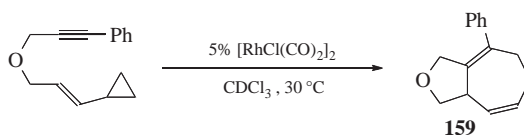
⁸⁶³ See Lautens, M.; Maddess, M.L. *Org. Lett.* **2004**, *6*, 1883.

⁸⁶⁴ Rückert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* **2001**, *42*, 5245.

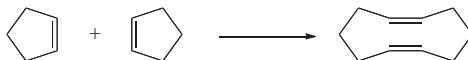
⁸⁶⁵ Choi, T.-L.; Grubbs, R.H. *Chem. Commun.* **2001**, 2648.

reported,⁸⁶⁶ and a triple metathesis was reported to for a dihydropyran with two dihydropyran substituents.⁸⁶⁷ Cross-metathesis of vinylcyclopropanes leads to an alkene with two cyclopropyl substituents.⁸⁶⁸ Vinylcyclopropane-alkyne metathesis reactions have been reported.⁸⁶⁹ Cyclic alkenes can be opened, usually with polymerization using metathesis catalysts. Ring-opening metathesis generates dienes from cyclic alkenes.⁸⁷⁰ Allenes undergo a metathesis reaction to give symmetrical allenenes.⁸⁷¹ An interesting variation reacts an α,ω -diene with a cyclic alkene. The combination of ring-opening metathesis and ring-closing cross-metathesis leads to ring expansion to give a macrocyclic nonconjugated diene.⁸⁷² Note that an alkane metathesis reaction is known.⁸⁷³

Dienes can react intermolecularly or intramolecularly.⁸⁷⁴ Intramolecular reactions generate rings, including small rings,⁸⁷⁵ usually alkenes or dienes. Alkene metathesis can be used to form very large rings, including 21-membered lactone rings.⁸⁷⁶ Diynes undergo both cross-metathesis and ring-closing metathesis.⁸⁷⁷ Diynes can also react intramolecularly to give large-ring alkynes.⁸⁷⁸ Metathesis with vinyl-cyclopropyl-alkynes is also known, producing a ring-expanded product (see **159**).⁸⁷⁹ Vinyl halides undergo metathesis reactions.⁸⁸⁰



Two cyclic alkenes react to give dimeric dienes,⁸⁸¹ for example,



With many catalysts, the products can then react with additional monomers and with each other, so that polymers are produced, and the cyclic dienes are obtained only in low yield.

⁸⁶⁶ BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, 3, 1451; van Otterlo, W.A.L.; Ngidi, E.L.; de Koning, C.D.; Fernandes, M.A. *Tetrahedron Lett.* **2004**, 45, 659.

⁸⁶⁷ Sundararajan, G.; Prabakaran, N.; Varghese, B. *Org. Lett.* **2001**, 3, 1973.

⁸⁶⁸ Verbicky, C.A.; Zercher, C.K. *Tetrahedron Lett.* **2000**, 41, 8723.

⁸⁶⁹ López, F.; Delgado, A.; Rodríguez, J.R.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* **2004**, 126, 10262.

⁸⁷⁰ See Randl, S.; Connon, S.J.; Blechert, S. *Chem. Commun.* **2001**, 1796; Morgan, J.P.; Morrill, C.; Grubbs, R.H. *Org. Lett.* **2002**, 4, 67.

⁸⁷¹ Ahmed, M.; Arnauld, T.; Barrett, A.G.M.; Braddock, D.C.; Flack, K.; Procopiou, P.A. *Org. Lett.* **2000**, 2, 551.

⁸⁷² Lee, C.W.; Choi, T.-L.; Grubbs, R.H. *J. Am. Chem. Soc.* **2002**, 124, 3224.

⁸⁷³ Basset, J.-M.; Copret, C.; Soulivong, D.; Taoufik, M.; Cazat, J.T. *Acc. Chem. Res.* **2010**, 43, 323; Basset, J.-M.; Copéret, C.; Lefort, L.; Maunders, B.M.; Maury, O.; Le Roux, E.; Saggio, G.; Soignier, S.; Soulivong, D.; Sunley, G.J.; Taoufik, M.; Thivolle-Cazat, J. *J. Am. Chem. Soc.* **2005**, 127, 8604; Basset, J.-M.; Copéret, C.; Soulivong, D.; Taoufik, M.; Thivolle-Cazat, J. *Angew. Chem. Int. Ed.* **2006**, 45, 6082.

⁸⁷⁴ See Grubbs, R.H.; Miller, S.J.; Fu, G.C. *Accts. Chem. Res.* **1995**, 28, 446.

⁸⁷⁵ Grela, K. *Angew. Chem. Int. Ed.* **2008**, 47, 5504.

⁸⁷⁶ Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, 61, 3942. Also see, Goldring, W.P.D.; Hodder, A.S.; Weiler, L. *Tetrahedron Lett.* **1998**, 39, 4955; Ghosh, A.K.; Hussain, K.A. *Tetrahedron Lett.* **1998**, 39, 1881.

⁸⁷⁷ See Kim, M.; Miller, R.L.; Lee, D. *J. Am. Chem. Soc.* **2005**, 127, 12818.

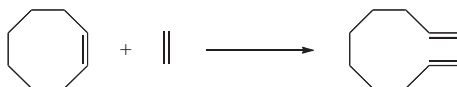
⁸⁷⁸ Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* **2003**, 2629.

⁸⁷⁹ Wender, P.A.; Sperandio, D. *J. Org. Chem.* **1998**, 63, 4164.

⁸⁸⁰ Macnaughtan, M.L.; Johnson, M.J.A.; Kampf, J.W. *J. Am. Chem. Soc.* **2007**, 129, 7708.

⁸⁸¹ Calderon N.; Ofstead, E.A.; Judy, W.A. *J. Polym. Sci. Part A-1* **1967**, 5, 2209; Wasserman, E.; Ben-Efraim, D.A.; Wolovsky, R. *J. Am. Chem. Soc.* **1968**, 90, 3286; Wolovsky, R.; Nir, Z. *Synthesis* **1972**, 134.

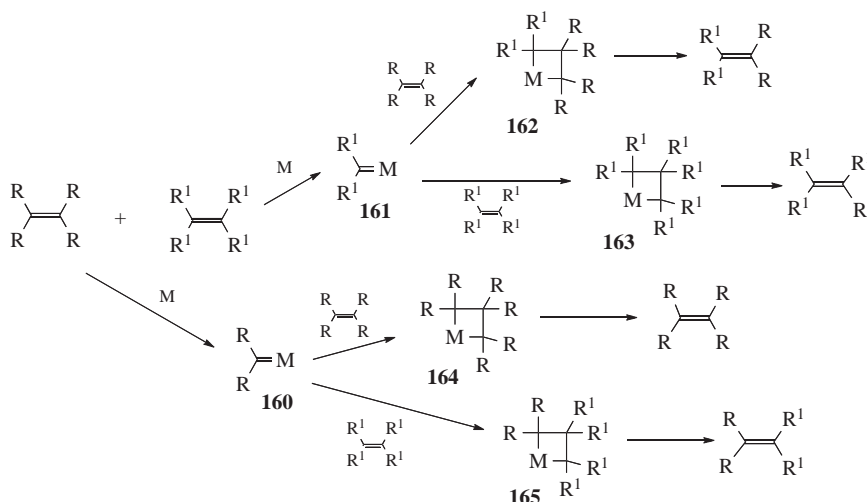
The reaction between a cyclic and a linear alkene can give a ring-opened diene⁸⁸²:



The reaction has also been applied to internal alkynes⁸⁸³:



and some success has been reported for terminal triple bonds.⁸⁸⁴ As noted above, molecules with a terminal alkene and a terminal alkyne react quite well (ene-yne metathesis).⁸⁸⁵ Intramolecular reactions of a double bond with a triple bond are known⁸⁸⁶ and a tetracyclic tetraene has been prepared from a poly-yne-diene.⁸⁸⁷ Cross-metathesis of terminal alkynes and terminal alkenes (en-yne)⁸⁸⁸ to give a diene has also been reported.⁸⁸⁹ Enyne metathesis generates 1,3-dienes.⁸⁹⁰



⁸⁸² Rossi, R.; Diversi, P.; Lucherini, A.; Porri, L. *Tetrahedron Lett.* **1974**, 879; Lal, J.; Smith, R.R. *J. Org. Chem.* **1975**, 40, 775.

⁸⁸³ See Weissman, H.; Plunkett, K.N.; Moore, J.S. *Angew. Chem. Int. Ed.* **2006**, 45, 585. For reviews, see Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539; Fürstner, A.; Davies, P.W. *Chem. Commun.* **2005**, 2307.

⁸⁸⁴ Couteliera, O.; Mortreux, A. *Adv. Synth. Catal.* **2006**, 348, 2038; Mortreux, A.; Petit, F.; Petit, M.; Szymanska-Buza, T. *J. Mol. Catal. A: Chemical* **1995**, 96, 95. However, see McCullough, L.G.; Listemann, M.L.; Schrock, R.R.; Churchill, M.R.; Ziller, J.W. *J. Am. Chem. Soc.* **1983**, 105, 6729.

⁸⁸⁵ See Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, 2, 543; Kitamura, T.; Mori, M. *Org. Lett.* **2001**, 3, 1161.

⁸⁸⁶ See Gilbertson, S.R.; Hoge, G.S. *Tetrahedron Lett.* **1998**, 39, 2075.

⁸⁸⁷ Zuercher, W.J.; Scholl, M.; Grubbs, R.H. *J. Org. Chem.* **1998**, 63, 4291.

⁸⁸⁸ See Kang, B.; Lee, J.M.; Kwak, J.; Lee, Y.S.; Chang, S. *J. Org. Chem.* **2004**, 69, 7661. See Diver, S.T.; Giessert, A.J. *Chem. Rev.* **2004**, 104, 1317.

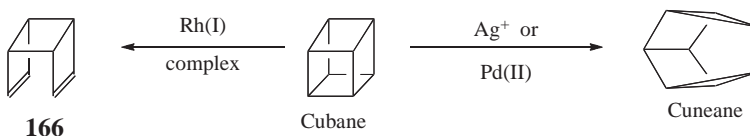
⁸⁸⁹ Poulsen, C.S.; Madsen, R. *Synthesis* **2003**, 1. See Lee, H.-Y.; Kim, B.G.; Snapper, M.L. *Org. Lett.* **2003**, 5, 1855; Giessert, A.J.; Brazis, N.J.; Diver, S.T. *Org. Lett.* **2003**, 5, 3819; Kim, M.; Park, S.; Maifeld, S.V.; Lee, D. *J. Am. Chem. Soc.* **2004**, 126, 10242. See also, Kang, B.; Kim, D.-h.; Do, Y.; Chang, S. *Org. Lett.* **2003**, 5, 3041.

⁸⁹⁰ Hansen, E.C.; Lee, D. *Acc. Chem. Res.* **2006**, 39, 509; Debleds, O.; Campagne, J.-M. *J. Am. Chem. Soc.* **2008**, 130, 1562; Giessert, A.J.; Diver, S.T. *J. Org. Chem.* **2005**, 70, 1046. For a mechanistic study, see Galan, B.R.; Giessert, A.J.; Keister, J.B.; Diver, S.T. *J. Am. Chem. Soc.* **2005**, 127, 5762.

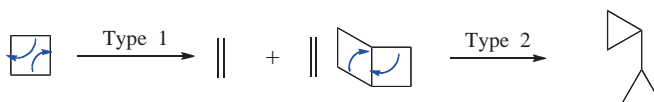
The generally accepted mechanism is a chain mechanism,⁸⁹¹ involving the intervention of a metal–carbene complex (**160** and **161**)⁸⁹² and a four-membered ring containing a metal⁸⁹³ (**162–165**).⁸⁹⁴ In the cross-metathesis reaction shown as an example, $R_2C=CR_2$ reacts with $R^1_2C=CR^1_2$ in the presence of a metal catalyst (M). Initial reaction with the catalyst leads to the two expected metal carbenes, (**160** and **161**). Metal carbene (**161**) can react with both alkenes to form metallocyclobutanes **162** and **163**. Each of these intermediates loses the metal to form the alkenes, the product of metathesis ($R_2C=CR^1_2$) and one of the original alkenes. In a likewise manner, **160** reacts with each alkene to form metallocyclobutanes **164** and **165**, which decomposes to $R_2C=CR_2$ and the metathesis product. It has been shown that the phosphine-containing methyldiene complexes decompose to methylphosphonium salts,⁸⁹⁵

OS 80, 85; **81**, 1.

18-38 Metal-Ion-Catalyzed σ -Bond Rearrangements



Many highly strained cage molecules undergo rearrangement when treated with metallic ions [e.g., Ag^+ , Rh(I), or Pd(II)].⁸⁹⁶ The bond rearrangements observed can be formally classified into two main types: (Type 1)



[2 + 2]-ring openings of cyclobutanes and (Type 2) conversion of a bicyclo[2.2.0] system to a bicyclic system. The molecule cubane supplies an example of each type

⁸⁹¹ See Sanford, M.S.; Ulman, M.; Grubbs, R.H. *J. Am. Chem. Soc.* **2001**, 123, 749; Sanford, M.S.; Love, J.A.; Grubbs, R.H. *J. Am. Chem. Soc.* **2001**, 123, 6543; Cavallo, L. *J. Am. Chem. Soc.* **2002**, 124, 8965; Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* **2004**, 126, 3496.

⁸⁹² See Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, Wiley, NY, **1988**, pp. 244–267; Kingsbury, J.S.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2005**, 127, 4510; Poater, A.; Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2007**, 129, 8207; Vyboishchikov, S.F.; Thiel, W. *Chemistry: European J.* **2005**, 11, 3921.

⁸⁹³ See Collman, J.C.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, **1987**, pp. 459–520; Lindner, E. *Adv. Heterocycl. Chem.* **1986**, 39, 237. See Romero, P.E.; Piers, W.E. *J. Am. Chem. Soc.* **2005**, 127, 5032; Romero, P.E.; Piers, W.E. *J. Am. Chem. Soc.* **2007**, 129, 1698.

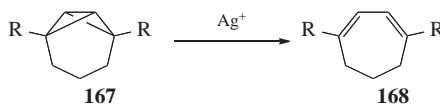
⁸⁹⁴ See Grubbs, R.H. *Prog. Inorg. Chem.* **1978**, 24, 1; Katz, T.J. *Adv. Organomet. Chem.* **1977**, 16, 283; Calderon N.; Ofstead, E.A.; Judy, W.A. *Angew. Chem. Int. Ed.* **1976**, 15, 401. See also, Kress, J.; Osborn, J.A.; Greene, R.M. E.; Ivin, K.J.; Rooney, J.J. *J. Am. Chem. Soc.* **1987**, 109, 899; Feldman, J.; Davis, W.M.; Schrock, R.R. *Organometallics* **1989**, 8, 2266.

⁸⁹⁵ Hong, S.H.; Wenzel, A.G.; Salguero, T.T.; Day, M.W.; Grubbs, R.H. *J. Am. Chem. Soc.* **2007**, 129, 7961.

⁸⁹⁶ Halpern, J. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, **1977**, pp. 705–721; Bishop, III, K.C. *Chem. Rev.* **1976**, 76, 461; Cardin, D.J.; Cetinkaya, B.; Doyle, M.J.; Lappert, M.F. *Chem. Soc. Rev.* **1973**, 2, 99, pp. 132–139; Paquette, L.A. *Synthesis* **1975**, 347; *Acc. Chem. Res.* **1971**, 4, 280.

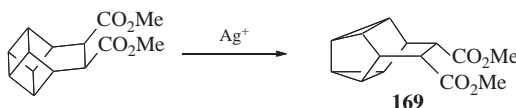
(see above). Treatment with Rh(I) complexes converts cubane to tricyclo[4.2.0.0^{2,5}]octa-3,7-diene (**166**),⁸⁹⁷ an example of type 1, while Ag⁺ or Pd(II) causes the second type of reaction, producing cuneane.⁸⁹⁸ Other examples are the conversion of **167** to **168**, and formation of **159**, the 9,10-dicarbomethoxy derivative of *snoutane* (pentacyclo[3.3.2.0^{2,4}.0^{3,7}.0^{6,8}]decane).

Type 1



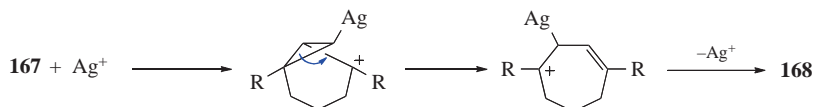
Ref. 899

Type 2⁹⁰⁰

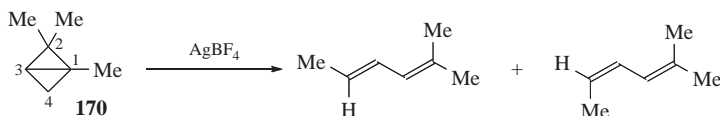


Ref. 901

The mechanisms of these reactions are not completely understood, although relief of strain undoubtedly supplies the driving force. The reactions are thermally forbidden by the orbital-symmetry rules, and the role of the catalyst is to provide low-energy pathways so that the reactions can take place. Type 1 reactions are the reverse of the catalyzed [2 + 2] ring closures discussed at Reaction **15-63**. The following mechanism, in which Ag⁺ attacks one of the edge bonds, has been suggested for the conversion of **167** to **168**.⁹⁰²



Simpler bicyclobutanes can also be converted to dienes, but in this case the products usually result from cleavage of the central bond and one of the edge bonds.⁹⁰³ For example, treatment of **170** with AgBF₄,⁹⁰⁴



or [(π -allyl)PdCl]₂⁹⁰⁵ gives a mixture of the two dienes shown, resulting from a formal cleavage of the C-1—C-3 and C-1—C-2 bonds (note that a hydride shift has taken place). Dienes can also be converted to bicyclobutanes under photochemical conditions.⁹⁰⁶

⁸⁹⁷ Eaton, P.E.; Chakraborty, U.R. *J. Am. Chem. Soc.* **1978**, *100*, 3634.

⁸⁹⁸ Cassar, L.; Eaton, P.E.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 6336.

⁸⁹⁹ Sakai, M.; Westberg, H.H.; Yamaguchi, H.; Masamune, S. *J. Am. Chem. Soc.* **1972**, *93*, 4611; Paquette, L.A.; Wilson, S.E.; Henzel, R.P. *J. Am. Chem. Soc.* **1972**, *94*, 7771.

⁹⁰⁰ The starting compound here is a derivative of basketane, or 1,8-bishomocubane. For a review of homo-, bishomo-, and trishomocubanes, see Marchand, A.P. *Chem. Rev.* **1989**, *89*, 1011.

⁹⁰¹ See Paquette, L.A.; Beckley, R.S.; Farnham, W.B. *J. Am. Chem. Soc.* **1975**, *97*, 1089.

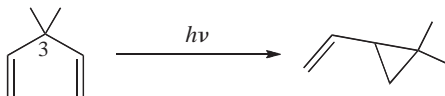
⁹⁰² See Sakai, M.; Westberg, H.H.; Yamaguchi, H.; Masamune, S. *J. Am. Chem. Soc.* **1972**, *93*, 4611.

⁹⁰³ See Paquette, L.A.; Zon, G. *J. Am. Chem. Soc.* **1974**, *96*, 203, 224.

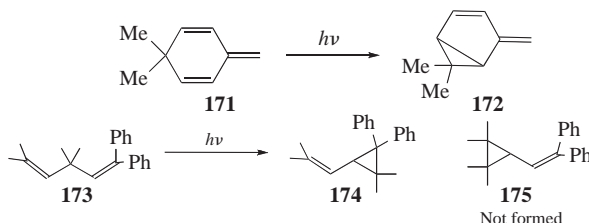
⁹⁰⁴ Paquette, L.A.; Henzel, R.P.; Wilson, S.E. *J. Am. Chem. Soc.* **1971**, *93*, 2335.

⁹⁰⁵ Gassman, P.G.; Meyer, R.G.; Williams, F.J. *Chem. Commun.* **1971**, 842.

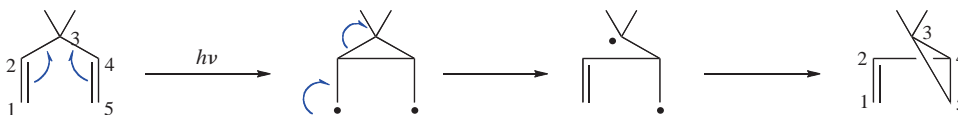
⁹⁰⁶ Garavelli, M.; Frabboni, B.; Fato, M.; Celani, P.; Bernardi, F.; Robb, M.A.; Olivucci, M. *J. Am. Chem. Soc.* **1999**, *121*, 1537.

18-39 The Di- π -methane and Related RearrangementsDi- π -methane rearrangement

1,4-Dienes carrying alkyl or aryl substituents on C-3⁹⁰⁷ can be photochemically rearranged to vinylcyclopropanes in a reaction called the *di- π -methane rearrangement*.⁹⁰⁸ An example is conversion of **171** to **172**.⁹⁰⁹ For most 1,4-dienes, it is only the singlet excited state that gives the reaction; triplet states generally take other pathways.⁹¹⁰ For unsymmetrical dienes, the reaction is regioselective. For example, **173** gave **174**, not **175**.⁹¹¹



The mechanism can be described by the diradical pathway given⁹¹² (the C-3 substituents act to stabilize the radical), although the species shown are not necessarily intermediates, but may represent transition states. It has been shown, for the case of certain substituted substrates, that configuration is retained at C-1 and C-5 and inverted at C-3.⁹¹³



The reaction has been extended to allylic benzenes⁹¹⁴ (in this case C-3 substituents are not required), to β,γ -unsaturated ketones⁹¹⁵ (the latter reaction, which is called the *oxa-di-*

⁹⁰⁷ Zimmerman, H.E.; Pincock, J.A. *J. Am. Chem. Soc.* **1973**, 95, 2957.

⁹⁰⁸ Zimmerman, H.E. *Org. Photochem.* **1991**, 11, 1; Zimmerman, H.E. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, **1980**, pp. 131–166; Hixson, S.S.; Mariano, P.S.; Zimmerman, H.E. *Chem. Rev.* **1973**, 73, 531. See also, Roth, W.R.; Wildt, H.; Schlemenat, A. *Eur. J. Org. Chem.* **2001**, 4081.

⁹⁰⁹ Zimmerman, H.E.; Hackett, P.; Juers, D.F.; McCall, J.M.; Schröder, B. *J. Am. Chem. Soc.* **1971**, 93, 3653.

⁹¹⁰ However, some substrates, generally rigid bicyclic molecules, (e.g., barrelene, which is converted to semi-bullvalene) give the di- π -methane rearrangement only from triplet states.

⁹¹¹ Zimmerman, H.E.; Baum, A.A. *J. Am. Chem. Soc.* **1971**, 93, 3646. See also, Paquette, L.A.; Bay, E.; Ku, A.Y.; Rondan, N.G.; Houk, K.N. *J. Org. Chem.* **1982**, 47, 422.

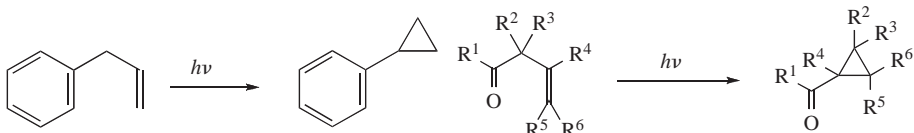
⁹¹² See Zimmerman, H.E.; Boettcher, R.J.; Buehler, N.E.; Keck, G.E. *J. Am. Chem. Soc.* **1975**, 97, 5635. However, see Adam, W.; De Lucchi, O.; Dörr, M. *J. Am. Chem. Soc.* **1989**, 111, 5209.

⁹¹³ Zimmerman, H.E.; Robbins, J.D.; McKelvey, R.D.; Samuel, C.J.; Sousa, L.R. *J. Am. Chem. Soc.* **1989**, 111, 5209.

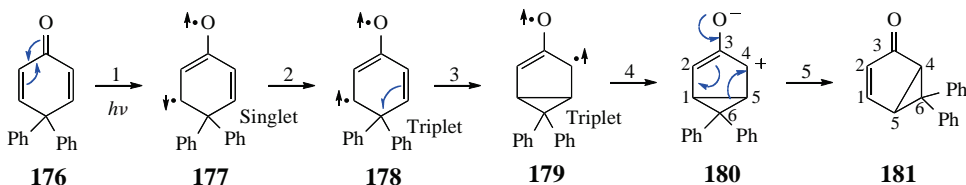
⁹¹⁴ See Paquette, L.A.; Bay, E. *J. Am. Chem. Soc.* **1984**, 106, 6693; Zimmerman, H.E.; Swafford, R.L. *J. Org. Chem.* **1984**, 49, 3069.

⁹¹⁵ See Schuster, D.I. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, **1980**, pp. 167–279; Houk, K.N. *Chem. Rev.* **1976**, 76, 1; Schaffner, K. *Tetrahedron* **1976**, 32, 641; Dauben, W.G.; Lodder, G.; Ipaktschi, J. *Top. Curr. Chem.* **1975**, 54, 73.

π -methane rearrangement,⁹¹⁶ generally occurs only from the triplet state), to β,γ -unsaturated imines,⁹¹⁷ and to triple-bond systems.⁹¹⁸



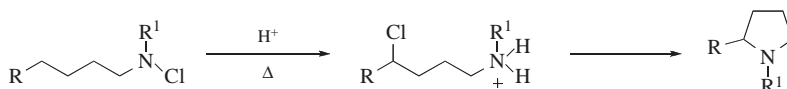
When photolyzed, 2,5-cyclohexadienones can undergo a number of different reactions, one of which is formally the same as the di- π -methane rearrangement.⁹¹⁹ In this reaction, photolysis of the substrate **176** gives the bicyclo[3.1.0]hexenone (**181**). Although the reaction is formally the same (note the conversion of **171** to **172**),



the mechanism is different from that of the di- π -methane rearrangement, because irradiation of a ketone can cause an $n \rightarrow \pi^*$ transition, which is of course not possible for a diene lacking a carbonyl group. The mechanism⁹²⁰ in this case has been formulated as proceeding through the excited triplet states **178** and **179**. In step 1, the molecule undergoes an $n \rightarrow \pi^*$ excitation to the singlet species **177**, which cross to the triplet **178**. Step 3 is a rearrangement from one excited state to another. Step 4 is a $\pi^* \rightarrow n$ electron demotion (an intersystem crossing from $T_1 \rightarrow S_0$, see Sec. 7.A.vi, category 4). The conversion of **180** to **181** consists of two 1,2-alkyl migrations (a one-step process would be a 1,3-migration of alkyl to a carbocation center): The old C-6—C-5 bond becomes the new C-6—C-4 bond and the old C-6—C-1 bond becomes the new C-6—C-5 bond.⁹²¹

2,4-Cyclohexadienones also undergo photochemical rearrangements, but the products are different, generally involving ring opening.⁹²²

18-40 The Hofmann–Löffler and Related Reactions



⁹¹⁶ For a review, see Demuth, M. *Org. Photochem.* **1991**, 11, 37.

⁹¹⁷ See Armesto, D.; Horspool, W.M.; Langa, F.; Ramos, A. *J. Chem. Soc. Perkin Trans. 1* **1991**, 223.

⁹¹⁸ See Griffin, G.W.; Chihal, D.M.; Perreten, J.; Bhacca, N.S. *J. Org. Chem.* **1976**, 41, 3931.

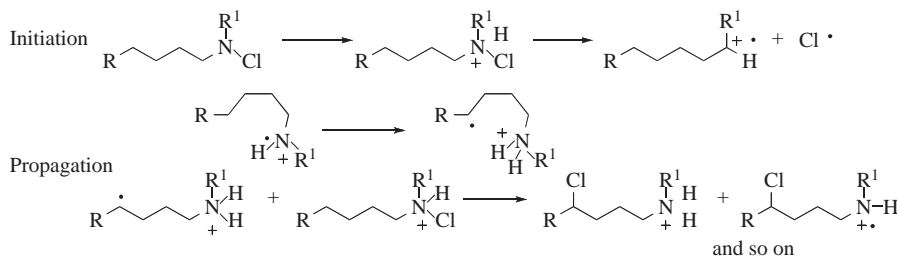
⁹¹⁹ See Schaffner, K.; Demuth, M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, **1980**, pp. 281–348; Zimmerman, H.E. *Angew. Chem. Int. Ed.* **1969**, 8, 1; Kropp, P.J. *Org. Photochem.* **1967**, 1, 1; Schaffner, K. *Adv. Photochem.* **1966**, 4, 81; Schultz, A.G.; Lavieri, F.P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc.* **1987**, 109, 3991, and references cited therein.

⁹²⁰ Schuster, D.I. *Acc. Chem. Res.* **1978**, 11, 65; Zimmerman, H.E.; Pasteris, R.J. *J. Org. Chem.* **1980**, 45, 4864, 4876; Schuster, D.I.; Liu, K. *Tetrahedron* **1981**, 37, 3329.

⁹²¹ Zimmerman, H.E.; Crumine, D.S.; Döpp, D.; Huyffer, P.S. *J. Am. Chem. Soc.* **1969**, 91, 434.

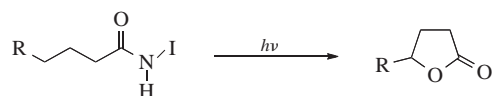
⁹²² Schaffner, K.; Demuth, M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, **1980**, p. 281; Quinkert, G. *Angew. Chem. Int. Ed.* **1972**, 11, 1072; Kropp, P.J. *Org. Photochem.* **1967**, 1, 1.

A common feature of the reactions in this section⁹²³ is that they serve to introduce functionality at a position remote from functional groups already present. As such, they have proved very useful in synthesizing many compounds, especially in the steroid field (see also, Reactions **19-2** and **19-17**). When *N*-haloamines in which one alkyl group has a hydrogen in the 4 or 5 position are heated with sulfuric acid, pyrrolidines, or piperidines are formed, in a reaction known as the *Hofmann-Löffler reaction* (also called the *Hofmann-Löffler-Freytag reaction*).⁹²⁴ The R' group is normally alkyl, but the reaction has been extended to R' = H by the use of concentrated sulfuric



acid solution and ferrous salts.⁹²⁵ The first step of the reaction is a rearrangement, with the halogen migrating from the nitrogen to the 4 or 5 position of the alkyl group. It is possible to isolate the resulting haloamine salt, but usually this is not done, and the second step, the ring closure (Reaction **10-31**), takes place. The reaction is most often induced by heat, but this is not necessary, and irradiation and chemical initiators (e.g., peroxides) have been used instead. The mechanism is of a free radical type, with the main step involving an internal hydrogen abstraction.⁹²⁶

A similar reaction has been carried out on *N*-halo amides, which give γ -lactones⁹²⁷:



Another related reaction is the *Barton reaction*,⁹²⁸ by which a methyl group in a unique position relative to an OH group can be oxidized to a CHO group. The alcohol is first converted to the nitrite ester. Photolysis of the nitrite results in conversion of the nitrite group to the OH group and nitrosation of the methyl group. Formation of a radical and with the methyl group in the appropriate position, hydrogen-atom transfer via a six-center transition state leads to a nitrite. Hydrolysis of the oxime tautomer gives the aldehyde, for example⁹²⁹

⁹²³ See Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed., Cambridge University Press, Cambridge, **1986**, pp. 263–279.

⁹²⁴ See Stella, L. *Angew. Chem. Int. Ed.* **1983**, 22, 337; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free Radical Chem.* **1972**, 4, 203, see pp. 249–259; Deno, N.C. *Methods Free-Radical Chem.* **1972**, 3, 135, see pp. 136–143.

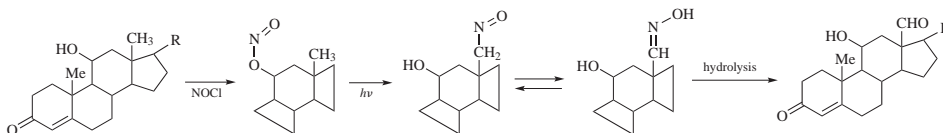
⁹²⁵ Schmitz, E.; Murawski, D. *Chem. Ber.* **1966**, 99, 1493.

⁹²⁶ Wawzonek, S.; Thelan, P.J. *J. Am. Chem. Soc.* **1950**, 72, 2118.

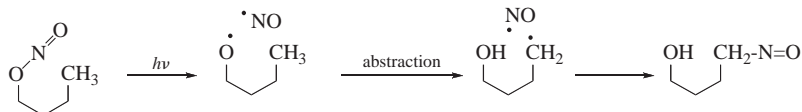
⁹²⁷ Barton, D.H.R.; Beckwith, A.L.J.; Goosen, A. *J. Chem. Soc.* **1965**, 181; Neale, R.S.; Marcus, N.L.; Schepers, R.G. *J. Am. Chem. Soc.* **1966**, 88, 3051. See Neale, R.S. *Synthesis* **1971**, 1.

⁹²⁸ See Hesse, R.H. *Adv. Free-Radical Chem.* **1969**, 3, 83; Barton, D.H.R. *Pure Appl. Chem.* **1968**, 16, 1; Saraiva, M.F.; Couri, M.R.C.; Le Hyaric, M.; de Almeida, M.V. *Tetrahedron* **2009**, 65, 3563.

⁹²⁹ Barton, D.H.R.; Beaton, J.M. *J. Am. Chem. Soc.* **1961**, 83, 4083. Also see, Barton, D.H.R.; Beaton, J.M.; Geller, L.E.; Pechet, M.M. *J. Am. Chem. Soc.* **1960**, 82, 2640.



This reaction takes place only when the methyl group is in a favorable steric position.⁹³⁰ The mechanism is similar to that of the *Hofmann-Löffler reaction*.⁹³¹

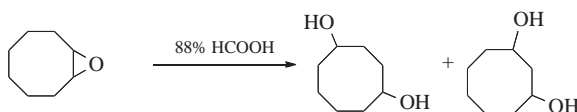


This is one of the few known methods for effecting substitution at an angular methyl group. Not only CH_3 groups but also alkyl groups of the form RCH_2 and R_2CH can give the Barton reaction if the geometry of the system is favorable. An RCH_2 group is converted to the oxime $\text{R}(\text{C}=\text{NOH})$, which is hydrolyzable to a ketone, or to a nitroso dimer, while an R_2CH group gives a nitroso compound $[\text{R}_2\text{C}(\text{NO})]$. With very few exceptions, the only carbons that become nitrosated are those in the position δ to the original OH group, indicating that a six-membered transition state is necessary for the hydrogen abstraction.⁹³²

OS III, 159.

D. Noncyclic Rearrangements

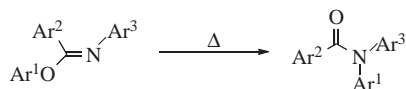
18-41 Hydride Shifts



The example shown is typical of a transannular hydride shift. The 1,2-diol is formed by a normal epoxide hydrolysis reaction (10-7).⁹³³ For a discussion of 1,3 and longer hydride shifts, see Sec. 18.B.

18-42 The Chapman Rearrangement

1/O—3/ N-Aryl-migration



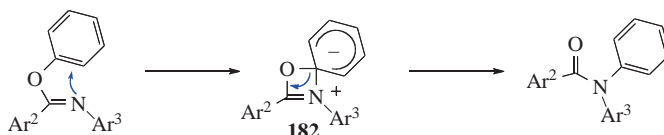
⁹³⁰ See Burke, S.D.; Silks III, L.A.; Strickland, S.M.S. *Tetrahedron Lett.* **1988**, 29, 2761.

⁹³¹ See Green, M.M.; Boyle, B.A.; Vairamani, M.; Mukhopadhyay, T.; Saunders Jr., W.H.; Bowen, P.; Allinger, N.L. *J. Am. Chem. Soc.* **1986**, 108, 2381; Grossi, L. *Chemistry: European J.* **2005**, 11, 5419.

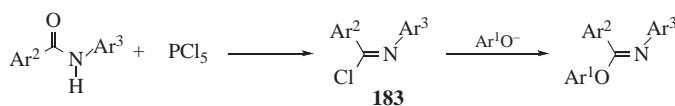
⁹³² See Nickon, A.; Ferguson, R.; Bosch, A.; Iwadare, T. *J. Am. Chem. Soc.* **1977**, 99, 4518.

⁹³³ Cope, A.C.; Fournier, Jr., A.; Simmons Jr., H.E. *J. Am. Chem. Soc.* **1957**, 79, 3905.

In the *Chapman rearrangement*, *N,N*-diaryl amides are formed when aryl imino esters are heated.⁹³⁴ Best yields are obtained in refluxing tetraethylene glycol dimethyl ether (tetraglyme),⁹³⁵ although the reaction can also be carried out without any solvent at all. Many groups may be present in the rings (e.g., alkyl, halo, OR, CN, and CO₂R). Aryl migrates best when it contains electron-withdrawing groups. On the other hand, electron-withdrawing groups in Ar² or Ar³ decrease the reactivity. The products can be hydrolyzed to

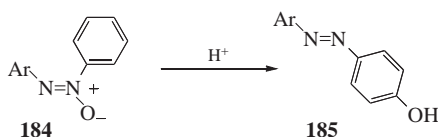


diarylamines, and this is a method for preparing these compounds. The mechanism probably involves an intramolecular⁹³⁶ aromatic nucleophilic substitution, resulting in a 1,3 oxygen-to-nitrogen shift via a species (e.g., **182**). Aryl imino esters can be prepared from *N*-aryl amides by reaction with PCl₅, followed by treatment



of the resulting imino chloride (**183**) with an aroxide ion.⁹³⁷ Imino esters with any or all of the three groups being alkyl also rearrange, but they require catalysis by H₂SO₄ or a trace of methyl iodide or methyl sulfate.⁹³⁸ The mechanism is different, involving an intermolecular process.⁹³⁹ This is also true for derivatives for formamide (Ar² = H).

18-43 The Wallach Rearrangement



The conversion of azoxy compounds (e.g., **184**), upon acid treatment, to *p*-hydroxy azo compounds (e.g., **185**, or sometimes the *o*-hydroxy isomers⁹⁴⁰) is called the *Wallach rearrangement*.⁹⁴¹ When both para positions are occupied, the *o*-hydroxy product may be

⁹³⁴ Schulenberg, J.W.; Archer, S. *Org. React.* **1965**, *14*, 1; McCarty, C.G. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 439–447; McCarty, C.G.; Garner, L.A. in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, **1975**, pp. 189–240. For a review of 1,3-migrations of R in general, see Landis, P.S. *Mech. Mol. Migr.* **1969**, *2*, 43.

⁹³⁵ Wheeler, O.H.; Roman, F.; Santiago, M.V.; Quiles, F. *Can. J. Chem.* **1969**, *47*, 503.

⁹³⁶ See Wheeler, O.H.; Roman, F.; Rosado, O. *J. Org. Chem.* **1969**, *34*, 966; Kimura, M. *J. Chem. Soc. Perkin Trans. 2* **1987**, 205.

⁹³⁷ See Bonnett, R. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 597–662.

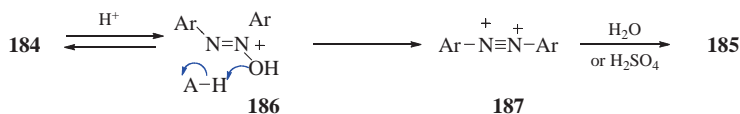
⁹³⁸ Landis, P.S. *Mech. Mol. Migr.* **1969**, *2*, 43.

⁹³⁹ See Challis, B.C.; Frenkel, A.D. *J. Chem. Soc. Perkin Trans. 2* **1978**, 192.

⁹⁴⁰ See Yamamoto, J.; Nishigaki, Y.; Umez, M.; Matsuura, T. *Tetrahedron* **1980**, *36*, 3177.

⁹⁴¹ See Buncel, E. *Mech. Mol. Migr.* **1968**, *1*, 61; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, **1969**, pp. 272–284, 357–359; Cox, R.A.; Buncel, E. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, **1975**, pp. 808–837.

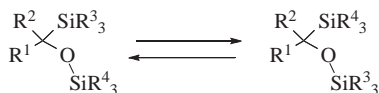
obtained, but ipso substitution at one of the para positions is also possible.⁹⁴² The following facts are known for the proposed mechanism⁹⁴³: (1) The para rearrangement is intermolecular.⁹⁴⁴ (2) When the reaction was carried out with an azoxy compound in which the N—O nitrogen was labeled with ¹⁵N, *both* nitrogens of the product carried the label equally,⁹⁴⁵ demonstrating that the oxygen did not have a preference for migration to either the near or the far ring. This shows that there is a symmetrical intermediate. (3) Kinetic studies show that two protons are normally required for the reaction.⁹⁴⁶ The following mechanism,⁹⁴⁷ involving the symmetrical intermediate (**187**), has been proposed to explain the facts.⁹⁴⁸ It has proved possible to obtain **186** and **187** as stable species in superacid solutions.⁹⁴⁹ Another mechanism, involving an intermediate with only one positive charge, has been proposed for certain substrates at low acidities.⁹⁴⁹



A photochemical *Wallach rearrangement*⁹⁵⁰ is also known: The product is the *o*-hydroxy azo compound, the OH group is found in the farther ring, and the rearrangement is intramolecular.⁹⁵¹

18-44 Dyotropic Rearrangements

1/*C*-Trialkylsilyl,2/*O*-trialkylsilyl-interchange



A *dyotropic rearrangement*⁹⁵² is an uncatalyzed process in which two σ bonds simultaneously migrate intramolecularly.⁹⁵³ There are two types. The above is an example of type 1, which consists of reactions in which the two σ bonds interchange positions.

⁹⁴² See Shimao, I.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, 56, 643.

⁹⁴³ Furin, G.G. *Russ. Chem. Rev.* **1987**, 56, 532; Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* **1980**, 5, 184; Buncel, E. *Acc. Chem. Res.* **1975**, 8, 132.

⁹⁴⁴ See Oae, S.; Fukumoto, T.; Yamagami, M. *Bull. Chem. Soc. Jpn.* **1963**, 36, 601.

⁹⁴⁵ Shemyakin, M.M.; Maimind, V.I.; Vaichunaite, B.K. *Chem. Ind. (London)* **1958**, 755; *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1960**, 808. Also see, Behr, L.C.; Hendley, E.C. *J. Org. Chem.* **1966**, 31, 2715.

⁹⁴⁶ See Cox, R.A. *J. Am. Chem. Soc.* **1974**, 96, 1059.

⁹⁴⁷ See Buncel, E.; Keum, S. *J. Chem. Soc., Chem. Commun.* **1983**, 578.

⁹⁴⁸ Also see Shemyakin, M.M.; Agadzhanian, Ts.E.; Maimind, V.I.; Kudryavtsev, R.V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1963**, 1216; Hendley, E.C.; Duffey, D. *J. Org. Chem.* **1970**, 35, 3579.

⁹⁴⁹ Cox, R.A.; Dolenko, A.; Buncel, E. *J. Chem. Soc. Perkin Trans. 2* **1975**, 471; Cox, R.A.; Buncel, E. *J. Am. Chem. Soc.* **1975**, 97, 1871.

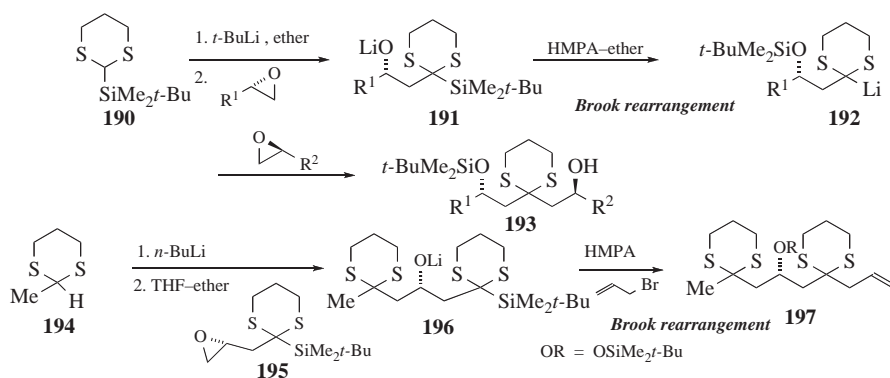
⁹⁵⁰ See Shimao, I.; Hashidzume, H. *Bull. Chem. Soc. Jpn.* **1976**, 49, 754.

⁹⁵¹ See Shine, H.J.; Subotkowski, W.; Gruszecka, E. *Can. J. Chem.* **1986**, 64, 1108.

⁹⁵² See Davis, R.L.; Tantillo, D.J. *J. Org. Chem.* **2010**, 75, 1693.

⁹⁵³ Minkin, V.I.; Olekhovich, L.P.; Zhdanov, Yu.A. *Molecular Design of Tautomeric Compounds*, D. Reidel Publishing Co., Dordrecht, **1988**, pp. 221–246; Minkin, V.I. *Sov. Sci. Rev. Sect. B* **1985**, 7, 51; Reetz, M.T. *Adv. Organomet. Chem.* **1977**, 16, 33. Also see, Mackenzie, K.; Gravaatt, E.C.; Gregory, R.J.; Howard, J.A.K.; Maher, J.P. *Tetrahedron Lett.* **1992**, 33, 5629.

The *Brook rearrangement* has been used in two important synthetic applications, a multicomponent coupling protocol initiated by a *Brook rearrangement* involving silyl dithianes as mentioned, and anion relay chemistry (ARC) involving a *Brook rearrangement*. An example of the former is the conversion of the 2-silyl dithiane (**190**) to the anion with *tert*-butyllithium followed by ring opening of an epoxide to give **191**.⁹⁶⁵ Treatment with HMPA triggers a solvent-controlled *Brook rearrangement* that gives a new dithiane anion (**192**), which then reacts with a different epoxide to give the final product **193**. An example of the anion relay chemistry treats dithiane (**194**) with *n*-butyllithium, and then **195** to give **196**.⁹⁶⁶ Subsequent treatment with a variety of electrophiles (e.g., allyl bromide, in HMPA), leads to **197** via a *Brook rearrangement*, and then alkylation of the resultant dithiane anion. This reaction can be initiated by nucleophiles other than dithiane anion.



⁹⁶⁵ Smith, III, A.B.; Pitram, S.M.; Boldi, A.M.; Gaunt, M.J.; Sfougataakis, C.; Moser, W.H. *J. Am. Chem. Soc.* **2003**, *125*, 14435. See Smith, III, A.B.; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66.

⁹⁶⁶ Smith, III, A.B.; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66.








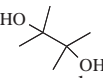
Oxidations and Reductions

First, the terms oxidation and reduction must be clarified. Inorganic chemists define oxidation in two ways: loss of electrons and an increase in oxidation number. In organic chemistry, these definitions, while still technically correct, are not easy to apply. While electrons are directly transferred in some organic oxidations and reductions, and electrons are certainly transferred by making and breaking bonds, the mechanisms of most of these reactions do not involve a direct electron transfer. As for oxidation number, while this is easy to apply in some cases (e.g., the oxidation number of carbon in CH_4 is -4), in most cases attempts to apply the concept lead to fractional values or to apparent absurdities. Thus carbon in propane has an oxidation number of -2.67 and in butane of -2.5 , although organic chemists seldom think of these two compounds as being in different oxidation states. An improvement could be made by assigning different oxidation states to different carbon atoms in a molecule, depending on what is bonded to them (e.g., the two carbons in acetic acid are obviously in different oxidation states), but for this a whole set of arbitrary assumptions would be required, since the oxidation number of an atom in a molecule is assigned on the basis of the oxidation numbers of the atoms attached to it. There would seem little to be gained by such a procedure. The practice in organic chemistry has been to set up a series of functional groups, in a qualitative way, arranged in order of increasing oxidation state, and then to define oxidation as *the conversion of a functional group in a molecule from one category to a higher one*. Reduction is the opposite. For the simple functional groups, this series is shown in Table 19.1.¹ Note that this classification applies only to a single carbon atom or to two adjacent carbon atoms. Thus 1,3-dichloropropane is in the same oxidation state as chloromethane, but 1,2-dichloropropane is in a higher one. Obviously, such distinctions are somewhat arbitrary, and if we attempt to carry them too far, we will find ourselves painted into a corner. Nevertheless, the basic idea has served organic chemistry well. Note that conversion of any compound to another in the same category is not an oxidation or a reduction. Most oxidations in organic chemistry involve a gain of oxygen and/or a loss of hydrogen (Lavoisier's original definition of oxidation). The reverse is true for reductions.

Of course, there is no oxidation without a concurrent reduction. However, reactions are classified as oxidations or reductions depending on whether the *organic compound* is oxidized or reduced. In some cases, both the oxidant and reductant are organic; those reactions are treated separately at the end of the chapter.

¹ For more extensive tables, see Soloveichik, S.; Krakauer, H. *J. Chem. Educ.* **1966**, *43*, 532.

TABLE 19.1 Categories of Simple Functional Groups Arranged According to Oxidation State^a

RH		$\text{—C}\equiv\text{C—}$		CO ₂
	ROH			CO ₄
	RCl			
	RNH ₂			
	... and so on			
			... and so on	
				
		... and so on		
Approximate Oxidation Number				
−4	−2	0	+2	+4

^aOxidation is the conversion of a functional group in a molecule to a higher category; reduction is conversion to a lower one. Conversions within a category are neither oxidations nor reductions. The numbers given at the bottom are only approximations.

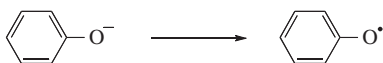
19.A. MECHANISMS

Note that our definition of oxidation has nothing to do with mechanism. Thus the conversion of bromomethane to methanol with KOH (Reaction 10-1) and to methane with LiAlH₄ (Reaction 19-53) have the same S_N2 mechanisms, but one is a reduction (according to our definition) and the other is not. It is impractical to consider the mechanisms of oxidation and reduction reactions in broad categories in this chapter as done for the reactions considered in Chapters 10–18.² The main reason is that the mechanisms are too diverse, and this in turn is because the bond changes are too different. For example, in Chapter 15, most reactions involved the bond change C=C → W—C—C—Y yet a relatively few mechanisms covered those reactions. But for oxidations and reductions the bond changes are far more diverse. Another reason is that the mechanism of a given oxidation or reduction reaction can vary greatly with the oxidizing or reducing agent employed. Very often the mechanism has been studied intensively for only one or a few of many possible agents.

² See Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, 1980; *Oxidation in Organic Chemistry*, Academic Press, NY, pt. A [Wiberg, K.B.], 1965, pts. B, C, and D [Trahanovsky, W.S.], 1973, 1978, 1982; Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, 1964; Stewart, R. *Oxidation Mechanisms*; W. A. Benjamin, NY, 1964. For a review, see Stewart, R. *Isot. Org. Chem.* 1976, 2, 271.

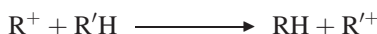
Although oxidation and reduction mechanisms are not covered in the same way as other mechanisms, it is still possible to list a few broad mechanistic categories. The scheme of Wiberg is followed.³

1. *Direct Electron Transfer*.⁴ Several reactions have been encountered in which the reduction is a direct gain of electrons or the oxidation is a direct loss of them. An example is the *Birch reduction* (Reaction **15-13**), where sodium directly transfers an electron to an aromatic ring. An example from this chapter is found in the bimolecular reduction of ketones with a metal (**19-76**), where again it is a metal that supplies the electrons. This kind of mechanism is found largely in three types of reaction:⁵ (a) the oxidation or reduction of a free radical (oxidation to a positive or reduction to a negative ion), (b) the oxidation of a negative ion or the reduction of a positive ion to a comparatively stable free radical, and (c) electrolytic oxidations or reductions (an example is the *Kolbe reaction*, **14-29**). An important example of (b) is oxidation of phenolate ions:

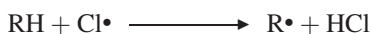


These reactions occur easily because of the relative stability of the radicals involved.⁶ The (SET) mechanism, which has been seen several times (see Sec. 10.B) is an important case.

2. *Hydride Transfer*.⁷ In some reactions, a hydride ion is transferred to or from the substrate. The reduction of epoxides with LiAlH_4 is an example (**19-35**). Another is the *Cannizzaro reaction* (**19-81**). Reactions in which a hydride ion is transferred to a carbocation belong in this category:⁸

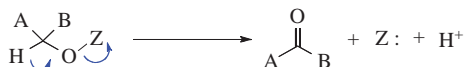


3. *Hydrogen-Atom Transfer*. Many oxidation and reduction reactions are free radical substitutions and involve the transfer of a hydrogen atom. For example, one of the two main propagation steps of Reaction **14-1** involves abstraction of hydrogen:



This is the case for many of the reactions of Chapter 14.

4. *Formation of Ester Intermediates*. A number of oxidations involve the formation of an ester intermediate (usually of an inorganic acid), and then the cleavage of this intermediate:



³ Wiberg, K.B. *Surv. Prog. Chem.* **1963**, *1*, 211.

⁴ See Ebersson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer, NY, **1987**; Ebersson, L. *Adv. Phys. Org. Chem.* **1982**, *18*, 79; Deuchert, K.; Hünig, S. *Angew. Chem. Int. Ed.* **1978**, *17*, 875.

⁵ Littler, J.S.; Sayce, I.G. *J. Chem. Soc.* **1964**, 2545.

⁶ See Mihailovic, M.Lj.; Cekovic, Z. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, **1971**, pp. 505–592.

⁷ For a review, see Watt, C.I.F. *Adv. Phys. Org. Chem.* **1988**, *24*, 57.

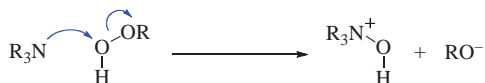
⁸ See Nenitzescu, C.D. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, **1970**, pp. 463–520.

Z is usually CrO_3H , MnO_3 , or a similar inorganic acid moiety. One example of this mechanism will be seen in Reaction **19-23**, where A was an alkyl or aryl group, B was OH, and Z was CrO_3H . Another is the oxidation of a secondary alcohol to a ketone (Reaction **19-3**), where A and B are alkyl or aryl groups and Z is also CrO_3H . In the lead tetraacetate oxidation of glycols (Reaction **19-7**), the mechanism also follows this pattern, but the positive leaving group is carbon instead of hydrogen. Note that the cleavage shown is an example of an E2 elimination.

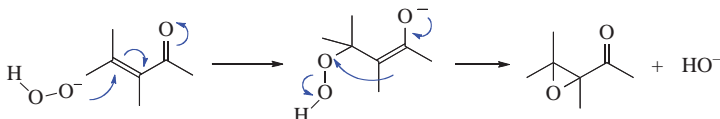
5. *Displacement Mechanisms.* In these reactions, the organic substrate uses its electrons to cause displacement on an electrophilic oxidizing agent. One example is the addition of bromine to an alkene (Reaction **15-39**).



An example from this chapter is found in Reaction **19-29**:



6. *Addition-Elimination Mechanisms.* In the reaction between α,β -unsaturated ketones and alkaline peroxide (**15-50**), the oxidizing agent adds to the substrate and then part of it is lost:



In this case, the oxygen of the oxidizing agent is in oxidation state -1 and the hydroxide ion departs with its oxygen in the -2 state, so it is reduced and the substrate is oxidized. There are several reactions that follow this pattern of addition of an oxidizing agent and the loss of part of the agent, usually in a different oxidation state. Another example is the oxidation of ketones with SeO_2 (Reaction **19-17**). This reaction is also an example of category 4, since it involves formation and E2 cleavage of an ester. This example shows that these six categories are not mutually exclusive.

19.B. REACTIONS

In this chapter, the reactions are classified by the type of bond change occurring to the organic substrate, in conformity with other chapters.⁹ This means that there is no discussion in any one place of the use of a particular oxidizing or reducing agent (e.g., acid dichromate or LiAlH_4 ; except for a discussion of selectivity of reducing agents Sec. 19.B.ii, A). Some oxidizing or reducing agents are fairly specific in their action,

⁹ See Hudlicky, M. J. *Chem. Educ.* **1977**, *54*, 100.

attacking only one or a few types of substrate. Others, like acid dichromate, permanganate, LiAlH_4 , and catalytic hydrogenation, are much more versatile.^{10,11}

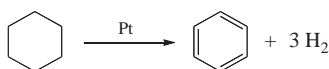
19.B.i. Oxidations¹¹

In some cases, oxidations have been placed in another chapter. The oxidations of an alkene to a diol (Reaction 15-48), and an aromatic compound to a diol (Reaction 15-49), or oxidations to an epoxide (Reaction 15-50) are placed in Chapter 15, for consistency with the concept of addition to a π bond. Diamination of an alkene (Reaction 15-53) and formation of aziridines (Reaction 15-54) are in Chapter 15 for the same reason. Most other oxidations have been placed here. The reactions in this section are classified into groups depending on the type of bond change involved. These groups are Section (A) eliminations of hydrogen, Section (B) oxidations involving cleavage of carbon-carbon bonds, Section (C) reactions involving replacement of hydrogen by oxygen, Section (D) reactions in which oxygen is added to the substrate, and Section (E) oxidative coupling.

A. Eliminations of Hydrogen

19-1 Aromatization of Six-Membered Rings

Hexahydro-terelimination



¹⁰ See Mijs, W.J.; de Jonge, C.R.J.I. *Organic Synthesis by Oxidation with Metal Compounds*, Plenum, NY, **1986**; Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, **1984**; Arndt, D. *Manganese Compounds as Oxidizing Agents in Organic Chemistry*, Open Court Publishing Company, La Salle, IL, **1981**; Lee, D.G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*; Open Court Publishing Company: La Salle, IL, **1980**. For some reviews, see Curci, R. *Adv. Oxygenated Processes* **1990**, 2, 1 (dioxiranes); Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* **1989**, 22, 205 (dioxiranes); Murray, R.W. *Chem. Rev.* **1989**, 89, 1187 (dioxiranes); Ley, S.V. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, **1987**, pp. 163–206 (seleninic anhydrides and acids); Fatiadi, A.J. *Synthesis* **1987**, 85 (KMnO_4); Rubottom, G.M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D, Academic Press, NY, **1982**, pp. 1–145 (lead tetraacetate); Fatiadi, A.J. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, **1981**, pp. 147–335; *Synthesis* **1974**, 229 (HIO_4); Fatiadi, A.J. *Synthesis* **1976**, 65, 133 (MnO_2); Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, **1974**, pp. 143–174 (MnO_2); George, M.V.; Balachandran, K.S. *Chem. Rev.* **1975**, 75, 491 (nickel peroxide); Courtney, J.L.; Swansborough, K.F. *Rev. Pure Appl. Chem.* **1972**, 22, 47 (ruthenium tetroxide); Ho, T.L. *Synthesis* **1973**, 347 (ceric ion); Aylward, J.B. *Q. Rev. Chem. Soc.* **1971**, 25, 407 (lead tetraacetate); Sklarz, B. *Q. Rev. Chem. Soc.* **1967**, 21, 3 (HIO_4); Korshunov, S.P.; Vereshchagin, L.I. *Russ. Chem. Rev.* **1966**, 35, 942 (MnO_2). For reviews of the behavior of certain reducing agents, see Keefer, L.K.; Lunn, G. *Chem. Rev.* **1989**, 89, 459 (Ni-Al alloy); Málek, J. *Org. React.* **1988**, 36, 249; **1985**, 34, 1–317 (metal alkoxyaluminum hydrides); Caubère, P. *Angew. Chem. Int. Ed.* **1983**, 22, 599 (modified sodium hydride); Nagai, Y. *Org. Prep. Proced. Int.* **1980**, 12, 13 (hydrosilanes); Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, **1974**, pp. 101–294 (LiAlH_4); Winterfeldt, E. *Synthesis* **1975**, 617 (diisobutylaluminum hydride and triisobutylaluminum); Hüchel, W. *Fortschr. Chem. Forsch.* **1966**, 6, 197 (metals in ammonia or amines). See also Ref. 9.

¹¹ For books on oxidation reactions, see Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, **1990**; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, 2 vols., Academic Press, NY, **1985**, **1988** [The first volume pertains to hydrocarbon substrates; the second mostly to oxygen- and nitrogen-containing substrates]; Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, **1971**; Augustine, R.L.; Trecker, D.J. *Oxidation*, 2 Vols., Marcel Dekker, NY, **1969**, **1971**.

Six-membered alicyclic rings can be aromatized in a number of ways.¹² Aromatization is accomplished most easily if there are already one or two double bonds in the ring or if the ring is fused to an aromatic ring. The reaction can also be applied to heterocyclic five- and six-membered rings. Many groups may be present on the ring without interference, and even *gem*-dialkyl substitution does not always prevent the reaction: In such cases, one alkyl group often migrates or is eliminated, but more drastic conditions are usually required for this. In some cases, OH and COOH groups are lost from the ring. Cyclic ketones are converted to phenols. Seven-membered and larger rings are often isomerized to six-membered aromatic rings, although this is not the case for partially hydrogenated azulene systems, which are frequently found in nature; these are converted to azulenes.

There are three types of reagents most frequently used to effect aromatization.

1. Hydrogenation catalysts¹³ (e.g., Pt, Pd,¹⁴ and Ni). Palladium trifluoroacetate also facilitates oxidative aromatization of cyclohexene.¹⁵ In this case, the reaction is the reverse of double-bond hydrogenation (**15-11** and **15-15**), and presumably the mechanism is also the reverse, although not much is known.¹⁶ Cyclohexene has been detected as an intermediate in the conversion of cyclohexane to benzene, using Pt.¹⁷ The substrate is heated with the catalyst at ~300–350 °C. The reactions can often be carried out under milder conditions if a hydrogen acceptor (e.g., maleic acid, cyclohexene, or benzene) is present to remove hydrogen as it is formed. The acceptor is reduced to the saturated compound. Other transition metals can be used.¹⁸ It has been reported that dehydrogenation of 1-methylcyclohexene-1-¹³C over an alumina catalyst gave toluene with the label partially scrambled throughout the aromatic ring.¹⁹ For polycyclic systems, heating with oxygen on activated carbon generates the aromatic compound, as in the conversion of dihydroanthracene to anthracene.²⁰
2. The elements sulfur and selenium, which combine with the hydrogen evolved to give, respectively, H₂S and H₂Se. Little is known about this mechanism either.²¹

¹² See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1985**, pp. 16–22, 217–222; Fu, P.P.; Harvey, R.G. *Chem. Rev.* **1978**, 78, 317; Valenta, Z. in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, **1973**, pp. 1–76; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 34–44.

¹³ See Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, **1973**, pp. 1–59.

¹⁴ See Cossy, J.; Belotti, D. *Org. Lett.* **2002**, 4, 2557. See Cho, C.S.; Patel, D.B.; Shim, S.C. *Tetrahedron* **2005**, 61, 9490.

¹⁵ Bercaw, J.E.; Hazari, N.; Labinger, J.A. *J. Org. Chem.* **2008**, 73, 8654.

¹⁶ See Tsai, M.; Friend, C.M.; Muetterties, E.L. *J. Am. Chem. Soc.* **1982**, 104, 2539. See also, Augustine, R.L.; Thompson, M.M. *J. Org. Chem.* **1987**, 52, 1911.

¹⁷ Land, D.P.; Pettiette-Hall, C.L.; McIver Jr., R.T.; Hemminger, J.C. *J. Am. Chem. Soc.* **1989**, 111, 5970.

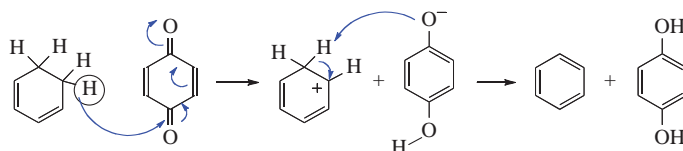
¹⁸ Srinivas, G.; Periasamy, M. *Tetrahedron Lett.* **2002**, 43, 2785.

¹⁹ Marshall, J.L.; Miiller, D.E.; Ihrig, A.M. *Tetrahedron Lett.* **1973**, 3491.

²⁰ Nakamichi, N.; Kawabata, H.; Hiyashi, M. *J. Org. Chem.* **2003**, 68, 8272.

²¹ Silverwood, H.A.; Orchin, M. *J. Org. Chem.* **1962**, 27, 3401.

3. Quinones²² become reduced to the corresponding hydroquinones. Two important quinones often used for aromatizations are chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).²³ The latter is more reactive and can be used in cases where the substrate is difficult to dehydrogenate. It is likely that the mechanism involves a transfer of hydride to the quinone oxygen, followed by the transfer of a proton to the phenolate ion.²⁴



Other reagents²⁵ have been used for aromatization of six-membered rings, including atmospheric oxygen, MnO_2 ,²⁶ SeO_2 , H_2SO_4 , and a Ru catalyst.²⁷ The last-mentioned reagent also dehydrogenates cyclopentanes to cyclopentadienes. In some instances, the hydrogen is not released as H_2 or transferred to an external oxidizing agent, but instead serves to reduce another molecule of substrate. This is a disproportionation reaction and can be illustrated by the conversion of cyclohexene to cyclohexane and benzene.

Heteroatom rings, as found in quinoline derivatives, for example, can be generated from amino-ketones with [hydroxy(tosyloxy)iodo]benzene and perchloric acid²⁸ or with $\text{NaHSO}_4\text{--Na}_2\text{Cr}_2\text{O}_7$ on wet silica.²⁹ Dihydropyridines are converted to pyridines with $\text{NaNO}_2\text{--oxalic acid}$ and wet silica,³⁰ BaMnO_4 ,³¹ $\text{FeCl}_3\text{--acetic acid}$,³² or SeO_2 .³³ *Hantzsch 1,4-dihydropyridines* (see Reactions **15-14** and **16-17**) are aromatized by treatment with ferric perchlorate in acetic acid.³⁴ Cyclic imines are converted to pyridine derivatives with NCS and then excess sodium methoxide.³⁵ Enamines are aromatized with Sn or Sb compounds.³⁶

²² Becker, H.; Turner, A.B. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, **1988**, pp. 1351–1384; Becker, H. in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, **1974**, pp. 335–423.

²³ See Turner, A.B. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, **1977**, pp. 193–225; Walker, D.; Hiebert, J.D. *Chem. Rev.* **1967**, 67, 153.

²⁴ Trost, B.M. *J. Am. Chem. Soc.* **1967**, 89, 1847. See also, Radtke, R.; Hintze, H.; Rösler, K.; Heesing, A. *Chem. Ber.* **1990**, 123, 627; Höfler, C.; Rüchardt, C. *Liebigs Ann. Chem.* **1996**, 183. See also Ref. 22.

²⁵ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 187–191.

²⁶ See Leffingwell, J.C.; Bluhm, H.J. *Chem. Commun.* **1969**, 1151.

²⁷ Tanaka, H.; Ikeno, T.; Yamada, T. *Synlett* **2003**, 576.

²⁸ Varma, R.S.; Kumar, D. *Tetrahedron Lett.* **1998**, 39, 9113.

²⁹ Damavandi, J.A.; Zolfigol, M.A.; Karami, B. *Synth. Commun.* **2001**, 31, 3183.

³⁰ Zolfigol, M.A.; Kiany-Borazjani, M.; Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R. *Synth. Comm.* **2000**, 30, 551.

³¹ Memarian, H.R.; Sadeghi, M.M.; Momeni, A.R. *Synth. Commun.* **2001**, 31, 2241.

³² Lu, J.; Bai, Y.; Wang, Z.; Yang, B.Q.; Li, W. *Synth. Commun.* **2001**, 31, 2625.

³³ Cai, X.-h.; Yang, H.-j.; Zhang, G.-l. *Can. J. Chem.* **2005**, 83, 273.

³⁴ Heravi, M.M.; Behbahani, F.K.; Oskooie, H.A.; Shoar, R.H. *Tetrahedron Lett.* **2005**, 46, 2775.

³⁵ DeKimpe, N.; Keppens, M.; Fonck, G. *Chem. Commun.* **1996**, 635.

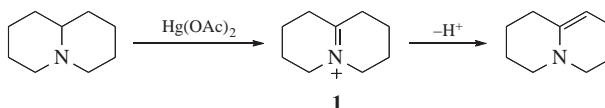
³⁶ Bigdeli, M.A.; Rahmati, A.; Abbasi-Ghadim, H.; Mahdavinia, G.H. *Tetrahedron Lett.* **2007**, 48, 4575.

Note that hydrogenolysis of cyclohexane leads to *n*-hexane with hydrogen and an Ir catalyst.³⁷

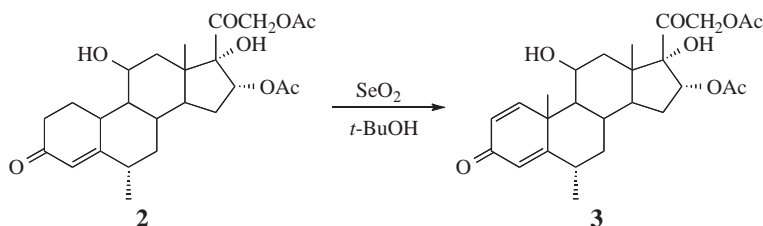
OS **II**, 214, 423; **III**, 310, 358, 729, 807; **IV**, 536; **VI**, 731. Also see, OS **III**, 329.

19-2 Dehydrogenations Yielding Carbon–Carbon Double Bonds

Dihydro-elimination



Dehydrogenation of an aliphatic compound to give a double bond in a specific location is not usually a feasible process, although industrially mixtures of alkenes are obtained in this way from mixtures of alkanes (generally by heating with chromia–alumina catalysts). There are, however, some notable exceptions. Heating cyclooctane with an Ir catalyst leads to cyclooctene.³⁸ Treating alkenes that have an allylic hydrogen with CrCl_2 converts them to allenes.³⁹ It is not surprising, however, that most of the exceptions generally involve cases where the new double bond can be in conjugation with a double bond or with an unshared pair of electrons already present.⁴⁰ One example is the synthesis developed by Leonard and Musker,⁴¹ in which tertiary amines give enamines (Reaction **10-69**) when treated with mercuric acetate⁴² (see the example above). In this case, the initial product is the iminium ion (**1**) that loses a proton to give the enamine. Other transition metal catalysts convert amines to enamines, including Co compounds.⁴³ *Hünig's base* (diisopropylethylamine) was converted to the enamine *N,N*-diisopropyl-*N*-vinylamine by heating with an Ir catalyst.⁴⁴



³⁷ Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* **2001**, *123*, 1658.

³⁸ Göttker-Schnetmann, I.; White, P.; Brookhart, M. *J. Am. Chem. Soc.* **2004**, *126*, 1804.

³⁹ Takai, K.; Kokumai, R.; Toshikawa, S. *Synlett* **2002**, 1164.

⁴⁰ See Haines, A.J. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, **1985**, pp. 6–16, 206–216. For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 251–256.

⁴¹ See Leonard, N.J.; Musker, W.K. *J. Am. Chem. Soc.* **1959**, *81*, 5631; **1960**, *82*, 5148.

⁴² See Haynes, L.W.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed. Marcel Dekker, NY, **1988**, pp. 103–163; Lee, D.G. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, **1969**, pp. 102–107.

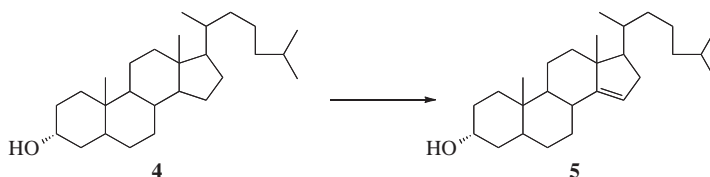
⁴³ Bolig, A.D.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 14544.

⁴⁴ Zhang, X.; Fried, A.; Knapp, S.; Goldman, A.S. *Chem. Commun.* **2003**, 2060.

The oxidizing agent SeO_2 can in certain cases convert a carbonyl compound to an α,β -unsaturated carbonyl compound by removing H_2 ⁴⁵ (note that this reagent more often gives Reaction 19-17). This reaction has been most often applied in the steroid series, an example being formation of **2** from **3**.⁴⁶ Similarly, SeO_2 has been used to dehydrogenate 1,4-diketones⁴⁷ and 1,2-diaryllkanes. These conversions can also be carried out by certain quinones, most notably DDQ (see Reaction 19-1).²⁴ Molecular oxygen has been used to convert cyclic ketones to the conjugated ketone in the presence of a Pd catalyst.⁴⁸

Simple aldehydes and ketones have been dehydrogenated (e.g., cyclopentanone \rightarrow cyclopentenone) by PdCl_2 ,⁴⁹ by FeCl_3 ,⁵⁰ and by benzeneseleninic anhydride⁵¹ (this reagent also dehydrogenates lactones in a similar manner), among other reagents. In an indirect method of achieving this conversion, the silyl enol ether of a simple ketone is treated with DDQ⁵² or with triphenylmethyl cation⁵³ (for another indirect method, see Reaction 17-12). Silyl enol ethers give the conjugated ketone upon treatment with ceric ammonium nitrate in DMF⁵⁴ or with $\text{Pd}(\text{OAc})_2/\text{NaOAc}/\text{O}_2$.⁵⁵

Simple linear alkanes have been converted to alkenes by treatment with certain transition metal compounds.⁵⁶



An entirely different approach (remote functionalization) allows specific dehydrogenation, as reported by R. Breslow⁵⁷ and by J.E. Baldwin et al.⁵⁸ 3 α -Cholesterol (**4**) was converted to 5 α -cholest-14-en-3 α -ol (**5**), for example, thus introducing a double bond at a specific site remote from any functional group.⁵⁹

⁴⁵ See Back, T.G. in Patai, S. *The Chemistry of Organic Selenium and Tellurium Compounds*, pt. 2, Wiley, NY, **1987**, pp. 91–213, 110–114; Jerussi, R.A. *Sel. Org. Transform.* **1970**, *1*, 301, see pp. 315–321.

⁴⁶ Bernstein, S.; Littell, R. *J. Am. Chem. Soc.* **1960**, *82*, 1235.

⁴⁷ See Barnes, C.S.; Barton, D.H.R. *J. Chem. Soc.* **1953**, 1419.

⁴⁸ Tokunaga, M.; Harada, S.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *Tetrahedron Lett.* **2007**, *48*, 6860. For a review, see Muzart, J. *Eur. J. Org. Chem.* **2010**, 3779.

⁴⁹ See Mukaiyama, T.; Ohshima, M.; Nakatsuka, T. *Chem. Lett.* **1983**, 1207. See also, Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, **1985**, pp. 103–110.

⁵⁰ Cardinale, G.; Laan, J.A.M.; Russell, S.W.; Ward, J.P. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 199.

⁵¹ Barton, D.H.R.; Hui, R.A.H.F.; Ley, S.V.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1919; Barton, D.H.R.; Godfrey, C.R.A.; Morzycki, J.W.; Motherwell, W.B.; Ley, S.V. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1947.

⁵² Jung, M.E.; Pan, Y.; Rathke, M.W.; Sullivan, D.F.; Woodbury, R.P. *J. Org. Chem.* **1977**, *42*, 3961.

⁵³ Ryu, I.; Murai, S.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* **1978**, 3455. Also see Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 5635, 5639.

⁵⁴ Evans, P.A.; Longmire, J.M.; Modi, D.P. *Tetrahedron Lett.* **1995**, *36*, 3985.

⁵⁵ Larock, R.C.; Hightower, T.R.; Kraus, G.A.; Hahn, P.; Zheng, O. *Tetrahedron Lett.* **1995**, *36*, 2423.

⁵⁶ See Maguire, J.A.; Boese, W.T.; Goldman, A.S. *J. Am. Chem. Soc.* **1989**, *111*, 7088; Sakakura, T.; Ishida, K.; Tanaka, M. *Chem. Lett.* **1990**, 585, and references cited therein.

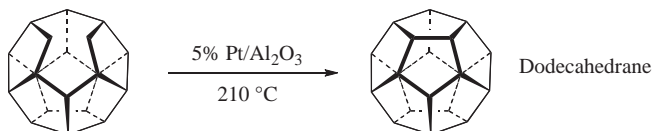
⁵⁷ See Breslow, R. *Chemtracts: Org. Chem.* **1988**, *1*, 333; *Acc. Chem. Res.* **1980**, *13*, 170; *Isr. J. Chem.* **1979**, *18*, 187; *Chem. Soc. Rev.* **1972**, *1*, 553.

⁵⁸ Baldwin, J.E.; Bhatnagar, A.K.; Harper, R.W. *Chem. Commun.* **1970**, 659.

⁵⁹ See Czekay, G.; Drewello, T.; Schwarz, H. *J. Am. Chem. Soc.* **1989**, *111*, 4561. See also, Bégué, J. *J. Org. Chem.* **1982**, *47*, 4268; Nagata, R.; Saito, I. *Synlett* **1990**, 291; Breslow, R.; Brandl, M.; Hunger, J.; Adams, A.D. *J. Am. Chem. Soc.* **1987**, *109*, 3799; Batr, R.; Breslow, R. *Tetrahedron Lett.* **1989**, *30*, 535; Orito, K.; Ohto, M.; Sugimoto, H. *J. Chem. Soc. Chem. Commun.* **1990**, 1076.

Certain 1,2-diarylalkenes ($\text{ArCH}=\text{CHAR}'$) have been converted to the corresponding alkynes ($\text{ArC}\equiv\text{CAR}'$) by treatment with *t*-BuOK in DMF.⁶⁰ Dihydroindoles are converted to indoles with *N,N',N''*-trichloro-1,3,5-triazin-2,4,6-trione and DBU.⁶¹

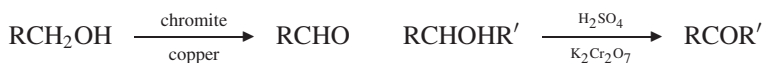
A different kind of dehydrogenation was used in the final step of Paquette's synthesis of dodecahedrane⁶²:



OS V, 428, VII, 4, 473.

19-3 Oxidation or Dehydrogenation of Alcohols to Aldehydes and Ketones

C,O-Dihydro-elimination



Primary alcohols can be converted to aldehydes and secondary alcohols to ketones in seven main ways:⁶³

1. *With Chromium Reagents.*⁶⁴ Secondary alcohols are easily oxidized to ketones by dichromate in acidic media⁶⁵ at room temperature or slightly above. A solution of chromic and sulfuric acid in water is known as the *Jones reagent*.⁶⁶ Secondary alcohols are oxidized to ketones rapidly and in high yield without disturbing any double or triple bonds that may be present (see Reaction **19-10**) and without epimerizing an adjacent stereogenic center.⁶⁷ Mixing sodium dichromate with an alcohol, without solvent, provides a method for oxidation when the mixture is shaken.⁶⁸ Chromium trioxide (CrO_3)⁶⁹ has been used to oxidize primary and alcohols under solvent-free conditions. Chromium trioxide on silica gel, in supercritical CO_2 ,

⁶⁰ Akiyama, S.; Nakatsuji, S.; Nomura, K.; Matsuda, K.; Nakashima, K. *J. Chem. Soc. Chem. Commun.* **1991**, 948.

⁶¹ Tilstam, U.; Harre, M.; Heckrodt, T.; Weinmann, H. *Tetrahedron Lett.* **2001**, 42, 5385.

⁶² Paquette, L.A.; Doherty, A.M. *Polyquinane Chemistry*, Springer, NY, **1987**. See in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, **1990**, the reviews by Paquette, L.A. pp. 313–352, and by Fessner, W.; Prinzbach, H. pp. 353–405; Paquette, L.A. *Chem. Rev.* **1989**, 89, 1051; in Lindberg, T. *Strategies and Tactics in Organic Synthesis*, Academic Press, NY, **1984**, pp. 175–200.

⁶³ Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, pp. 114–126, 132–149; Haines, A.M. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, **1988**, pp. 5–148, 326–390; Müller, P. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, **1980**, pp. 469–538. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1234–1250.

⁶⁴ See Lee, D.G. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, **1971**, pp. 56–81; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 257–273.

⁶⁵ See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, **1981**, pp. 118–216; Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1, Wiley, NY, **1967**, pp. 142–147, 1059–1064, and subsequent volumes in this series.

⁶⁶ Bowers, A.; Halsall, T.G.; Jones, E.R.H.; Lemin, A.J. *J. Chem. Soc.* **1953**, 2548. Also see, Ali, M.H.; Wiggin, C.J. *Synth. Commun.* **2001**, 31, 1389; Ali, M.H.; Wiggin, C.J. *Synth. Commun.* **2001**, 31, 3383.

⁶⁷ See Djerassi, C.; Hart, P.A.; Warawa, E.J. *J. Am. Chem. Soc.* **1964**, 86, 78.

⁶⁸ Lou, J.-D.; Gao, C.-L.; Ma, Y.-C.; Huang, L.-H.; Li, L. *Tetrahedron Lett.* **2006**, 47, 311.

⁶⁹ Lou, J.-D.; Xu, Z.-N. *Tetrahedron Lett.* **2002**, 43, 6095.

oxidizes alcohols to the corresponding carbonyl.⁷⁰ For acid-sensitive compounds, trimethylsilyl chromates⁷¹ can be used. Chromium trioxide with aq *tert*-butylhydroperoxide oxidizes benzylic alcohols with microwave irradiation.⁷² Phase-transfer catalysis is particularly useful,⁷³ especially when the substrates are generally insoluble in water (see Sec. 10.G.v). A catalytic amount of Cr(acac)₃ in conjunction with H₃IO₅ oxidizes benzylic alcohols to aldehydes.⁷⁴

The Jones reagent can also oxidize primary allylic alcohols to the corresponding aldehydes,⁷⁵ although overoxidation to the carboxylic acid is a problem.⁷⁶ Oxidative cleavage of primary alcohols has been observed in the presence of molecular sieves 3 Å.⁷⁷ One way to mitigate overoxidation is to distil the aldehyde as it is formed, but this is not always possible. Due to these problems, other oxidizing conditions have been used to convert at least some primary alcohols to aldehydes.⁷⁸ Perhaps the three most commonly used Cr(VI) reagents used for the oxidation of allylic alcohols include⁷⁹ dipyridine Cr(VI) oxide (*Collins' reagent*),⁸⁰ pyridinium chlorochromate (PCC),⁸¹ and pyridinium dichromate (PDC).⁸² The PCC is somewhat acidic, and acid-catalyzed rearrangements have been observed.⁸³

Analogous to the use of pyridine for PCC and PDC, a variety of amines and diamines have been converted to tetraalkylammonium halochromates or dichromates, including *N*-benzyl 1,4-diazabicyclo[2.2.2]octane ammonium dichromate with microwave irradiation,⁸⁴ γ -picolinium chlorochromate,⁸⁵ and quinolinium fluorochromate.⁸⁶ Benzyltriphenylphosphonium chlorochromate has been used in a similar manner.⁸⁷ Oxidizing agents have been supported on a polymer,⁸⁸

⁷⁰ González-Núñez, M.E.; Mello, R.; Olmos, A.; Acerete, R.; Asensio, G. *J. Org. Chem.* **2006**, *71*, 1039.

⁷¹ Moiseenkov, A.M.; Cheskis, B.A.; Veselovskii, A.B.; Veselovskii, V.V.; Romanovich, A.Ya.; Chizhov, B.A. *J. Org. Chem. USSR* **1987**, *23*, 1646.

⁷² Singh, J.; Sharma, M.; Chhibber, M.; Kaur, J.; Kad, G.L. *Synth. Commun.* **2000**, *30*, 3941. Also see Heravi, M.M.; Ajami, D.; Tabar-Hydar, K. *Synth. Commun.* **1999**, *29*, 163; Mirza-Ayhayan, M.; Heravi, M.M. *Synth. Commun.* **1999**, *29*, 785.

⁷³ For a review, see Patel, S.; Mishra, B.K. *Tetrahedron* **2007**, *63*, 4367.

⁷⁴ Xu, L.; Trudell, M.L. *Tetrahedron Lett.* **2003**, *44*, 2553.

⁷⁵ Harding, K.E.; May, L.M.; Dick, K.F. *J. Org. Chem.* **1975**, *40*, 1664.

⁷⁶ Though ketones are much less susceptible to further oxidation than aldehydes, such oxidation is possible (**19-8**), and care must be taken to avoid it, usually by controlling the temperature and/or the oxidizing agent.

⁷⁷ Fernandes, R.A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1275.

⁷⁸ Also see Nishiguchi, T.; Asano, F. *J. Org. Chem.* **1989**, *54*, 1531; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1234–1250.

⁷⁹ See Warrenner, R.N.; Lee, T.S.; Russell, R.A.; Paddon-Row, M.N. *Aust. J. Chem.* **1978**, *31*, 1113.

⁸⁰ Collins, J.C.; Hess, W.W. *Org. Synth.* **VI**, 644; Sharpless, K.B.; Akashi, K. *J. Am. Chem. Soc.* **1975**, *97*, 5927.

⁸¹ Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* **1975**, 2647. See Luzzio, F.A.; Guzic, Jr., F.S. *Org. Prep. Proced. Int.* **1988**, *20*, 533; Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245; Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* **1990**, *46*, 4417; Salehi, P.; Firouzabadi, H.; Farrokhi, A.; Gholizadeh, M. *Synthesis* **2001**, 2273.

⁸² See Czernecki, S.; Georgoulis, C.; Stevens, C.L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699.

⁸³ See Ren, S.-K.; Wang, F.; Dou, H.-N.; Fan, C.-A.; He, L.; Song, Z.-L.; Xia, W.-J.; Li, D.-R.; Jia, Y.-X.; Li, X.; Tu, Y.-Q. *Synthesis* **2001**, 2384.

⁸⁴ Hajipour, A.R.; Mallakpour, S.E.; Khoee, S. *Synlett* **2000**, 740.

⁸⁵ Khodaei, M.M.; Salehi, P.; Goodarzi, M. *Synth. Commun.* **2001**, *31*, 1253.

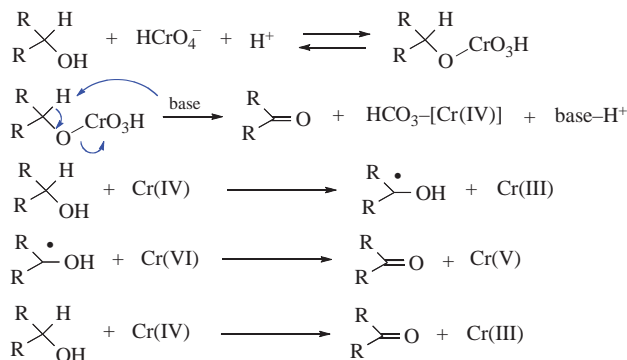
⁸⁶ Rajkumar, G.A.; Arabindoo, B.; Murugesan, V. *Synth. Commun.* **1999**, *29*, 2105.

⁸⁷ Hajipour, A.R.; Mallakpour, S.E.; Backnejad, H. *Synth. Commun.* **2000**, *30*, 3855.

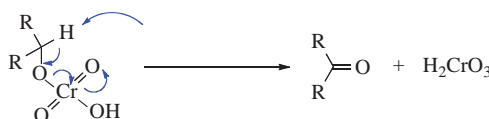
⁸⁸ For a review, see McKillop, A.; Young, D.W. *Synthesis* **1979**, 401. See also, Shirini, F.; Dabiri, M.; Dezyani, S.; Jalili, F. *Russ. J. Org. Chem.* **2005**, *41*, 390.

including chromic acid,⁸⁹ as well as poly[vinyl(pyridinium fluorochromate)].⁹⁰ Triphenylmethylphosphonium dichromate is effective for selective oxidation of benzylic alcohols.⁹¹

Studies on the mechanism of oxidation with acid dichromate⁹² led to the currently accepted mechanism as proposed by Westheimer⁹³ (cf. the first two steps with Sec. 19.A, category 4).



The base in the second step may be water, although it is also possible⁹⁴ that in some cases no external base is involved and that the proton is transferred directly to one of the CrO₃H oxygen atoms in which case the Cr(IV) species produced would be H₂CrO₃. Part of the evidence for this mechanism was the isotope effect of ~6 found on use of MeCDOHMe, showing that the α hydrogen is removed in the rate-determining step.⁹⁵ Note that, as in Reaction 19-23 the substrate is oxidized by three different oxidation states of chromium.⁹⁶



⁸⁹ Cainelli, G.; Cardillo, G.; Orena, M.; Sandri, S. *J. Am. Chem. Soc.* **1976**, 98, 6737; Santaniello, E.; Ponti, F.; Manzocchi, A. *Synthesis* **1978**, 534. See also, San Filippo, Jr., J.; Chern, C. *J. Org. Chem.* **1977**, 42, 2182.

⁹⁰ Srinivasan, R.; Balasubramanian, K. *Synth. Commun.* **2000**, 30, 4397.

⁹¹ Hajipour, A.R.; Safaei, S.; Ruoho, A.E. *Synth. Commun.* **2009**, 39, 3687.

⁹² See Müller, P. *Chimia* **1977**, 31, 209; Wiberg, K.B. in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, **1965**, pp. 142–170; Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, **1964**, pp. 49–71; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, **1964**, pp. 37–48; Sengupta, K.K.; Samanta, T.; Basu, S.N. *Tetrahedron* **1985**, 41, 205.

⁹³ Westheimer, F.H. *Chem. Rev.* **1949**, 45, 419, see p. 434; Holloway, F.; Cohen, M.; Westheimer, F.H. *J. Am. Chem. Soc.* **1951**, 73, 65.

⁹⁴ Kwart, H.; Nickle, J.H. *J. Am. Chem. Soc.* **1979**, 98, 2881 and cited references; Sengupta, K.K.; Samanta, T.; Basu, S.N. *Tetrahedron* **1986**, 42, 681. See also, Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* **1990**, 46, 1963.

⁹⁵ Westheimer, F.H.; Nicolaides, N. *J. Am. Chem. Soc.* **1949**, 71, 25. Also see Wiberg, K.B.; Schäfer, H. *J. Am. Chem. Soc.* **1969**, 91, 927, 933; Lee, D.G.; Raptis, M. *Tetrahedron* **1973**, 29, 1481.

⁹⁶ Doyle, M.P.; Swedo, R.J.; Rocek, J. *J. Am. Chem. Soc.* **1973**, 95, 8352; Wiberg, K.B.; Mukherjee, S.K. *J. Am. Chem. Soc.* **1974**, 96, 1884, 6647.

With other oxidizing agents discussed below, mechanisms are less clear.⁹⁷ It seems certain that some oxidizing agents operate by a hydride-shift mechanism,⁹⁸ for example, dehydrogenation with triphenylmethyl cation⁹⁹ and the *Oppenauer oxidation*, and some by a free radical mechanism (e.g., oxidation with $\text{S}_3\text{O}_8^{2-}$ ¹⁰⁰ and with VO_2^{+} ¹⁰¹). A summary of many proposed mechanisms is given by Littler.¹⁰²

2. *With Manganese and Other Metal Oxidizing Agents.* Potassium permanganate (KMnO_4) has been used for the oxidation of alcohols.¹⁰³ Benzylic and allylic alcohols have been selectively oxidized to the aldehydes in the presence of saturated alcohols by the use of potassium permanganate (KMnO_4) under phase-transfer conditions.¹⁰⁴ Phase-transfer catalysis has also been used with chromic acid,¹⁰⁵ and ruthenium tetroxide.¹⁰⁶ Ultrasound has been used for KMnO_4 oxidations.¹⁰⁷ Permanganate supported on a polymer has been used.¹⁰⁸

Permanganate¹⁰⁹ is an important reagent for the selective oxidation of benzylic alcohols primary and benzylic alcohols, in preference to aliphatic substrates.¹¹⁰ A variation oxidizes alcohols with $\text{MnO}_2/\text{AlCl}_3$.¹¹¹

An alternative to MnO_2 is the oxidation of allylic and benzylic alcohols with Me_3NO in the presence of $\text{CHDFe}(\text{CO})_3$.¹¹² Similar oxidation occurs with NaBrO_3 in aq MeCN ¹¹³ or K_2FeO_4 on clay.¹¹⁴ The reaction of AuCl with an anionic ligand leads to oxidation of primary alcohols to aldehydes.¹¹⁵ The *Grubbs' catalyst*, $\text{PhCH}=\text{Ru}(\text{PCy}_3)_2\text{Cl}_2$, where Cy = cyclohexyl, (see **156** in Reaction **18-37**), in the presence of KOH , oxidized alcohols.¹¹⁶

⁹⁷ See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, **1977**, pp. 264–277.

⁹⁸ Barter, R.M.; Littler, J.S. *J. Chem. Soc. B* **1967**, 205. See Moodie, R.B.; Richards, S.N. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1833; Ross, D.S.; Gu, C.; Hum, G.P.; Malhotra, R. *Int. J. Chem. Kinet.* **1986**, 18, 1277.

⁹⁹ Bonthron, W.; Reid, D.H. *J. Chem. Soc.* **1959**, 2773.

¹⁰⁰ Walling, C.; Camaioni, D.M. *J. Org. Chem.* **1978**, 43, 3266; Clerici, A.; Minisci, F.; Ogawa, K.; Surzur, J. *Tetrahedron Lett.* **1978**, 1149; Beylerian, N.M.; Khachatryan, A.G. *J. Chem. Soc. Perkin Trans. 2* **1984**, 1937.

¹⁰¹ Littler, J.S.; Waters, W.A. *J. Chem. Soc.* **1959**, 4046.

¹⁰² Littler, J.S. *J. Chem. Soc.* **1962**, 2190.

¹⁰³ See Takemoto, T.; Yasuda, K.; Ley, S.V. *Synlett* **2001**, 1555. For oxidation in an ionic liquid, see Kumar, A.; Jain, N.; Chauhan, S.M.S. *Synth. Commun.* **2004**, 34, 2835.

¹⁰⁴ Kim, K.S.; Chung, S.; Cho, I.H.; Hahn, C.S. *Tetrahedron Lett.* **1989**, 30, 2559. See Lee, D.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D Academic Press, NY, **1982**, pp. 147–206.

¹⁰⁵ See Landini, D.; Montanari, F.; Rolla, F. *Synthesis* **1979**, 134; Pletcher, D.; Tait, S.J.D. *J. Chem. Soc. Perkin Trans. 2* **1979**, 788.

¹⁰⁶ Morris Jr., P.E.; Kiely, D.E. *J. Org. Chem.* **1987**, 52, 1149.

¹⁰⁷ Yamawaki, J.; Sumi, S.; Ando, T.; Hanfusa, T. *Chem. Lett.* **1983**, 379.

¹⁰⁸ See Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* **1981**, 22, 4889. See also, Menger, F.M.; Lee, C. *J. Org. Chem.* **1979**, 44, 3446.

¹⁰⁹ Lou, J.D.; Xu, Z.-N. *Tetrahedron Lett.* **2002**, 43, 6149.

¹¹⁰ Taylor, R.J.K.; Reid, M.; Foot, J.; Raw, S.A. *Acc. Chem. Res.* **2005**, 38 851. See Varma, R.S.; Saini, R.K.; Dahiya, R. *Tetrahedron Lett.* **1997**, 38, 7823.

¹¹¹ Firouzabadi, H.; Etemadi, S.; Karimi, B.; Jarrahpour, A.A. *Synth. Commun.* **1999**, 29, 4333.

¹¹² Pearson, A.J.; Kwak, Y. *Tetrahedron Lett.* **2005**, 46, 5417.

¹¹³ Shaabani, A.; Karimi, A.-R. *Synth. Commun.* **2001**, 31, 759.

¹¹⁴ Tajbakhsh, M.; Heravi, M.M.; Habibzadeh, S.; Ghassemzadeh, M. *J. Chem. Res. (S)* **2001**, 39.

¹¹⁵ Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2005**, 127, 18004.

¹¹⁶ Adair, G.R.A.; Williams, J.M.J. *Tetrahedron Lett.* **2005**, 46, 8233.

Tetrapropylammonium perruthenate ($\text{Pr}_4\text{N}^+ \text{RuO}_4^-$; also called TPAP; the *Ley reagent*)¹¹⁷ is an important oxidizing agent that is compatible with the presence of other functionality in the molecule.¹¹⁸ In the presence of molecular oxygen, oxidation of alcohols is catalytic in TPAP.¹¹⁹ This reagent has been bound to a polymer.¹²⁰ Methods have been developed for recovery of the catalyst and reuse of TPAP.¹²¹

Many other oxidizing agents have been employed. Examples include ruthenium tetroxide,¹²² MeReO_3 ,¹²³ HNO_3 with a $\text{Yb}(\text{OTf})_3$ catalyst,¹²⁴ $\text{FeBr}_3\text{—H}_2\text{O}_2$,¹²⁵ ceric ammonium nitrate in an ionic liquid,¹²⁶ a Bi catalyst,¹²⁷ O_2 with transition metal catalysts,¹²⁸ and with RuO_2 and a zeolite catalyst.¹²⁹ Microwave induced oxidation of benzylic alcohols was reported using zeolite-supported ferric nitrate.¹³⁰

Reagents that can be used specifically to oxidize a secondary OH group in the presence of a primary OH group¹³¹ are H_2O_2 –ammonium molybdate,¹³² or urea– H_2O_2 with MgBr_2 ,¹³³ while $\text{RuCl}_2(\text{PPh}_3)_3$ –benzene,¹³⁴ osmium tetroxide,¹³⁵ and

¹¹⁷ Griffith, W.P.; Ley, S.V. *Aldrichimica Acta* **1990**, 23, 13; Chandler, W.D.; Wang, Z.; Lee, D.G. *Can. J. Chem.* **2005**, 83, 1212.

¹¹⁸ With organotrifluoroborates: Molander, G.A.; Petrillo, D.E. *J. Am. Chem. Soc.* **2006**, 128, 9634.

¹¹⁹ Lenz, R.; Ley, S.V. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3291.

¹²⁰ Hinzen, B.; Lenz, R.; Ley, S.V. *Synthesis* **1998**, 977. Also see Brown, D.S.; Kerr, W.J.; Lindsay, D.M.; Pike, K.G.; Ratcliffe, P.D. *Synlett* **2001**, 1257.

¹²¹ Ley, S.V.; Ramarao, C.; Smith, M.D. *Chem. Commun.* **2001**, 2278.

¹²² See Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B Academic Press, NY, **1973**, pp. 197–222.

¹²³ Divalentin, C.; Gandolfi, R.; Gisdakis, P.; Rösch, N. *J. Am. Chem. Soc.* **2001**, 123, 2365; Jain, S.L.; Sharma, V.B.; Sain, B. *Tetrahedron Lett.* **2004**, 45, 1233.

¹²⁴ Barrett, A.G.M.; Braddock, D.C.; McKinnell, R.M.; Waller, F.J. *Synlett* **1999**, 1489.

¹²⁵ Martín, S.E.; Garrone, A. *Tetrahedron Lett.* **2003**, 44, 549.

¹²⁶ Mehdi, H.; Bodor, A.; Lantos, D.; Horváth, I.T.; De Vos, D.E.; Binnemans, K. *J. Org. Chem.* **2007**, 72, 517.

¹²⁷ Matano, Y.; Nomura, H. *J. Am. Chem. Soc.* **2001**, 123, 6443. With *tert*-butylhydroperoxide, see Malik, P.; Chakraborty, D. *Synthesis* **2010**, 3736.

¹²⁸ See Schultz, M.J.; Sigman, M.S. *Tetrahedron* **2006**, 62, 8227; Lenoir, D. *Angew. Chem. Int. Ed.* **2006**, 45, 3206; Zhan, B.-Z.; Thompson, A. *Tetrahedron* **2004**, 60, 2917; Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, 104, 3037; Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, 103, 27. Catalysts of **Au**: Abad, A.; Almela, C.; Corma, A.; García, H. *Tetrahedron* **2006**, 62, 6666; Li, H.; Guan, B.; Wang, W.; Xing, D.; Fang, Z.; Wan, X.; Yang, L.; Shi, Z. *Tetrahedron* **2007**, 63, 8430; Miyamura, H.; Matsubara, R.; Miyazaki, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2007**, 46, 4151; Abad, A.; Almela, C.; Corma, A.; García, H. *Chem. Commun.* **2006**, 3178; Kim, S.; Bae, S.W.; Lee, J.S.; Park, J. *Tetrahedron* **2009**, 65, 1461. **Cu**: Lipshutz, B.H.; Shimizu, H. *Angew. Chem. Int. Ed.* **2004**, 43, 2228; Jiang, N.; Ragauskas, A.J. *Org. Lett.* **2005**, 7, 3689. **Co**: Jiang, N.; Ragauskas, A.J. *J. Org. Chem.* **2006**, 71, 7087. **Mo**: Velusamy, S.; Ahamed, M.; Punniyamurthy, T. *Org. Lett.* **2004**, 6, 4821. **Pd**: Nielsen, R.J.; Goddard III, W.A. *J. Am. Chem. Soc.* **2006**, 128, 9651; Steinhoff, B.A.; King, A.E.; Stahl, S.S. *J. Org. Chem.* **2006**, 71, 1861; Batt, F.; Bourcet, E.; Kassab, Y.; Fache, F. *Synlett* **2007**, 1869. **Ru**: Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2002**, 41, 4538. **V**: Jiang, N.; Ragauskas, A.J. *Tetrahedron Lett.* **2007**, 48, 273.

¹²⁹ Zhan, B.-Z.; White, M.A.; Sham, T.-K.; Pincok, J.A.; Doucet, R.J.; Rao, K.V.R.; Robertson, K.N.; Cameron, T.S. *J. Am. Chem. Soc.* **2003**, 125, 2195.

¹³⁰ Heravi, M.M.; Ajami, D.; Aghapoor, K.; Ghassemzadeh, M. *Chem. Commun.* **1999**, 833.

¹³¹ For a review, see Arterburn, J.B. *Tetrahedron* **2001**, 57, 9765.

¹³² See Sakata, Y.; Ishii, Y. *J. Org. Chem.* **1991**, 56, 6233.

¹³³ Park, H.J.; Lee, J.C. *Synlett* **2009**, 79.

¹³⁴ Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, 22, 1605.

¹³⁵ Maione, A.M.; Romeo, A. *Synthesis* **1984**, 955.

$\text{Br}_2\text{—Ni}(\text{OBz})_2$ ¹³⁶ all oxidize primary OH groups in the presence of a secondary OH group.¹³⁷ Certain zirconocene complexes can selectively oxidize only one OH group of a diol, even if both are primary.¹³⁸ α -Hydroxy ketones are oxidized to 1,2-diketones with $\text{Bi}(\text{NO}_3)_3$ and a $\text{Cu}(\text{OAc})_2$ catalyst,¹³⁹ ferric chloride (solid state),¹⁴⁰ or O_2 and a V catalyst.¹⁴¹ 1,2-Diols are oxidized to chiral α -hydroxy-ketones using NBS with a chiral Cu catalyst.¹⁴²

3. *The Oppenauer Oxidation.* When a ketone in the presence of an aluminum alkoxide is used as the oxidizing agent (it is reduced to a secondary alcohol), the reaction is known as the *Oppenauer oxidation*.¹⁴³ This is the reverse of the *Meerwein–Ponndorf–Verley reaction* (19-36) and the mechanism is also the reverse. The ketones most commonly used are acetone, butanone, and cyclohexanone. A common base is aluminum *tert*-butoxide. The chief advantage of the method is its high selectivity. Although the method is most often used for the preparation of ketones, it has also been used for aldehydes. An Ir catalyst¹⁴⁴ has been developed for the *Oppenauer oxidation*, and also a water-soluble Ir catalyst.¹⁴⁵ Homogeneous water-soluble complexes catalyze the reaction.¹⁴⁶ An uncatalyzed reaction under supercritical conditions was reported.¹⁴⁷
4. *DMSO Based Reagents.* The use of oxalyl chloride and DMSO at low temperature is called the *Swern oxidation*¹⁴⁸ and is widely used. A sulfonium salt is produced *in situ*, which reacts with the alcohol to generate the key intermediate required for oxidation.¹⁴⁹ Maintaining the low-reaction temperature is essential in this reaction, however, since the reagent generated *in situ* decomposes at temperatures significantly below ambient. Note that *Swern oxidation* of molecules having alcohol moieties, as well as a disulfide, leads to the ketone without oxidation of the sulfur.¹⁵⁰ Sulfoxides other than DMSO can be used in conjunction with oxalyl chloride for the oxidation of alcohols,¹⁵¹ including fluorinated sulfoxides¹⁵² and a polymer-bound sulfoxide.¹⁵³

¹³⁶ Doyle, M.P.; Dow, R.L.; Bagheri, V.; Patrie, W.J. *J. Org. Chem.* **1983**, 48, 476.

¹³⁷ For a list of references, see Kulkarni, M.G.; Mathew T.S. *Tetrahedron Lett.* **1990**, 31, 4497.

¹³⁸ Nakano, T.; Terada, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1986**, 774.

¹³⁹ Tymonko, S.A.; Nattier, B.A.; Mohan, R.S. *Tetrahedron Lett.* **1999**, 40, 7657.

¹⁴⁰ Zhou, Y.-M.; Ye, X.-R.; Xin, X.-Q. *Synth. Commun.* **1999**, 29, 2229.

¹⁴¹ Kirahara, M.; Ochiai, Yy.; Takizawa, S.; Takahata, H.; Nemoto, H. *Chem. Commun.* **1999**, 1387. See also, Sigman, M.S.; Jensen, D.R. *Acc. Chem. Res.* **2006**, 39, 221.

¹⁴² Onomura, O.; Arimoto, H.; Matsumura, Y.; Demizu, Y. *Tetrahedron Lett.* **2007**, 48, 8668.

¹⁴³ See Djerassi, C. *Org. React.* **1951**, 6, 207. See Ooi, T.; Miura, T.; Itagaki, Y.; Ichikawa, H.; Maruoka, K. *Synthesis* **2002**, 279; Graves, C.R.; Zeng, B.-S.; Nguyen, S.T. *J. Am. Chem. Soc.* **2006**, 128, 12596.

¹⁴⁴ Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *J. Org. Chem.* **2003**, 68, 1601.

¹⁴⁵ Ajjou, A.N. *Tetrahedron Lett.* **2001**, 42, 13.

¹⁴⁶ Ajjou, A.N.; Pinet, J.-L. *Can. J. Chem.* **2005**, 83, 702.

¹⁴⁷ Sominsky, L.; Rozental, E.; Gottlieb, H.; Gedanken, A.; Hoz, S. *J. Org. Chem.* **2004**, 69, 1492.

¹⁴⁸ Omura, K.; Swern, D. *Tetrahedron* **1978**, 34, 1651. See Ohsugi, S.-i.; Nishide, K.; Oono, K.; Okuyama, K.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron* **2003**, 59, 8393.

¹⁴⁹ For a mechanism study, see Giagou T.; Meyer, M.P. *J. Org. Chem.* **2010**, 75, 8088.

¹⁵⁰ Fang, X.; Bandarage, U.K.; Wang, T.; Schroeder, J.D.; Garvey, D.S. *J. Org. Chem.* **2001**, 66, 4019.

¹⁵¹ Nishida, K.; Ohsugi, S.-i.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* **2002**, 43, 5177.

¹⁵² Crich, D.; Neelamkavil, S. *Tetrahedron* **2002**, 58, 3865.

¹⁵³ Choi, M.K.W.C.; Toy, P.H. *Tetrahedron* **2003**, 59, 7171.

Similar oxidation of alcohols has been carried out with DMSO and other reagents¹⁵⁴ in place of DCC: acetic anhydride,¹⁵⁵ SO₃–pyridine–triethylamine,¹⁵⁶ trifluoroacetic anhydride,¹⁵⁷ pivaloyl chloride,¹⁵⁸ tosyl chloride,¹⁵⁹ Ph₃P⁺Br[−],¹⁶⁰ trimethylamine *N*-oxide,¹⁶¹ a Mo catalyst and O₂,¹⁶² and methanesulfonic anhydride.⁵¹⁷ Dimethyl sulfoxide in 48% HBr oxidizes benzylic alcohols to aryl aldehydes.¹⁶³ An alcohol is treated with DMSO, DCC,¹⁶⁴ and anhydrous phosphoric acid¹⁶⁵ in what is called *Moffatt oxidation*. In this way, a primary alcohol can be converted to the aldehyde with no carboxylic acid being produced. The strong acid conditions are sometimes a problem, and complete removal of the dicyclohexylurea byproduct can be difficult.

5. *TEMPO and Related Reagents*. The nitroxyl radical TEMPO (**6**) has been used in conjunction with coreagents, including mcpba,¹⁶⁶ O₂ with transition metal catalysts,¹⁶⁷ O₂ with HBr and *tert*-butylnitrite,¹⁶⁸ CuBr₂(bpy)–air (bpy = 2,2′-bipyridyl),¹⁶⁹ CuBr•SMe₂ in perfluorous solvents,¹⁷⁰ bromohydantoins,¹⁷¹ enzymes,¹⁷² carbenes,¹⁷³ NaNO₂–HCl,¹⁷⁴ NaIO₄,¹⁷⁵ and H₅IO₆.¹⁷⁶ Silica-supported TEMPO,¹⁷⁷ polymer-bound TEMPO,¹⁷⁸ and PEG–TEMPO¹⁷⁹ have been used. The TEMPO derived ionic liquids,¹⁸⁰ or ionic liquid-supported TEMPO¹⁸¹ have

¹⁵⁴ For a review, see Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165.

¹⁵⁵ Albright, J.D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, 89, 2416.

¹⁵⁶ Parikh, J.R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, 89, 5507.

¹⁵⁷ Huang, S.L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297.

¹⁵⁸ Dubey, A.; Kandula, S.R.V.; Kumar, P. *Synth. Commun.* **2008**, 38, 746.

¹⁵⁹ Albright, J.D. *J. Org. Chem.* **1974**, 39, 1977.

¹⁶⁰ Bisai, A.; Chandrasekhar, M.; Singh, V.K. *Tetrahedron Lett.* **2002**, 43, 8355.

¹⁶¹ Godfrey, A.G.; Ganem, B. *Tetrahedron Lett.* **1990**, 31, 4825.

¹⁶² Khenkin, A.M.; Neumann, R. *J. Org. Chem.* **2002**, 67, 7075.

¹⁶³ Li, C.; Xu, Y.; Lu, M.; Zhao, Z.; Liu, L.; Zhao, Z.; Cui, Y.; Zheng, P.; Ji, X.; Gao, G. *Synlett* **2002**, 2041.

¹⁶⁴ The DCC is converted to dicyclohexylurea, which in some cases is difficult to separate from the product. One way to avoid this problem is to use a carbodiimide linked to an insoluble polymer: Weinshenker, N.M.; Shen, C. *Tetrahedron Lett.* **1972**, 3285.

¹⁶⁵ Fenselau, A.H.; Moffatt, J.G. *J. Am. Chem. Soc.* **1966**, 88, 1762; Albright, J.D.; Goldman, L. *J. Org. Chem.* **1965**, 30, 1107.

¹⁶⁶ Rychnovsky, S.D.; Vaidyanathan, R. *J. Org. Chem.* **1999**, 64, 310.

¹⁶⁷ **Mn/Co**: Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* **2001**, 42, 6651. **Mo**: Ben-Daniel, R.; Alsteers, P.; Neumann, R. *J. Org. Chem.* **2001**, 66, 8650. **Ru**: Dijkman, A.; Marino-González, A.; Payeras, A.M.; Arends, I.W.C.E.; Sheldon, R.A. *J. Am. Chem. Soc.* **2001**, 123, 6826.

¹⁶⁸ Xie, Y.; Mo, W.; Xu, D.; Shen, Z.; Sun, N.; Hu, B.; Hu, X. *J. Org. Chem.* **2007**, 72, 4288.

¹⁶⁹ Gamez, P.; Arends, I.W.C.E.; Reedijk, J.; Sheldon, R.A. *Chem. Commun.* **2003**, 2414.

¹⁷⁰ Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* **2000**, 41, 4343.

¹⁷¹ Liu, R.; Dong, C.; Liang, X.; Wang, X.; Hu, X. *J. Org. Chem.* **2005**, 70, 729.

¹⁷² Fabbrini, M.; Galli, C.; Gentili, P.; Macchitella, D. *Tetrahedron Lett.* **2001**, 42, 7551.

¹⁷³ Guin, J.; Sarkar, S.D.; Grimme, S.; Studer, A. *Angew. Chem. Int. Ed.* **2008**, 47, 8727.

¹⁷⁴ Wang, X.; Liu, R.; Jin, Y.; Liang, X. *Chemistry: European J.* **2008**, 14, 2679. For an Fe–TEMPO system, see Wang, N.; Liu, R.; Chen, J.; Liang, X. *Chem. Commun.* **2005**, 5322.

¹⁷⁵ Lei, M.; Hu, R.-J.; Wang, Y.-G. *Tetrahedron* **2006**, 62, 8928.

¹⁷⁶ Kim, S.S.; Nehru, K. *Synlett* **2002**, 616.

¹⁷⁷ Bolm, C.; Fey, T. *Chem. Commun.* **1999**, 1795.

¹⁷⁸ Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C. *J. Org. Chem.* **2002**, 66, 8154.

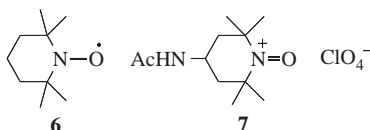
¹⁷⁹ Benaglia, M.; Puglisi, A.; Holczknecht, O.; Quici, S.; Pozzi, G. *Tetrahedron* **2005**, 61, 12058. See Miao, C.-X.; He, L.-N.; Wang, J.-Q.; Gao, J. *Synlett* **2009**, 3291.

¹⁸⁰ Wu, X.-E.; Ma, L.; Ding, M.-X.; Gao, L.-X. *Synlett* **2005**, 607.

¹⁸¹ Fall, A.; Sene, M.; Gaye, M.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2010**, 51, 4501.

been used for the oxidation of alcohols. The TEMPO compound has also been used with a polymer-bound hypervalent iodine reagent.¹⁸² A catalytic reaction using 5% TEMPO and 5% CuCl with O₂ in an ionic liquid oxidizes benzylic alcohols to the corresponding aldehyde.¹⁸³ Ion-supported TEMPO oxidation in water is possible.¹⁸⁴

Other nitroxyl radical oxidizing agents are known.¹⁸⁵ A related oxidizing agent is oxoammonium salt **7** (*Bobbitt's reagent*), a stable and nonhygroscopic salt that oxidizes primary and secondary alcohols in dichloromethane.¹⁸⁶ The mechanism of oxidation for **7** has been examined.¹⁸⁷



6. *With Hypervalent Iodine Reagents.*¹⁸⁸ Treatment of 2-iodobenzoic acid with KBrO₃ in H₂SO₄ and heating the resulting product to 100 °C with acetic anhydride and acetic acid¹⁸⁹ gives hypervalent iodine reagent (**8**), the so-called *Dess–Martin Periodinane*.¹⁹⁰ This reagent reacts with alcohols at ambient temperature to give the corresponding aldehyde or ketone.¹⁹¹ The reaction is accelerated by water¹⁹² and a water-soluble periodinane [*o*-iodoxybenzoic acid (**9**), IBX]¹⁹³ has been prepared that oxidized allylic alcohols to conjugated aldehydes.¹⁹⁴ 2-Methyl-2-propanol has been used as a solvent.¹⁹⁵ The reagent has an indefinite shelf-life in a sealed container, but hydrolysis occurs upon long-term exposure to atmospheric moisture. A note of CAUTION! The *Dess–Martin reagent* can be shock sensitive under some conditions and explode ~200 °C.¹⁹⁶

¹⁸² Sakuratani, K.; Togo, H. *Synthesis* **2003**, 21.

¹⁸³ Ansar, I.A.; Gree, R. *Org. Lett.* **2002**, 4, 1507.

¹⁸⁴ Qian, W.; Jin, E.; Bao, W.; Zhang, Y. *Tetrahedron* **2006**, 62, 556.

¹⁸⁵ de Nooy, A.E.J.; Besemer, A.C.; van Bekkum, H. *Synthesis* **1996**, 1153; Gilhespy, M.; Lok, M.; Baucherel, X. *Chem. Commun.* **2005**, 1085.

¹⁸⁶ See Merbouh, N.; Bobbitt, J.M.; Brückner, C. *Org. Prep. Proceed. Int.* **2004**, 36, 1.

¹⁸⁷ Bailey, W.F.; Bobbitt, J.M.; Wiberg, K.B. *J. Org. Chem.* **2007**, 72, 4504.

¹⁸⁸ See Su, J.T.; Goddard, III, W.A. *J. Am. Chem. Soc.* **2005**, 127, 14146; Wirth, T. *Angew. Chem. Int. Ed.* **2005**, 44, 3656. See Duschek, A.; Kirsch, S.F. *Chemistry: Eur. J.* **2009**, 15, 10713.

¹⁸⁹ See Lin, C.-K.; Lu, T.-J. *Tetrahedron* **2010**, 66, 9688.

¹⁹⁰ Dess, D.B.; Martin, J.C. *J. Am. Chem. Soc.* **1991**, 113, 7277. See Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, 64, 4537.

¹⁹¹ See Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, 35, 8019.

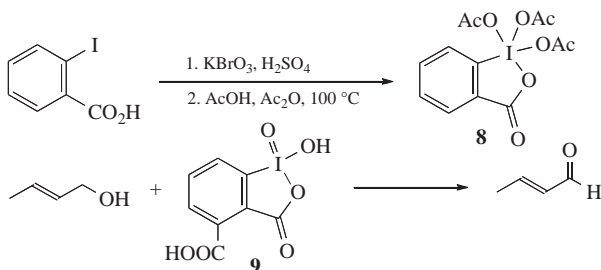
¹⁹² Meyer, S.D.; Schreiber, S.L. *J. Org. Chem.* **1994**, 59, 7549. In aqueous β-cyclodextrin-acetone solution, see Surendra, K.; Krishnaveni, N.S.; Reddy, M.A.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* **2003**, 68, 2058.

¹⁹³ Gallen, M.J.; Goumont, R.; Clark, T.; Terrier, F.; Williams, C.M. *Angew. Chem. Int. Ed.* **2006**, 45, 2929.

¹⁹⁴ Thottumkara, A.P.; Vinod, T.K. *Tetrahedron Lett.* **2001**, 43, 569.

¹⁹⁵ Van Arman, S.A. *Tetrahedron Lett.* **2009**, 50, 4693.

¹⁹⁶ Plumb, J.B.; Harper, D.J. *Chem. Eng. News*, **1990**, July 16, p. 3. For an improved procedure, see Ireland, R.E.; Liu, L. *J. Org. Chem.* **1993**, 58, 2899.



Iodine has been used as a cocatalyst.¹⁹⁷ Other hypervalent iodine oxidizing reagents are known,¹⁹⁸ including $\text{PhI}(\text{OAc})_2/\text{TEMPO}$,¹⁹⁹ $\text{PhI}(\text{OAc})_2$ -chromium salen,²⁰⁰ $\text{PhI}(\text{OAc})_2$ supported on alumina with microwave irradiation,²⁰¹ and an ion-supported hypervalent iodine(III) reagent.²⁰² Microwave irradiation of benzylic alcohols with $\text{PhI}(\text{OH})\text{OTs}$ gave the corresponding aldehyde.²⁰³ Hypervalent iodine compounds have been used in ionic liquids.²⁰⁴ Heating benzylic alcohols with *o*-iodoxybenzoic acid under solvent-free conditions gave the aldehyde.²⁰⁵ 2-Iodobenzenesulfonic acid is a very active catalyst for oxidation of alcohols using Oxone.²⁰⁶

7. *By Catalytic Dehydrogenation.* For the conversion of primary alcohols to aldehydes, dehydrogenation catalysts have the advantage over strong oxidizing agents that further oxidation to the carboxylic acid is prevented. Copper chromite is often used, but other catalysts (e.g., Ag and Cu), have also been employed. Many ketones were prepared in this manner. Catalytic dehydrogenation is more often used industrially than as a laboratory method. However, procedures using $\text{Cu}(\text{II})$ complexes,²⁰⁷ Rh complexes,²⁰⁸ Ru complexes,²⁰⁹ Raney nickel,²¹⁰ and Pd complexes²¹¹ (under phase transfer conditions)²¹² have been reported. Allylic alcohols²¹³ are oxidized to the corresponding saturated aldehyde or ketone by heating with a Rh catalyst, and benzylic alcohols are converted to the aldehyde with a Rh

¹⁹⁷ Karade, N.N.; Tiwari, G.B.; Huple, D.B. *Synlett* **2005**, 2039.

¹⁹⁸ Moriarty, R.M.; Prakash, O. *Accs. Chem. Res.* **1986**, *19*, 244; Dohi, T.; Takenaga, N.; Fukushima, K.-i.; Uchiyama, T.; Kato, D.; Motoo, S.; Fujioka, H.; Kita, Y. *Chem. Commun.* **2010**, 7697.

¹⁹⁹ DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

²⁰⁰ Adam, W.; Hajra, S.; Herderich, M.; Saha-Möller, C.R. *Org. Lett.* **2000**, *2*, 2773.

²⁰¹ Varma, R.S.; Saini, R.K.; Dahiya, R. *J. Chem. Res. (S)* **1998**, 120.

²⁰² Qian, W.; Jin, E.; Bao, W.; Zhang, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 952.

²⁰³ Lee, J.C.; Lee, J.Y.; Lee, S.J. *Tetrahedron Lett.* **2004**, *45*, 4939.

²⁰⁴ Liu, Z.; Chen, Z.-C.; Zheng, Q.-C. *Org. Lett.* **2003**, *5*, 3321; Karthikeyan, G.; Perumal, P.T. *Synlett* **2003**, 2249.

²⁰⁵ Moorthy, J.N.; Singhal, N.; Venkatakrishnan, P. *Tetrahedron Lett.* **2004**, *45*, 5419.

²⁰⁶ Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251.

²⁰⁷ Muldoon, J.; Brown, S.N. *Org. Lett.* **2002**, *4*, 1043.

²⁰⁸ Takahashi, M.; Oshima, K.; Matsubara, S. *Tetrahedron Lett.* **2003**, *44*, 9201.

²⁰⁹ Meijer, R.H.; Ligthart, G.B.W.L.; Meuldijk, J.; Vekemans, J.A.J.M.; Hulshof, L.A.; Mills, A.M.; Kooijman, H.; Spek, A.L. *Tetrahedron* **2004**, *60*, 1065.

²¹⁰ Krafft, M.E.; Zorc, B. *J. Org. Chem.* **1986**, *51*, 5482.

²¹¹ See Mandal, S.K.; Jensen, D.R.; Pugsley, J.S.; Sigman, M.S. *J. Org. Chem.* **2003**, *68*, 4600. See also, Mandal, S.K.; Sigman, M.S. *J. Org. Chem.* **2003**, *68*, 7535; Guram, A.S.; Bei, X.; Turner, H.W. *Org. Lett.* **2003**, *5*, 2485. For a review, see Muzart, J. *Tetrahedron* **2003**, *59*, 5789.

²¹² Choudary, B.M.; Reddy, N.P.; Kantam, M.L.; Jamil, Z. *Tetrahedron Lett.* **1985**, *26*, 6257.

²¹³ Tanaka, K.; Fu, G.C. *J. Org. Chem.* **2001**, *66*, 8177.

catalyst.²¹⁴ Propargylic alcohols are oxidized by heating with a V catalyst.²¹⁵ Secondary alcohols are oxidized with $\text{Bi}(\text{NO}_3)_3$ on Montmorillonite.²¹⁶ Biooxidation is possible as well via hydrogen transfer.²¹⁷

8. *Miscellaneous Reagents.*²¹⁸ Nitric acid in dichloromethane oxidizes benzylic alcohols to the corresponding ketone.²¹⁹ Bromine is an effective oxidant, and iodine under photochemical conditions has been used.²²⁰ Heating a 1,2-diol with NBS in CCl_4 gave the 1,2-diketone.²²¹ Iodine has been used in conjunction with DMSO and hydrazine.²²² Enzymatic oxidations have been reported.²²³ Oxidation of alcohols in water is possible using I_2O_5 .²²⁴ Dimethyl dioxirane²²⁵ oxidizes benzylic alcohols to the corresponding aldehyde,²²⁶ and dioxirane reagents are sufficiently mild that an α,β -epoxy alcohol was oxidized to the corresponding ketone, without disturbing the epoxide, using methyl trifluoromethyl dioxirane.²²⁷ Hydrogen peroxide with urea oxidizes aryl aldehydes in formic acid.²²⁸ *tert*-Butylhydroperoxide with a Cu catalyst gives oxidation in an ionic liquid.²²⁹ Potassium monoperoxysulfate in the presence of a chiral ketone oxidizes 1,2-diols to α -hydroxy ketones enantioselectively.²³⁰ Potassium monoperoxysulfate also oxidizes secondary alcohols in the presence of O_2 .²³¹ Air, in the presence of a zeolite oxidizes benzylic alcohols.²³² Periodic acid oxidizes aldehydes or ketones in the presence of a PCC catalyst.²³³ Sodium hypochlorite in acetic acid²³⁴ or in water with β -cyclodextrin²³⁵ is a useful oxidizing agent. Calcium hypochlorite on moist alumina with microwave

²¹⁴ Miyata, A.; Murakami, M.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2001**, 42, 7067; Csjermyik, G.; Ell, A.H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, 67, 1657.

²¹⁵ Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Uemura, S. *Tetrahedron Lett.* **2001**, 42, 8877.

²¹⁶ Samajdar, S.; Becker, F.F.; Banik, B.K. *Synth. Commun.* **2001**, 31, 2691.

²¹⁷ See Orbegozo, T.; de Vries, J.G.; Kroutil, W. *Eur. J. Org. Chem.* **2010**, 3445; Orbegozo, T.; Lavandera, I.; Fabian, W.M.F.; Mautner, B.; de Vries, J.G.; Kroutil, W. *Tetrahedron* **2009**, 65, 6805.

²¹⁸ See Sheldon, R.A.; Arends, I.W.C.E.; ten Brink, G.-J.; Dijkman, A. *Acc. Chem. Res.* **2002**, 35, 774.

²¹⁹ Strazzolini, P.; Runcio, A. *Eur. J. Org. Chem.* **2003**, 526.

²²⁰ Itoh, A.; Kodama, T.; Masaki, Y. *Chem. Lett.* **2001**, 686.

²²¹ Khurana, J.M.; Kandpal, B.M. *Tetrahedron Lett.* **2003**, 44, 4909.

²²² Gogoi, P.; Sarmah, G.K.; Konwar, D. *J. Org. Chem.* **2004**, 69, 5153.

²²³ *Bacillus stearothermophilus*: Fantin, G.; Fogagnolo, M.; Giovannini, P.P.; Medici, A.; Pedrini, P.; Poli, S. *Tetrahedron Lett.* **1995**, 36, 441. *Chloroperoxidase*: Hu, S.; Dordick, J.S. *J. Org. Chem.* **2002**, 67, 314. *Gluconobacter oxydans* DSM 2343: Villa, R.; Romano, A.; Gandolfi, R.; Gargo, J.V.S.; Molinari, F. *Tetrahedron Lett.* **2002**, 43, 6059.

²²⁴ Liu, Z.-Q.; Zhao, Y.; Luo, H.; Chai, L.; Sheng, Q. *Tetrahedron Lett.* **2007**, 48, 3017.

²²⁵ See Deubel, D.V. *J. Org. Chem.* **2001**, 66, 3790.

²²⁶ Baumstark, A.L.; Kovac, F.; Vasquez, P.C. *Can. J. Chem.* **1999**, 77, 308. See Angelis, Y.S.; Hatzakis, N.S.; Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* **2001**, 42, 3753.

²²⁷ D'Accolti, L.; Fusco, C.; Annese, C.; Rella, M.R.; Turteltaub, J.S.; Williard, P.G.; Curci, R. *J. Org. Chem.* **2004**, 69, 8510.

²²⁸ Balicki, R. *Synth. Commun.* **2001**, 31, 2195.

²²⁹ Liu, C.; Han, J.; Wang, J. *Synlett* **2007**, 643.

²³⁰ Adam, W.; Saha-Möller, C.R.; Zhao, C.-G. *J. Org. Chem.* **1999**, 64, 7492.

²³¹ Döbler, C.; Mehlretter, G.M.; Sundermeier, U.; Eckert, M.; Militzer, H.-C.; Beller, M. *Tetrahedron Lett.* **2001**, 42, 8447.

²³² Son, Y.-C.; Makwana, V.D.; Howell, A.R.; Suib, S.L. *Angew. Chem. Int. Ed.* **2001**, 40, 4280.

²³³ Hunsen, M. *Tetrahedron Lett.* **2005**, 46, 1651. See also, Zhang, S.; Xu, L.; Trudell, M.L. *Synthesis* **2005**, 1757.

²³⁴ Stevens, R.V.; Chapman, K.T.; Weller, H.N. *J. Org. Chem.* **1980**, 45, 2030. See also, Mohrig, J.R.; Nienhuis, D.M.; Linck, C.F.; van Zoeren, C.; Fox, B.G.; Mahaffy, P.G. *J. Chem. Educ.* **1985**, 62, 519; Xie, H.; Zhang, S.; Duan, H. *Tetrahedron Lett.* **2004**, 45, 2013.

²³⁵ Ji, H.-B.; Shi, D.-P.; Shao, M.; Li, Z.; Wang, L.-F. *Tetrahedron Lett.* **2005**, 46, 2517.

irradiation has been used to oxidize benzylic alcohols.²³⁶ Hydrogen bromide in aq H_2O_2 oxidizes secondary alcohols to ketones.²³⁷ With ultrasound, DDQ selectively oxidizes a benzylic or allylic hydroxyl group of 1,2-diols with those substituents.²³⁸ Photooxidation of alcohols is possible in the presence of a catalytic amount of NBS.²³⁹ A mixture of $\text{I}_2\text{—KI—K}_2\text{CO}_3\text{—H}_2\text{O}$ oxidizes alcohols to aldehydes or ketones under anaerobic conditions.²⁴⁰ Similarly $\text{KBrO}_3/\text{ZrClO}_2\cdot 8\text{H}_2\text{O}$ can be used to oxidize alcohols.²⁴¹ Oxone oxidizes alcohols, catalyzed by AlCl_3 .²⁴²

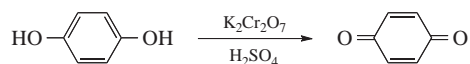
Tetrabutylammonium periodate²⁴³ and benzyltriphenylphosphonium periodate.²⁴⁴ oxidizes primary alcohols to aldehydes. On the other hand, *Fremy's salt* (see Reaction 19-4) selectively oxidizes benzylic alcohols and not allylic or saturated ones.²⁴⁵

In a related reaction to the oxidation of alcohols, it is possible to oxidize ethers to aldehydes. Oxidation of trimethylsilyl ethers with O_2 , a catalytic amount of *N*-hydroxyphthalimide and a Co catalyst, give an aldehyde.²⁴⁶ Microwave irradiation with BiCl_2 oxidizes benzylic TMS ethers to the aldehyde.²⁴⁷ Microwave irradiation on zeolite supported ferric nitrate has been used.²⁴⁸ *O*-Tetrahydropyranyl ethers (*O*-THP) have been oxidized to the aldehyde with ferric nitrate on zeolites,²⁴⁹ and the Pd catalyzed oxidation of allylic esters to conjugated ketones is known.²⁵⁰ *N*-Bromosuccinimide with β -cyclodextrin oxidizes tetrahydropyranyl ethers in water.²⁵¹

OS I, 87, 211, 241, 340; II, 139, 541; III, 37, 207; IV, 189, 192, 195, 467, 813, 838; V, 242, 310, 324, 692, 852, 866; VI, 218, 220, 373, 644, 1033; VII, 102, 112, 114, 177, 258, 297; VIII, 43, 367, 386; IX, 132, 432. Also see, OS IV, 283; VIII, 363, 501.

19-4 Oxidation of Phenols and Aromatic Amines to Quinones

1/*O*,6/*O*-Dihydro-elimination



²³⁶ Mojtahedi, M.M.; Saidi, M.R.; Bolourtchian, M.; Shirzi, J.S. *Monat. Chem.* **2001**, 132, 655.

²³⁷ Sharma, V.B.; Jain, S.L.; Sain, B. *Synlett* **2005**, 173.

²³⁸ Peng, K.; Chen, F.; She, X.; Yang, C.; Cui, Y.; Pan, X. *Tetrahedron Lett.* **2005**, 46, 1217.

²³⁹ Kuwabara, K.; Itoh, A. *Synthesis* **2006**, 1949.

²⁴⁰ Gogoi, P.; Konwar, D. *Org. Biomol. Chem.* **2005**, 3, 3473.

²⁴¹ Shirini, F.; Zolfigol, M.A.; Mollarazi, E. *Synth. Commun.* **2005**, 35, 1541.

²⁴² Wu, S.; Ma, H.; Le, Z. *Tetrahedron* **2010**, 66, 8641.

²⁴³ Friedrich, H.B.; Khan, F.; Singh, N.; van Staden, M. *Synlett* **2001**, 869.

²⁴⁴ Hajipour, A.R.; Mallakpour, S.E.; Samimi, H.A. *Synlett* **2001**, 1735.

²⁴⁵ Morey, J.; Dzielenziak, A.; Saá, J.M. *Chem. Lett.* **1985**, 263.

²⁴⁶ Karimi, B.; Rajabi, J. *Org. Lett.* **2004**, 6, 2841.

²⁴⁷ Hajipour, A.R.; Mallakpour, S.E.; Baltork, I.M.; Adibi, H. *Synth. Commun.* **2001**, 31, 1625.

²⁴⁸ Heravi, M.M.; Ajami, D.; Ghassemzadeh, M.; Tabar-Hydar, K. *Synth. Commun.* **2001**, 31, 2097.

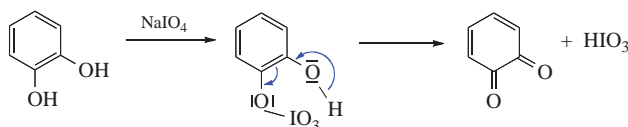
²⁴⁹ Mohajerani, B.; Heravi, M.M.; Ajami, D. *Monat. Chem.* **2001**, 132, 871.

²⁵⁰ Trost, B.M.; Richardson, J.; Yong, K. *J. Am. Chem. Soc.* **2006**, 128, 2540.

²⁵¹ Narender, M.; Reddy, M.S.; Rao, K.R. *Synthesis* **2004**, 1741. See Reddy, M.S.; Narender, M.; Nageswar, Y.V.D.; Rao, K.R. *Synthesis* **2005**, 714.

Ortho and para diols are easily oxidized to o- and p-quinones, respectively.²⁵² Either or both OH groups can be replaced by NH₂ groups to give the same products, although for the preparation of o-quinones only OH groups are normally satisfactory. The reaction has been successfully carried out with other groups para to OH or NH₂; halogen, OR, Me, *t*-Bu, and even H, although yields are poor with the latter. Many oxidizing agents have been used: acid dichromate,²⁵³ silver oxide, silver carbonate, lead tetraacetate, HIO₄, NBS—H₂O—H₂SO₄,²⁵⁴ dimethyl dioxirane,²⁵⁵ and atmospheric oxygen.²⁵⁶ Oxidation has been done photochemically with O₂ and tetraphenylporphine.²⁵⁷ A particularly effective reagent for rings with only one OH or NH₂ group is (KSO₃)₂N—O• (dipotassium nitrosodisulfonate; *Fremy's salt*), which is a stable free radical.²⁵⁸ A mixture of 4-iodophenoxyacetic acid and Oxone is an effective catalyst for the oxidation of *p*-alkoxyphenols to *p*-quinones.²⁵⁹ A supported iron phthalocyanine facilitates the aromatic oxidation of phenols.²⁶⁰

Less is known about the mechanism than is the case for oxidizing simple alcohols in Reaction 19-3, and it seems to vary with the oxidizing agent. For oxidation of catechol with NaIO₄, it was found that the reaction conducted in H₂¹⁸O gave unlabeled quinone.²⁶¹ Therefore the following mechanism²⁶² was proposed:



When catechol was oxidized with MnO₄[−] under aprotic conditions, a semiquinone radical ion intermediate was involved.²⁶³ For autoxidations²⁶⁴ (i.e., with atmospheric O₂) a free radical mechanism is known to operate.²⁶⁵

OS I, 383, 482, 511; II, 175, 254, 430, 553; III, 663, 753; IV, 148; VI, 412, 480, 1010.

19-5 Dehydrogenation of Amines to Nitriles or Imines

1/1/N,2/2/C-Tetrahydro-bielimination



²⁵² See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, **1988**, pp. 305–323, 438–447; Naruta, Y.; Maruyama, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, **1988**, pp. 247–276; Thomson, R.H. in Patai, S. *The Chemistry of the Quinoid Compounds*, Vol. 1, pt. 1, Wiley, NY, **1974**, pp. 112–132.

²⁵³ See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, **1981**, pp. 92–117.

²⁵⁴ Kim, D.W.; Choi, H.Y.; Lee, K.Y.; Chi, D.Y. *Org. Lett.* **2001**, 3, 445.

²⁵⁵ Adam, W.; Schönberger, A. *Tetrahedron Lett.* **1992**, 33, 53.

²⁵⁶ See Hashemi, M.M.; Beni, Y.A. *J. Chem. Res. (S)* **1998**, 138.

²⁵⁷ Cossy, J.; Belotti, S. *Tetrahedron Lett.* **2001**, 42, 4329.

²⁵⁸ See Zimmer, H.; Lankin, D.C.; Horgan, S.W. *Chem. Rev.* **1971**, 71, 229.

²⁵⁹ Yakura, T.; Konishi, T. *Synlett* **2007**, 765.

²⁶⁰ Zalomaeva, O.V.; Sorokin, A.B. *New J. Chem.* **2006**, 30, 1768.

²⁶¹ Adler, E.; Falkehag, I.; Smith, B. *Acta Chem. Scand.* **1962**, 16, 529.

²⁶² This mechanism is an example of category 4 (Sec. 19.A).

²⁶³ Bock, H.; Jaculi, D. *Angew. Chem. Int. Ed.* **1984**, 23, 305.

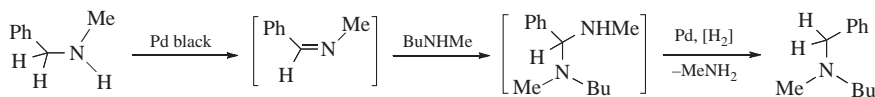
²⁶⁴ For an example, see Rathore, R.; Bosch, E.; Kochi, J.K. *Tetrahedron Lett.* **1994**, 35, 1335.

²⁶⁵ Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, **1981**, pp. 368–381; Walling, C. *Free Radicals in Solution*, Wiley, NY, **1957**, pp. 457–461.

Primary amines at a primary carbon can be dehydrogenated to nitriles. The reaction has been carried out with a variety of reagents, among others, I_2 in aq NH_3 ,²⁶⁶ IBX see **19-3**, category 6),²⁶⁷ $NaOCl$,²⁶⁸ Me_3N-O/OsO_4 ,²⁶⁹ $Ru/Al_2O_3/O_2$,²⁷⁰ and $CuCl/O_2/pyridine$.²⁷¹ Iodine and 1,3-diiodo-5,5-dimethylhydantoin in aq ammonia converted both amines and alcohols to nitriles.²⁷² Dehydrogenation of amines has been done in aq micelles.²⁷³

Several methods have been reported for the dehydrogenation of secondary amines to imines.²⁷⁴ Among them²⁷⁵ are treatment with (1) iodosylbenzene (PhIO) alone or in the presence of a Ru complex,²⁷⁶ (2) DMSO and oxalyl chloride,²⁷⁷ and (3) *t*-BuOOH and a Rh catalyst.²⁷⁸ *N*-Tosyl aziridines are converted to *N*-tosyl imines when heated with a Pd catalyst.²⁷⁹ An interesting variation treats pyrrolidine with iodobenzene and a Rh catalyst to give 2-phenylpyrroline.²⁸⁰

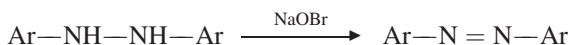
A reaction that involves dehydrogenation to an imine that then reacts further is the reaction of primary or secondary amines²⁸¹ with Pd black.²⁸² The imine initially formed by the dehydrogenation reacts with another molecule of the same or a different amine to give an aminal, which loses NH_3 or RNH_2 to give a secondary or tertiary amine. An example is the reaction between *N*-methylbenzylamine and butylmethylamine, which produces 95% *N*-methyl-*N*-butylbenzylamine.



In a related reaction, alkyl azides react with BrF_3 to give the corresponding nitrile.²⁸³

19-6 Oxidation of Hydrazines, Hydrazones, and Hydroxylamines

1/*N*,2/*N*-Dihydro-elimination



²⁶⁶ Iida, S.; Togo, H. *Synlett* **2006**, 2633.

²⁶⁷ Chiampanichayakul, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Kuhakarn, C. *Synthesis* **2008**, 2045.

²⁶⁸ Yamazaki, S. *Synth. Commun.* **1997**, 27, 3559; Jursic, B. *J. Chem. Res. (S)* **1988**, 168.

²⁶⁹ Gao, S.; Herzig, D.; Wang, B. *Synthesis* **2001**, 544.

²⁷⁰ Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2003**, 42, 1480.

²⁷¹ Capdevielle, P.; Lavigne, A.; Maumy, M. *Tetrahedron* **1990**, 2835; Capdevielle, P.; Lavigne, A.; Sparfel, D.; Baranne-Lafont, J.; Cuong, N.K.; Maumy, M. *Tetrahedron Lett.* **1990**, 31, 3305.

²⁷² Iida, S.; Togo, H. *Tetrahedron* **2007**, 63, 8274.

²⁷³ Biondini, D.; Brinchi, L.; Germani, R.; Goracci, L.; Savelli, G. *Eur. J. Org. Chem.* **2005**, 3060.

²⁷⁴ See Dayagi, S.; Degani, Y. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 117-124.

²⁷⁵ See Cornejo, J.J.; Larson, K.D.; Mendenhall, G.D. *J. Org. Chem.* **1985**, 50, 5382; Nishinaga, A.; Yamazaki, S.; Matsuura, T. *Tetrahedron Lett.* **1988**, 29, 4115.

²⁷⁶ Müller, P.; Gilabert, D.M. *Tetrahedron* **1988**, 44, 7171.

²⁷⁷ Keirs, D.; Overton, K. *J. Chem. Soc. Chem. Commun.* **1987**, 1660.

²⁷⁸ Murahashi, S.; Naot, T.; Taki, H. *J. Chem. Soc. Chem. Commun.* **1985**, 613.

²⁷⁹ Wolfe, J.P.; Ney, J.E. *Org. Lett.* **2003**, 5, 4607.

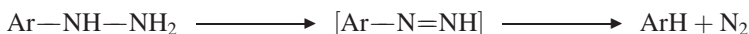
²⁸⁰ Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2004**, 126, 13244.

²⁸¹ See Larsen, J.; Jørgensen, K.A. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1213. Also see, Yamaguchi, J.; Takeda, T. *Chem. Lett.* **1992**, 1933; Yamazaki, S. *Chem. Lett.* **1992**, 823.

²⁸² Murahashi, S.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, 105, 5002. See also, Wilson, Jr., R.B.; Laine, R.M. *J. Am. Chem. Soc.* **1985**, 107, 361.

²⁸³ Sasson, R.; Rozen, S. *Org. Lett.* **2005**, 7, 2177.

N,N'-Diarylhydrazines (hydrazo compounds) are oxidized to azo compounds by several oxidizing agents, including NaOBr, $\text{K}_3\text{Fe}(\text{CN})_6$ under phase-transfer conditions²⁸⁴ FeCl_3 ,²⁸⁵ MnO_2 (this reagent yields *cis* azobenzenes),²⁸⁶ CuCl_2 , and air and NaOH.²⁸⁷ The reaction is also applicable to *N,N'*-dialkyl- and *N,N'*-diacylhydrazines. Hydrazines (both alkyl and aryl) substituted on only one side also give azo compounds,²⁸⁸ but these are unstable and decompose to nitrogen and the hydrocarbon:



Aniline derivatives are converted to azo compounds by heating with cetyltrimethylammonium dichromate in chloroform.²⁸⁹ When hydrazones are oxidized with HgO , Ag_2O , MnO_2 , PbO_4 , or certain other oxidizing agents, diazo compounds ($\text{R}_2\text{C}=\text{N}-\text{NH}_2 \rightarrow \text{R}_2\text{C}=\text{N}^+=\text{N}^-$) are obtained²⁹⁰:

Hydrazones of the form $\text{ArCH}=\text{NNH}_2$ react with HgO in solvents, (e.g., diglyme or ethanol) to give nitriles (ArCN).²⁹¹ It is possible to oxidize dimethylhydrazones ($\text{R}-\text{C}=\text{N}-\text{NMe}_2$) to the corresponding nitrile ($\text{R}-\text{C}\equiv\text{N}$) with magnesium monoperoxyphthalate (MMP),²⁹² or with dimethyl dioxirane.²⁹³ Oxone on wet alumina also converts hydrazones to nitriles with microwave irradiation.²⁹⁴ Oximes of aromatic aldehydes are converted to aryl nitriles with InCl_3 ²⁹⁵ (ketoximes give a *Beckmann rearrangement*, Reaction 18-17).

In a related reaction, primary aromatic amines have been oxidized to azo compounds by a variety of oxidizing agents, among them MnO_2 , lead tetraacetate, O_2 and a base, BaMnO_4 ,²⁹⁶ and sodium perborate in acetic acid. *tert*-Butyl hydroperoxide has been used to oxidize certain primary amines to azoxy compounds.²⁹⁷

Nitrones [$\text{C}=\text{N}^+(\text{R})-\text{O}^-$] are generated by the oxidation of *N*-hydroxyl secondary amines with 5% aq NaOCl.²⁹⁸ Secondary amines (e.g., dibenzylamine) can be converted to the corresponding nitrone by heating with cumyl hydroperoxide in the presence of a titanium catalyst.²⁹⁹

OS II, 496; III, 351, 356, 375, 668; IV, 66, 411; V, 96, 160, 897; VI, 78, 161, 334, 392, 803, 936; VII, 56. Also see, OS V, 258. For oxidation of primary amines, see OS V, 341.

²⁸⁴ Dimroth, K.; Tüncher, W. *Synthesis* **1977**, 339.

²⁸⁵ Wang, C.-L.; Wang, X.-X.; Wang, X.-Y.; Xiao, J.-P.; Wang, Y.-L. *Synth. Commun.* **1999**, 29, 3435.

²⁸⁶ Hyatt, J.A. *Tetrahedron Lett.* **1977**, 141.

²⁸⁷ See Newbold, B.T. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, **1975**, pp. 543–557, 564–573.

²⁸⁸ See Mannen, S.; Itano, H.A. *Tetrahedron* **1973**, 29, 3497.

²⁸⁹ Patel, S.; Mishra, B.K. *Tetrahedron Lett.* **2004**, 45, 1371.

²⁹⁰ For a review, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, **1986**, pp. 233–256.

²⁹¹ Mobbs, D.B.; Suschitzky, H. *Tetrahedron Lett.* **1971**, 361.

²⁹² Fernández, R.; Gasch, C.; Lassaletta, J.-M.; Llera, J.-M.; Vázquez, J. *Tetrahedron Lett.* **1993**, 34, 141.

²⁹³ Altamura, A.; D'Accolti, L.; Detomaso, A.; Dinoi, A.; Fiorentino, M.; Fusco, C.; Curci, R. *Tetrahedron Lett.* **1998**, 39, 2009.

²⁹⁴ Ramalingam, T.; Reddy, B.V.S.; Srinivas, R.; Yadav, J.S. *Synth. Commun.* **2000**, 30, 4507.

²⁹⁵ Barman, D.C.; Thakur, A.J.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* **2000**, 1196.

²⁹⁶ Firouzabadi, H.; Mostafavipoor, Z. *Bull. Chem. Soc. Jpn.* **1983**, 56, 914.

²⁹⁷ Kosswig, K. *Liebigs Ann. Chem.* **1971**, 749, 206.

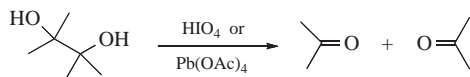
²⁹⁸ Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* **1999**, 64, 7243.

²⁹⁹ Forcato, M.; Nugent, W.A.; Licini, G. *Tetrahedron Lett.* **2003**, 44, 49.

B. Oxidations Involving Cleavage of Carbon–Carbon Bonds³⁰⁰

19-7 Oxidative Cleavage of Glycols and Related Compounds

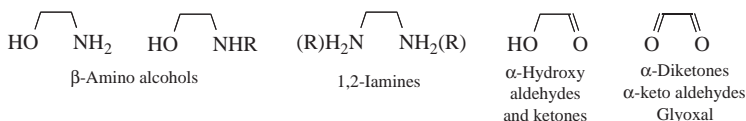
2/O-De-hydrogen-uncoupling



1,2-Diols (glycols) are easily cleaved under mild conditions and in good yield with periodic acid or lead tetraacetate.³⁰¹ The reaction generates 2 molar equivalents of aldehyde, or 2 molar equivalents of ketone, or 1 molar equivalent of each, depending on the groups attached to the two carbons. The yields are so good that alkenes are often converted to diols (Reaction 15-48), and then cleaved with HIO_4 or $\text{Pb}(\text{OAc})_4$ rather than being cleaved directly with ozone (Reaction 19-9) or dichromate or permanganate (Reaction 19-10). The diol can be generated and cleaved *in situ* from an alkene to give the carbonyl compounds.³⁰² A number of other oxidizing agents also give the same products, among them³⁰³ aq sodium hypochlorite (NaOCl),³⁰⁴ activated MnO_2 ,³⁰⁵ O_2 and a Ru catalyst,³⁰⁶ or PCC.³⁰⁷ Permanganate, dichromate, and several other oxidizing agents³⁰⁸ also cleave glycols, giving carboxylic acids rather than aldehydes, but these reagents are seldom used synthetically.

The two reagents (periodic acid and lead tetraacetate) are complementary, since periodic acid is best used in water and lead tetraacetate in organic solvents. Chiral lead carboxylates have been prepared for the oxidative cleavage of 1,2-diols.³⁰⁹ When three or more OH groups are located on adjacent carbons, the middle one (or ones) is converted to formic acid.

Other compounds that contain oxygen atoms or nitrogen atoms on adjacent carbons undergo similar cleavage:



³⁰⁰ See Bentley, K.W. in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, **1973**, pp. 137–254.

³⁰¹ See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, **1988**, pp. 277–301, 432–437; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 3353–363; Perlín, A.S. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, **1969**, pp. 189–212; Bunton, C.A. in Wiberg, K.B. in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, **1965**, pp. 367–407. Also see Rubottom, G.M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D Academic Press, NY, **1982**, p. 1; Aylward, J.B. *Q. Rev. Chem. Soc.* **1971**, 25, 407; Fatiadi, A.J. *Synthesis* **1976**, 65,133.

³⁰² Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, 6, 3217.

³⁰³ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1250–1255.

³⁰⁴ Khurana, J.M.; Sharma, P.; Gogia, A.; Kandpal, B.M. *Org. Prep. Proceed. Int.* **2007**, 39, 185.

³⁰⁵ See Ohloff, G.; Giersch, W. *Angew. Chem. Int. Ed.* **1973**, 12, 401.

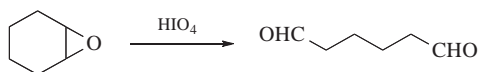
³⁰⁶ Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **1999**, 1, 713.

³⁰⁷ Cisneros, A.; Fernández, S.; Hernández, J.E. *Synth. Commun.* **1982**, 12, 833.

³⁰⁸ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1650–1652.

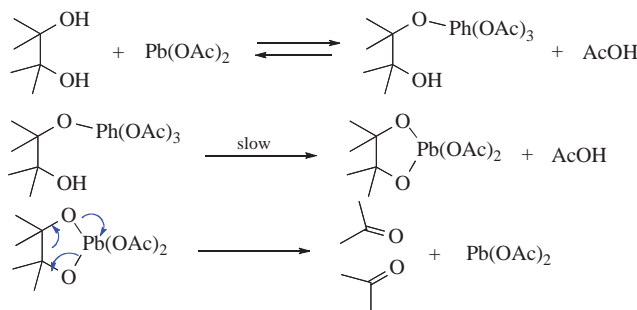
³⁰⁹ Lena, J.I.C.; Sesenoglu, Ö.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Lett.* **2001**, 42, 21.

Cyclic 1,2-diamines are cleaved to diketones with dimethyl dioxirane.³¹⁰ α -Diketones and α -hydroxy ketones are also cleaved by alkaline H_2O_2 .³¹¹ Periodic acid (HIO_4) has been used to cleave epoxides to aldehydes,³¹² for example,

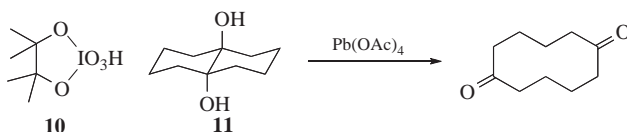


α -Hydroxy and α -keto acids are not cleaved by HIO_4 but are cleaved by NaIO_4 in methanol in the presence of a crown ether $\text{Pb}(\text{OAc})_4$,³¹³ alkaline H_2O_2 , and other reagents. These are oxidative decarboxylations. α -Hydroxy acids give aldehydes or ketones, and α -keto acids give carboxylic acids. Also see, Reaction **19-12** and **19-13**.

The mechanism of glycol oxidation with $\text{Pb}(\text{OAc})_4$ was proposed by Criegee et al.:³¹⁴



This mechanism is supported by (1) the kinetics are second order (first order in each reactant); (2) added acetic acid retards the reaction (drives the equilibrium to the left); and (3) *cis*-glycols react much more rapidly than *trans* glycols.³¹⁵ For periodic acid, the mechanism is similar, with the intermediate (**10**)³¹⁶



However, the cyclic-intermediate mechanism cannot account for all glycol oxidations, since some glycols that cannot form such an ester (e.g., **11**) are nevertheless cleaved by lead tetraacetate (although other glycols that cannot form cyclic esters are *not* cleaved, by either reagent³¹⁷). To account for cases like **11**, a cyclic transition state has been proposed:³¹⁵

OS IV, 124; VII, 185; VIII, 396.

³¹⁰ Gagnon, J.L.; Zajac Jr., W.W. *Tetrahedron Lett.* **1995**, 36, 1803.

³¹¹ See Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* **1977**, 42, 4061.

³¹² Nagarkatti, J.P.; Ashley, K.R. *Tetrahedron Lett.* **1973**, 4599.

³¹³ Kore, A.R.; Sagar, A.D.; Salunkhe, M.M. *Org. Prep. Proceed. Int.* **1995**, 27, 373.

³¹⁴ Criegee, R.; Kraft, L.; Rank, B. *Liebigs Ann. Chem.* **1933**, 507, 159. For reviews, see Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, **1964**, pp. 72–81; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, **1964**, pp. 97–106.

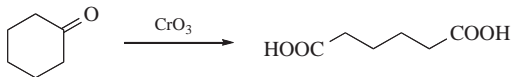
³¹⁵ See Criegee, R.; Höger, E.; Huber, G.; Kruck, P.; Marktscheffel, F.; Schellenberger, H. *Liebigs Ann. Chem.* **1956**, 599, 81.

³¹⁶ Buist, G.J.; Bunton, C.A.; Hipperson, W.C.P. *J. Chem. Soc. B* **1971**, 2128.

³¹⁷ Angyal, S.J.; Young, R.J. *J. Am. Chem. Soc.* **1959**, 81, 5251.

19-8 Oxidative Cleavage of Ketones, Aldehydes, and Alcohols

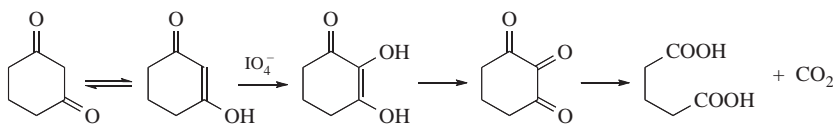
Cycloalkanone oxidative ring opening



Oxidative cleavage of open-chain ketones or alcohols³¹⁸ is a preparative procedure that is seldom useful, not because these compounds do not undergo oxidation (they do, except for diaryl ketones), but because the result is generally a hopeless mixture. Aryl methyl ketones (e.g., acetophenone), however, are readily oxidized to aryl carboxylic acids with Re_2O_7 and 70% aq *tert*-butyl hydroperoxide.³¹⁹ Oxygen with a mixture of Mn and Co catalysts give similar oxidative cleavage,³²⁰ as do hypervalent iodine compounds.³²¹ Aldehydes, (e.g., PhCH_2CHO) are cleaved to benzaldehyde with phosphonium dichromate in refluxing acetonitrile.³²² 1,3-Diketones (e.g., 1,3-diphenyl-1,3-propanedione) are oxidatively cleaved with aq Oxone to give benzoic acid.³²³ Cyclic α -chloro ketones are cleaved to give an α,ω -functionalized compound (acetal-ester) when treated with cerium (IV) sulfate tetrahydrate and O_2 .³²⁴

Despite problems with acyclic ketones, the reaction is useful for the conversion of cyclic ketones and the corresponding secondary alcohols to the dicarboxylic acid in good yield. The formation of adipic acid from cyclohexanone (shown above) is an important industrial procedure. Dichromate in acidic media and permanganate are the most common oxidizing agents, although autoxidation (oxidation with atmospheric oxygen) in alkaline solution³²⁵ and potassium superoxide under phase-transfer conditions³²⁶ have also been used. *O*-Silyl-ketones have been cleaved to esters using electrolysis in alcohol solvents.³²⁷

Cyclic 1,3-diketones, which exist mainly in the mono-enolic form, can be cleaved with sodium periodate with loss of one carbon, for example,³²⁸



The species actually undergoing the cleavage is the triketone, so this is an example of Reaction 19-7. Cyclic 1,3-diketones are converted to α,ω -diesters with an excess of KHSO_5 in methanol.³²⁹

OS I, 18; IV, 19; VI, 690. See also, OS VI, 1024.

³¹⁸ See Trahanovsky, W.S. *Methods Free-Radical Chem.* **1973**, 4, 133–169; Verter, H.S. in Zabicky, J. *The Chemistry of the Carbonyl Group*, pt. 2, Wiley, NY, **1970**, pp. 71–156.

³¹⁹ Gurunath, S.; Sudalai, A. *Synlett* **1999**, 559.

³²⁰ Minisci, F.; Recupero, F.; Fontana, F.; Bjørsvik, H.-R.; Liguori, L. *Synlett* **2002**, 610.

³²¹ Lee, J.C.; Choi, J.-H.; Lee, Y.C. *Synlett* **2001**, 1563.

³²² Hajipour, A.R.; Mohammadpoor-Baltork, I.; Niknam, K. *Org. Prep. Proceed. Int.* **1999**, 31, 335.

³²³ Ashford, S.W.; Grega, K.C. *J. Org. Chem.* **2001**, 66, 1523.

³²⁴ He, L.; Horiuchi, C.A. *Bull. Chem. Soc. Jpn.* **1999**, 72, 2515.

³²⁵ Bjørsvik, H.-R.; Liguori, L.; González, R.R.; Merinero, J.A.V. *Tetrahedron Lett.* **2002**, 43, 4985. See also, Osowska-Pacewicz, K.; Alper, H. *J. Org. Chem.* **1988**, 53, 808.

³²⁶ Sotiriou, C.; Lee, W.; Giese, R.W. *J. Org. Chem.* **1990**, 55, 2159.

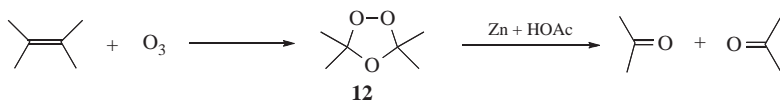
³²⁷ Yoshida, J.; Itoh, M.; Matsunaga, S.; Isoe, S. *J. Org. Chem.* **1992**, 57, 4877.

³²⁸ Wolfrom, M.L.; Bobbitt, J.M. *J. Am. Chem. Soc.* **1956**, 78, 2489.

³²⁹ Yan, J.; Travis, B.R.; Borhan, B. *J. Org. Chem.* **2004**, 69, 9299.

19-9 Ozonolysis

Oxo-uncoupling



When compounds containing double bonds are treated with ozone, usually at low temperatures, initial formation of a 1,2,3-trioxolane is followed by formation of compounds called 1,2,4-trioxolanes (*ozonides*, **12**). These compounds can be isolated but, because some of them are explosive, they are decomposed with Zn and acetic acid or catalytic hydrogenation. More commonly they are decomposed with DMS³³⁰ to give 2 molar equivalents of aldehyde, or 2 molar equivalents of ketone, or 1 molar equivalent of each, depending on the groups attached to the alkene.³³¹ The decomposition of **12** has also been carried out with triethylamine³³² and with reducing agents (e.g., trimethyl phosphite³³³ or thiourea).³³⁴ However, ozonides can also be *oxidized* with oxygen, peroxyacids, or H₂O₂ to give ketones and/or carboxylic acids. Note that the presence of a hydrogen atom on the C=C unit (C=C—H) leads to differences in oxidation or reduction of **12**. In such a system, oxidation leads to the acid, whereas reduction leads to the aldehyde. Note that the presence of a hydrogen atom on the C=C unit (C=C—H) leads to differences in oxidation or reduction of **12**. In such a system, oxidation leads to the acid, whereas reduction leads to the aldehyde. It is also possible to reduce **12** with LiAlH₄, NaBH₄, BH₃, or catalytic hydrogenation with excess H₂ to give 2 molar equivalents of alcohol.³³⁵ Ozonides can be treated with ammonia, hydrogen, and a catalyst to give the corresponding amines,³³⁶ or with an alcohol and anhydrous HCl to give the corresponding carboxylic esters.³³⁷ Ozonolysis is therefore an important synthetic reaction.³³⁸ Ozonolysis can be done in solvent–water mixtures.³³⁹

Many alkenes undergo ozonolysis, including cyclic alkenes, where cleavage gives rise to one bifunctional product (an α,ω -difunctional molecule). Alkenes in which the double bond is connected to electron-donating groups react many times faster than those in which it is connected to electron-withdrawing groups.³⁴⁰ Ozonolysis of compounds containing more than one double bond generally leads to cleavage of all the bonds. In some cases,

³³⁰ Pappas, J.J.; Keaveney, W.P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.

³³¹ See Razumovskii, S.D.; Zaikov, G.E. *Ozone and its Reactions with Organic Compounds*; Elsevier, NY, **1984**; Bailey, P.S. *Ozonation in Organic Chemistry*, 2 Vols., Academic Press, NY, **1978**, **1982**. For reviews, see Odinkov, V.N.; Tolstikov, G.A. *Russ. Chem. Rev.* **1981**, 50, 636; Belew, J.S. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, **1969**, pp. 259–335; Menyailo, A.T.; Pospelov, M.V. *Russ. Chem. Rev.* **1967**, 36, 284.

³³² Hon, Y.-S.; Lin, S.-W.; Chen, Y.-J. *Synth. Commun.* **1993**, 23, 1543.

³³³ Knowles, W.S.; Thompson, Q.E. *J. Org. Chem.* **1960**, 25, 1031.

³³⁴ Gupta, D.; Soman, R.; Dev, S. *Tetrahedron* **1982**, 38, 3013.

³³⁵ See Flippin, L.A.; Gallagher, D.W.; Jalali-Araghi, K. *J. Org. Chem.* **1989**, 54, 1430.

³³⁶ See White, R.W.; King, S.W.; O'Brien, J.L. *Tetrahedron Lett.* **1971**, 3591.

³³⁷ Neumeister, J.; Keul, H.; Saxena, M.P.; Griesbaum, K. *Angew. Chem. Int. Ed.* **1978**, 17, 939. See also, Cardinale, G.; Grimmlikhuysen, J.C.; Laan, J.A.M.; Ward, J.P. *Tetrahedron* **1984**, 40, 1881.

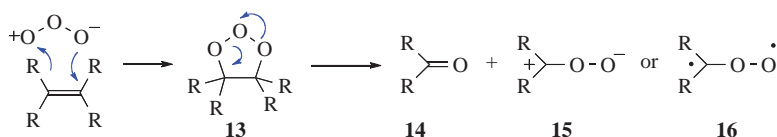
³³⁸ Drug synthesis: see Van Ornum, S.G.; Champeau, R.M.; Pariza, R. *Chem. Rev.* **2006**, 106, 2990.

³³⁹ Schiaffo, C.E.; Dussault, P.H. *J. Org. Chem.* **2008**, 73, 4688.

³⁴⁰ Pryor, W.A.; Giamalva, D.; Church, D.F. *J. Am. Chem. Soc.* **1985**, 107, 2793. See Kuczkowski, R.L. *Adv. Oxygenated Processes* **1991**, 3, 1; Gillies, C.W.; Kuczkowski, R.L. *Isr. J. Chem.* **1983**, 23, 446.

especially when bulky groups are present, conversion of the substrate to an epoxide (**15-50**) becomes an important side reaction and can be the main reaction.³⁴¹ Rearrangement is possible in some cases.³⁴² Ozonolysis of triple bonds³⁴³ is less common and the reaction proceeds less easily, since ozone is an electrophilic agent³⁴⁴ and prefers double to triple bonds (Sec. 15.B.i). Compounds that contain triple bonds generally give carboxylic acids, although sometimes ozone oxidizes them to α -diketones (Reaction **19-26**).

Aromatic compounds are attacked less readily than alkenes, but cleavage is known. Aromatic compounds behave as if the double bonds in the Kekulé structures were really there. Thus benzene gives 3 molar equivalents of glyoxal (HCOCHO), and *o*-xylene gives a glyoxal/MeCOCHO/MeCOCOMe ratio of 3 : 2 : 1, which shows that in this case cleavage is statistical. With polycyclic aromatic compounds the site of attack depends on the structure of the molecule and on the solvent.³⁴⁵



Although a large amount of work has been done on the mechanism of ozonization (formation of **12**), not all the details are known. Note that a primary ozonide has been trapped.³⁴⁶ Criegee³⁴⁷ formulated the basic mechanism. The first step of the *Criegee mechanism*³⁴⁸ is a 1,3-dipolar addition (Reaction **15-58**) of ozone to the substrate to give the “initial” or “primary” ozonide, the structure of which has been shown to be the 1,2,3-trioxolane (**13**) by microwave and other spectral methods.³⁴⁹ However, **13** is highly unstable and cleaves to an aldehyde or ketone (**14**) and an intermediate³⁵⁰ that Criegee showed as a zwitterion (**15**), but which may be a diradical (**16**). This intermediate is usually referred to as a carbonyl oxide.³⁵¹ The carbonyl oxide, which will be represented as **15**, can then undergo various reactions, three of which lead to normal products. One is a recombination with **14**, which leads to ozonide **12**. The second is a dimerization to the bis(peroxide) **17**, and the third a kind of dimerization to **18**.³⁵² If the first path is taken (this

³⁴¹ See Bailey, P.S.; Hwang, H.H.; Chiang, C. *J. Org. Chem.* **1985**, 50, 231.

³⁴² Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Cuerva, J.M.; Segovia, A. *Synlett.* **2000**, 1269.

³⁴³ See Pryor, W.A.; Govindan, C.K.; Church, D.F. *J. Am. Chem. Soc.* **1982**, 104, 7563.

³⁴⁴ See Williamson, D.G.; Cvetanovic, R.J. *J. Am. Chem. Soc.* **1968**, 90, 4248; Razumovskii, S.D.; Zaikov, G.E. *J. Org. Chem. USSR* **1972**, 8, 468, 473; Klutsch, G.; Fliszár, S. *Can. J. Chem.* **1972**, 50, 2841.

³⁴⁵ See O'Murchu, C. *Synthesis* **1989**, 880.

³⁴⁶ Jung, M.E.; Davidov, P. *Org. Lett.* **2001**, 3, 627.

³⁴⁷ See Kuczkowski, R.L. *Acc. Chem. Res.* **1983**, 16, 42; Criegee, R. *Angew. Chem. Int. Ed.* **1975**, 14, 745; Murray, R.W. *Acc. Chem. Res.* **1968**, 1, 313.

³⁴⁸ Also see Ponc, R.; Yuzhakov, G.; Haas, Y.; Samuni, U. *J. Org. Chem.* **1997**, 62, 2757.

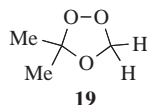
³⁴⁹ Gillies, J.Z.; Gillies, C.W.; Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* **1988**, 110, 7991. See also, Kohlmeier, C.K.; Andrews, L. *J. Am. Chem. Soc.* **1981**, 103, 2578; McGarrity, J.F.; Prodolliet, J. *J. Org. Chem.* **1984**, 49, 4465.

³⁵⁰ See Fajgar, R.; Vítek, J.; Haas, Y.; Pola, J. *Tetrahedron Lett.* **1996**, 37, 3391.

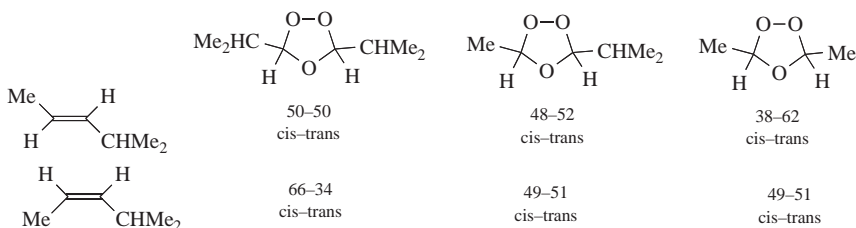
³⁵¹ See Sander, W. *Angew. Chem. Int. Ed.* **1990**, 29, 344; Brunelle, W.H. *Chem. Rev.* **1991**, 91, 335.

³⁵² Fliszár, S.; Chylinska, J.B. *Can. J. Chem.* **1967**, 45, 29; **1968**, 46, 783.

(photooxidation of diazo compounds), reacted with aldehydes to give ozonides³⁶⁰; and (3) *cis*- and *trans*-alkenes generally give the same ozonide, which would be expected if they cleave first.³⁶¹ However, this was not true for $\text{Me}_3\text{CCH}=\text{CHCMe}_3$, where the *cis*-alkene gave the *cis*-ozonide (chiefly), and the *trans* gave the *trans*.³⁶²



The latter result is not compatible with the Criegee mechanism. Also incompatible with the Criegee mechanism was the finding that the *cis*/*trans* ratios of symmetrical (cross) ozonides obtained from *cis*- and *trans*-4-methyl-2-pentene were not the same.³⁶³ If the Criegee mechanism operated as shown above, the *cis*/*trans* ratio for each of the two cross ozonides would have to be identical for the *cis*- and *trans*-alkenes, since in this mechanism they are completely cleaved.



The above stereochemical results have been explained³⁶⁴ on the basis of the Criegee mechanism with the following refinements: (1) The formation of **13** is stereospecific, as expected from a 1,3-dipolar cycloaddition. (2) Once formed, **15** and **14** remain attracted to each other, much like an ion pair. (3) Intermediate **15** exists in *syn* and *anti* forms, which are produced in different amounts and can hold their shapes, at least for a time. This is plausible if we remember that a $\text{C}=\text{O}$ canonical form contributes to the structure of **19**. (4) The combination of **15** and **14** is also a 1,3-dipolar cycloaddition, so configuration is retained in this step too.³⁶⁵

Evidence that the basic Criegee mechanism operates even in these cases comes from ¹⁸O labeling experiments, making use of the fact, mentioned above, that mixed ozonides (e.g., **15**) can be isolated when an external aldehyde is added. Both the normal and modified Criegee mechanisms predict that if ¹⁸O-labeled aldehyde is added to the ozonolysis mixture, the label will appear in the ether oxygen (see the reaction between **15** and **14**), and this is what is found.³⁶⁶ There is evidence that the *anti*-**15** couples much more readily than the *syn*-**15**.³⁶⁷

³⁶⁰ Higley, D.P.; Murray, R.W. *J. Am. Chem. Soc.* **1974**, *96*, 3330.

³⁶¹ See Murray, R.W.; Williams, G.J. *J. Org. Chem.* **1969**, *34*, 1896.

³⁶² See Kolsaker, P. *Acta Chem. Scand. Ser. B* **1978**, *32*, 557.

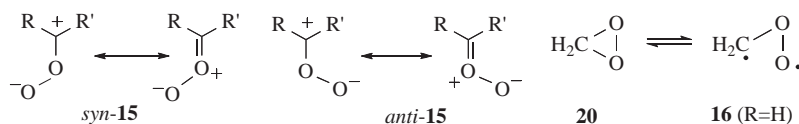
³⁶³ Murray, R.W.; Youssefyeh, R.D.; Story, P.R. *J. Am. Chem. Soc.* **1966**, *88*, 3143, 3655; Story, P.R.; Murray, R.W.; Youssefyeh, R.D. *J. Am. Chem. Soc.* **1966**, *88*, 3144. Also see, Choe, J.; Srinivasan, M.; Kuczkowski, R.L. *J. Am. Chem. Soc.* **1983**, *105*, 4703.

³⁶⁴ Keul, H.; Kuczkowski, R.L. *J. Am. Chem. Soc.* **1985**, *50*, 3371.

³⁶⁵ See Choe, J.; Painter, M.K.; Kuczkowski, R.L. *J. Am. Chem. Soc.* **1984**, *106*, 2891.

³⁶⁶ See Mazur, U.; Kuczkowski, R.L. *J. Org. Chem.* **1979**, *44*, 3185.

³⁶⁷ Mile, B.; Morris, G.M. *J. Chem. Soc. Chem. Commun.* **1978**, 263.



The ozonolysis of ethylene³⁶⁸ in the liquid phase (without a solvent) was shown to take place by the Criegee mechanism.³⁶⁹ This reaction has been used to study the structure of the intermediate **15** or **16**. The compound dioxirane (**20**) was identified in the reaction mixture³⁷⁰ at low temperatures and is probably in equilibrium with the biradical **16** (R = H). Dioxirane has been produced in solution, but it oxidatively cleaves dialkyl ethers (e.g., Et—O—Et) via a chain-radical process,³⁷¹ so the choice of solvent is important.

Ozonolysis in the gas phase is not generally carried out in the laboratory. However, the reaction is important because it takes place in the atmosphere and contributes to air pollution.³⁷² There is much evidence that the Criegee mechanism operates in the gas phase too, although the products are more complex because of other reactions that also take place.³⁷³

OS V, 489, 493; VI, 976; VII, 168; IX, 314. Also see, OS IV, 554. For the preparation of ozone, see OS III, 673.

19-10 Oxidative Cleavage of Double Bonds and Aromatic Rings

Oxo-de-alkylidene-bisubstitution, and so on



Carbon–carbon double bonds can be cleaved by many oxidizing agents,³⁷⁴ the most common of which are permanganate in neutral or acid media and dichromate in acid media. The products are generally 2 molar equivalents of ketone, 2 molar equivalents of carboxylic acid, or 1 molar equivalent of each, depending on what groups are attached to the alkene. With ordinary solutions of permanganate or dichromate, yields are generally low and the reaction is seldom a useful synthetic method; but high yields can be obtained by oxidizing with KMnO_4 dissolved in benzene containing the crown ether dicyclohexano-18-crown-6 (see Sec. 3.C.ii).³⁷⁵ The crown ether coordinates with K^+ , permitting the KMnO_4 to dissolve in benzene. Another reagent frequently used for synthetic purposes is the *Lemieux-von Rudloff reagent*: HIO_4 containing a trace of MnO_4^- .³⁷⁶ The MnO_4^- is the actual oxidizing agent, being reduced to the manganate stage, and the

³⁶⁸ See Samuni, U.; Fraenkel, R.; Haas, Y.; Fajgar, R.; Pola, J. *J. Am. Chem. Soc.* **1996**, *118*, 3687.

³⁶⁹ Fong, G.D.; Kuczkowski, R.L. *J. Am. Chem. Soc.* **1980**, *102*, 4763.

³⁷⁰ Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* **1978**, *100*, 5117. See, however, Ishiguro, K.; Hirano, Y.; Sawaki, Y. *J. Org. Chem.* **1988**, *53*, 5397.

³⁷¹ Ferrer, M.; Sánchez-Baeza, F.; Casas, J.; Messegue, A. *Tetrahedron Lett.* **1994**, *35*, 2981.

³⁷² See Atkinson, R.; Carter, W.P.L. *Chem. Rev.* **1984**, *84*, 437.

³⁷³ See Atkinson, R.; Carter, W.P.L. *Chem. Rev.* **1984**, *84*, 437, pp. 452–454; Martinez, R.I.; Herron J.T. *J. Phys. Chem.* **1988**, *92*, 4644.

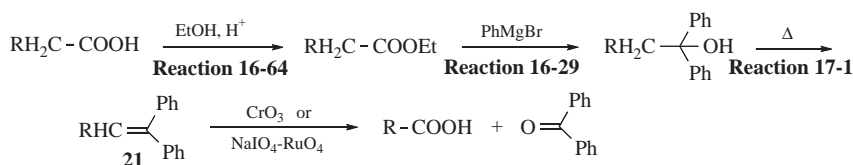
³⁷⁴ See Henry, P.M.; Lange, G.L. in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, **1977**, pp. 965–1098; Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, D.C., **1990**, pp. 77–84, 96–98; Badanyan, Sh.O.; Minasyan, T.T.; Vardapetyan, S.K. *Russ. Chem. Rev.* **1987**, *56*, 740; Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, **1981**, pp. 59–92. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, p. 1634.

³⁷⁵ Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* **1972**, *94*, 4024. See also, Lee, D.G.; Chang, V.S. *J. Org. Chem.* **1978**, *43*, 1532.

³⁷⁶ von Rudloff, E. *Can. J. Chem.* **1955**, *33*, 1714; **1956**, *34*, 1413; **1965**, *43*, 1784.

purpose of the HIO_4 is to reoxidize the manganate back to MnO_4^- . Another reagent that behaves similarly is NaIO_4 –ruthenium tetroxide.³⁷⁷ Oxidative cleavage of alkenes is catalyzed by Ru with $\text{IO}(\text{OH})_5$.³⁷⁸ Cyclic alkenes are cleaved to α,ω -diketones, keto-acids, or dicarboxylic acids. Cyclic alkenes are cleaved to dialdehydes with $\text{KMnO}_4\cdot\text{CuSO}_4$ in dichloromethane.³⁷⁹ A combination of $\text{RuCl}_3/\text{HIO}_5$ oxidatively cleaves cyclic alkenes to dicarboxylic acids.³⁸⁰

The *Barbier–Wieland procedure* for decreasing the length of a chain by one carbon involves oxidative cleavage by acid dichromate (NaIO_4 – RuO_4 has also been used), but this is cleavage of a 1,1-diphenyl alkene (**21**), which generally gives good yields. Addition of a catalytic amount of OsO_4 to *Jones reagent* (Reaction **19-3**) leads to good yields of the carboxylic acid from simple alkenes.³⁸¹ A combination of Oxone and OsO_4 in DMF cleaves alkenes to carboxylic acids.³⁸² Cleavage of alkynes is generally rather difficult, but treatment of internal alkynes with an excess of Oxone with a Ru catalyst leads to aliphatic carboxylic acids.³⁸³



With certain reagents, the oxidation of double bonds can be stopped at the aldehyde stage, and in these cases the products are the same as in the ozonolysis procedure. Among these reagents are *tert*-butyl iodoxybenzene,³⁸⁴ KMnO_4 in $\text{THF}-\text{H}_2\text{O}$,³⁸⁵ and NaIO_4 – OsO_4 .³⁸⁶ Enol ethers, $[\text{RC}(\text{OR}')=\text{CH}_2]$ have been cleaved to carboxylic esters $[\text{RC}(\text{OR}')=\text{O}]$ by atmospheric oxygen.³⁸⁷ Oxidative cleavage of alkenes is catalyzed by a Mn–porphyrin complex.³⁸⁸

The mechanism of oxidation probably involves in most cases the initial formation of a glycol (Reaction **15-29**) or cyclic ester,³⁸⁹ and then further oxidation as in Reaction **19-7**.³⁹⁰ In line with the electrophilic attack on the alkene, triple bonds are more resistant to oxidation than double bonds. Terminal triple-bond compounds can be cleaved to

³⁷⁷ Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B Academic Press, NY, **1973**, pp. 186–192. See Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *Synthesis* **1989**, 47.

³⁷⁸ Shoair, A.G.F.; Mohamed, R.H. *Synth. Commun.* **2006**, 36, 59.

³⁷⁹ Göksu, S.; Altundaş, R.; Sütbeyaz, Y. *Synth. Commun.* **2000**, 30, 1615.

³⁸⁰ Griffith, W.P.; Shoair, A.G.; Suriaatmaja, M. *Synth. Commun.* **2000**, 30, 3091.

³⁸¹ Henry, J.R.; Weinreb, S.M. *J. Org. Chem.* **1993**, 58, 4745.

³⁸² Travis, B.R.; Narayan, R.S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, 124, 3824. See also, Whitehead, D.C.; Travis, B.R.; Borhan, B. *Tetrahedron Lett.* **2006**, 47, 3797.

³⁸³ Yang, D.; Chen, F.; Dong, Z.-M.; Zhang, D.-W. *J. Org. Chem.* **2004**, 69, 2221.

³⁸⁴ Ranganathan, S.; Ranganathan, D.; Singh, S.K. *Tetrahedron Lett.* **1985**, 26, 4955.

³⁸⁵ Viski, P.; Szeverényi, Z.; Simándi, L.I. *J. Org. Chem.* **1986**, 51, 3213.

³⁸⁶ Pappo, R.; Allen, Jr., D.S.; Lemieux, R.U.; Johnson, W.S. *J. Org. Chem.* **1956**, 21, 478.

³⁸⁷ Taylor, R. *J. Chem. Res. (S)* **1987**, 178. See Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* **1985**, 50, 4980.

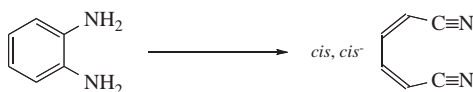
³⁸⁸ Liu, S.-T.; Reddy, K.V.; Lai, R.-Y. *Tetrahedron* **2007**, 63, 1821.

³⁸⁹ See Lee, D.G.; Spitzer, U.A. *J. Org. Chem.* **1976**, 41, 3644; Lee, D.G.; Chang, V.S.; Helliwell, S. *J. Org. Chem.* **1976**, 41, 3644, 3646.

³⁹⁰ There is evidence for an epoxide intermediate: Rocek, J.; Drozd, J.C. *J. Am. Chem. Soc.* **1970**, 92, 6668.

carboxylic acids with Ti(III)NO_3 ³⁹¹ or with [bis(trifluoroacetoxy)iodo]pentafluorobenzene [i.e., $\text{C}_6\text{F}_5\text{I(OCOCF}_3)_2$].³⁹²

Aromatic rings can be cleaved with strong enough oxidizing agents. An important laboratory reagent for this purpose is RuO_4 along with a cooxidant (e.g., NaIO_4 or NaOCl and household bleach can be used). Ruthenium tetroxide is an expensive reagent, but the cost can be greatly reduced by the use of an inexpensive cooxidant (e.g., NaOCl), the function of which is to oxidize RuO_2 back to ruthenium tetroxide. Examples³⁹³ are the oxidation of naphthalene to phthalic acid³⁹⁴ and, even more remarkably, of cyclohexylbenzene to cyclohexanecarboxylic acid³⁹⁵ (note the contrast with Reaction 19-11). The latter conversion was also accomplished with ozone.³⁹⁶ Another reagent that oxidizes aromatic rings is air catalyzed by V_2O_5 . The oxidations of naphthalene to phthalic anhydride and of benzene to maleic anhydride by this reagent are important industrial procedures.³⁹⁷ *o*-Diamines have been oxidized with nickel peroxide, with lead tetraacetate,³⁹⁸ and with O_2 catalyzed by CuCl .³⁹⁹

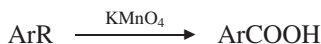


The last-named reagent also cleaves *o*-dihydroxybenzenes (catechols) to give, in the presence of MeOH , the monomethylated dicarboxylic acids ($\text{HO}_2\text{C}-\text{C}=\text{C}-\text{C}=\text{C}-\text{CO}_2\text{Me}$).⁴⁰⁰

OS II, 53, 523; III, 39, 234, 449; IV, 136, 484, 824; V, 393; VI, 662, 690; VII, 397; VIII, 377, 490; IX, 530. Also see, OS II, 551.

19-11 Oxidation of Aromatic Side Chains

Oxo,hydroxy-de-dihydro,methyl-tersubstitution



Alkyl chains on aromatic rings can be oxidized to CO_2H groups by many oxidizing agents, including permanganate, nitric acid, and acid dichromate.⁴⁰¹ The method is most often applied to the methyl group ($\text{CH}_3 \rightarrow \text{CO}_2\text{H}$), although longer side chains can also be cleaved. Tertiary alkyl groups are resistant to oxidation, and when they *are* oxidized, ring cleavage usually occurs too.⁴⁰² It is usually difficult to oxidize an R group on a fused

³⁹¹ McKillop, A.; Oldenzel, O.H.; Swann, B.P.; Taylor, E.C.; Robey, R.L. *J. Am. Chem. Soc.* **1973**, 95, 1296.

³⁹² Moriarty, R.M.; Penmasta, R.; Awasthi, A.K.; Prakash, I. *J. Org. Chem.* **1988**, 53, 6124.

³⁹³ See Nuñez, M.T.; Martín, V.S. *J. Org. Chem.* **1990**, 55, 1928.

³⁹⁴ Spitzer, U.A.; Lee, D.G. *J. Org. Chem.* **1974**, 39, 2468.

³⁹⁵ Caputo, J.A.; Fuchs, R. *Tetrahedron Lett.* **1967**, 4729.

³⁹⁶ Klein, H.; Steinmetz, A. *Tetrahedron Lett.* **1975**, 4249. See Liotta, R.; Hoff, W.S. *J. Org. Chem.* **1980**, 45, 2887; Chakraborti, A.K.; Ghatak, U.R. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2605.

³⁹⁷ See Pyatnitskii, Yu.I. *Russ. Chem. Rev.* **1976**, 45, 762.

³⁹⁸ Nakagawa, K.; Onoue, H. *Tetrahedron Lett.* **1965**, 1433; *Chem. Commun.* **1966**, 396.

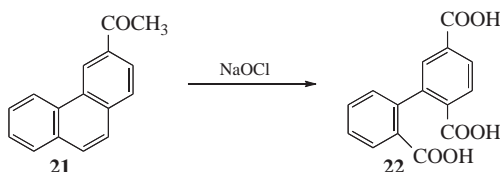
³⁹⁹ Kajimoto, T.; Takahashi, H.; Tsuji, J. *J. Org. Chem.* **1976**, 41, 1389.

⁴⁰⁰ Tsuji, J.; Takayanag, H. *Tetrahedron* **1978**, 34, 641; Bankston, D. *Org. Synth.* 66, 180.

⁴⁰¹ Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, pp. 105–109; Lee, D.G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*, Open-Court Publishing Co., La Salle, IL, **1980**, pp. 43–64. See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, **1981**, pp. 23–33.

⁴⁰² Brandenberger, S.G.; Maas, L.W.; Dvoretzky, I. *J. Am. Chem. Soc.* **1961**, 83, 2146.

aromatic system without cleaving the ring or oxidizing it to a quinone (Reaction **19-19**). However, this has been done (e.g., 2-methylnaphthalene was converted to 2-naphthoic acid) with aq $\text{Na}_2\text{Cr}_2\text{O}_7$.⁴⁰³ Aryl methyl groups are oxidized to aryl CO_2H with NaOCl in acetonitrile,⁴⁰⁴ or with NBS in aqueous NaOH under photochemical conditions.⁴⁰⁵ Functional groups can be present anywhere on the side chain and, if in the α position, greatly increase the ease of oxidation. An exception is an α phenyl group. In such cases, the reaction stops at the diaryl ketone stage. Molecules containing aryl groups on different carbons cleave so that each ring gets one carbon atom, as in the cleavage of the 9,10-bond of dihydrophenanthrenes (**21** to **22**).



It is possible to oxidize only one alkyl group of a ring that contains more than one. The order of reactivity⁴⁰⁶ toward most reagents is $\text{CH}_2\text{Ar} > \text{CHR}_2 > \text{CH}_2\text{R} > \text{CH}_3$.⁴⁰⁷ Groups on the ring susceptible to oxidation (OH , NHR , NH_2 , etc.) must be protected. The oxidation can be performed with oxygen, in which case it is autoxidation, and the mechanism is like that in Reaction **14-7**, with a hydroperoxide intermediate.⁴⁰⁸ With this procedure it is possible to isolate ketones from ArCH_2R , and this is often done.⁴⁰⁹

The mechanism has been studied for the following closely related reaction: $\text{Ar}_2\text{CH}_2 + \text{CrO}_3 \rightarrow \text{Ar}_2\text{C}=\text{O}$.⁴¹⁰ A deuterium isotope effect of 6.4 was found, indicating that the rate-determining step is either $\text{Ar}_2\text{CH}_2 \rightarrow \text{Ar}_2\text{CH}\cdot$ or $\text{Ar}_2\text{CH}_2 \rightarrow \text{Ar}_2\text{CH}^+$. Either way this explains why tertiary groups are not converted to CO_2H and why the reactivity order is $\text{CHR}_2 > \text{CH}_2\text{R} > \text{CH}_3$, as mentioned above. Both free radicals and carbocations exhibit this order of stability (Chapter 5). The two possibilities are examples of categories 2 and 3 in Section 19.A. Just how the radical or the cation goes on to the product is not known.

When the alkyl group is one oxidizable to CO_2H (Reaction **19-11**), cupric salts are oxidizing agents, and the OH group is found in a position ortho to that occupied by the alkyl group.⁴¹¹ This reaction is used industrially to convert toluene to phenol.

In another kind of reaction, an aromatic aldehyde (ArCHO) or ketone (ArCOR') is converted to a phenol (ArOH) on treatment with alkaline H_2O_2 ,⁴¹² but there must be an OH or NH_2 group in the ortho or para position. This is called the *Dakin reaction*.⁴¹³ The

⁴⁰³ Friedman, L.; Fishel, D.L.; Shechter, H. *J. Org. Chem.* **1965**, 30, 1453.

⁴⁰⁴ Yamazaki, S. *Synth. Commun.* **1999**, 29, 2211.

⁴⁰⁵ Itoh, A.; Kodama, T.; Hashimoto, S.; Masaki, Y. *Synthesis* **2003**, 2289.

⁴⁰⁶ Onopchenko, A.; Schulz, J.G.D.; Seekircher, R. *J. Org. Chem.* **1972**, 37, 1414.

⁴⁰⁷ See Foster, G.; Hickinbottom, W.J. *J. Chem. Soc.* **1960**, 680; Ferguson, L.N.; Wims, A.I. *J. Org. Chem.* **1960**, 25, 668.

⁴⁰⁸ Hermans, I.; Peeters, J.; Jacobs, P.A. *J. Org. Chem.* **2007**, 72, 3057.

⁴⁰⁹ Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, **1977**, pp. 508–543.

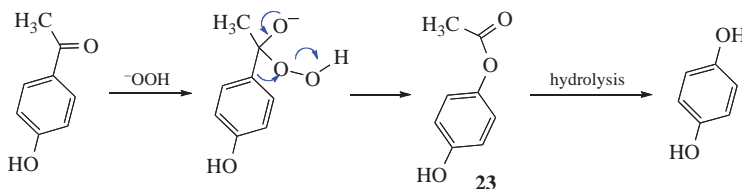
⁴¹⁰ Wiberg, K.B.; Evans, R.J. *Tetrahedron* **1960**, 8, 313.

⁴¹¹ Kaeding, W.W. *J. Org. Chem.* **1961**, 26, 3144. See Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B Academic Press, NY, **1973**, pp. 91–94.

⁴¹² For a convenient procedure, see Hocking, M.B. *Can. J. Chem.* **1973**, 51, 2384.

⁴¹³ See Schubert, W.M.; Kintner, R.R. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 749–752.

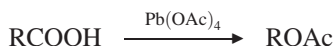
mechanism may be similar to that of the *Baeyer–Villiger Reaction* (18-19).⁴¹⁴ The intermediate **23** has been isolated.⁴¹⁵ The reaction has been performed on aromatic aldehydes with an alkoxy group in the ring, and no OH or NH₂. In this case, acidic H₂O₂ was used.⁴¹⁶ The Dakin reaction has been done in ionic liquids.⁴¹⁷



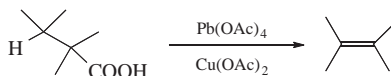
OS I, 159, 385, 392, 543; II, 135, 428; III, 334, 420, 740, 791, 820, 822; V, 617, 810. OS I, 149; III, 759.

19-12 Oxidative Decarboxylation

Acetoxy-de-carboxy-substitution



Hydro-carboxyl-elimination



Carboxylic acids can be decarboxylated⁴¹⁸ with lead tetraacetate to give a variety of products: an ester (ROAc), the alkane (RH) (see Reaction 12-40), an alkene if α,β hydrogen is present, as well as numerous other products arising from rearrangements, internal cyclizations,⁴¹⁹ and reactions with solvent molecules. When R is tertiary, the chief product is usually the alkene. High yields of alkenes can also be obtained when R is primary or secondary using Cu(OAc)₂ along with the Pb(OAc)₄.⁴²⁰ In the absence of Cu(OAc)₂, primary acids give mostly alkanes (though yields are generally low) and secondary acids may give carboxylic esters or alkenes. Other oxidizing agents,⁴²¹ including Co(III), Ag(II), Mn(III), and Ce(IV), have also been used to effect oxidative decarboxylation.⁴²²

⁴¹⁴ See Hocking, M.B.; Bhandari, K.; Shell, B.; Smyth, T.A. *J. Org. Chem.* **1982**, 47, 4208.

⁴¹⁵ Hocking, M.B.; Ko, M.; Smyth, T.A. *Can. J. Chem.* **1978**, 56, 2646.

⁴¹⁶ Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* **1984**, 49, 4740.

⁴¹⁷ Zambrano, J.L.; Dorta, R. *Synlett* **2003**, 1545.

⁴¹⁸ See Serguchev, Yu.A.; Beletskaya, I.P. *Russ. Chem. Rev.* **1980**, 49, 1119; Sheldon, R.A.; Kochi, J.K. *Org. React.* **1972**, 19, 279.

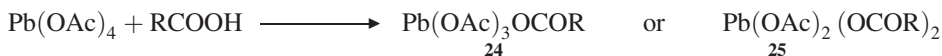
⁴¹⁹ See Davies, D.I.; Waring, C. *J. Chem. Soc. C* **1968**, 1865, 2337.

⁴²⁰ Ogibin, Yu.N.; Katzin, M.I.; Nikishin, G.I. *Synthesis* **1974**, 889.

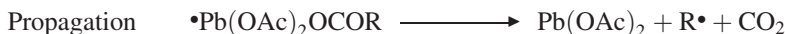
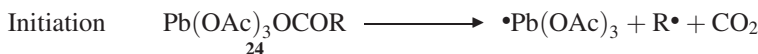
⁴²¹ See Trahanovsky, W.S.; Cramer, J.; Brixius, D.W. *J. Am. Chem. Soc.* **1974**, 96, 1077; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, **1978**, pp. 99–106. See also.; Fristad, W.E.; Fry, M.A.; Klang, J.A. *J. Org. Chem.* **1983**, 48, 3575; Barton, D.H.R.; Crich, D.; Motherwell, W.B. *J. Chem. Soc. Chem. Commun.* **1984**, 242.

⁴²² For another method, see Barton, D.H.R.; Bridon, D.; Zard, S.Z. *Tetrahedron* **1989**, 45, 2615.

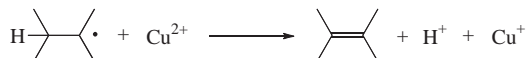
The mechanism with lead tetraacetate is generally accepted to be of the free radical type.⁴²³ First, there is an interchange of ester groups:



A free radical chain mechanism follows (shown for **24** although **25** and other lead esters can behave similarly)



Products can then be formed either from $\text{R}\bullet$ or R^+ . Primary $\text{R}\bullet$ abstract H from solvent molecules to give RH. The R^+ ion can lose H^+ to give an alkene, react with HOAc to give the carboxylic ester, react with solvent molecules or with another functional group in the same molecule, or rearrange, thus accounting for the large number of possible products. The radical $\text{R}\bullet$ can also dimerize to give RR. The effect of Cu^{2+} ions⁴²⁴ is to oxidize the radicals to alkenes, thus producing good yields of alkenes from primary and secondary substrates. The Cu^{2+} ion has no effect on tertiary radicals, because these are efficiently oxidized to alkenes by lead tetraacetate.

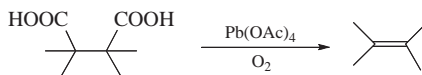


In another type of oxidative decarboxylation, arylacetic acids can be oxidized to aldehydes with one less carbon ($\text{ArCH}_2\text{COOH} \rightarrow \text{ArCHO}$) by tetrabutylammonium periodate.⁴²⁵ Simple aliphatic carboxylic acids were converted to nitriles with one less carbon ($\text{RCH}_2\text{COOH} \rightarrow \text{RC}\equiv\text{N}$) by treatment with trifluoroacetic anhydride and NaNO_2 in $\text{F}_3\text{CCO}_2\text{H}$.⁴²⁶

See also, Reaction **14-37**.

19-13 Bis(decarboxylation)

Dicarboxy-elimination



Compounds containing carboxyl groups on adjacent carbons (succinic acid derivatives) can be bis(decarboxylated) with lead tetraacetate in the presence of O_2 .⁴¹⁷ The reaction is of wide scope. The elimination is stereoselective, but not stereospecific (both *meso*- and

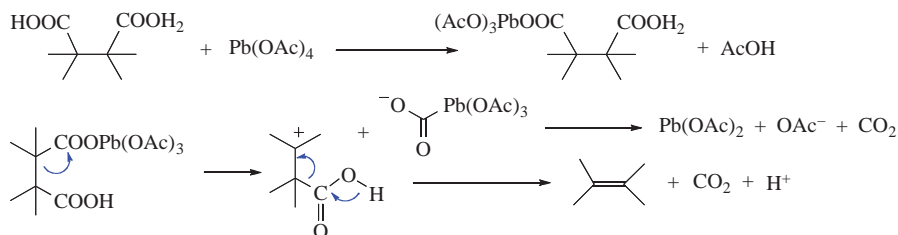
⁴²³ See Cantello, B.C.C.; Mellor, J.M.; Scholes, G. *J. Chem. Soc. Perkin Trans. 2* **1974**, 348; Beckwith, A.L.J.; Cross, R.T.; Gream, G.E. *Aust. J. Chem.* **1974**, 27, 1673, 1693.

⁴²⁴ Kochi, J.K.; Bacha, J.D. *J. Org. Chem.* **1968**, 33, 2746; Torrsell, K. *Ark. Kemi*, **1970**, 31, 401.

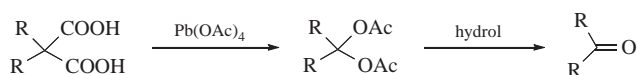
⁴²⁵ Santaniello, E.; Ponti, F.; Manzocchi, A. *Tetrahedron Lett.* **1980**, 21, 2655. Also see Doleschall, G.; Tóth, G. *Tetrahedron* **1980**, 36, 1649.

⁴²⁶ Smushkevich, Yu.I.; Usorov, M.I.; Suvorov, N.N. *J. Org. Chem. USSR* **1975**, 11, 653.

dl-2,3-diphenylsuccinic acid gave *trans*-stilbene)⁴²⁷; a concerted mechanism is thus unlikely. The following mechanism is compatible with the data:



though a free radical mechanism seems to hold in some cases. Bis(decarboxylation) of succinic acid derivatives to give alkenes⁴²⁸ has also been carried out by other methods.⁴²⁹ Compounds containing geminal carboxyl groups (disubstituted malonic acid derivatives) can be bis(decarboxylated) with lead tetraacetate,⁴³⁰ *gem*-diacetates (acylals) being produced, which are easily hydrolyzable to ketones:⁴³¹

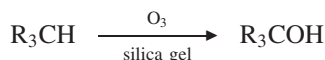


A related reaction involves α -substituted aryl nitriles having a sufficiently acidic α hydrogen, which can be converted to ketones by oxidation with air under phase-transfer conditions.⁴³² The nitrile is added to NaOH in benzene or DMSO, containing a catalytic amount of triethylbenzylammonium chloride (TEBA).⁴³³ This reaction could not be applied to aliphatic nitriles, but an indirect method for achieving this conversion is given in Reaction 19-60.

C. Reactions Involving Replacement of Hydrogen by Heteroatoms

19-14 Hydroxylation at an Aliphatic Carbon

Hydroxylation or Hydroxy-de-hydrogenation



Compounds containing susceptible C—H bonds can be oxidized to alcohols.⁴³⁴ Nearly always, the C—H bond involved is tertiary, so the product is a tertiary alcohol. This is partly because tertiary C—H bonds are more susceptible to free radical attack than primary and secondary bonds and partly because the reagents involved would oxidize primary and

⁴²⁷ Corey, E.J.; Casanova, J. *J. Am. Chem. Soc.* **1963**, 85, 165.

⁴²⁸ For a review, see De Lucchi, O.; Modena, G. *Tetrahedron* **1984**, 40, 2585, pp. 2591–2608.

⁴²⁹ Radlick, P.; Klem, R.; Spurlock, S.; Sims, J.J.; van Tamelen, E.E.; Whitesides, T. *Tetrahedron Lett.* **1968**, 5117; Westberg, H.H.; Dauben Jr., H.J. *Tetrahedron Lett.* **1968**, 5123. For additional references, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, **1989**, pp. 253–254.

⁴³⁰ See Salomon, R.G.; Roy, S.; Salomon, R.G. *Tetrahedron Lett.* **1988**, 29, 769.

⁴³¹ Tufariello, J.J.; Kissel, W.J. *Tetrahedron Lett.* **1966**, 6145.

⁴³² For other methods of achieving this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, p. 1260.

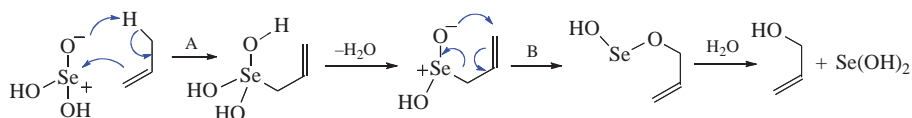
⁴³³ See Kulp, S.S.; McGee, M.J. *J. Org. Chem.* **1983**, 48, 4097.

⁴³⁴ Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, **1971**, pp. 7–11; Lee, D.G. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, **1969**, pp. 2–6; Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, **1989**.

secondary alcohols further. In the best method, the reagent is ozone and the substrate is absorbed on silica gel.⁴³⁵ Yields as high as 99% have been obtained by this method. Other reagents are chromic acid,⁴³⁶ ruthenium tetroxide (RuO_4),⁴³⁷ thallium acetate,⁴³⁸ sodium chlorite (NaClO_2) with a metalloporphyrin catalyst,⁴³⁹ OsO_4 ,⁴⁴⁰ and certain peroxybenzoic acids.⁴⁴¹ Alkanes and cycloalkanes have been oxidized at secondary positions, to a mixture of alcohols and trifluoroacetates, by 30% aq H_2O_2 in trifluoroacetic acid.⁴⁴² This reagent does not oxidize the alcohols further and ketones are not found. As in the case of chlorination with *N*-haloamines and sulfuric acid (see Reaction 14-1), the $\omega - 1$ position is the most favored. Another reagent⁴⁴³ that oxidizes secondary positions is iodosylbenzene, catalyzed by Fe(III)–porphyrin catalysts.⁴⁴⁴ Use of an optically active Fe(III)–porphyrin gave modest enantioselective hydroxylation.⁴⁴⁵

When chromic acid is the reagent, the mechanism is probably as follows: a Cr^{6+} species abstracts a hydrogen to give $\text{R}_3\text{C}^\bullet$, which is held in a solvent cage near the resulting Cr^{5+} species. The two species then combine to give $\text{R}_3\text{COCr}^{4+}$, which is hydrolyzed to the alcohol. This mechanism predicts retention of configuration; this is largely observed.⁴⁴⁶ The oxidation by permanganate also involves predominant retention of configuration, and a similar mechanism has been proposed.⁴⁴⁷

Treatment of double-bond compounds with selenium dioxide introduces an OH group into the allylic position (see also, Reaction 19-17).⁴⁴⁸ This reaction also produces conjugated aldehydes in some cases.⁴⁴⁹ Allylic rearrangements are common. There is evidence that the mechanism does not involve free radicals, but includes two pericyclic steps (A and B):⁴⁵⁰



The step marked **A** is similar to the ene reaction (Reaction 15-23). The step marked **B** is a [2,3]-sigmatropic rearrangement (see Reaction 18-35). The reaction can also be

⁴³⁵ Cohen, Z.; Keinan, E.; Mazur, Y.; Varkony, T.H. *J. Org. Chem.* **1975**, *40*, 2141; *Org. Synth.* **VI**, 43; Keinan, E.; Mazur, Y. *Synthesis* **1976**, 523; McKillop, A.; Young, D.W. *Synthesis* **1979**, 401, see pp. 418–419.

⁴³⁶ Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, **1984**, pp. 8–23.

⁴³⁷ Bakke, J.M.; Braenden, J.E. *Acta Chem. Scand.* **1991**, *45*, 418.

⁴³⁸ Lee, J.C.; Park, C.; Choi, Y. *Synth. Commun.* **1997**, *27*, 4079.

⁴³⁹ Collman, J.P.; Tanaka, H.; Hembre, R.T.; Brauman, J.I. *J. Am. Chem. Soc.* **1990**, *112*, 3689.

⁴⁴⁰ Bales, B.C.; Brown, P.; Dehestani, A.; Mayer, J.M. *J. Am. Chem. Soc.* **2005**, *127*, 2832.

⁴⁴¹ Schneider, H.; Müller, W. *J. Org. Chem.* **1985**, *50*, 4609; Tori, M.; Sono, M.; Asakawa, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2669. See also, Querci, C.; Ricci, M. *Tetrahedron Lett.* **1990**, *31*, 1779.

⁴⁴² Deno, N.C.; Jedziniak, E.J.; Messer, L.A.; Meyer, M.D.; Stroud, S.G.; Tomezsko, E.S. *Tetrahedron* **1977**, *33*, 2503.

⁴⁴³ For other procedures, see Sharma, S.N.; Sonawane, H.R.; Dev, S. *Tetrahedron* **1985**, *41*, 2483; Nam, W.; Valentine, J.S. *New J. Chem.* **1989**, *13*, 677.

⁴⁴⁴ See Groves, J.T.; Nemo, T.E. *J. Am. Chem. Soc.* **1983**, *105*, 6243.

⁴⁴⁵ Groves, J.T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628.

⁴⁴⁶ Wiberg, K.B.; Eisenthal, R. *Tetrahedron* **1964**, *20*, 1151.

⁴⁴⁷ Stewart, R.; Spitzer, U.A. *Can. J. Chem.* **1978**, *56*, 1273.

⁴⁴⁸ See Rabjohn, N. *Org. React.* **1976**, *24*, 261; Jerussi, R.A. *Sel. Org. Transform.* **1970**, *1*, 301; Trachtenberg, E. N. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, **1969**, pp. 123–153.

⁴⁴⁹ Singh, J.; Sharma, M.; Kad, G.L.; Chhabra, B.R. *J. Chem. Res. (S)* **1997**, 264.

⁴⁵⁰ Arigoni, D.; Vasella, A.; Sharpless, K.B.; Jensen, H.P. *J. Am. Chem. Soc.* **1973**, *95*, 7917; Woggon, W.; Ruther, F.; Egli, H. *J. Chem. Soc. Chem. Commun.* **1980**, 706. Also see Stephenson, L.M.; Speth, D.R. *J. Org. Chem.* **1979**, *44*, 4683.

accomplished with *tert*-butyl hydroperoxide, if SeO_2 is present in catalytic amounts (the *Sharpless method*).⁴⁵¹ The SeO_2 is the actual reagent; the peroxide reoxidizes the $\text{Se}(\text{OH})_2$.⁴⁵² This method makes work up easier, but gives significant amounts of side products when the double bond is in a ring.⁴⁵³ Alkynes generally give α, α' dihydroxylation.⁴⁵⁴ Allylic hydroxylation⁴⁵⁵ with selenium dioxide often gives aldehydes, but in the presence of acetic anhydride and oxygen, SeO_2 converts alkenes to homoallylic acetates as the major product, $\text{C}=\text{C}-\text{C}-\text{C} \rightarrow \text{C}=\text{C}-\text{C}-\text{C}-\text{OAc}$.⁴⁵⁶

Hydroxylation of unactivated sp^3 hybridized bonds is possible using an oxaziridine-mediated, organocatalyzed reaction.⁴⁵⁷ Ruthenium tetroxide oxidizes alkanes.⁴⁵⁸ Nanocrystalline cobalt oxide is another catalyst for alkane oxidation.⁴⁵⁹ The $\text{H}_2\text{O}_2-\text{NaVO}_3-\text{H}_2\text{SO}_4$ system facilitates alkane oxidation in aqueous acetonitrile.⁴⁶⁰

Benzylic methylene groups are more readily oxidized to benzylic alcohols when compared to simple alkanes. Typical reagents include manganese salen and PhIO^{461} or peroxides.⁴⁶² Oxidation to an acetoxy benzyl derivative was accomplished with $\text{PhI}(\text{OAc})_2$ in acetic acid with a Pd catalyst,⁴⁶³ and with $\text{PhI}(\text{OH})\text{OTs}$ in aq DMSO.⁴⁶⁴ With minimal water, cerium (IV) triflate converts benzylic arenes to benzylic alcohols, although the major product is the ketone when >15% of water is present.⁴⁶⁵

Allylic benzyloxylation occurs when an alkene is treated with *t*-BuOOCOPh and a Cu—Na zeolite,⁴⁶⁶ a Cu catalyst,⁴⁶⁷ or with a chiral Cu catalyst to give modest enantioselectivity.⁴⁶⁸ Allylic methylene groups can be converted to ester ($-\text{CH}-\text{OCOR}$) derivatives in a similar manner using copper triflate.⁴⁶⁹ Cupric acetate has been used,⁴⁷⁰ as well as Cu_2O .⁴⁷¹ A chiral Lewis acid has been used for an enantioselective allylic CH oxidation to an allylic acyl derivative.⁴⁷² α -Acetoxylation of allylic alkenes can proceed with allylic rearrangement.⁴⁷³

⁴⁵¹ Umbreit, M.A.; Sharpless, K.B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. See also Singh, J.; Sabharwal, A.; Sayal, P.K.; Chhabra, B.R. *Chem. Ind. (London)* **1989**, 533.

⁴⁵² See Sabol, M.R.; Wigglesworth, C.; Watt, D.S. *Synth. Commun.* **1988**, *18*, 1.

⁴⁵³ Warpehoski, M.A.; Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* **1982**, *47*, 2897.

⁴⁵⁴ Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* **1979**, *44*, 4202.

⁴⁵⁵ For a review, see Andrus, M.B.; Lashley, J.C. *Tetrahedron* **2002**, *58*, 845.

⁴⁵⁶ Koltun, E.S.; Kass, S.R. *Synthesis* **2000**, 1366.

⁴⁵⁷ Brodsky, B.H.; Du Bois, J. *J. Am. Chem. Soc.* **2005**, *127*, 15391.

⁴⁵⁸ Drees, M.; Strassner, T. *J. Org. Chem.* **2006**, *71*, 1755.

⁴⁵⁹ Davies, T.E.; García, T.; Solsona, B.; Taylor, S.H. *Chem. Commun.* **2006**, 3417.

⁴⁶⁰ Shul'pina, L.S.; Kirillova, M.V.; Pombeiro, A.J.L.; Shul'pin, G.B. *Tetrahedron* **2009**, *65*, 2424.

⁴⁶¹ Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10017.

⁴⁶² Kawasaki, K.; Tsumura, S.; Katsuki, T. *Synlett* **1995**, 1245.

⁴⁶³ Dick, A.R.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.

⁴⁶⁴ Xie, Y.-Y.; Chen, Z.-C. *Synth. Commun.* **2002**, *32*, 1875.

⁴⁶⁵ Laali, K.K.; Herbert, M.; Cushnyr, B.; Bhatt, A.; Terrano, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 578.

⁴⁶⁶ Carloni, S.; Frullanti, B.; Maggi, R.; Mazzacani, A.; Bigi, F.; Sartori, G. *Tetrahedron Lett.* **2000**, *41*, 8947.

⁴⁶⁷ LeBras, J.; Muzart, J. *Tetrahedron Asymmetry* **2003**, *14*, 1911; Fache, F.; Piva, O. *Synlett* **2002**, 2035.

⁴⁶⁸ Lee, W.-S.; Kwong, H.-L.; Chan, H.-L.; Choi, W.-W.; Ng, L.-Y. *Tetrahedron Asymmetry* **2001**, *12*, 1007.

⁴⁶⁹ Sekar, G.; Datta Gupta, A.; Singh, V.K. *J. Org. Chem.* **1998**, *63*, 2961; Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941.

⁴⁷⁰ Södergren, M.J.; Andersson, P.G. *Tetrahedron Lett.* **1996**, *37*, 7577; Rispen, M.T.; Zondervan, C.; Feringa, B.L. *Tetrahedron Asymmetry*, **1995**, *6*, 661.

⁴⁷¹ Levina, A.; Muzart, J. *Tetrahedron Asymmetry*, **1995**, *6*, 147.

⁴⁷² Covell, D.J.; White, M.C. *Angew. Chem. Int. Ed.* **2008**, *47*, 6448.

⁴⁷³ Chen, M.S.; White, M.C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.

Hydroxylation can be accomplished using enzymatic systems. In the presence of *Bacillus megaterium* and oxygen, cyclohexane is converted to cyclohexanol.⁴⁷⁴ Allylic oxidation to an allylic alcohol was accomplished with cultured cells of *Gossypium hirsutum*.⁴⁷⁵ Benzylic arenes are converted to the corresponding α -hydroxy compound by treatment with the enzymes of *B. megaterium*, with modest enantioselectivity.⁴⁷⁶ The reaction of tetradecanoic acid with the α -oxidase from *Pisum sativum*, in the presence of molecular oxygen, gives 2(*R*)-hydroxytetradecanoic acid with high asymmetric induction.⁴⁷⁷

Simple alkanes can be converted to esters with dialkyloxiranes. Cyclic alkanes are oxidized to alcohols with dimethyl dioxirane.⁴⁷⁸ Cyclohexane was converted to cyclohexyl trifluoroacetate with di(trifluoromethyl) dioxirane and trifluoroacetic anhydride⁴⁷⁹ and also with $\text{RuCl}_3/\text{MeCO}_3\text{H}/\text{CF}_3\text{CO}_2\text{H}$.⁴⁸⁰ Dimethyl dioxirane converts alkanes to alcohols in some cases.⁴⁸¹ Adamantane is converted to adamantyl alcohol with DDQ (see Reaction 19-1, category 3) and triflic acid.⁴⁸² The mechanism of oxygen insertion into alkanes has been examined.⁴⁸³

It is possible to perform the conversion $\text{CH}_2 \rightarrow \text{C}=\text{O}$ on an alkane, with no functional groups at all, although the most success has been achieved with substrates in which all CH_2 groups are equivalent (e.g., unsubstituted cycloalkanes). Hydrogen peroxide and trifluoroacetic acid has also been used for oxidation of alkanes.⁴⁸⁴ With this method, cyclohexane was converted with 72% efficiency to give 95% cyclohexanone and 5% cyclohexanol.⁴⁸⁵ The same type of conversion, with lower yields (20–30%), has been achieved with the *Gif* system.⁴⁸⁶ There are several variations. One consists of pyridine–acetic acid, with H_2O_2 as oxidizing agent and tris(picolinato)iron(III) as catalyst.⁴⁸⁷ Other *Gif* systems use O_2 as oxidizing agent and Zn as a reductant.⁴⁸⁸ The selectivity of the *Gif* systems toward alkyl carbons is $\text{CH}_2 > \text{CH} \geq \text{CH}_3$, which is unusual, and shows that a simple free radical mechanism (see Sec. 14.A.iv) is not involved.⁴⁸⁹ Another reagent that can oxidize the CH_2 of an alkane is methyl(trifluoromethyl)dioxirane, but this produces $\text{CH}-\text{OH}$ more often

⁴⁷⁴ Adam, W.; Lukacs, Z.; Saha-Möller, C.R.; Weckerle, B.; Schreier, P. *Eur. J. Org. Chem.* **2000**, 2923.

⁴⁷⁵ Hamada, H.; Tanaka, T.; Furuya, T.; Takahata, H.; Nemoto, H. *Tetrahedron Lett.* **2001**, 42, 909.

⁴⁷⁶ Adam, W.; Lukacs, Z.; Harmsen, D.; Saha-Möller, C.R.; Schreier, P. *J. Org. Chem.* **2000**, 65, 878.

⁴⁷⁷ Adam, W.; Boland, W.; Hartmann-Schreier, J.; Humpf, H.-U.; Lazarus, M.; Saffert, A.; Saha-Möller, C.R.; Schreier, P. *J. Am. Chem. Soc.* **1998**, 120, 11044.

⁴⁷⁸ Curci, R.; D'Accolti, L.; Fusco, C. *Tetrahedron Lett.* **2001**, 42, 7087.

⁴⁷⁹ Asensio, G.; Mello, R.; González-Núñez, M.E.; Castellano, G.; Corral, J. *Angew. Chem. Int. Ed.* **1996**, 35, 217.

⁴⁸⁰ Komiya, N.; Noji, S.; Murahashi, S.-I. *Chem. Commun.* **2001**, 65.

⁴⁸¹ Murray, R.W.; Gu, D. *J. Chem. Soc. Perkin Trans. 2* **1994**, 451.

⁴⁸² Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3230.

⁴⁸³ Freccero, M.; Gandolfi, R.; Sarzi-Amadé, M.; Rastelli, A. *Tetrahedron* **2001**, 57, 9843.

⁴⁸⁴ Camaioni, D.M.; Bays, J.T.; Shaw, W.J.; Linehan, J.C.; Birnbaum, J.C. *J. Org. Chem.* **2001**, 66, 789.

⁴⁸⁵ Sheu, C.; Richert, S.A.; Cofré, P.; Ross Jr., B.; Sobkowiak, A.; Sawyer, D.T.; Kanofsky, J.R. *J. Am. Chem. Soc.* **1990**, 112, 1936. See also, Sheu, C.; Sobkowiak, A.; Jeon, S.; Sawyer, D.T. *J. Am. Chem. Soc.* **1990**, 112, 879; Tung, H.; Sawyer, D.T. *J. Am. Chem. Soc.* **1990**, 112, 8214.

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⁴⁸⁷ About-Jaudet, E.; Barton, D.H.R.; Cshui, E.; Ozbalik, N. *Tetrahedron Lett.* **1990**, 31, 1657. For a review of the mechanism, see Barton, D.H.R. *Chem. Soc. Rev.* **1996**, 25, 237.

⁴⁸⁸ See Barton, D.H.R.; Cshui, E.; Ozbalik, N. *Tetrahedron* **1990**, 46, 3743 and references cited therein.

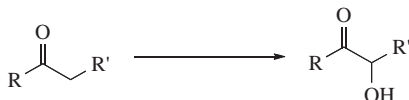
⁴⁸⁹ Barton, D.H.R.; Cshui, E.; Doller, D.; Ozbalik, N.; Senglet, N. *Tetrahedron Lett.* **1990**, 31, 3097. For mechanistic studies, see Barton, D.H.R.; Doller, D.; Geletii, Y.V. *Tetrahedron Lett.* **1991**, 32, 3911 and references cited therein; Knight, C.; Perkins, M.J. *J. Chem. Soc. Chem. Commun.* **1991**, 925. Also see, Minisci, F.; Fontana, F. *Tetrahedron Lett.* **1994**, 35, 1427; Barton, D.H.R.; Hill, D.R. *Tetrahedron Lett.* **1994**, 35, 1431.

than C=O (see Reactions **19-14** and **19-15**).⁴⁹⁰ Cyclic alkanes are oxidized to a mixture of the alcohol and the ketone with $\text{PhI}(\text{OAc})_2$ and a manganese complex in an ionic liquid.⁴⁹¹ Oxidation of cyclic alkanes to cyclic ketones was accomplished using a Ru catalyst.⁴⁹²

OS IV, 23; VI, 43, 946; VII, 263, 277, 282.

19-15 Oxidation of Methylene to OH, O_2CR , or OR

Hydroxy (or alkoxy) - α -dihydro-bisubstitution



Methyl or methylene groups α to a carbonyl can be oxidized to give α -hydroxy ketones, aldehydes, or carboxylic acid derivatives. Ketones can be α hydroxylated in good yields, without conversion to the enolates, by treatment with the hypervalent iodine reagents⁴⁹³ *o*-iodosobenzoic acid.⁴⁹⁴ Dioxygen (O_2) and a chiral phase-transfer catalyst gave enantioselective α hydroxylation of ketones, if the α position was tertiary.⁴⁹⁵ Dimethyl dioxirane is quite effective for hydroxylation of 1,3-dicarbonyl compounds,⁴⁹⁶ and O_2 with a Mn catalyst also gives hydroxylation.⁴⁹⁷ Oxygen with a Ce catalyst α -hydroxylates β -keto esters.⁴⁹⁸ The Pd—C catalyzed α -oxygenation of 1,3-dicarbonyl compounds can be accomplished using O_2 .⁴⁹⁹ An engineered Cytochrome P450 BM-3 is effective for the enantioselective α -hydroxylation of esters of benzylic acids.⁵⁰⁰ The reaction of ketones with $\text{Ti}(\text{O}i\text{Pr})_4$, diethyl tartrate and *tert*-butylhydroperoxide gave the α -hydroxy ketone with good enantioselectivity, albeit in low yield.⁵⁰¹ α -Hydroxylation of ketones was reported using H_2O_2 and 12-tungstophosphoric acid—cetylpyridinium chloride as a catalyst.⁵⁰² Hypervalent iodine(III) sulfonate has been used for the α -hydroxylation of aryl ketones.⁵⁰³

Ketones and carboxylic esters can be α hydroxylated by treatment of their enolate anions (prepared by adding the ketone or ester to LDA) with a Mo peroxide reagent (MoO_5 —pyridine—HMPA; called MoOPH) in THF—hexane at -70°C .⁵⁰⁴ The enolate forms of amides and esters⁵⁰⁵ and the enamine derivatives of ketones⁵⁰⁶ can similarly be

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⁴⁹¹ Li, Z.; Xiu, C.-G.; Xu, C.-Z. *Tetrahedron Lett.* **2003**, 44, 9229.

⁴⁹² Che, C.-M.; Cheng, K.-W.; Chan, M.C.W.; Lau, T.-C.; Mak, C.-K. *J. Org. Chem.* **2000**, 65, 7996.

⁴⁹³ See Moriarty, R.M.; Prakash, O. *Acc. Chem. Res.* **1986**, 19, 244. Also see, Reddy, D.R.; Thornton, E.R. *J. Chem. Soc. Chem. Commun.* **1992**, 172.

⁴⁹⁴ Moriarty, R.M.; Hou, K.; Prakash, O.; Arora, S.K. *Org. Synth.* **VII**, 263.

⁴⁹⁵ Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, 29, 2835.

⁴⁹⁶ Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, 39, 1.

⁴⁹⁷ Christoffers, J. *J. Org. Chem.* **1999**, 64, 7668.

⁴⁹⁸ Christoffers, J.; Werner, T. *Synlett* **2002**, 119.

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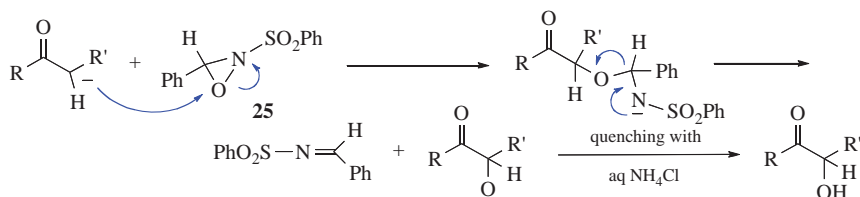
⁵⁰³ Huang, H.-Y.; Hou, R.-S.; Wang, H.-M.; Chen, L.-C. *Org. Prep. Proceed. Int.* **2006**, 38, 473.

⁵⁰⁴ Vedejs, E.; Larsen, S. *Org. Synth.* **VII**, 277; Gamboni, R.; Tamm, C. *Tetrahedron Lett.* **1986**, 27, 3999; *Helv. Chim. Acta* **1986**, 69, 615. See also, Hara, O.; Takizawa, J.-i.; Yamatake, T.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* **1999**, 40, 7787.

⁵⁰⁵ Wasserman, H.H.; Lipshutz, B.H. *Tetrahedron Lett.* **1975**, 1731. For another method, see Pohmakotr, M.; Winotai, C. *Synth. Commun.* **1988**, 18, 2141.

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converted to their α -hydroxy derivatives by reaction with molecular oxygen. The MoO_5 method can also be applied to certain nitriles.⁵⁰⁷



Ketones are converted to α -hydroxy ketones by reaction of the enolate anion with a 2-sulfonyloxaziridine (e.g., **25**).⁵⁰⁸ This is not a free radical process; the mechanism shown is likely. The method is also successful for carboxylic esters⁵⁰⁹ and *N,N*-disubstituted amides,⁵¹⁰ and can be made enantioselective by the use of a chiral oxaziridine.⁵¹¹ Dimethyldioxirane also oxidizes the enolate anions of ketones to α -hydroxy ketones.⁵¹² Titanium enolates are oxidized with *tert*-butyl hydroperoxide⁵¹³ or with dimethyldioxirane⁵¹⁴ and hydrolyzed with aq ammonium fluoride to give the α -hydroxy ketone. Ketones are converted to the α -oxamino derivative ($\text{O}=\text{C}-\text{CH}_2-\rightarrow \text{O}=\text{C}-\text{CHONHPh}$) with excellent enantioselectivity using $\text{PhN}=\text{O}$ and L-proline⁵¹⁵ or (S)-proline.⁵¹⁶ Aldehydes undergo a similar oxidation.⁵¹⁷ α -Lithio sulfones have been hydroxylated with $\text{Me}_3\text{SiOO}t\text{-Bu}$.⁵¹⁸



Dimethyldioxirane

Ketones have been α hydroxylated by conversion to the silyl enol ether, followed by treatment with *m*-chloroperoxybenzoic acid,¹⁶⁶ or with certain other oxidizing agents.⁵¹⁹ α -Hydroxyketones can be accomplished from silyl enol ethers with a catalytic amount of MeReO_3 and H_2O_2 .⁵²⁰ When the silyl enol ethers are treated with iodobenzene in the presence of trimethylsilyl trifluoromethyl sulfonate, the product is the α -keto triflate.⁵²¹

⁵⁰⁷ Rubottom, G.M.; Gruber, J.M.; Juve, Jr., H.D.; Charleson, D.A. *Org. Synth.* **VII**, 282. See also, Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, 30, 3323.

⁵⁰⁸ Davis, F.A.; Vishwakarma, L.C.; Billmers, J.M.; Finn, J. *J. Org. Chem.* **1984**, 49, 3241.

⁵⁰⁹ For formation of α -benzyloxy lactones, see Brodsky, B.H.; DuBois, J. *Org. Lett.* **2004**, 6, 2619.

⁵¹⁰ Davis, F.A.; Vishwakarma, L.C. *Tetrahedron Lett.* **1985**, 26, 3539.

⁵¹¹ Davis, F.A.; Sheppard, A.C.; Chen, B.; Haque, M.S. *J. Am. Chem. Soc.* **1990**, 112, 6679; Davis, F.A.; Weismiller, M.C. *J. Org. Chem.* **1990**, 55, 3715.

⁵¹² Guertin, K.R.; Chan, T.H. *Tetrahedron Lett.* **1991**, 32, 715.

⁵¹³ Schulz, M.; Kluge, R.; Schüßler, M.; Hoffmann, F. *Tetrahedron* **1995**, 51, 3175.

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⁵¹⁶ Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem. Int. Ed.* **2004**, 43, 1109.

⁵¹⁷ Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, 44, 8293.

⁵¹⁸ Chemla, F.; Julia, M.; Uguen, D. *Bull. Soc. Chim. Fr.* **1993**, 130, 547; **1994**, 131, 639.

⁵¹⁹ See Davis, F.A.; Sheppard, A.C. *J. Org. Chem.* **1987**, 52, 954; Takai, T.; Yamada, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* **1991**, 281.

⁵²⁰ Stankovic, S.; Espenson, J.H. *J. Org. Chem.* **1998**, 63, 4129.

⁵²¹ Moriarty, R.M.; Epa, W.R.; Penmasta, R.; Awasthi, A.K. *Tetrahedron Lett.* **1989**, 30, 667.

Silyl ketene ethers are converted to α -hydroxy esters with H_2O_2 and methyl trioxorhenium.⁵²² The α' -position of α,β -unsaturated ketones can be selectively oxidized.⁵²³ *N*-Acyl amines are converted to the α -hydroxy derivative with PhIO and a Mn salen catalyst.⁵²⁴ Note that homoallylic-type oxidation occurs when an α,α -dimethyl oxime ether is treated with $\text{PhI}(\text{OAc})_2$ and a Pd catalyst in acetic acid/acetic anhydride, converting one of the methyl groups to an acetoxymethyl.⁵²⁵

α -Acetoxylation of ketones with concurrent α -arylation occurs when ketones react with $\text{Mn}(\text{OAc})_3$ in benzene.⁵²⁶ α -Acetoxylation of ketones can occur under similar conditions without arylation.⁵²⁷ α -Methyl ketones are converted to the α -acetoxy derivative under the same conditions.⁵²⁸ Iodobenzene with 30% aq H_2O_2 and acetic anhydride generates α -acetoxy ketones.⁵²⁹ Thallium(III) triflate converts acetophenone to α -formyloxy acetophenone.⁵³⁰ Methanesulfonic acid and CuO converts ketones to α -mesyloxy ($-\text{OMs}$) ketones⁵³¹ and $\text{PhI}(\text{OH})\text{OTs}$ converts ketones to α -tosyloxy ($-\text{OTs}$) ketones.⁵³² *N*-Methyl-*O*-tosylhydroxylamine is another reagent that effects direct α -oxytosylation of ketones and aldehydes.⁵³³ α -Acetoxylation of ketones results from *in situ* generation of hypervalent iodine species in the presence of acetic acid.⁵³⁴

OSCV 7, 277; OSCV 7, 263; OSCV 6, 43

19-16 Oxidation of Methylene to Heteroatom Functional Groups Other Than Oxygen or Carbonyl

Amino (or amido) -de-dihydro-bisubstitution



α -Amination or amidation of a CH unit is possible in some cases. Cyclic alkanes are converted to the *N*-alkyl *N*-tosylamine with $\text{PhI}=\text{NTs}$ and a Cu complex.⁵³⁵ Benzylic (CH) as in ethylbenzene, is oxidized with $\text{PhI}(\text{OAc})_2$ in the presence of TsNH_2 and a fluorinated manganese porphyrin to give the corresponding *N*-tosylamine [$\text{PhCHMe}(\text{NHTs})$].⁵³⁶ Alkenes with an allylic CH react with $\text{PhI}=\text{NTs}$ and a Ru catalysts to give an allylic

⁵²² Stankovic, S.; Espenson, J.H. *J. Org. Chem.* **2000**, 65, 5528.

⁵²³ Demir, A.S.; Jeganathan, A. *Synthesis* **1992**, 235.

⁵²⁴ Punniyamurthy, T.; Katsuki, T. *Tetrahedron* **1999**, 55, 9439.

⁵²⁵ Desai, L.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2004**, 126, 9542.

⁵²⁶ Tanyeli, C.; Özdemirhan, D.; Sezen, B. *Tetrahedron* **2002**, 58, 9983.

⁵²⁷ Demir, A.S.; Reis, Ö.; Iğdir, A.C. *Tetrahedron* **2004**, 60, 3427.

⁵²⁸ Tanyeli, C.; Iyigün, C. *Tetrahedron* **2003**, 59, 7135.

⁵²⁹ Sheng, J.; Li, X.; Tang, M.; Gao, B.; Huang, G. *Synthesis* **2007**, 1165.

⁵³⁰ Lee, J.C.; Jin, Y.S.; Choi, J.-H. *Chem. Commun.* **2001**, 956.

⁵³¹ Lee, J.C.; Choi, Y. *Tetrahedron Lett.* **1998**, 39, 3171.

⁵³² Nabana, T.; Togo, H. *J. Org. Chem.* **2002**, 67, 4362. See Yamamoto, Y.; Togo, H. *Synlett* **2006**, 708; Richardson, R.D.; Page, T.K.; Altermann, S.; Paradine, S.M.; French, A.N.; Wirth, T. *Synlett* **2007**, 538; Akiike, J.; Yamamoto, Y.; Togo, H. *Synlett* **2007**, 2168.

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⁵³⁵ Diaz-Requejo, M.M.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* **2003**, 125, 12078.

⁵³⁶ Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, 2, 2233.

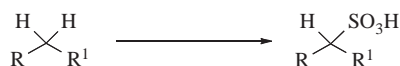
N-tosylamine.⁵³⁷ When an α -keto ester reacts with DEAD and a chiral Cu complex, an α -carbamate is formed, $\text{RCH}(\text{NHCO}_2\text{Et})\text{C}(=\text{O})\text{CO}_2\text{Et}$, with modest enantioselectivity.⁵³⁸

Cyclic amines react with *Pseudomonas oleovorans* GPOL to give hydroxy amines; *N*-benzylpyrrolidine is converted to 3-hydroxy *N*-benzylpyrrolidine.⁵³⁹ *Sphingomonas* sp. HXN-200 gives similar results,⁵⁴⁰ and lactams are converted to the corresponding 3-hydroxy lactam with *sphingomonas* sp. HXN-200.⁵⁴¹ *N*-Benzyl piperidine is converted to the 4-hydroxy derivative under the same conditions.⁵⁴² *N*-Benzyl phthalimide reacts with NBS, NaOAc, and acetic acid to give *N*-(α -acetoxybenzyl)phthalimide.⁵⁴³

Tetrahydrofuran was converted to the hemiacetal 2-hydroxytetrahydrofuran, which was relatively stable under the conditions used, by electrolysis in water.⁵⁴⁴ α -Hydroxy ethers are generated by reaction of SO_2/O_2 and a V catalyst with ethers.⁵⁴⁵

Similar reactions are possible, in some cases, to produce sulfur containing compounds.

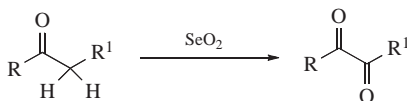
Sulfo-de-dihydro-bisubstitution



Cyclic alkanes are converted to the corresponding alkylsulfonic acid with SO_2/O_2 and a V catalyst.⁵⁴⁶

19-17 Oxidation of Methylene to Carbonyl

Oxo-de-dihydro-bisubstitution



Methyl or methylene groups α to a carbonyl can be oxidized with selenium dioxide to give, respectively, α -keto aldehydes (see Reaction 19-18) and α -diketones.⁵⁴⁷ The reaction can also be carried out α to an aromatic ring or to a double bond, although in the latter case, hydroxylation (see 19-14) is the more common result. Selenium dioxide, (SeO_2) is often used, but the reaction has also been carried out with other oxidizing agents,⁵⁴⁸ including hypervalent iodine compounds.⁵⁴⁹ Sodium nitrite/HCl oxidizes cyclic ketones to the diketone.⁵⁵⁰ Substrates most easily oxidized contain two aryl groups on CH_2 , and these substrates can be oxidized with many oxidizing agents (see Reaction 19-11). The benzylic

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⁵⁴¹ Chang, D.; Witholt, B.; Li, Z. *Org. Lett.* **2000**, *2*, 3949.

⁵⁴² Chang, D.; Feiten, H.-J.; Engesser, K.-H.; van Beilen, J.; Witholt, B.; Li, Z. *Org. Lett.* **2002**, *4*, 1859.

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⁵⁴⁵ Miyafuji, A.; Katsuki, T. *Synlett* **1997**, 836.

⁵⁴⁶ Ishii, Y.; Matsunaka, K.; Sakaguchi, S. *J. Am. Chem. Soc.* **200**, *122*, 7390.

⁵⁴⁷ See Krief, A.; Hevesi, L. *Organoselenium Chemistry I*, Springer, NY, **1988**, pp. 115–180; Krongauz, E.S. *Russ. Chem. Rev.* **1977**, *46*, 59; Rabjohn, N. *Org. React.* **1976**, *24*, 261; Trachtenberg, E.N. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Marcel Dekker, NY, pp. 119–187.

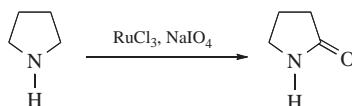
⁵⁴⁸ See Wasserman, H.H.; Ives, J.L. *J. Org. Chem.* **1985**, *50*, 3573.

⁵⁴⁹ Lee, J.C.; Park, H.-J.; Park, J.Y. *Tetrahedron Lett.* **2002**, *43*, 5661.

⁵⁵⁰ Rüedi, G.; Oberli, M.A.; Nagel, M.; Weymuth, C.; Hansen, H.-J. *Synlett* **2004**, 2315.

position of arenes have been oxidized to alkyl aryl ketones with several oxidizing agents, including the Jones reagent,⁵⁵¹ CrO_3 on silica,⁵⁵² PCC,⁵⁵³ DDQ,⁵⁵⁴ KMnO_4 supported on MnO_2 ,⁵⁵⁵ $\text{KMnO}_4/\text{CuSO}_4$ neat⁵⁵⁶ or with ultrasound,⁵⁵⁷ manganese salen/ PhIO ,⁵⁵⁸ *tert*-butylhydroperoxide and a Ru catalyst,⁵⁵⁹ or H_2O_2 with a Cu catalyst.⁵⁶⁰ The combination of O_2 and mcpba oxidizes benzylic arenes to aryl ketones.⁵⁶¹ The combination of HBr and H_2O_2 gives a similar oxidation.⁵⁶² Methyl ketones are oxidized to the α -keto ester in a two-step procedure using a fluorous selenic acid with an iodoxy benzene, followed by treatment with sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$).⁵⁶³

Alkenes of the form $\text{C}=\text{C}-\text{CH}_2$ (an allylic position) have been oxidized to α,β -unsaturated ketones⁵⁶⁴ by sodium dichromate in $\text{HOAc}-\text{Ac}_2\text{O}$, by *t*-BuOOH and Cr compounds,⁵⁶⁵ *t*-BuOOH and a Pd⁵⁶⁶ or Rh⁵⁶⁷ catalyst. Thallium(III) nitrate in aq acetic acid converts allylic alkenes to the corresponding saturated ketone, even in the presence of a primary alcohol elsewhere in the molecule.⁵⁶⁸ The propargylic position of internal alkynes are oxidized to give propargylic ketones with an iron catalyst,⁵⁶⁹ with a dirhodium catalyst in water,⁵⁷⁰ or with O_2/t -BuOOH in the presence of a Cu catalyst.⁵⁷¹ Chloramine-T (see Reaction 15-54), O_2 , and an Fe catalyst give selective oxidation of hydrocarbons to ketones.⁵⁷²



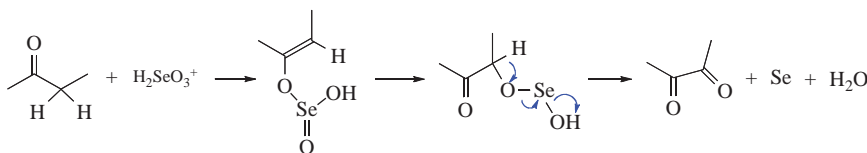
Cyclic amines are oxidized to lactams using a mixture of RuCl_3 and NaIO_4 .⁵⁷³ Lactams are also formed using KMnO_4 with benzyltriethylammonium chloride.⁵⁷⁴ Tertiary amines are converted to amides⁵⁷⁵ and cyclic tertiary amines can be converted to lactams by oxidation with

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⁵⁶³ Crich, D.; Zou, Y. *J. Org. Chem.* **2005**, 70, 3309.
⁵⁶⁴ See Muzart, J. *Bull. Soc. Chim. Fr.* **1986**, 65. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1207–1210.
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⁵⁶⁷ Catino, A.J.; Forslund, R.E.; Doyle, M.P. *J. Am. Chem. Soc.* **2004**, 126, 13622.
⁵⁶⁸ Ferraz, H.M.C.; Longo, Jr., L.S.; Zukerman-Schpector, J. *J. Org. Chem.* **2002**, 67, 3518.
⁵⁶⁹ Pérollier, C.; Sorokin, A.B. *Chem. Commun.* **2002**, 1548.
⁵⁷⁰ McLaughlin, E.C.; Doyle, M.P. *J. Org. Chem.* **2008**, 73, 4317.
⁵⁷¹ Ajjou, A.N.; Ferguson, G. *Tetrahedron Lett.* **2006**, 47, 3719.
⁵⁷² Li, S.-J.; Wan, Y.-G. *Tetrahedron Lett.* **2005**, 46, 8013.
⁵⁷³ Sharma, N.K.; Ganesh, K.N. *Tetrahedron Lett.* **2004**, 45, 1403.
⁵⁷⁴ Markgraf, J.H.; Stickney, C.A. *J. Heterocyclic Chem.* **2000**, 37, 109.
⁵⁷⁵ Markgraf, J.H.; Sangani, P.K.; Finkelstein, M. *Synth. Commun.* **1995**, 27, 1285.

a Hg(II)—EDTA (EDTA = ethylenediaminetetraacetic acid) complex in basic solution.⁵⁷⁶ Lactams, which need not be *N*-substituted, can be converted to cyclic imides by oxidation with a hydroperoxide or peroxyacid and an Mn(II) or Mn(III) salt.⁵⁷⁷ Lactams are oxidized to cyclic imides with oxygen and Co(OAc)₂ in the presence *N*-hydroxysuccinimide.⁵⁷⁸

Ethers in which at least one group is a primary alkyl can be oxidized to the corresponding carboxylic esters in high yields with ruthenium tetroxide.⁵⁷⁹ Molecular oxygen with a binuclear Cu(II) complex⁵⁸⁰ or PdCl₂/CuCl₂/CO⁵⁸¹ also converts ethers to esters. Cyclic ethers are oxidized to lactones.⁵⁸² Cyclic ethers are oxidized to lactones with CrO₃/Me₃SiONO₂.⁵⁸³ Lactones are also formed from cyclic ethers with NaBrO₃—KHSO₄ in water.⁵⁸⁴ The reaction has also been accomplished with CrO₃ in H₂SO₄,⁵⁸⁵ and with benzyltriethylammonium permanganate.⁵⁸⁶

Two mechanisms have been suggested for the reaction with SeO₂. One of these involves a selenate ester of the enol:⁵⁸⁷



In the other proposed mechanism,⁵⁸⁸ the principal intermediate is α,β -ketoseleninic acid ($\text{O}=\text{C}-\text{CH}=\text{SeO}_2\text{H}$) and a selenate ester is not involved.

Oxidation of CH_2 to $\text{C}=\text{O}$ groups is possible even if they are not near any functional groups, indirectly, by the remote oxidation method of Breslow⁵⁷ (see Reaction 19-2). One of the CH_2 groups of *n*-hexadecanol monosuccinate [$\text{CH}_3(\text{CH}_2)_{14}\text{CH}_2\text{OCOCH}_2\text{CH}_2\text{CO}_2\text{H}$] was oxidized to a $\text{C}=\text{O}$ group to give a mixture of it and benzophenone-4-carboxylic acid [*p*-PhCOC₆H₄CO₂H] in CCl₄.⁵⁸⁹ Other remote oxidations⁵⁹⁰ also have been reported. Among these are conversion of aryl ketones [$\text{ArCO}(\text{CH}_2)_3\text{R}$] to 1,4-diketones [$\text{ArCO}(\text{CH}_2)_4\text{COR}$] by photoirradiation in the presence of such oxidizing agents as K₂Cr₂O₇ or KMnO₄,⁵⁹¹ and conversion of alkyl ketones [$\text{RCO}(\text{CH}_2)_3\text{R}'$] to 1,3- and 1,4-diketones with

⁵⁷⁶ Wenkert, E.; Angell, E.C. *Synth. Commun.* **1988**, 18, 1331.

⁵⁷⁷ Doumaux Jr., A.R.; Trecker, D.J. *J. Org. Chem.* **1970**, 35, 2121.

⁵⁷⁸ Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G.F. *J. Org. Chem.* **2002**, 67, 2671.

⁵⁷⁹ Bakke, J.M.; Frøhaug, A. *Acta Chem. Scand. B* **1995**, 49, 615; Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, **1973**, pp. 222–225; Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* **1981**, 46, 3936.

⁵⁸⁰ Minakata, S.; Imai, E.; Ohshima, Y.; Inaki, K.; Ryu, I.; Komatsu, M.; Ohshiro, Y. *Chem. Lett.* **1996**, 19.

⁵⁸¹ Miyamoto, M.; Minami, Y.; Ukaji, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1994**, 1149.

⁵⁸² See Ferraz, H.M.C.; Longo, Jr., L.S. *Org. Lett.* **2003**, 5, 1337.

⁵⁸³ Shahi, S.P.; Gupta, A.; Pitre, S.V.; Reddy, M.V.R.; Kumareswaran, R.; Vankar, Y.D. *J. Org. Chem.* **1999**, 64, 4509.

⁵⁸⁴ Metsger, L.; Bittner, S. *Tetrahedron* **2000**, 56, 1905.

⁵⁸⁵ Harrison, I.T.; Harrison, S. *Chem. Commun.* **1966**, 752.

⁵⁸⁶ Schmidt, H.; Schäfer, H.J. *Angew. Chem. Int. Ed.* **1979**, 18, 69.

⁵⁸⁷ Corey, E.J.; Schaefer, J.P. *J. Am. Chem. Soc.* **1960**, 82, 918.

⁵⁸⁸ Sharpless, K.B.; Gordon, K.M. *J. Am. Chem. Soc.* **1976**, 98, 300.

⁵⁸⁹ Breslow, R.; Scholl, P.C. *J. Am. Chem. Soc.* **1971**, 93, 2331. See also, Breslow, R.; Heyer, D. *Tetrahedron Lett.* **1983**, 24, 5039.

⁵⁹⁰ See also, Beckwith, A.L.J.; Duong, T. *J. Chem. Soc. Chem. Commun.* **1978**, 413.

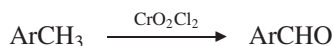
⁵⁹¹ Mitani, M.; Tamada, M.; Uehara, S.; Koyama, K. *Tetrahedron Lett.* **1984**, 25, 2805. For an alternative photochemical procedure, see Negele, S.; Wieser, K.; Severin, T. *J. Org. Chem.* **1998**, 63, 1138.

$\text{Na}_2\text{S}_2\text{O}_8$ and FeSO_4 .⁵⁹² 2-Octanol was oxidized to give 2-propyl-5-methyl γ -butyrolactone with lead tetraacetate in a CO atmosphere.⁵⁹³

OS I, 266; II, 509; III, 1, 420, 438; IV, 189, 229, 579; VI, 48; IX, 396. Also see, OS IV, 23.

19-18 Oxidation of Arylmethanes to Aldehydes

Oxo-de-dihydro-bisubstitution



Methyl groups on an aromatic ring can be oxidized to an aldehyde by several oxidizing agents. The reaction is a special case of **19-17**. When the reagent is chromyl chloride (CrO_2Cl_2), the reaction is called the *Étard reaction*⁵⁹⁴ and the yields are high.⁵⁹⁵ Another oxidizing agent is a mixture of CrO_3 and Ac_2O , where the reaction stops at the aldehyde stage because the initial product is $\text{ArCH}(\text{OAc})_2$ (an acylal), which is resistant to further oxidation. Hydrolysis of the acylal gives the aldehyde.

Among other oxidizing agents⁵⁹⁶ that have been used to accomplish the conversion of ArCH_3 to ArCHO are ceric ammonium nitrate,⁵⁹⁷ PCC,⁵⁹⁸ hypervalent iodoso compounds (see Reaction **19-3**),⁵⁹⁹ Bi-*t*-BuOOH,⁶⁰⁰ and urea- H_2O_2 with microwave irradiation.⁶⁰¹ Oxidative of benzylic positions to the corresponding carbonyl has been reported using two heterogeneous catalysts.⁶⁰² Oxidation of ArCH_3 to carboxylic acids is considered at Reaction **19-11**.

Conversion of ArCH_3 to ArCHO can also be achieved indirectly by bromination to give ArCHBr_2 (**14-1**), followed by hydrolysis (Reaction **10-2**).

The mechanism of the *Étard reaction* is not completely known.⁶⁰³ An insoluble complex is formed on addition of the reagents, which is hydrolyzed to the aldehyde. The complex is probably a kind of acylal, but the identity of the structure is not fully settled, although many proposals have been made as to its structure and as to how it is hydrolyzed. It is known that ArCH_2Cl is not an intermediate (see Reaction **19-20**), since it reacts only very slowly with chromyl chloride. Magnetic susceptibility measurements⁶⁰⁴ indicate that the complex from toluene is **26**, a structure first proposed by Étard. According to this proposal, the reaction

⁵⁹² Nikishin, G.I.; Troyansky, E.I.; Lazareva, M.I. *Tetrahedron Lett.* **1984**, 25, 4987.

⁵⁹³ Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, 120, 8692. Also see, Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1994**, 116, 5473.

⁵⁹⁴ The name *Étard reaction* is often applied to any oxidation with chromyl chloride, for example, oxidation of glycols (**19-7**), alkenes (**19-10**), and so on.

⁵⁹⁵ See Hartford, W.H.; Darrin, M. *Chem. Rev.* **1958**, 58, 1, see pp. 25–53.

⁵⁹⁶ See Steckhan, E. *Top. Curr. Chem.* **1987**, 142, 1; pp. 12–17.

⁵⁹⁷ Trahanovsky, W.S.; Young, L.B. *J. Org. Chem.* **1966**, 31, 2033; Syper, L. *Tetrahedron Lett.* **1967**, 4193. See Ganin, E.; Amer, I. *Synth. Commun.* **1995**, 25, 3149.

⁵⁹⁸ Hosseinzadeh, R.; Tajbakhsh, M.; Vahedi, H. *Synlett* **2005**, 2769.

⁵⁹⁹ Nicolaou, K.C.; Baran, P.S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, 123, 3183.

⁶⁰⁰ Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D.A.; Oldham, J.; Burton, A.J.; Barrett, A.G.M. *Org. Lett.* **2005**, 7, 4549.

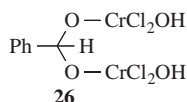
⁶⁰¹ Paul, S.; Nanda, P.; Gupta, R. *Synlett* **2004**, 531.

⁶⁰² Rajabi, F.; Clark, J.H.; Karimi, B.; Macquarrie, D.J. *Org. Biomol. Chem.* **2005**, 3, 725.

⁶⁰³ For a review, see Nenitzescu, C.D. *Bull. Soc. Chim. Fr.* **1968**, 1349.

⁶⁰⁴ Wheeler, O.H. *Can. J. Chem.* **1960**, 38, 2137. See also, Makhija, R.C.; Stairs, R.A. *Can. J. Chem.* **1968**, 46, 1255.

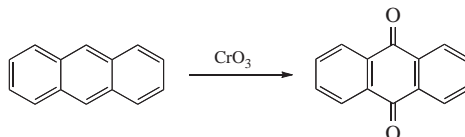
stops after only two hydrogen atoms have been replaced because of the insolubility of **26**. There is a disagreement on how **26** is formed, assuming that the complex has this structure. Both an ionic⁶⁰⁵ and a free radical⁶⁰⁶ process have been proposed. An entirely different structure for the complex was proposed by Nenitzescu et al.⁶⁰⁷ On the basis of ESR studies, they proposed that the complex is $\text{PhCH}_2\text{OCrCl}_2\text{OCrCl}_2\text{OH}$, which is isomeric with **26**. However, this view has been challenged by Wiberg and Eisenthal,⁶⁰⁶ who interpret the ESR result as being in accord with **26**. Still another proposal is that the complex is composed of benzaldehyde coordinated with reduced chromyl chloride.⁶⁰⁸



OS II, 441; III, 641; IV, 31, 713.

19-19 Oxidation of Aromatic Hydrocarbons to Quinones

Arene-quinone transformation



Condensed aromatic systems (including naphthalenes) can be directly oxidized to quinones by various oxidizing agents.⁶⁰⁹ Yields are generally not high, although good yields have been reported with ceric ammonium sulfate.⁶¹⁰ Benzene cannot be so oxidized by strong oxidizing agents, but can be electrolytically oxidized to benzoquinone.⁶¹¹ Naphthalene derivatives, however, are oxidized to naphthoquinones with H_5IO_6 and CrO_3 .⁶¹² 1,4-Dimethoxy aromatic compounds are oxidized to *p*-quinones with an excess of CoF_3 in water–dioxane.⁶¹³

OS IV, 698, 757. Also see, OS II, 554.

⁶⁰⁵ Stairs, R.A. *Can. J. Chem.* **1964**, 42, 550.

⁶⁰⁶ Wiberg, K.B.; Eisenthal, R. *Tetrahedron* **1964**, 20, 1151. See also, Gragerov, I.P.; Ponomarchuk, M.P. *J. Org. Chem. USSR* **1969**, 6, 1125.

⁶⁰⁷ Necsoiu, I.; Przemetchi, V.; Ghenculescu, A.; Rentea, C.N.; Nenitzescu, C.D. *Tetrahedron* **1966**, 22, 3037.

⁶⁰⁸ Duffin, H.C.; Tucker, R.B. *Chem. Ind. (London)* **1966**, 1262; *Tetrahedron* **1968**, 24, 6999.

⁶⁰⁹ Naruta, Y.; Maruyama, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, **1988**, pp. 242–247; Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, pp. 94–96; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, **1985**, pp. 182–185, 358–360; Thomson, R.H. in Patai, S. *The Chemistry of the Quinoid Compounds*, Vol. 1, pt. 1, Wiley, NY, **1974**, pp. 132–134.

⁶¹⁰ Periasamy, M.; Bhatt, M.V. *Synthesis* **1977**, 330; Balanikas, G.; Hussain, N.; Amin, S.; Hecht, S.S. *J. Org. Chem.* **1988**, 53, 1007.

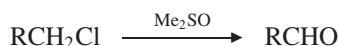
⁶¹¹ See Ito, S.; Katayama, R.; Kunai, A.; Sasaki, K. *Tetrahedron Lett.* **1989**, 30, 205.

⁶¹² Yamazaki, S. *Tetrahedron Lett.* **2001**, 42, 3355.

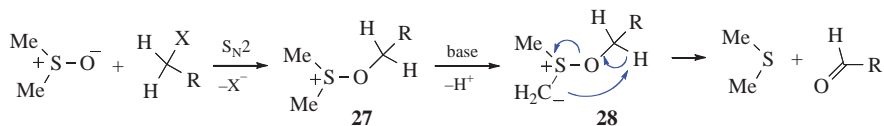
⁶¹³ Tomatsu, A.; Takemura, S.; Hashimoto, K.; Nakata, M. *Synlett* **1999**, 1474.

19-20 Oxidation of Primary Halides and Esters of Primary Alcohols to Aldehydes⁶¹⁴

Oxo-de-hydro,halo-bisubstitution



Primary alkyl halides (chlorides, bromides, and iodides) can be oxidized to aldehydes easily and in good yields with DMSO,⁶¹⁵ in what has been called the *Kornblum reaction*. In Kornblum's original work, the reaction of α -halo ketones with DMSO at elevated temperatures gave good yields of the corresponding glyoxal (an α -keto-aldehyde).⁶¹⁶ If the glyoxal could be removed from the reaction medium by distillation as it was formed, the reaction was very efficient. In many cases, it was difficult to isolate high-boiling glyoxals from DMSO. Primary and secondary⁶¹⁷ alkyl iodides or tosylates⁶¹⁸ can be converted to aldehydes or ketones, although they are much less reactive than α -halo ketones. Primary chlorides with DMSO, NaBr, and ZnO give the corresponding aldehyde when heated to 140 °C.⁶¹⁹ Benzylic halides are oxidized to aryl aldehydes with MnO_2 ⁶²⁰ or with $\text{NaIO}_4\text{—LiBr}$.⁶²¹ Hydrogen peroxide in ethanol oxidizes organic halides to carbonyl compounds.⁶²² Pyridine *N*-oxide in the presence of silver oxide oxidizes benzylic and allylic halides.⁶²³



The mechanism of these DMSO oxidations is probably that shown with **27** and **28**,⁶²⁴ although in some cases the base abstracts a proton directly from the carbon being oxidized, in which case the ylide (**28**) is not an intermediate. Alkoxysulfonium salts (**27**) have been isolated.⁶²⁵ This mechanism predicts that secondary compounds should be oxidizable to ketones, and this is the case. In a related procedure for the oxidation of alcohols, the

⁶¹⁴ For reviews, see Tidwell, T.T. *Org. React.* **1990**, 39, 297; *Synthesis* **1990**, 857; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, **1988**, pp. 171–181, 402–406; Durst, T. *Adv. Org. Chem.* **1969**, 6, 285, pp. 343–356; Epstein, W.W.; Sweat, F.W. *Chem. Rev.* **1967**, 67, 247; Moffatt, J.G. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, **1971**, pp. 1–64. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1222–1225.

⁶¹⁵ Nace, H.R.; Monagle, J.J. *J. Org. Chem.* **1959**, 24, 1792; Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* **1959**, 81, 4113. Also see Villemin, D.; Hammadi, M. *Synth. Commun.* **1995**, 25, 3141.

⁶¹⁶ Kornblum, N.; Powers, J.W.; Anderson, G.J.; Jones, W.J.; Larson, H.O.; Levand, O.; Weaver, W.M. *J. Am. Chem. Soc.* **1957**, 79, 6562. Mg—Al hydrotalcites have been used as heterogeneous basic catalysts: see Kshirsagar, S.W.; Patil, N.R.; Samant, S.D. *Tetrahedron Lett.* **2008**, 49, 1160.

⁶¹⁷ Baizer, M.M. *J. Org. Chem.*, **1960**, 25, 670.

⁶¹⁸ Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* **1959**, 81, 4113.

⁶¹⁹ Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* **2001**, 31, 667; Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* **2001**, 31, 3395.

⁶²⁰ Goswami, S.; Jana, S.; Adak, A.K. *Chem. Lett.* **2005**, 34, 194.

⁶²¹ Ali Shaikh, T.M.; Emmanuvel, L.; Sudalai, A. *Synth. Commun.* **2007**, 37, 2641.

⁶²² Tang, J.; Zhu, J.; Shen, Z.; Zhang, Y. *Tetrahedron Lett.* **2007**, 48, 1919.

⁶²³ Chen, D.X.; Ho, C.M.; Wu, Q.Y.R.; Wu, P.R.; Wong, F.M.; Wu, W. *Tetrahedron Lett.* **2008**, 49, 4147.

⁶²⁴ See Johnson, C.R.; Phillips, W.G. *J. Org. Chem.* **1967**, 32, 1926; Torrsell, K. *Acta Chem. Scand.* **1967**, 21, 1.

⁶²⁵ Khuddus, M.A.; Swern, D. *J. Am. Chem. Soc.* **1973**, 95, 8393.

intermediate **27**⁶²⁶ is formed without the use of DMSO by treating the substrate with a complex generated from chlorine or NCS and DMS.⁶²⁷ Also see the *Swern oxidation* in Reaction **19-3**.

Another way to oxidize primary alkyl halides to aldehydes is by the use of hexamethylenetetramine followed by water. However, this reaction, called the *Sommelet reaction*,⁶²⁸ is limited to benzylic halides. The reaction is seldom useful when the R in RCH₂Cl is alkyl. The first part of the reaction is conversion to the amine (ArCH₂NH₂), which can be isolated. Reaction of the amine with excess hexamethylenetetramine gives the aldehyde. It is this last step that is the actual *Sommelet reaction*, although the entire process can be conducted without isolation of intermediates. Once the amine is formed, it is converted to an imine (ArCH₂N=CH₂) with formaldehyde liberated from the reagent. The key step then follows: transfer of hydrogen from another mole of the arylamine to the imine. This last imine is then hydrolyzed by water to the aldehyde. Alternatively, the benzylamine may transfer hydrogen directly to hexamethylenetetramine.

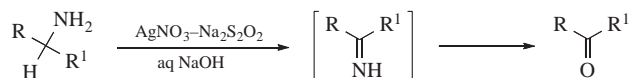
Pyridine followed by *p*-nitrosodimethylaniline and then water converts benzylic halides to aldehydes, and is called the *Kröhnke reaction*. Primary halides and tosylates have been oxidized to aldehydes by trimethylamine *N*-oxide,⁶²⁹ and by pyridine *N*-oxide with microwave irradiation.⁶³⁰

Epoxides⁶³¹ have been used to give α-hydroxy ketones or aldehydes.⁶³²

OS **II**, 336; **III**, 811; **IV**, 690, 918, 932; **V**, 242, 668, 825, 852, 872. Also see, OS **V**, 689; **VI**, 218.

19-21 Oxidation of Amines or Nitro Compounds to Aldehydes, Ketones, or Dihalides

Oxo-de-hydro-amino-bisubstitution (overall transformation)



Primary aliphatic amines can be oxidized to aldehydes or ketones, using silver compounds as shown.⁶³³ Other reagents have been used,⁶³⁴ including *N*-bromoacetamide⁶³⁵ (for benzylic amines), or aq NaOCl with phase-transfer catalysts.⁶³⁶ Several indirect methods for achieving the conversion RR'CHNH₂ → RR'C=O (R' = alkyl, aryl, or H) have been reported.⁶³⁷

⁶²⁶ For an alternative, see Moffatt, J.G. *J. Org. Chem.* **1971**, 36, 1909 and references cited therein.

⁶²⁷ See Katayama, S.; Fukuda, K.; Watanabe, T.; Yamauchi, M. *Synthesis* **1988**, 178.

⁶²⁸ See Angyal, S.J. *Org. React.* **1954**, 8, 197.

⁶²⁹ Franzen, V.; Otto, S. *Chem. Ber.* **1961**, 94, 1360. For the use of other amine oxides, see Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.* **1986**, 59, 3287.

⁶³⁰ Barbry, D.; Champagne, P. *Tetrahedron Lett.* **1996**, 37, 7725.

⁶³¹ See Olah, G.A.; Vankar, Y.D.; Arvanaghi, M. *Tetrahedron Lett.* **1979**, 3653.

⁶³² Santosusso, T.M.; Swern, D. *J. Org. Chem.* **1975**, 40, 2764.

⁶³³ See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, **1988**, pp. 200–220, 411–415.

⁶³⁴ For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1225–1227; Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, p. 240.

⁶³⁵ Banerji, K.K. *Bull. Chem. Soc. Jpn.* **1988**, 61, 3717.

⁶³⁶ Lee, G.A.; Freedman, H.H. *Tetrahedron Lett.* **1976**, 1641.

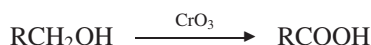
⁶³⁷ See Babler, J.H.; Invergo, B.J. *J. Org. Chem.* **1981**, 46, 1937.

Primary, secondary, and tertiary aliphatic amines have been cleaved to give aldehydes, ketones, or carboxylic acids with aq bromine⁶³⁸ and with neutral permanganate.⁶³⁹ The other product of this reaction is the amine with one less alkyl group. Reaction of a primary amine with benzoyl peroxide/CsCO₃ and subsequent heating of the hydroxylamine product gives the ketone.⁶⁴⁰ In a different type of procedure, primary alkyl primary amines can be converted to *gem*-dihalides [RCH₂NH₂ → RCHX₂ (X = Br or Cl)] by treatment with an alkyl nitrite and the anhydrous copper(I) halide.⁶⁴¹

Primary and secondary aliphatic nitro compounds have been oxidized to aldehydes and ketones, respectively (RR'CHNO₂ → RR'C=O), with sodium chlorite under phase-transfer conditions,⁶⁴² tetrapropylammonium perruthenate (TPAP),⁶⁴³ as well as with other reagents.⁶⁴⁴

19-22 Oxidation of Primary Alcohols to Carboxylic Acids or Carboxylic Esters

Oxo-de-dihydro-bisubstitution



Primary alcohols can be oxidized to carboxylic acids by many strong oxidizing agents including chromic acid, permanganate,⁶⁴⁵ nitric acid,⁶⁴⁶ or H₅IO₆/CrO₃.⁶⁴⁷ The reaction can be looked on as a combination of **19-3** and **19-23**. Aliphatic primary alcohols are converted to the carboxylic acid with 30% aq H₂O₂, tetrabutylammonium hydrogen sulfate and a W catalyst with microwave irradiation.⁶⁴⁸ Benzylic alcohols are oxidized to benzoic acid derivatives by treatment first with TEMPO⁶⁴⁹ (Sec. 5.C.i), and then NaClO₂.⁶⁵⁰ Oxidation with 5% aq NaOCl and a Ni catalyst oxidizes primary alcohols to the corresponding acid.⁶⁵¹ Similar oxidation to the acid occurred with NaIO₄/RuCl₃ in aq acetonitrile,⁶⁵² or 30% aq H₂O₂ and a Co salen catalyst.⁶⁵³ Oxammonium salts and NaClO₂ oxidize alcohols to carboxylic acids.⁶⁵⁴

⁶³⁸ Deno, N.C.; Fruit Jr., R.E. *J. Am. Chem. Soc.* **1968**, *90*, 3502.

⁶³⁹ Rawalay, S.S.; Shechter, H. *J. Org. Chem.* **1967**, *32*, 3129. For another procedure, see Monkovic, I.; Wong, H.; Bachand, C. *Synthesis* **1985**, 770.

⁶⁴⁰ Knowles, D.A.; Mathews, C.J.; Tomkinson, N.C.O. *Synlett* **2008**, 2769.

⁶⁴¹ Doyle, M.P.; Siegfried, B. *J. Chem. Soc. Chem. Commun.* **1976**, 433.

⁶⁴² Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1989**, *30*, 5329.

⁶⁴³ Tokunaga, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1997**, 207.

⁶⁴⁴ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1227–1228.

⁶⁴⁵ See Rankin, K.N.; Liu, Q.; Hendry, J.; Yee, H.; Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* **1998**, *39*, 1095.

⁶⁴⁶ See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, pp. 127–132; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, **1988**, 148–165, 391–401. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1646–1650.

⁶⁴⁷ Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschäen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Lett.* **1998**, *39*, 5323.

⁶⁴⁸ Bogdal, D.; Lukaszewicz, M. *Synlett* **2000**, 143.

⁶⁴⁹ See DeLuca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999.

⁶⁵⁰ Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschäen, D.M.; Grabowski, E.J.J.; Reider, P.J. *J. Org. Chem.* **1999**, *64*, 2564.

⁶⁵¹ Grill, J.M.; Ogle, J.W.; Miller, S.A. *J. Org. Chem.* **2006**, *71*, 9291.

⁶⁵² Prashad, M.; Lu, Y.; Kim, H.-Y.; Hu, B.; Repic, O.; Blacklock, T.J. *Synth. Commun.* **1999**, *29*, 2937.

⁶⁵³ Das, S.; Punniyamurthy, T. *Tetrahedron Lett.* **2003**, *44*, 6033.

⁶⁵⁴ Shibuya, M.; Sato, T.; Tomizawa, M.; Iwabuchi, Y. *Chem. Commun.* **2009**, 1739.

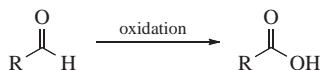
When acidic conditions are used, a considerable amount of carboxylic ester (RCOOCH_2R) is often isolated, although this is probably not formed by a combination of the acid with unreacted alcohol, but by a combination of intermediate aldehyde with unreacted alcohol to give an acetal or hemiacetal, which is oxidized to the ester.⁶⁵⁵ A mixture of Oxone and NaCl converts alcohols to symmetrical esters.⁶⁵⁶ Aliphatic alcohols are converted to a symmetrical ester ($\text{RCH}_2\text{OH} \rightarrow \text{RCOOCH}_2\text{R}$) by oxidation with PCC on aluminum without solvent.⁶⁵⁷ Hydrogen with a Ru—CO complex converts primary alcohols (ROH) to an ester (RCO_2R).⁶⁵⁸ Iodine has been used to convert alcohols to esters.⁶⁵⁹ Hydrogen transfer with a Ru catalyst has been used to convert primary alcohols to methyl esters.⁶⁶⁰ Oxone in aq methanol also converts aryl aldehydes to the corresponding ester.⁶⁶¹ Allylic alcohols are converted to conjugated esters with MnO_2 and NaCN in methanol–acetic acid.⁶⁶² Primary alcohols are oxidized to the methyl ester with trichloroisocyanuric acid in methanol.⁶⁶³ This reagent also converts diols to lactones. Lactones can be prepared by oxidizing diols in which at least one OH is primary,⁶⁶⁴ and addition of a chiral additive (e.g., sparteine) leads to lactones with high asymmetric induction.⁶⁶⁵

Primary alcohols (RCH_2OH) can be directly oxidized to acyl fluorides (RCOF) with cesium fluoroxysulfate.⁶⁶⁶ 2-(3-Hydroxypropyl)aniline was oxidized to an acyl derivative that cyclized to give a lactam when heated with a Rh catalyst.⁶⁶⁷

OS I, 138, 168; IV, 499, 677; V, 580; VII, 406; IX, 462; **81**, 195. Also see, OS III, 745.

19-23 Oxidation of Aldehydes to Carboxylic Acids, Carboxylic Esters, and Related Compounds

Hydroxylation or Hydroxy-de-hydrogenation



Oxidation of aldehydes to carboxylic acids is quite common⁶⁶⁸ and has been carried out with many oxidizing agents, including permanganate in acid, basic, or neutral solution,⁶⁶⁹

⁶⁵⁵ Craig, J.C.; Horning, E.C. *J. Org. Chem.* **1960**, 25, 2098. See also, Nwaukwa, S.O.; Keehn, P.M. *Tetrahedron Lett.* **1982**, 23, 35.

⁶⁵⁶ Schulze, A.; Pagona, G.; Giannis, A. *Synth. Commun.* **2006**, 36, 1147.

⁶⁵⁷ Bhar, S.; Chaudhuri, S.K. *Tetrahedron* **2003**, 59, 3493.

⁶⁵⁸ Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, 127, 10840.

⁶⁵⁹ Mori, N.; Togo, H. *Tetrahedron* **2005**, 61, 5915.

⁶⁶⁰ Owston, N.A.; Parker, A.J.; Williams, J.M.J. *Chem. Commun.* **2008**, 624.

⁶⁶¹ Koo, B.-S.; Kim, E.-H.; Lee, K.-J. *Synth. Commun.* **2002**, 32, 2275.

⁶⁶² Foot, J.S.; Kanno, H.; Giblin, G.M.P.; Taylor, R.J.K. *Synlett* **2002**, 1293.

⁶⁶³ Hiegel, G.A.; Gilley, C.B. *Synth. Commun.* **2003**, 33, 2003.

⁶⁶⁴ See Ito, M.; Osaku, A.; Shiihashi, A.; Ikariya, T. *Org. Lett.* **2007**, 9, 1821. For a list of reagents used to effect this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1650–1652.

⁶⁶⁵ Yanagisawa, Y.; Kashiwagi, Y.; Kurashima, F.; Anzai, J.; Osa, T.; Bobbitt, J.M. *Chem. Lett.* **1996**, 1043.

⁶⁶⁶ Stavber, S.; Planinsek, Z.; Zupan, M. *Tetrahedron Lett.* **1989**, 30, 6095.

⁶⁶⁷ Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, 6, 2785.

⁶⁶⁸ See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1988**, pp. 241–263, 423–428; Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, **1971**, pp. 63–70; Lee, D.G. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, **1969**, pp. 81–86.

⁶⁶⁹ See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, pp. 174–180; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1653–1661; Srivastava, R.G.; Venkataramani, P.S. *Synth. Commun.* **1988**, 18, 2193. See also, Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1988**.

chromic acid,⁶⁷⁰ bromine, and Oxone.⁶⁷¹ Silver oxide is a fairly specific oxidizing agent for aldehydes and does not readily attack other groups. *Benedict's* and *Fehling's solutions* oxidize aldehydes,⁶⁷² and there is a test for aldehydes that depends on this reaction, but the method is seldom used for preparative purposes and gives very poor results with aromatic aldehydes. α,β -Unsaturated aldehydes can be oxidized by sodium chlorite without disturbing the double bond.⁶⁷³ Aldehydes are also oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peroxy acid (RCO_3H),⁶⁷⁴ which with another molecule of aldehyde disproportionates to give two molecules of acid (see Reaction 14-7).⁶⁷⁵ The air oxidation of aldehydes to carboxylic acids is mediated by a mixture of Pd/C — NaBH_4 and KOH .⁶⁷⁶ An aldehyde can be converted to the carboxylic acid by treatment with 30% H_2O_2 and methyl(trioctyl) ammonium hydrogen sulfate at 90 °C.⁶⁷⁷ Aryl aldehydes are similarly oxidized by a mixture of H_2O_2 and selenium dioxide (SeO_2).⁶⁷⁸ Polymer-bound hypervalent iodine + TEMPO oxidizes aldehydes to acids.⁶⁷⁹ Hydrogen peroxide oxidizes aldehydes to carboxylic acids in the presence of a AgNO_3 catalyst⁶⁸⁰ or a Pd catalyst.⁶⁸¹

Aryl aldehydes are converted to the corresponding aryl carboxylic ester with H_2O_2 and a V_2O_5 catalyst⁶⁸² or a titanosilicate⁶⁸³ in an alcohol solvent. Esterification of aldehydes with alcohols uses an Ir catalyst.⁶⁸⁴ The reaction of aldehydes with aq alcohols, in the presence of iodine and NaNO_2 , gives an ester.⁶⁸⁵ Organoboronic acids and molecular oxygen convert aldehydes to an ester using a Pd catalyst.⁶⁸⁶ *N*-heterocyclic carbenes catalyze oxidation of aldehydes to the corresponding ester.⁶⁸⁷ Aldehydes (RCHO) can be directly converted to carboxylic esters (RCOOR') by treatment with Br_2 in the presence of an alcohol.⁶⁸⁸

⁶⁷⁰ See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, **1984**, pp. 217–225.

⁶⁷¹ See Travis, B.R.; Sivakumar, M.; Hollist, G.O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.

⁶⁷² See Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, **1973**, pp. 31–34.

⁶⁷³ Dalcanele, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567. See also, Bayle, J.P.; Perez, F.; Courtieu, J. *Bull. Soc. Chim. Fr.* **1990**, 565.

⁶⁷⁴ See Swern, D. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, **1970**, pp. 313–516.

⁶⁷⁵ For reviews of the autoxidation of aldehydes, see Vardanyan, I.A.; Nalbandyan, A.B. *Russ. Chem. Rev.* **1985**, *54*, 532 (gas phase); Sajus, L.; Séré de Roch, I. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, **1980**, pp. 89–124 (liquid phase); Maslov, S.A.; Blyumberg, E.A. *Russ. Chem. Rev.* **1976**, *45*, 155 (liquid phase). See Niclaude, M.; Lemaire, J.; Letort, M. *Adv. Photochem.* **1966**, *4*, 25. See Larkin, D.R. *J. Org. Chem.* **1990**, *55*, 1563.

⁶⁷⁶ Lim, M.; Yoon, C.M.; An, G.; Rhee, H. *Tetrahedron Lett.* **2007**, *48*, 3835.

⁶⁷⁷ Sato, K.; Hyodo, M.; Takagi, J.; Aoki, M.; Noyori, R. *Tetrahedron Lett.* **2000**, *41*, 1439.

⁶⁷⁸ Wójtowicz, H.; Brzasczcz, M.; Kloc, K.; Młochowski, J. *Tetrahedron* **2001**, *57*, 9743.

⁶⁷⁹ Tashino, Y.; Togo, H. *Synlett* **2004**, 2010.

⁶⁸⁰ Chakraborty, D.; Gowda, R.R.; Malik, P. *Tetrahedron Lett.* **2009**, *50*, 6553.

⁶⁸¹ Kon, Y.; Imao, D.; Nakashima, T.; Sato, K. *Chem. Lett.* **2009**, *38*, 430.

⁶⁸² Gopinath, R.; Patel, B.K. *Org. Lett.* **2000**, *2*, 577.

⁶⁸³ Chavan, S.P.; Dantale, S.W.; Govande, C.A.; Venkatraman, M.S.; Praveen, C. *Synlett* **2002**, 267.

⁶⁸⁴ Kiyooka, S.-i.; Wada, Y.; Ueno, M.; Yokoyama, T.; Yokoyama, R. *Tetrahedron* **2007**, *63*, 12695.

⁶⁸⁵ Kiran, Y.B.; Ikeda, R.; Sakai, N.; Konakahara, T. *Synthesis* **2010**, 276.

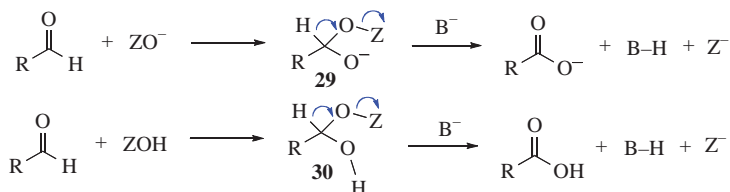
⁶⁸⁶ Qin, C.; Wu, H.; Chen, J.; Liu, M.; Cheng, J.; Su, W.; Ding, J. *Org. Lett.* **2008**, *10*, 1537.

⁶⁸⁷ Maki, B.E.; Scheidt, K.A. *Org. Lett.* **2008**, *10*, 4331. Using boronic acids: see Rosa, J.N.; Reddy, R.S.; Candeias, N.R.; Cal, P.M.S.D.; Gois, P.M.P. *Org. Lett.* **2010**, *12*, 2686.

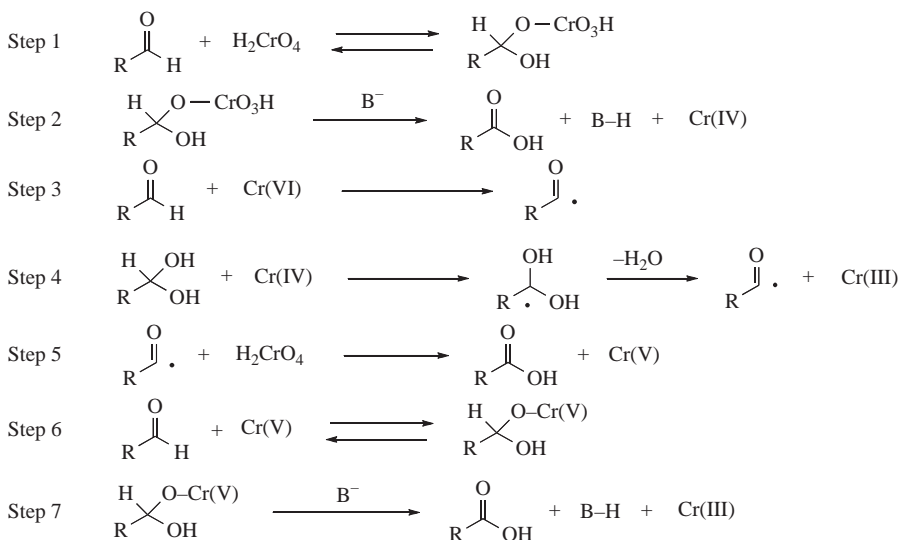
⁶⁸⁸ Al Neirabeyeh, M.; Pujol, M.D. *Tetrahedron Lett.* **1990**, *31*, 2273; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* **1989**, *54*, 1212. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1661–1669.

Aldehydes react with amines, mediated by La catalysts, to give amides.⁶⁸⁹

Mechanisms of aldehyde oxidation⁶⁹⁰ are not firmly established, but there are at least two main types: a free radical mechanism and an ionic one. In the free radical process, the aldehyde hydrogen is abstracted to leave an acyl radical, which obtains OH from the oxidizing agent. In the ionic process, the first step is addition of a species ^-OZ to the carbonyl bond to give **29** in alkaline solution and **30** in acid or neutral solution. The aldehyde hydrogen of **29** or **30** is then lost as a proton to a base, while Z leaves with its electron pair.



For oxidation with acid dichromate the picture seems to be quite complex, with several processes of both types going on:⁶⁹¹



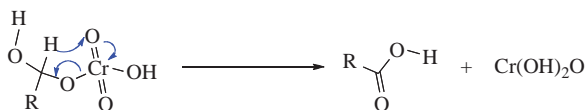
Steps 1 and 2 constitute an oxidation by the ionic pathway by Cr(VI), and steps 6 and 7 a similar oxidation by Cr(V), which is produced by an electron-transfer process. Either Cr(VI) (step 3) or Cr(IV) (step 4) [Cr(IV) is produced in step 2] may abstract a hydrogen and the resulting acyl radical is converted to carboxylic acid in step 5. Thus, Cr in three oxidation states is instrumental in oxidizing aldehydes. Still another possible process has been proposed in which the chromic acid ester decomposes as follows:⁶⁹²

⁶⁸⁹ Seo, S.Y.; Marks, T.J. *Org. Lett.* **2008**, *10*, 317.

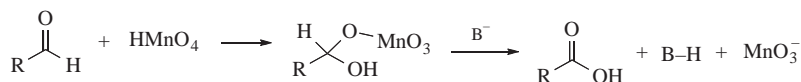
⁶⁹⁰ See Rocek, J., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 461–505.

⁶⁹¹ Wiberg, K.B.; Szeimies, G. *J. Am. Chem. Soc.* **1974**, *96*, 1889. See also, Sen Gupta, S.; Dey, S.; Sen Gupta, K.K. *Tetrahedron* **1990**, *46*, 2431.

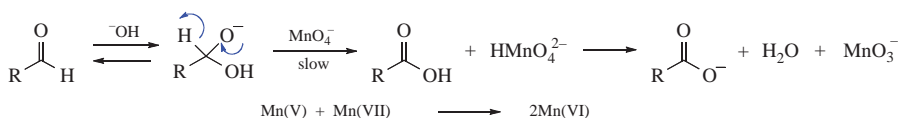
⁶⁹² See Rocek, J.; Ng, C. *J. Org. Chem.* **1973**, *38*, 3348.



The mechanism with permanganate is less well known, but an ionic mechanism has been proposed⁶⁹³ for neutral and acid permanganate, similar to steps 1 and 2 for dichromate:



For alkaline permanganate, the following mechanism has been proposed:⁶⁹⁴

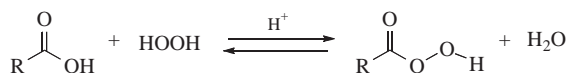


OS I, 166; II, 302, 315, 538; III, 745; IV, 302, 493, 499, 919, 972, 974.

The conversion of thioketones to sulfoxes ($\text{R}_2\text{C}=\text{S}=\text{O}$) is difficult to categorize into the sections available, and it placed after oxidation of ketones and aldehydes. The reaction of a thioketone with H_2O_2 and a catalytic amount of MTO (methyl trioxorhenium) gives the sulfoxine.⁶⁹⁵

19-24 Oxidation of Carboxylic Acids to Peroxy Acids

Peroxy-de-hydroxy-substitution

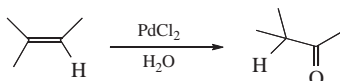


The oxidation of carboxylic acids with H_2O_2 and an acid catalyst is the best general method for the preparation of peroxy acids.⁶⁹⁶ A mixture of $\text{Me}_2\text{C}(\text{OMe})\text{OOH}$ and DCC has also been used.⁶⁹⁷ Concentrated H_2SO_4 is a common catalyst for aliphatic R. The reaction is in equilibrium and is driven to the right by removal of water or by the use of excess reagents. For aromatic R, the best catalyst is methanesulfonic acid, which is also used as the solvent.

D. Reactions in which Oxygen Is Added to the Substrate

19-25 Oxidation of Alkenes to Aldehydes and Ketones

1/Oxo-(1/→2/hydro)-migr-attachm



⁶⁹³ See Freeman, F.; Lin, D.K.; Moore, G.R. *J. Org. Chem.* **1982**, 47, 56; Jain, A.L.; Banerji, K.K. *J. Chem. Res. (S)* **1983**, 60.

⁶⁹⁴ Freeman, F.; Brant, J.B.; Hester, N.B.; Kamego, A.A.; Kasner, M.L.; McLaughlin, T.G.; Paul, E.W. *J. Org. Chem.* **1970**, 35, 982.

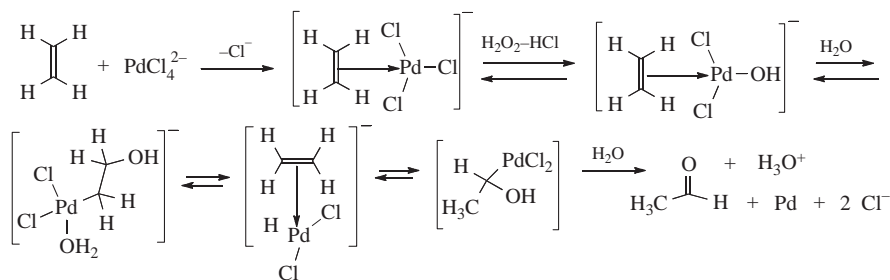
⁶⁹⁵ Huang, R.; Espenson, J.H. *J. Org. Chem.* **1999**, 64, 6935.

⁶⁹⁶ See Swern, D. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, **1970**, pp. 313–516.

⁶⁹⁷ Dussault, P.; Sahli, A. *J. Org. Chem.* **1992**, 57, 1009.

Monosubstituted and 1,2-disubstituted alkenes can be oxidized to aldehydes and ketones by PdCl_2 , where the PdCl_2 is reduced to Pd.⁶⁹⁸ Similar salts of noble metals also work, but 1,1-disubstituted alkenes generally give poor results. The reaction is used industrially to prepare acetaldehyde from ethylene (the *Wacker process*),⁶⁹⁹ but it is also suitable for laboratory preparations. The reagent is expensive, so the reaction is usually carried out with a cooxidant, often CuCl_2 , whose function is to reoxidize the Pd to Pd(II) . The CuCl_2 is reduced to Cu(I) , which itself is reoxidized to Cu(II) by air, so that atmospheric oxygen is the only oxidizing agent actually used up. Many other cooxidants have been tried, among them O_3 , Fe^{3+} , and PbO_2 . Terminal alkenes are oxidized to methyl ketones with O_2 and a Pd catalyst.⁷⁰⁰ The principal product is an aldehyde only from ethylene: With other alkenes *Markovnikov's rule* is followed, and ketones are formed predominantly.

The generally accepted mechanism shown below involves π complexes of Pd.⁷⁰¹ This mechanism accounts for the fact, established by deuterium labeling, that the four hydrogen atoms of the acetaldehyde all come from the original ethylene and none from the solvent.



Similar reactions have been carried out with other oxidizing agents. An example involving migration of an alkyl group instead of hydrogen is oxidation of $\text{Me}_2\text{C}=\text{CMe}_2$ with peroxytrifluoroacetic acid–boron trifluoride to give Me_3COMe (pinacolone).⁷⁰² This reaction consists of epoxidation (**15-50**) followed by pinacol rearrangement of the epoxide (**18-2**). A migration is also involved in the conversion of $\text{ArCH}=\text{CHCH}_3$ to $\text{ArCH}(\text{CH}_3)\text{CHO}$ by treatment with $\text{I}_2\text{—Ag}_2\text{O}$ in aq dioxane.⁷⁰³

⁶⁹⁸ See Henry, P.M. *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Reidel Publishing Co., Dordrecht, **1980**; Tsuji, J. *Organic Synthesis with Palladium Compounds*, Springer, NY, **1980**, pp. 6–12; *Synthesis* **1990**, 739; Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, **1985**, pp. 59–80; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, **1981**, pp. 189–193, 299–303; Jira, R.; Freiesleben, W. *Organomet. React.* **1972**, 3, 1, pp. 1–44; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, **1974**, pp. 77–91; Hüttel, R. *Synthesis* **1970**, 225, see pp. 225–236; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, **1967**, pp. 88–111.

⁶⁹⁹ Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem. Int. Ed.* **1962**, 1, 80; Jira, R.; Freiesleben, W. *Organomet. React.* **1972**, 3, 1; *The Merck Index*, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, **2006**, p ONR-98; Mundy, B.P.; Ellerd, M.G.; Favaloro, Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley–Interscience, New Jersey, **2005**, pp. 676–677. See Muzart, J. *Tetrahedron* **2007**, 63, 7505.

⁷⁰⁰ See Cornell, C.N.; Sigman, M.S. *Org. Lett.* **2006**, 8, 4117.

⁷⁰¹ See Cornell, C.N.; Sigman, M.S. *J. Am. Chem. Soc.* **2005**, 127, 2796; Keith, J.A.; Nielsen, R.J.; Oxgaard, J.; Goddard III, W.A. *J. Am. Chem. Soc.* **2007**, 129, 12342.

⁷⁰² Hart, H.; Lerner, L.R. *J. Org. Chem.* **1967**, 32, 2669.

⁷⁰³ Kikuchi, H.; Kogure, K.; Toyoda, M. *Chem. Lett.* **1984**, 341.

Other reagents used have been $\text{Pb}(\text{OAc})_4\text{—F}_3\text{CCO}_2\text{H}$ ⁷⁰⁴ (e.g., $\text{PhCH=CH}_2 \rightarrow \text{PhCH}_2\text{CHO}$), H_2O_2 and a Pd catalyst,⁷⁰⁵ $\text{H}_2\text{O—PdCl}_2\text{—polyethylene glycol}$.⁷⁰⁶ Terminal alkenes react with ceric ammonium nitrate in methanol to give α -methoxy ketones.⁷⁰⁷

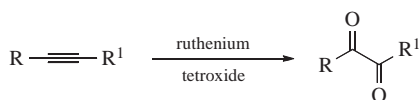
Alkenes have also been converted to more highly oxidized products. Examples are (1) Treatment with KMnO_4 in aq acetone containing acetic acid gives α -hydroxy ketones.⁷⁰⁸ (2) 1,2-Disubstituted and trisubstituted alkenes give α -chloro ketones when oxidized with chromyl chloride in acetone: $\text{RCH=CR}^1\text{R}^2 \rightarrow \text{RCOCClR}^1\text{R}^2$.⁷⁰⁹ (3) α -Iodo ketones can be prepared by treating alkenes with bis(*sym*-collidine)iodine(I) tetrafluoroborate.⁷¹⁰ (4) Potassium permanganate in acetic anhydride oxidizes large-ring cycloalkenes to 1,2-diketones.⁷¹¹

Enol ethers are oxidized to carboxylic esters ($\text{RCH=CHOR}' \rightarrow \text{RCH}_2\text{COOR}'$) with PCC ⁷¹² and enamines to α -amino ketones with *N*-sulfonyloxaziridines.⁷¹³ Enamines ($\text{R}^1\text{R}^4\text{C=CR}^2\text{NR}_2^3$, $\text{R}^4 \neq \text{H}$) do not give these products, but lose the amino group to give α -hydroxy ketones [$\text{R}^1\text{R}^4\text{C}(\text{OH})\text{COR}^2$].⁷¹³ Carboxylic acids can be prepared from terminal alkynes by conversion of the alkyne to its phenylthio ether ($\text{RC}\equiv\text{CPh}$) and treatment of this with HgSO_4 in $\text{HOAc—H}_2\text{SO}_4$.⁷¹⁴ *Aza-Wacker reactions* are known.⁷¹⁵

OS VI, 1028; VII, 137; VIII, 208.

19-26 The Oxidation of Alkynes to α -Diketones

Dioxo-biaddition



Internal alkynes have been oxidized⁷¹⁶ to α -diketones by several oxidizing agents,⁷¹⁷ including neutral KMnO_4 ,⁷¹⁸ bis(trifluoroacetoxy)iodobenzene,⁷¹⁹ $\text{NaIO}_4\text{—RuO}_2$,⁷²⁰

⁷⁰⁴ Lethbridge, A.; Norman, R.O.C.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* **1973**, 35.

⁷⁰⁵ Roussel, M.; Mimoun, H. *J. Org. Chem.* **1980**, 45, 5387.

⁷⁰⁶ Alper, H.; Januszkiewicz, K.; Smith, D.J.H. *Tetrahedron Lett.* **1985**, 26, 2263.

⁷⁰⁷ Nair, V.; Nair, L.G.; Panicker, S.B.; Sheeba, V.; Augustine, A. *Chem. Lett.* **2000**, 584.

⁷⁰⁸ Srinivasan, N.S.; Lee, D.G. *Synthesis* **1979**, 520. See also, Baskaran, S.; Das, J.; Chandrasekaran, S. *J. Org. Chem.* **1989**, 54, 5182.

⁷⁰⁹ Sharpless, K.B.; Teranishi, A.Y. *J. Org. Chem.* **1973**, 38, 185. See also, Kageyama, T.; Tobito, Y.; Katoh, A.; Ueno, Y.; Okawara, M. *Chem. Lett.* **1983**, 1481; Lee, J.G.; Ha, D.S. *Tetrahedron Lett.* **1989**, 30, 193.

⁷¹⁰ Evans, R.D.; Schauble, J.H. *Synthesis* **1986**, 727.

⁷¹¹ Jensen, H.P.; Sharpless, K.B. *J. Org. Chem.* **1974**, 39, 2314.

⁷¹² Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron Lett.* **1977**, 3483. See Baskaran, S.; Islam, I.; Raghavan, M.; Chandrasekaran, S. *Chem. Lett.* **1987**, 1175.

⁷¹³ Davis, F.A.; Sheppard, A.C. *Tetrahedron Lett.* **1988**, 29, 4365.

⁷¹⁴ Abrams, S. R. *Can. J. Chem.* **1983**, 61, 2423.

⁷¹⁵ Liu, G.; Stahl, S.S. *J. Am. Chem. Soc.* **2007**, 129, 6328; Zhang, Z.; Tan, J.; Wang, Z. *Org. Lett.* **2008**, 10, 173.

⁷¹⁶ See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, **1985**, pp. 153–162, 332–338; Simándi, L.I. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, **1983**, pp. 513–570.

⁷¹⁷ See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, p. 92.

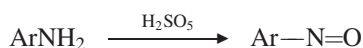
⁷¹⁸ See Tatlock, J.H. *J. Org. Chem.* **1995**, 60, 6221.

⁷¹⁹ Vasil'eva, V.P.; Khalfina, L.L.; Karpitskaya, L.G.; Merkushev, E.B. *J. Org. Chem. USSR* **1987**, 23, 1967.

⁷²⁰ See Al-Rashid, Z.F.; Johnson, W.L.; Hsung, R.P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* **2008**, 73, 8780.

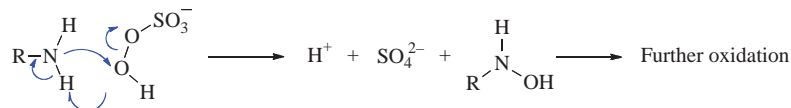
$\text{MeReO}_3/\text{H}_2\text{O}_2$,⁷²¹ or oxygen and a mixture of Pd and Cu catalysts.⁷²² A Ru complex with a small amount of trifluoroacetic acid converts internal alkynes to the α -diketone.⁷²³ Ozone generally oxidizes triple-bond compounds to carboxylic acids (Reaction 19-9), but α -diketones are sometimes obtained.⁷²⁴ Selenium dioxide (SeO_2) with a small amount of H_2SO_4 oxidizes alkynes to α -diketones, as well as arylacetylenes to α -keto acids ($\text{ArC}\equiv\text{CH} \rightarrow \text{ArCOCO}_2\text{H}$).⁷²⁵ A mixture of formic acid, methanesulfonic acid and DMSO with an HBr catalyst converts alkynes to α -diketones.⁷²⁶

19-27 Oxidation of Amines to Nitroso Compounds and Hydroxylamines and Related *N*-Oxo-de-dihydro-bisubstitution



Primary aromatic amines can be oxidized⁷²⁷ to nitroso compounds. Most often the conversion is accomplished by *Caro's acid* (H_2SO_5) or with H_2O_2 in HOAc.⁷²⁸ Other reagents used for this oxidation are sodium perborate⁷²⁹ H_2O_2 with a Ti complex,⁷³⁰ HOF generated *in situ*,⁷³¹ and $\text{Na}_2\text{WO}_4/\text{H}_2\text{O}_2$.⁷³² Hydroxylamines, which are probably intermediates in most cases, can sometimes be isolated, but under the reaction conditions they are generally oxidized to the nitroso compounds. Primary aliphatic amines can be oxidized in this manner, but the nitroso compound is stable only if there is no α hydrogen. If there is an α hydrogen, the compound tautomerizes to the oxime.⁷³³

The mechanism with H_2SO_5 has been postulated to be an example of category 5 (Sec. 19.A).⁷³⁴



Secondary amines (R_2NH) are oxidized to hydroxylamines (R_2NHOH), which are resistant to further oxidation, by dimethyldioxirane⁷³⁵ and by benzoyl peroxide and

⁷²¹ Zhu, Z.; Espenson, J.H. *J. Org. Chem.* **1995**, 60, 7728.

⁷²² Ren, W.; Xia, Y.; Ji, S.-J.; Zhang, Y.; Wan, X.; Zhao, J. *Org. Lett.* **2009**, 11, 1841.

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⁷²⁶ Wan, Z.; Jones, C.D.; Mitchell, D.; Pu, J.Y.; Zhang, T.Y. *J. Org. Chem.* **2006**, 71, 826.

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⁷²⁹ Zajac, Jr., W.W.; Darcy, M.G.; Subong, A.P.; Buzby, J.H. *Tetrahedron Lett.* **1989**, 30, 6495.

⁷³⁰ Dewkar, G.K.; Nikalje, M.D.; Ali, I.S.; Paraskar, A.S.; Jagtap, H.S.; Sadalai, A. *Angew. Chem. Int. Ed.* **2001**, 40, 405.

⁷³¹ Dirk, S.M.; Mickelson, E.T.; Henderson, J.C.; Tour, J.M. *Org. Lett.* **2002**, 2, 3405.

⁷³² Corey, E.J.; Gross, A.W. *Org. Synth.* 65, 166.

⁷³³ See Kahr, K.; Berther, C. *Chem. Ber.* **1960**, 93, 132.

⁷³⁴ Gragerov, I.P.; Levit, A.F. *J. Gen. Chem. USSR* **1960**, 30, 3690.

⁷³⁵ Murray, R.W.; Singh, M. *Synth. Commun.* **1989**, 19, 3509. This reagent also oxidizes primary amines to hydroxylamines: Wittman, M.D.; Halcomb, R.L.; Danishefsky, S.J. *J. Org. Chem.* **1990**, 55, 1981.

Na_2HPO_4 .⁷³⁶ Oxone on silica also oxidizes secondary alcohols to the hydroxylamine.⁷³⁷ Hydroxylamines are formed when secondary amines react with the enzyme cyclohexanone monooxygenase.⁷³⁸ Carbamates (e.g., *N*-Boc amines) are converted to the *N*-hydroxy compound with bis(trifluoromethyl)dioxirane.⁷³⁹ Dialkylamines are oxidized to the *N*-nitroso compound with N_2O_2 on poly(vinylpyrrolidinone).⁷⁴⁰

OS III, 334; VIII, 93; 80, 207.

19-28 Oxidation of Primary Amines, Oximes, Azides, Isocyanates, or Nitroso Compounds to Nitro Compounds



Tertiary alkyl primary amines can be oxidized to nitro compounds in excellent yields with KMnO_4 .⁷⁴¹ This type of nitro compound is not easily prepared in other ways. All classes of primary amine (including primary, secondary, and tertiary alkyl, as well as aryl) are oxidized to nitro compounds in high yields with dimethyldioxirane.⁷⁴² Other reagents that oxidize various types of primary amines to nitro compounds are dry ozone,⁷⁴³ various peroxyacids,⁷⁴⁴ $\text{MeReO}_3/\text{H}_2\text{O}_2$,⁷⁴⁵ Oxone,⁷⁴⁶ *tert*-butyl hydroperoxide in the presence of certain Mo and V compounds,⁷⁴⁷ and sodium perborate.⁷⁴⁸ An aqueous solution of fluorine oxidizes amino esters to α -nitro esters.⁷⁴⁹

Dimethyldioxirane in wet acetone oxidizes isocyanates to nitro compounds ($\text{RNCO} \rightarrow \text{RNO}_2$).⁷⁵⁰ Oximes can be oxidized to nitro compounds with peroxytrifluoroacetic acid, or sodium perborate,⁷⁵¹ among other ways.⁷⁴¹ Secondary hydroxylamines are also oxidized to nitrones with MnO_2 in dichloromethane.⁷⁵² Primary and secondary alkyl azides have been converted to nitro compounds by treatment with Ph_3P followed by ozone.⁷⁵³ An aqueous solution of fluorine also oxidizes azides to the corresponding nitro

⁷³⁶ Biloski, A.J.; Ganem, B. *Synthesis* **1983**, 537.

⁷³⁷ Fields, J.D.; Kropp, P.J. *J. Org. Chem.* **2000**, *65*, 5937.

⁷³⁸ Colonna, S.; Pironti, V.; Carrea, G.; Pasta, P.; Zambianchi, F. *Tetrahedron* **2004**, *60*, 569.

⁷³⁹ Detomaso, A.; Curci, R. *Tetrahedron Lett.* **2001**, *42*, 755.

⁷⁴⁰ Iranpoor, N.; Firouzabadi, H.; Pourali, A.R. *Synthesis* **2003**, 1591.

⁷⁴¹ Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, **1969**, pp. 306–310. See also, Barnes, M.W.; Patterson, J.M. *J. Org. Chem.* **1976**, *41*, 733. For reviews of oxidations of nitrogen compounds, see Butler, R.N. *Chem. Rev.* **1984**, *84*, 249; Boyer, J.H. *Chem. Rev.* **1980**, *80*, 495.

⁷⁴² Murray, R.W.; Rajadhyaksha, S.N.; Mohan, L. *J. Org. Chem.* **1989**, *54*, 5783. See also, Zabrowski, D.L.; Moorman, A.E.; Beck, Jr., K.R. *Tetrahedron Lett.* **1988**, *29*, 4501.

⁷⁴³ See Keinan, E.; Mazur, Y. *J. Org. Chem.* **1977**, *42*, 844.

⁷⁴⁴ See Gilbert, K.E.; Borden, W.T. *J. Org. Chem.* **1979**, *44*, 659.

⁷⁴⁵ See Cardona, F.; Soldaini, G.; Goti, A. *Synlett* **2004**, 1553.

⁷⁴⁶ Webb, K.S.; Seneviratne, V. *Tetrahedron Lett.* **1995**, *36*, 2377.

⁷⁴⁷ Howe, G.R.; Hiatt, R.R. *J. Org. Chem.* **1970**, *35*, 4007. See also, Nielsen, A.T.; Atkins, R.L.; Norris, W.P.; Coon, C.L.; Sitzmann, M.E. *J. Org. Chem.* **1980**, *45*, 2341.

⁷⁴⁸ McKillop, A.; Tarbin, J.A. *Tetrahedron* **1987**, *43*, 1753.

⁷⁴⁹ Harel, T.; Rozen, S. *J. Org. Chem.* **2007**, *72*, 6500.

⁷⁵⁰ Eaton, P.E.; Wicks, G.E. *J. Org. Chem.* **1988**, *53*, 5353.

⁷⁵¹ Olah, G.A.; Ramaiah, P.; Lee, G.K.; Prakash, G.K.S. *Synlett* **1992**, 337.

⁷⁵² Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **2001**, *42*, 6503.

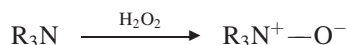
⁷⁵³ Corey, E.J.; Samuelsson, B.; Luzzio, F.A. *J. Am. Chem. Soc.* **1984**, *106*, 3682.

compound.⁷⁵⁴ Aromatic nitroso compounds are easily oxidized to nitro compounds by many oxidizing agents.⁷⁵⁵

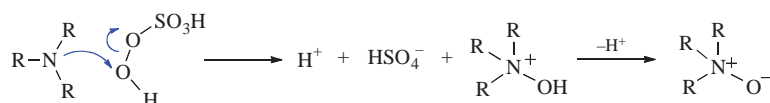
OS **III**, 334; **V**, 367, 845; **VI**, 803; **81**, 204.

19-29 Oxidation of Tertiary Amines to Amine Oxides

N-Oxygen-attachment



Tertiary amines can be converted to amine oxides by oxidation. Hydrogen peroxide is often used, but peroxyacids are also important reagents for this purpose. Pyridine and its derivatives are oxidized by peroxyacids⁷⁵⁶ rather than hydrogen peroxide. Note, however, that urea–H₂O₂ in formic acid does indeed oxidize pyridine.⁷⁵⁷ Oxidation with *Caro's acid* has been shown to proceed in this manner.⁷⁵⁸



This mechanism is the same as that of Reaction **19-27**; the products differ only because tertiary amine oxides cannot be further oxidized. The mechanism with other peroxyacids is probably the same. A green procedure for oxidation of tertiary amines has been developed, using a Mg–Al complex with aq H₂O₂.⁷⁵⁹ Nitrones can be prepared using a ball-mill.⁷⁶⁰

An alternative oxidation using O₂ and a RuCl₃ catalyst converted pyridine to pyridine *N*-oxide.⁷⁶¹ Bromamine-T and RuCl₃ in aq acetonitrile also oxidizes pyridine to the *N*-oxide.⁷⁶² Tertiary amines are oxidized to the *N*-oxide with O₂ and Fe₂O₃ in the presence of an aliphatic aldehyde.⁷⁶³ Oxygen and a Co–Schiff base complex also oxidizes tertiary amines, including pyridine.⁷⁶⁴

Analogous to the oxidation of tertiary amines, tertiary phosphines are oxidized to phosphine oxides (R₃P=O). Triphenylphosphine is converted to triphenylphosphine oxide with N₂O at 100 °C, for example. Triphenylphosphine is also oxidized with PhIO on Montmorillonite K-10.⁷⁶⁵ *tert*-Butylhydroperoxide oxides Ph₃P → BH₃ to Ph₃P=O.⁷⁶⁶ *P*-Stereogenic phosphine oxides have been prepared.⁷⁶⁷

OS **IV**, 612, 704, 828; **VI**, 342, 501; **VIII**, 87.

⁷⁵⁴ Carmeli, M.; Rozen, S. *J. Org. Chem.* **2006**, 71, 4585.

⁷⁵⁵ See Boyer, J.H. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, **1969**, pp. 264–265.

⁷⁵⁶ Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, **1991**, pp. 31–41; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, **1971**, pp. 21–72, 539–542.

⁷⁵⁷ Balicki, R.; Golinski, J. *Synth. Commun.* **2000**, 30, 1529.

⁷⁵⁸ Ogata, Y.; Tabushi, I. *Bull. Chem. Soc. Jpn.* **1958**, 31, 969.

⁷⁵⁹ Choudary, B.M.; Bharathi, B.; Reddy, Ch.V.; Kantam, M.L.; Raghavan, K.V. *Chem. Commun.* **2001**, 1736.

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⁷⁶¹ Jain, S.L.; Sain, B. *Chem. Commun.* **2002**, 1040.

⁷⁶² Sharma, V.B.; Jain, S.L.; Sain, B. *Tetrahedron Lett.* **2004**, 45, 4281.

⁷⁶³ Wang, F.; Zhang, H.; Song, G.; Lu, X. *Synth. Commun.* **1999**, 29, 11.

⁷⁶⁴ Jain, S.L.; Sain, B. *Angew. Chem. Int. Ed.* **2003**, 42, 1265.

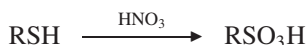
⁷⁶⁵ Mielniczak, G.; Lopusinski, A. *Synlett* **2001**, 505.

⁷⁶⁶ Uziel, J.; Darcel, C.; Moulin, D.; Bauduin, C.; Juge, S. *Tetrahedron Asymmetry* **2001**, 12, 1441.

⁷⁶⁷ Bergin, E.; O'Connor, C.T.; Robinson, S.B.; McGarrigle, E.M.; O'Mahony, C.P.; Gilheany, D.G. *J. Am. Chem. Soc.* **2007**, 129, 9566.

19-30 Oxidation of Thiols and Other Sulfur Compounds to Sulfonic Acids

Thiol-sulfonic acid oxidation

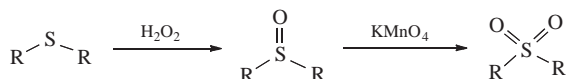


Thiols, sulfoxides, sulfones, disulfides,⁷⁶⁸ and other sulfur compounds can be oxidized to sulfonic acids with various oxidizing agents, but for synthetic purposes the reaction is most important for thiols.⁷⁶⁹ Among oxidizing agents used are boiling nitric acid, barium permanganate, and dimethyl dioxirane.⁷⁷⁰ Autoxidation (oxidation by atmospheric oxygen) can be accomplished in basic solution.⁷⁷¹ Oxidation of thiols with chlorine and water gives sulfonyl chlorides directly.⁷⁷² Thiols can also be oxidized to disulfides (Reaction 19-34).

OS II, 471; III, 226. Also see, OS V, 1070.

19-31 Oxidation of Thioethers to Sulfoxides and Sulfones

S-Oxygen-attachment



Thioethers can be oxidized to sulfoxides by 1 equiv of 30% H₂O₂ or by many other oxidizing agents,⁷⁷³ including NaIO₄,⁷⁷⁴ H₂O₂, and a Sc(OTf)₃ catalyst,⁷⁷⁵ HIO₃/wet SiO₂,⁷⁷⁶ dioxiranes,⁷⁷⁷ MeReO₃/H₂O₂,⁷⁷⁸ O₂ and a ceric ammonium nitrate catalyst,⁷⁷⁹ KO₂/Me₃SiCl,⁷⁸⁰ hexamethylene triamine-Br₂ with CHCl₃-H₂O,⁷⁸¹ H₅IO₆/FeCl₃,⁷⁸²

⁷⁶⁸ See Savige, W.E.; Maclaren, J.A. in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds*, Vol. 2; pp. 367–402, Pergamon, NY, **1966**.

⁷⁶⁹ See Capozzi, G.; Modena, G. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, **1974**, pp. 785–839; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, **1965**, pp. 217–239.

⁷⁷⁰ Gu, D.; Harpp, D.N. *Tetrahedron Lett.* **1993**, 34, 67. See Ballistreri, F.P.; Tomaselli, G.A.; Toscano, R.M. *Tetrahedron Lett.* **2008**, 49, 3291.

⁷⁷¹ Wallace, T.J.; Schriesheim, A. *Tetrahedron* **1965**, 21, 2271.

⁷⁷² See Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, **1965**, pp. 202–214.

⁷⁷³ See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, **1990**, pp. 252–263; Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulfoxides*, Wiley, NY, **1988**, pp. 233–378, pp. 235–255; Madesclaire, M. *Tetrahedron* **1986**, 42, 5459; Drabowicz, J.; Mikolajczyk, M. *Org. Prep. Proced. Int.* **1982**, 14, 45; Oae, S. in Oae, S. *The Organic Chemistry of Sulfur*, Plenum, NY, **1977**, pp. 385–390; Holland, H.L. *Chem. Rev.* **1988**, 88, 473.

⁷⁷⁴ Hiskey, R.G.; Harpold, M.A. *J. Org. Chem.* **1967**, 32, 3191; Varma, R.S.; Saini, R.K.; Meshram, H.M. *Tetrahedron Lett.* **1997**, 38, 6525.

⁷⁷⁵ Matteucci, M.; Bhalay, G.; Bradley, M. *Org. Lett.* **2003**, 5, 235.

⁷⁷⁶ Lakouraj, M.M.; Tajbakhsh, M.; Shirini, F.; Asady Tamami, M.V. *Synth. Commun.* **2005**, 35, 775.

⁷⁷⁷ Colonna, S.; Gaggero, N. *Tetrahedron Lett.* **1989**, 30, 6233. For a discussion of the mechanism, see González-Núñez, M.E.; Mello, R.; Royo, J.; Ríos, J.V.; Asensio, G. *J. Am. Chem. Soc.* **2002**, 124, 9154.

⁷⁷⁸ See Choi, S.; Yang, J.-D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K.-H.; Byeon, S.-H.; Baik, W.; Koo, S. *J. Org. Chem.* **2001**, 66, 8192.

⁷⁷⁹ See Ali, M.H.; Kriedelbaugh, D.; Wenciewicz, T. *Synthesis* **2007**, 3507.

⁷⁸⁰ Chen, Y.-J.; Huang, Y.-P. *Tetrahedron Lett.* **2000**, 41, 5233.

⁷⁸¹ Shaabani, A.; Teimouri, M.B.; Safaei, H.R. *Synth. Commun.* **2000**, 30, 265. See Kowalski, P.; Mitka, K.; Ossowska, K.; Kolarska, Z. *Tetrahedron* **2005**, 61, 1933.

⁷⁸² Kim, S.S.; Nehru, K.; Kim, S.S.; Kim, D.W.; Jung, H.C. *Synthesis* **2002**, 2484.

hypervalent iodine compounds,⁷⁸³ and peroxyacids.⁷⁸⁴ Sulfoxides can be further oxidized to sulfones by another equivalent of H₂O₂, KMnO₄, sodium perborate, or a number of other agents. If enough oxidizing agent is present, thioethers can be directly converted to sulfones without isolation of the sulfoxides.⁷⁸⁵ Thioethers can be oxidized directly to the sulfone by treatment with TPAP,⁷⁸⁶ H₂O₂,⁷⁸⁷ and an Fe catalyst,⁷⁸⁸ a Zr catalyst,⁷⁸⁹ a Ta catalyst,⁷⁹⁰ a V catalyst,⁷⁹¹ an Au catalyst,⁷⁹² a Mo catalyst,⁷⁹³ a flavin-ionic liquid catalyst,⁷⁹⁴ urea-H₂O₂,⁷⁹⁵ peroxy monosulfate and a Mn catalyst,⁷⁹⁶ or nitric acid with P₂O₅ on silica gel.⁷⁹⁷ These reactions give high yields, and many functional groups do not interfere.⁷⁹⁸

As with tertiary amines (Reaction 19-29), racemic thioethers can be kinetically resolved by oxidation to sulfoxides with an optically active reagent, and this has often been done.⁷⁹⁹ In addition, the use of chiral additives in conjunction with various oxidizing agents leads to chiral nonracemic sulfoxide with good-to-excellent enantioselectivity.⁸⁰⁰ Asymmetric oxidation using bacterial monooxygenases is known,⁸⁰¹ and horseradish peroxidase gives modest enantioselectivity.⁸⁰² Chiral sulfur reagents are also known.⁸⁰³ It is possible to oxidize a thioether to a sulfoxide in the presence of an alcohol moiety using MnO₂/HCl.⁸⁰⁴ *N*-Sulfonyloxaziridines can be used to oxidize sulfides to sulfoxides.⁸⁰⁵ Selenides (R₂Se) can be oxidized to selenoxides and selenones.⁸⁰⁶ Alkyl disulfides give oxidation of one

⁷⁸³ See Kopsosov, A.Y.; Zhdankin, V.V. *Synthesis* **2005**, 22.

⁷⁸⁴ See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**, p. 16.

⁷⁸⁵ See Schank, K. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulfoxides*, Wiley, NY, **1988**, pp. 165–231, pp. 205–213.

⁷⁸⁶ Guertin, K.R.; Kende, A.S. *Tetrahedron Lett.* **1993**, 34, 5369.

⁷⁸⁷ Kaczorowska, K.; Kolarska, Z.; Mitka, K.; Kowalski, P. *Tetrahedron* **2005**, 61, 8315. See Velusamy, S.; Kumar, A.V.; Saini, R.; Punniyamurthy, T. *Tetrahedron Lett.* **2005**, 46, 3819.

⁷⁸⁸ Margues, A.; Marin, M.; Ruasse, M.-F. *J. Org. Chem.* **2001**, 66, 7588.

⁷⁸⁹ Bahrami, K. *Tetrahedron Lett.* **2006**, 47, 2009.

⁷⁹⁰ Kirihaara, M.; Yamamoto, J.; Noguchi, T.; Hirai, Y. *Tetrahedron Lett.* **2009**, 50, 1180.

⁷⁹¹ Trivedi, R.; Lalitha, P. *Synth. Commun.* **2006**, 36, 3777.

⁷⁹² Yuan, Y.; Bian, Y. *Tetrahedron Lett.* **2007**, 48, 8518.

⁷⁹³ Jeyakumar, K.; Chand, D.K. *Tetrahedron Lett.* **2006**, 47, 4573; Gamelas, C.A.; Lourenço, T.; da Costa, A.P.; Simplicio, A.L.; Royo, B.; Romão, C.C. *Tetrahedron Lett.* **2008**, 49, 4708.

⁷⁹⁴ Lindén, A.A.; Johansson, M.; Hermanns, N.; Bäckvall, J.-E. *J. Org. Chem.* **2006**, 71, 3849.

⁷⁹⁵ Balicki, R. *Synth. Commun.* **1999**, 29, 2235.

⁷⁹⁶ Iranpoor, N.; Mohajer, D.; Rezaeifard, A.-R. *Tetrahedron Lett.* **2004**, 45, 3811.

⁷⁹⁷ Hajipour, A.R.; Kooshki, B.; Ruoho, A.E. *Tetrahedron Lett.* **2005**, 46, 2643.

⁷⁹⁸ See Venier, C.G.; Barager, III, H.J. *Org. Prep. Proced. Int.* **1974**, 6, 77, pp. 85–86.

⁷⁹⁹ For reviews, see Kagan, H.B.; Rebiere, F. *Synlett* **1990**, 643; Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *Org. Prep. Proceed. Int.* **1982**, 14, 45, see p. 288.

⁸⁰⁰ See Shibata, N.; Matsunaga, M.; Nakagawa, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2005**, 127, 1374; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, 129, 8940; del Río, R.E.; Wang, B.; Achab, S.; Bohé, L. *Org. Lett.* **2007**, 9, 2265; Gao, J.; Guo, H.; Liu, S.; Wang, M. *Tetrahedron Lett.* **2007**, 48, 8453; Yamaguchi, T.; Matsumoto, K.; Saito, B.; Katsuki, T. *Angew. Chem. Int. Ed.* **2007**, 46, 4729; Matsumoto, K.; Yamaguchi, T.; Katsuki, T. *Chem. Commun.* **2008**, 1704; Kelly, P.; Lawrence, S.E.; Maguire, A.R. *Synlett* **2007**, 1501; Jurok, R.; Cibulka, R.; Dvořáková, H.; Hampl, F.; Hodačová, J. *Eur. J. Org. Chem.* **2010**, 5217; Dieva, S.A.; Eliseenkova, R.M.; Efremov, Yu.Ya.; Sharafutdinova, D.R.; Bredikhin, A.A. *Russ. J. Org. Chem.* **2006**, 42, 12.

⁸⁰¹ Colonna, S.; Gaggero, N.; Pasta, P.; Ottolina, G. *Chem. Commun.* **1996**, 2303; Pasta, P.; Carrea, G.; Holland, H.L.; Dallavalle, S. *Tetrahedron Asymmetry*, **1995**, 6, 933.

⁸⁰² Ozaki, S.-i.; Watanabe, S.; Hayasaka, S.; Konuma, M. *Chem. Commun.* **2001**, 1654.

⁸⁰³ Mikolajczyk, M.; Drabowicz, J.; Kielbasinski, P. *Chiral Sulfur Reagents*, CRC Press, Boca Raton, FL, **1997**.

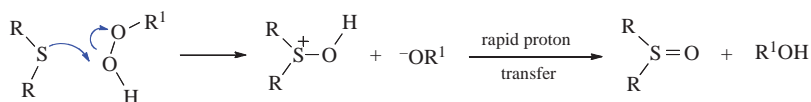
⁸⁰⁴ Gabbi, C.; Ghelfi, F.; Grandi, R. *Synth. Commun.* **1997**, 27, 2857.

⁸⁰⁵ See Jennings, W.B.; O'Shea, J.H.; Schweppe, A. *Tetrahedron Lett.* **2001**, 42, 101.

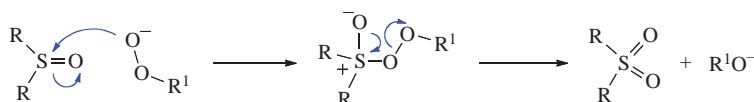
⁸⁰⁶ See Reich, H.J. in Trahanovsky, W.S. *Oxidations in Organic Chemistry*, pt. C, Academic Press, NY, **1978**, pp. 7–13; Kobayashi, M.; Ohkubo, H.; Shimizu, T. *Bull. Chem. Soc. Jpn.* **1986**, 59, 503.

sulfur to give a $\text{RS}-\text{S}(=\text{O})\text{R}$ compound with good enantioselectivity when using aq H_2O_2 , a catalytic amount of a V catalyst, and a chiral Schiff base ligand.⁸⁰⁷

When the oxidizing agent is a peroxide, the mechanism⁸⁰⁸ of oxidation to the sulfoxide is similar to that of Reaction 19-29.⁸⁰⁹



The second oxidation, which is normally slower than the first, which is why sulfoxides are so easily isolable, has the same mechanism in neutral or acid solution, but in basic solution it has been shown that the conjugate base of the peroxy compound ($\text{R}'\text{OO}^-$) also attacks the SO group as a nucleophile:⁸¹⁰



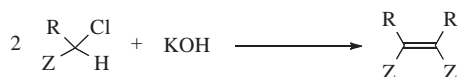
There are some reagents that oxidize sulfoxides in preference to sulfides (e.g., NaMnO_4).⁸¹¹

OS V, 791; VI, 403, 404, 482; VII, 453, 491; VIII, 464, 543; IX, 63; **80**, 190. Also see, OS V, 723; VI, 23.

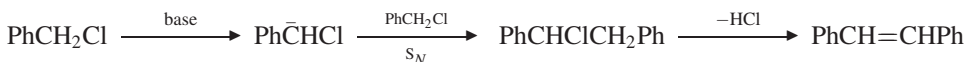
E. Oxidative Coupling

19-32 Coupling Involving Carbanions

De-hydro,chloro-coupling



Alkyl halides with an electron-withdrawing group on the halogen-bearing carbon can be dimerized to alkenes by treatment with bases. The Z group may be nitro, aryl, and so on. It is likely that in most cases the mechanism⁸¹² involves nucleophilic substitution followed by elimination⁸¹³ (illustrated for benzyl chloride):



α,α -Dibromotoluenes (ArCHBr_2) give tolanes ($\text{ArC}\equiv\text{CAr}$) by debromination of the intermediates $\text{ArCBr}=\text{CBrAr}$.⁸¹⁴ In a related reaction, diarylmethane dihalides

⁸⁰⁷ Blum, S.A.; Bergman, R.G.; Ellman, J.A. *J. Org. Chem.* **2003**, 68, 150.

⁸⁰⁸ See Agarwal, A.; Bhatt, P.; Banerji, K.K. *J. Phys. Org. Chem.* **1990**, 3, 174; Lee, D.G.; Chen, T. *J. Org. Chem.* **1991**, 56, 5346.

⁸⁰⁹ Modena, G.; Todesco, P.E. *J. Chem. Soc.* **1962**, 4920, and references cited therein.

⁸¹⁰ Curci, R.; Di Furia, F.; Modena, G. *J. Chem. Soc. Perkin Trans. 2* **1978**, 603 and references cited therein. See also, Akasaka, T.; Ando, W. *J. Chem. Soc. Chem. Commun.* **1983**, 1203.

⁸¹¹ See Henbest, H.B.; Khan, S.A. *Chem. Commun.* **1968**, 1036.

⁸¹² See Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, **1973**, pp. 548–554.

⁸¹³ See Reisdorf, D.; Normant, H. *Organomet. Chem. Synth.* **1972**, 1, 375; Hanna, S.B.; Wideman, L.G. *Chem. Ind. (London)* **1968**, 486. Also see Bethell, D.; Bird, R. *J. Chem. Soc. Perkin Trans. 2* **1977**, 1856.

⁸¹⁴ Vernigor, E.M.; Shalae, V.K.; Luk'yanets, E.A. *J. Org. Chem. USSR* **1981**, 17, 317.

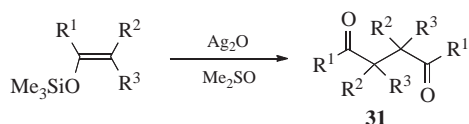
(Ar₂CX₂) have been dimerized to tetraaryl alkenes (Ar₂C=CAr₂) with Cu,⁸¹⁵ and with iron(II) oxalate dihydrate.⁸¹⁶

A somewhat different type of coupling is observed when salts of β-keto esters, arylacetoneitriles (ArCH₂CN), and other compounds of the form ZCH₂Z' are treated with an oxidizing agent (e.g., iodine,⁸¹⁷ or Cu(II) salts.)⁸¹⁸ Arylmethanesulfonyl chlorides (ArCH₂SO₂Cl) couple to give ArCH=CHAr when treated with Et₃N.⁸¹⁹

OS II, 273; IV, 372, 869, 914; VIII, 298. Also see, OS I, 46; IV, 877.

19-33 Dimerization of Silyl Enol Ethers or of Lithium Enolates

3/O-De-trimethylsilyl-1/C-coupling



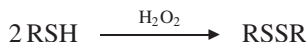
Silyl enol ethers can be dimerized to symmetrical 1,4-diketones by treatment with Ag₂O in DMSO or certain other polar aprotic solvents.⁸²⁰ The reaction has been performed with R², R³ = hydrogen or alkyl, although best yields are obtained when R² = R³ = H. In certain cases, unsymmetrical 1,4-diketones have been prepared by using a mixture of two silyl enol ethers. Other reagents that have been used to achieve either symmetrical or cross-coupled products are iodosobenzene–BF₃–OEt₂,⁸²¹ ceric ammonium nitrate,⁸²² and lead tetraacetate.⁸²³ If R¹ = OR (in which case the substrate is a ketene silyl acetal), dimerization with TiCl₄ leads to a dialkyl succinate (**31**, R¹ = OR).⁸²⁴

In a similar reaction, lithium enolates [RC(OLi)=CH₂] were dimerized to 1,4-diketones (RCOCH₂CH₂COR) with CuCl₂, FeCl₃, or copper(II) triflate, in a nonprotic solvent.⁸²⁵

OS VIII, 467.

19-34 Oxidation of Thiols to Disulfides

S-De-hydrogen-coupling



Thiols are easily oxidized to disulfides.⁸²⁶ Hydrogen peroxide is the most common reagent,⁸²⁷ but many oxidizing agents give the reaction, among them Br₂ on hydrated

⁸¹⁵ Buckles, R.E.; Matlack, G.M. *Org. Synth.* **IV**, 914.

⁸¹⁶ Khurana, J.M.; Maikap, G.C.; Mehta, S. *Synthesis* **1990**, 731.

⁸¹⁷ See Aurell, M.J.; Gil, S.; Tortajada, A.; Mestres, R. *Synthesis* **1990**, 317.

⁸¹⁸ Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, 93, 4605; Baudin, J.; Julia, M.; Rolando, C.; Verpeaux, J. *Bull. Soc. Chim. Fr.* **1987**, 493.

⁸¹⁹ Nakayama, J.; Tanuma, M.; Honda, Y.; Hoshino, M. *Tetrahedron Lett.* **1984**, 25, 4553.

⁸²⁰ Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, 97, 649.

⁸²¹ Moriarty, R.; Prakash, O.; Duncan, M.P. *J. Chem. Soc. Perkin Trans. 1* **1987**, 559.

⁸²² Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* **1989**, 30, 3707.

⁸²³ Moriarty, R.M.; Penmasta, R.; Prakash, I. *Tetrahedron Lett.* **1987**, 28, 873.

⁸²⁴ Inaba, S.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009. See also, Totten, G.E.; Wenke, G.; Rhodes, Y.E. *Synth. Commun.* **1985**, 15, 291, 301.

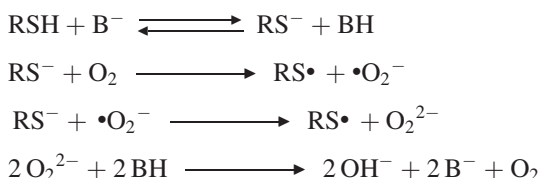
⁸²⁵ Frazier, Jr., R.H.; Harlow, R.L. *J. Org. Chem.* **1980**, 45, 5408.

⁸²⁶ See Capozzi, G.; Modena, G. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, **1974**, pp. 785–839; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**.

⁸²⁷ See, however, Evans, B.J.; Doi, J.T.; Musker, W.K. *J. Org. Chem.* **1990**, 55, 2337.

silica,⁸²⁸ sodium perborate,⁸²⁹ SmI_2 ,⁸³⁰ PPh_3 with a Rh catalyst,⁸³¹ cetyltrimethylammonium dichromate,⁸³² and NO. Hydrogen peroxide (30%) in hexafluoro-2-propanol converts thiols to disulfides,⁸³³ and solventless reactions on MnO_2 ,⁸³⁴ PCC (Reaction **19-3**, category 1)⁸³⁵ or SO_2Cl_2 ⁸³⁶ are also effective. A potassium phosphate catalyst has been used for the oxidative coupling of thiols to disulfides.⁸³⁷ Strong oxidizing agents may give Reaction **19-26**. Even oxygen in the air oxidizes thiols on standing, if a small amount of base is present. The reaction is reversible (see Reaction **19-75**), and the interconversion between cysteine and cystine is an important one in biochemistry.

The mechanism has been studied for several oxidizing agents and varies with the agent.⁸³⁸ For oxygen it is⁸³⁹



With respect to the sulfur, this mechanism is similar to that of Reaction **14-16**, involving as it does loss of a proton, oxidation to a free radical, and radical coupling.

Unsymmetrical disulfides can be prepared⁸⁴⁰ by treatment of a thiol RSH with diethyl azodicarboxylate ($\text{EtOOCN}=\text{NCOOEt}$) to give an adduct, to which another thiol ($\text{R}'\text{SH}$) is then added, producing the disulfide (RSSR').⁸⁴¹

OS **III**, 86, 116.

19.B.ii. Reductions

For the most part, reductions have been grouped into this chapter, with a few notable exceptions. Catalytic hydrogenation of alkenes and alkynes in Reactions **15-11** and **15-12**, hydrogenation of aromatic rings in Reaction **15-13**, and reductive cleavage of cyclopropanes in Reaction **15-15** were placed in Chapter 15 to coincide with addition reactions, and protonolysis of alkyl boranes in Reaction **15-16** was placed there also for continuity. In general, reductions of functional groups encompass a variety of reaction types. The reactions in this section are classified into groups depending on the type of bond change

⁸²⁸ Ali, M.H.; McDermott, M. *Tetrahedron Lett.* **2002**, 43, 6271.

⁸²⁹ McKillop, A.; Koyunçu, D. *Tetrahedron Lett.* **1990**, 31, 5007.

⁸³⁰ Zhan, Z.-P.; Lang, K.; Liu, F.; Hu, L.-m. *Synth. Commun.* **2004**, 34, 3203.

⁸³¹ Tanaka, K.; Ajiki, K. *Tetrahedron Lett.* **2004**, 45, 25.

⁸³² Patel, S.; Mishra, B.K. *Tetrahedron Lett.* **2004**, 45, 1371. See also, Tajbakhsh, M.; Hosseinzadeh, R.; Shakoori, A. *Tetrahedron Lett.* **2004**, 45, 1889.

⁸³³ Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Synthesis* **2000**, 223.

⁸³⁴ Firouzabadi, H.; Abbassi, M.; Karimi, B. *Synth. Commun.* **1999**, 129, 2527.

⁸³⁵ Salehi, P.; Farrokhi, A.; Gholizadeh, M. *Synth. Commun.* **2001**, 31, 2777.

⁸³⁶ Leino, R.; Lönnqvist, J.-E. *Tetrahedron Lett.* **2004**, 45, 8489.

⁸³⁷ Joshi, A.V.; Bhusare, S.; Baidossi, M.; Qafisheh, N.; Sasson, Y. *Tetrahedron Lett.* **2005**, 46, 3583.

⁸³⁸ Tarbell, D.S. in Kharasch, N. *Organic Sulfur Compounds*, Pergamon, Elmsford, NY, **1961**, pp. 97–102.

⁸³⁹ Wallace, T.J.; Schriesheim, A.; Bartok, W. *J. Org. Chem.* **1963**, 28, 1311.

⁸⁴⁰ Mukaiyama, T.; Takahashi, K. *Tetrahedron Lett.* **1968**, 5907.

⁸⁴¹ Also see Boustany, K.S.; Sullivan, A.B. *Tetrahedron Lett.* **1970**, 3547; Oae, S.; Fukushima, D.; Kim, Y.H. *J. Chem. Soc. Chem. Commun.* **1977**, 407.

involved. These groups are (1) attack at carbon (C—O and C=O), (2) attack at non-carbonyl multiple bonds to heteroatoms, (3) reactions in which a heteroatom is removed from the substrate, (4) reduction with cleavage, (5) reductive coupling, and (6) reactions in which an organic substrate is both oxidized and reduced. Most of the reagents in this section are metal hydrides, metals with an acid or a protic solvent, hydrogen gas with a catalyst, and so on. Other reducing agents are available, and will be introduced in the appropriate section. Note that plants can be used as reducing agents.⁸⁴²

A. Selectivity⁸⁴³

It is often necessary to reduce one group in a molecule without affecting another reducible group (this is called chemoselectivity), and reducing agents are available that will do this. The most common broad-spectrum reducing agents are the metal hydrides⁸⁴⁴ or hydrogen (with a catalyst).⁸⁴⁵ Many different metal hydride systems and hydrogenation catalysts have been investigated in order to find conditions under which a given group will be reduced chemoselectively. The ease of reduction for various functional groups toward catalytic hydrogenation is acyl halides > alkyl nitro compounds > alkynes > aldehydes > alkenes > ketones > benzylic ethers > nitriles > esters > amides.⁸⁴⁶ Futher, Table 19.2 and 19.4 list the reactivity of various functional groups with LiAlH_4 , and BH_3 , respectively.⁸⁴⁶ Table 19.5 shows which groups can be reduced by catalytic hydrogenation and various metal hydrides.⁸⁴⁷ Of course, the tables cannot be exact, because the nature of R and the reaction conditions obviously affect reactivity. Nevertheless, the tables do give a fairly good indication of which reagents reduce which groups.⁸⁴⁸ Lithium aluminum hydride is very powerful and unselective reagent.⁸⁴⁹ Other metal hydrides are generally used when chemoselectivity is required. As will be seen in Reaction 19-36, less reactive (and more selective) reagents have been prepared by replacing some of the hydrogen atoms of LiAlH_4 with alkoxy groups.⁸⁵⁰ Most of the metal hydrides are nucleophilic reagents and attack the

⁸⁴² Bruni, R.; Fantin, G.; Medici, A.; Pedrini, P.; Sacchetti, G. *Tetrahedron Lett.* **2002**, 43, 3377.

⁸⁴³ See Hudlicky, M. *Reductions in Organic Chemistry*, Wiley, NY, **1984**; Augustine, R.L. *Reduction*, Marcel Dekker, NY, **1968**; Candlin, J.P.; Rennie, R.A.C. in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, **1973**, pp. 77–135.

⁸⁴⁴ See Brown, H.C.; Krishnamurthy, S. *Tetrahedron* **1979**, 35, 567; Walker, E.R.H. *Chem. Soc. Rev.* **1976**, 5, 23; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**, pp. 209–251; Rerick, M.N. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, **1968**.

⁸⁴⁵ See Rylander, P.N. *Aldrichimica Acta* **1979**, 12, 53. See also, Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, **1985**.

⁸⁴⁶ Table 19.2 is from House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, p. 9. Tables 19.3 and 19.4 are from Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, **1972**, pp. 213 and 232, respectively.





⁸⁴⁷ The first 10 columns are from Brown, H.C.; Krishnamurthy, S. *Tetrahedron* **1979**, 35, 567, p. 604. The column on $(i\text{-Bu})_2\text{AlH}$ is from Yoon, N.M.; Gyoung, Y.S. *J. Org. Chem.* **1985**, 50, 2443; the one on $\text{NaAlEt}_2\text{H}_2$ from Stinson, S.R. *Chem. Eng. News*, Nov. 3, **1980**, 58, No. 44, 19; and the one on LiBEt_3H from Brown, H.C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, 45, 1. Also see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, p. 129; Hajós, A. *Complex Hydrides*, Elsevier, NY, **1979**, pp. 16–17; Hudlicky, M. *Reductions in Organic Chemistry*, Wiley, NY, **1984**, pp. 177–200.

⁸⁴⁸ See also, the table in Hudlicky, M. *J. Chem. Educ.* **1977**, 54, 100.


⁸⁴⁹ See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, **1974**, pp. 101–194.

⁸⁵⁰ See Málek, J. *J. Org. Chem.* **1988**, 36, 249; **1985**, 34, 1; Málek, J.; Cerny, M. *Synthesis* **1972**, 217.

TABLE 19.2 The Ease of Reduction of Various Functional Groups Toward Catalytic Hydrogenation⁸⁴⁶

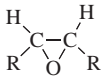
Reaction	Substrate ^a	Product	
19-39	RCOCl	RCHO	Easiest
19-45	RNO ₂	RNH ₂	
15-11	RC≡CR	RCH=CHR	
19-36	RCHO	RCH ₂ OH	
15-11	RCH=CHR	RCH ₂ CH ₂ R	
19-36	RCOR	RCHOHR	
19-56	ArCH ₂ OR	ArCH ₃ + ROH	
19-43	RC≡N	RCH ₂ NH ₂	
15-14			
19-38	RCOOR'	RCH ₂ OH + R'OH	
19-64	RCOHNHR'	RCH ₂ NHR'	
15-13			Most difficult
19-37	RCOO ⁻		Inert

^a The groups are listed in approximate order of ease of reduction.**TABLE 19.3 The Ease of Reduction of Various Functional Groups with LiAlH₄ in Ether^a**

Reaction	Substrate ^b	Product	
19-36	RCHO	RCH ₂ OH	Easiest
19-36	RCOR	RCHOHR	
19-63	RCOCl	RCH ₂ OH	
19-38	Lactone	Diol	
19-35		RCH ₂ CHOHR	
19-38	RCOOR'	RCH ₂ OH + R'OH	
19-37	RCOOH	RCH ₂ OH	
19-37	RCOO ⁻	RCH ₂ OH	
19-64	RCONR' ₂	RCH ₂ NR' ₂	
19-43	RC≡N	RCH ₂ NH ₂	
19-45	RNO ₂	RNH ₂	
19-80	ArNO ₂	ArN=NAr	Most difficult
15-11	RCH=CHR'		Inert

^aSee Ref. 846.^bHowever, LiAlH₄ is a very powerful reagent, and less chemoselective than most of the other metal hydrides. Adapted material from Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, 1972 p. 213, edited by Herbert C. Brown. Copyright © 1972 by Cornell University. Used by permission of the publisher, Cornell University Press.

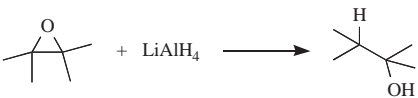
TABLE 19.4 The Ease of Reduction of Various Functional Groups With Borane^a

Reaction	Substrate ^b	Product	
19-37	RCOOH	RCH ₂ OH	Easiest
15-16	RCH=CHR	(RCH ₂ CHR) ₃ B	
19-36	RCOR	RCHOHR	
19-43	RCN	RCH ₂ NH ₂	
19-35		RCH ₂ CHOHR	Most difficult
19-38	RCOOR'	RCH ₂ OH + R'OH	
19-39,19-63	RCOCl		Inert

^aSee ref 846.^bIt is evident that this reagent and LiAlH₄ (Table 19.2) complement each other.Adapted material from Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, 1972, p. 232, edited by Herbert C. Brown. Copyright © 1972 by Cornell University. Used by permission of the publisher, Cornell University Press.TABLE 19.5 Reactivity of Various Functional Groups With Some Metal Hydrides and Toward Catalytic Hydrogenation^a

Reaction ^b	A ^c	B ^c	C ^c	D ^{c,d}	E ^{c,e}	F ^{c,f}	G ^c	H ^c	I ^c	J ^{c,g}	K ^{c,h}	L ^c	M ^c	N ^c
19-36 RCHO \longrightarrow RCH ₂ OH	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-36 RCOR \longrightarrow RCHOHR	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-39'														
19-63 RCOCl $\begin{cases} \longrightarrow \text{RCHO} \\ \longrightarrow \text{RCH}_2\text{OH} \end{cases}$	+	+	+	-	-	+	+	+	+	+	+	+	+	+
19-63 lactone \longrightarrow Diol	-	+	+	+	+	+	±	+	+	+	+	+	+	+
19-35 Epoxide \longrightarrow Alcohol	-	+	+	+	±	±	±	+	+	+	+	+	+	+
19-38 RCOOR' \longrightarrow RCH ₂ OH + R'OH	-	+	+	±	-	±	±	+	+	+	+	+	+	+
19-37 RCOOH \longrightarrow RCH ₂ OH	-	-	+	+	-	±	-	+	+	+	-	+	+	-
19-37 RCOO ⁻ \longrightarrow RCH ₂ OH	-	-	+	-	-	-	-	+	+	+	-	-	-	-
19-64														
19-41 RCONR ₂ ' $\begin{cases} \longrightarrow \text{RCH}_2\text{NR}_2' \\ \longrightarrow \text{RCHO} \end{cases}$	-	-	-	+	+	+	-	+	+	+	+	+	+	+
19-43 RC≡N \longrightarrow RCH ₂ NH ₂	-	-	-	+	-	±	-	+	+	+	±	+	+	+
19-45														
19-80 RCONR ₂ ' $\begin{cases} \longrightarrow \text{RCH}_2\text{NR}_2' \\ \longrightarrow \text{RCHO} \end{cases}$	-	-	-	-	-	-	-	+	+	-	-	+	+	+
15-11 RCH=CHR \longrightarrow RCH ₂ CH ₂ R	-	-	-	+	+	+	-	-	-	-	+	-	-	+

TABLE 19.5 (Continued)

Reaction ^b	A ^c	B ^c	C ^c	D ^{c,d}	E ^{c,e}	F ^{c,f}	G ^c	H ^c	I ^c	J ^{c,g}	K ^{c,h}	L ^c	M ^c	N ^c
19-53 $\text{RX} + \text{LiAlH}_4 \longrightarrow \text{RH}$														
19-57 $\text{R}-\text{OSO}_2\text{R}' + \text{LiAlH}_4 \longrightarrow \text{RH}$														
19-35 														

^asee Ref. 847.^bA ± indicates a borderline case.^cA = NaBH₄ in EtOH, B = NaBH₄ + LiCl in diglyme, C = NaBH₄ + AlCl₃ in diglyme, D = BH₃-THF, E = bis [3-methyl-2-butylborane (disiamylborane)] in THF, F = 9-BBN, G = LiAlH(O*i*-Bu)₃ in THF, H = LiAlH(OMe)₃ in THF, I = LiAlH₄ in ether, J = AlH₃ in THF, K = LiBEt₃H, L = (*i*Bu)₂AlH [DIBALH], M = NaAl(OCH₂CH₂OMe)₂H₂N = catalytic hydrogenation.^dsee Ref. 844.^esee Ref. 851^fsee Ref. 852^gsee Ref. 853^hsee Ref. 854ⁱsee Ref. 855^jsee Ref. 856

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carbon atom of a carbon-hetero single or multiple bond. However, BH₃^{857,858} and AlH₃⁸⁵⁹ are electrophiles (Lewis acids) and attack the heteroatom. This accounts for the different patterns of selectivity in the tables.

⁸⁵¹ Brown, H.C.; Bigley, D.B.; Arora, S.K.; Yoon, N.M. *J. Am. Chem. Soc.* **1970**, 92, 7161. For reductions with hexylborane, see Brown, H.C.; Heim, P.; Yoon, N.M. *J. Org. Chem.* **1972**, 37, 2942.

⁸⁵² Brown, H.C.; Krishnamurthy, S.; Yoon, N.M. *J. Org. Chem.* **1976**, 41, 1778.

⁸⁵³ See Yoon, N.M.; Brown, H.C. *J. Am. Chem. Soc.* 1968, 90, 2927.

⁸⁵⁴ Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, 45, 1. See Brown, H.C.; Singaram, B.; Singaram, S. *J. Organomet. Chem.* **1982**, 239, 43.

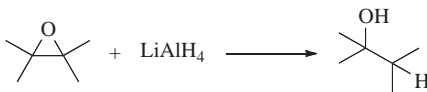
⁸⁵⁵ See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* **1970**, 92, 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, **1973**, pp. 319–371. Also see Wade, R.C. *J. Mol. Catal.*, **1983**, 18, 273; Lane, C.F. *Chem. Rev.* **1976**, 76, 773; *Aldrichimica Acta* **1977**, 10, 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* **1979**, 12, 3; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, pp. 125–164; Pelter, A. *Chem. Ind. (London)* **1976**, 888.

⁸⁵⁶ Reduced to a hydroxylamine (Reaction 19-46).

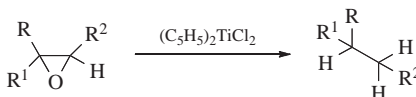
⁸⁵⁷ See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* **1970**, 92, 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, **1973**, pp. 319–371. For reviews of reductions with BH₃, see Wade, R.C. *J. Mol. Catal.* **1983**, 18, 273 (BH₃ and a catalyst); Lane, C.F. *Chem. Rev.* **1976**, 76, 773; *Aldrichimica Acta* **1977**, 10, 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* **1979**, 12, 3. For reviews of reduction with borane derivatives, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, **1988**, pp. 125–164; Pelter, A. *Chem. Ind. (London)* **1976**, 888.

⁸⁵⁸ Reacts with solvent, reduced in aprotic solvents.

⁸⁵⁹ Reduced to an aldehyde (Reaction 19-44).

B. Attack at Carbon (C—O And C=O)**19-35 Reduction of Epoxides****(3) *OC-seco*-Hydro-de-alkoxylation**

Reduction of epoxides is a special case of Reaction **19-56** and is easily carried out.⁸⁶⁰ A common reagent is LiAlH_4 ,⁸⁶¹ which reacts by the $\text{S}_{\text{N}}2$ -type mechanism, giving inversion of configuration. An epoxide on a substituted cyclohexane ring cleaves in such a direction as to give an axial alcohol. As expected for an $\text{S}_{\text{N}}2$ mechanism, the hydrogen atom is usually delivered to the less substituted carbon. The reaction has also been carried out with other reagents (e.g., sodium amalgam in EtOH, Li in ethylenediamine,⁸⁶² and by catalytic hydrogenolysis).⁸⁶³ Chemoselective and regioselective ring opening of allylic epoxides and of epoxy ketones and esters has been achieved with SmI_2 ,⁸⁶⁴ $\text{HCOOH}-\text{NEt}_3$ and a Pd catalyst,⁸⁶⁵ and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al; also known as Vitride).⁸⁶⁶ Highly hindered epoxides can be conveniently reduced, without rearrangement, with lithium triethylborohydride (called Super Hydride).⁸⁶⁷ For certain substrates, the epoxide ring can be opened the other way by reduction with $\text{NaBH}_4-\text{ZrCl}_4$,⁸⁶⁸ Pd/C and HCOONH_4 ,⁸⁶⁹ or with BH_3 in THF.⁸⁷⁰



Epoxy ketones are selectively reduced with lithium naphthalenide⁸⁷¹ or Cp_2TiCl in THF/MeOH⁸⁷² to the β -hydroxyketone. Other reduction methods can lead to the epoxy alcohol. Reduction of epoxy amides with SmI_2 in methanol gave the α -hydroxyamide.⁸⁷³

Epi-sulfides can be reduced to give the alkene using Bu_3SnH in the presence of BEt_3 .⁸⁷⁴

⁸⁶⁰ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1019–1027.

⁸⁶¹ See Healy, E.F.; Lewis, J.D.; Minniear, A.B. *Tetrahedron Lett.* **1994**, 35, 6647.

⁸⁶² Brown, H.C.; Ikegami, S.; Kawakami, J.H. *J. Org. Chem.* **1970**, 35, 3243.

⁸⁶³ See Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, **1967**, pp. 478–485; Oshima, M.; Yamazaki, H.; Shimizu, I.; Nizar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, 111, 6280.

⁸⁶⁴ Molander, G.A.; La Belle, B.E.; Hahn, G. *J. Org. Chem.* **1986**, 51, 5259; Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, 28, 4437. See also, Miyashita, M.; Hoshino, M.; Suzuki, T.; Yoshikoshi, A. *Chem. Lett.* **1988**, 507.

⁸⁶⁵ Noguchi, Y.; Yamada, T.; Uchiro, H.; Kobayashi, S. *Tetrahedron Lett.* **2000**, 41, 7493, 7499.

⁸⁶⁶ Gao, Y.; Sharpless, K.B. *J. Org. Chem.* **1988**, 53, 4081.

⁸⁶⁷ Krishnamurthy, S.; Schubert, R.M.; Brown, H.C. *J. Am. Chem. Soc.* **1973**, 95, 8486.

⁸⁶⁸ Laxmi, Y.R.S.; Iyengar, D.S. *Synth. Commun.* **1997**, 27, 1731.

⁸⁶⁹ Ley, S.V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.Q.; Zhou, W. *Org. Lett.* **2003**, 5, 4665.

⁸⁷⁰ See Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, **1973**, pp. 345–348. See also, Yamamoto, Y.; Toi, H.; Sonoda, A.; Murahashi, S. *J. Chem. Soc. Chem. Commun.* **1976**, 672.

⁸⁷¹ Jankowska, R.; Liu, H.-J.; Mhehe, G.L. *Chem. Commun.* **1999**, 1581.

⁸⁷² Hardouin, C.; Chevallier, F.; Rousseau, B.; Doris, E. *J. Org. Chem.* **2001**, 66, 1046.

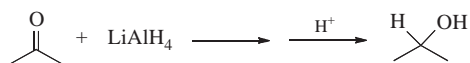
⁸⁷³ Concellón, J.M.; Bardales, E. *Org. Lett.* **2003**, 5, 4783.

⁸⁷⁴ Uenishi, J.; Kubo, Y. *Tetrahedron Lett.* **1994**, 35, 6697.

The usual product of epoxide reductions is the alcohol, but epoxides are reduced all the way to the alkane by titanocene dichloride⁸⁷⁵ and by $\text{Et}_3\text{SiH}-\text{BH}_3$.⁸⁷⁶

19-36 Reduction of Aldehydes and Ketones to Alcohols⁸⁷⁷

C,O-Dihydro-addition



Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, by a number of reducing agents.⁸⁷⁸ Among the most common are the metal hydrides (e.g., LiAlH_4 , NaBH_4 , and related compounds).⁸⁷⁹ These reagents have two main advantages over many other reducing agents: They do not reduce carbon-carbon double or triple bonds (with the exception of propargylic alcohols),⁸⁸⁰ and with LiAlH_4 all four hydrogen atoms are theoretically usable for reduction. Methods are available for titrating hydride reagents.⁸⁸¹ The scope of these reagents with ketones is similar to that with aldehydes. Lithium aluminum hydride reduces even sterically hindered ketones.

The reaction is broad and general. Lithium aluminum hydride easily reduces aliphatic, aromatic, alicyclic, and heterocyclic aldehydes or ketones, containing double or triple bonds and/or nonreducible groups (e.g., NR_3 , OH, OR, and F). If the molecule contains a group reducible by LiAlH_4 (e.g., NO_2 , CN, COOR), then that group is usually reduced. Since LiAlH_4 reacts readily with water and alcohols, protic solvents must be excluded. Despite limited solubility, common solvents are ether and THF.

The compound NaBH_4 (sodium borohydride) has a similar scope, but is less reactive, so it is more selective and so may be used with NO_2 , Cl, COOR, CN, and so on in the molecule. Another advantage of NaBH_4 is that it can be used in water or alcoholic solvents, and so reduces compounds, (e.g., sugars) that are not soluble in ethers.⁸⁸² Other solvents can be used with some modification of the borohydride. For example, butyltriphenylphosphonium borohydride reduces aldehydes to alcohols in dichloromethane.⁸⁸³ Reduction with solid acid activated NaBH_4 has been reported.⁸⁸⁴ A polymer-bound phase-transfer material with NaBH_4 in wet THF has also been used.⁸⁸⁵ Sodium borohydride on

⁸⁷⁵ van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* **1974**, 96, 5290.

⁸⁷⁶ Fry, J.L.; Mraz, T.J. *Tetrahedron Lett.* **1979**, 849.

⁸⁷⁷ See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 347-422.

⁸⁷⁸ See Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, **1984**, pp. 96-129. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1075-1113.

⁸⁷⁹ See Abdel-Magid, A.F. (Ed.) *Reductions in Organic Synthesis* American Chemical Society Washington, **1996**; Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, **1991**; Hajos, A. *Complex Hydrides*, Elsevier, NY, **1979**; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 49-71; Wheeler, O.H. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, **1966**, pp. 507-566.

⁸⁸⁰ See Meta, C.T.; Koide, K. *Org. Lett.* **2004**, 6, 1785.

⁸⁸¹ Hoye, T.R.; Aspaas, A.W.; Eklov, B.M.; Ryba, T.D. *Org. Lett.* **2005**, 7, 2205.

⁸⁸² See Toda, F.; Kiyoshige, K.; Yagi, M. *Angew. Chem. Int. Ed.* **1989**, 28, 320.

⁸⁸³ Hajipour, A.R.; Mallakpour, S.E. *Synth. Commun.* **2001**, 31, 1177.

⁸⁸⁴ Cho, B.T.; Kang, S.K.; Kim, M.S.; Ryu, S.R.; An, D.K. *Tetrahedron* **2006**, 62, 8164.

⁸⁸⁵ Tamami, B.; Mahdavi, H. *Tetrahedron* **2003**, 59, 821.

alumina, under microwave irradiation, is an effective reagent.⁸⁸⁶ Sodium borohydride has been used on silica gel.⁸⁸⁷

Red-Al was prepared by Vit in 1967,⁸⁸⁸ and its reducing power is close to that of LiAlH_4 . In addition, it is stable to dry air (it does not ignite in even moist air or oxygen), and is thermally stable up to 200 °C. The greatest practical utility of Red-Al is its solubility in aromatic hydrocarbon and ether solvents, which allows it to be conveniently used for applications that require inverse addition of hydrides. Red-Al essentially reacts the same as LiAlH_4 , reducing aldehydes, ketones⁸⁸⁹ and acid derivatives to alcohols.⁸⁹⁰ Reduction of conjugated carbonyls gives primarily 1,2-reduction to an allylic alcohol.⁸⁹¹ Other functional groups can be reduced.⁸⁹²

The $\text{C}=\text{C}$ units in compounds that contain double bonds are generally not affected by metallic hydrides, and the $\text{C}=\text{C}$ unit may be isolated or conjugated, but double bonds that are conjugated with the $\text{C}=\text{O}$ group may or may not be reduced, depending on the substrate, reagent, and reaction conditions.⁸⁹³ Some reagents that reduce only the $\text{C}=\text{O}$ bonds of α,β -unsaturated aldehydes and ketones are AlH_3 ,⁸⁹⁴ NaBH_4 , or LiAlH_4 in the presence of lanthanide salts,⁸⁹⁵ Co complexes,⁸⁹⁶ $\text{NaBH}_4\text{—LiClO}_4$,⁸⁹⁷ Ni compounds,⁸⁹⁸ $\text{NaBH}_3(\text{OAc})$,⁸⁹⁹ $\text{Zn}(\text{BH}_4)_2$ ⁹⁰⁰ on Y-zeolite,⁹⁰¹ and Et_3SiH .⁹⁰² Also, both LiAlH_4 ⁹⁰³ and NaBH_4 ⁹⁰⁴ predominantly reduce only the $\text{C}=\text{O}$ bonds of $\text{C}=\text{C—C}=\text{O}$ systems in most cases, although substantial amounts of fully saturated alcohols have been found in some cases⁹⁰³ (Reaction 15-14). For some reagents that reduce only the $\text{C}=\text{C}$ bonds of conjugated aldehydes and ketones, see Reaction 15-11. A mixture of InCl_3 and NaBH_4 reduced both the $\text{C}=\text{C}$ and $\text{C}=\text{O}$ units of conjugated ketones.⁹⁰⁵

⁸⁸⁶ Varma, R.S.; Saini, R.K. *Tetrahedron Lett.* **1997**, 38, 4337.

⁸⁸⁷ Liu, W.-y.; Xu, Q.-h.; Ma, Y.-x. *Org. Prep. Proceed. Int.* **2000**, 32, 596.

⁸⁸⁸ Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis Vol. 2*, Wiley, New York, **1969**, p. 382; Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis Vol. 3*, Wiley, New York, **1972**, p. 260; Vit, J.; Cásensky, B.; Macháček, J. *Fr. Pa.*, 1,515,582 1968 [*Chem. Abstr.* 70: 115009x, **1967**].

⁸⁸⁹ Capka, M.; Chvalovsky, V.; Kochloefl, K.; Kraus, M. *Collect. Czech. Chem. Commun.* **1969**, 34, 118; Stotter, P.L.; Friedman, M.D.; Minter, D.E. *J. Org. Chem.* **1985**, 50, 29.

⁸⁹⁰ Zurfliih, R.; Dunham, L.L.; Spain, V.L.; Siddall, J.B. *J. Am. Chem. Soc.* **1970**, 92, 425.

⁸⁹¹ Markezich, R.L.; Willy, W.E.; McCarry, B.E.; Johnson, W.S. *J. Am. Chem. Soc.* **1973**, 95, 4414; McCarry, B. E.; Markezich, R.L.; Johnson, W.S. *J. Am. Chem. Soc.* **1973**, 95, 4416.

⁸⁹² See Kesenheimer, C.; Groth, U. *Org. Lett.* **2006**, 8, 2507; White, J.D.; Choi, Y. *Org. Lett.* **2000**, 2, 2373; Gao, Y.; Sharpless, K.B. *J. Org. Chem.* **1988**, 53, 4081. Maloney, D.J.; Hecht, S.M. *Org. Lett.* **2005**, 7, 4297

⁸⁹³ See Keinan, E.; Greenspoon, N. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, **1989**, pp. 923–1022.

⁸⁹⁴ Dilling, W.L.; Plepys, R.A. *J. Org. Chem.* **1970**, 35, 2971.

⁸⁹⁵ See Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1929. See also, Chênevert, R.; Ampleman, G. *Chem. Lett.* **1985**, 1489; Varma, R.S.; Kabalka, G.W. *Synth. Commun.* **1985**, 15, 985.

⁸⁹⁶ Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, 3, 2543.

⁸⁹⁷ Halimjani, A.Z.; Saidi, M.R. *Synth. Commun.* **2005**, 35, 2271.

⁸⁹⁸ Khurana, J.M.; Chauhan, S. *Synth. Commun.* **2001**, 31, 3485.

⁸⁹⁹ Nutaitis, C.F.; Bernardo, J.E. *J. Org. Chem.* **1989**, 54, 5629.

⁹⁰⁰ For a review of the reactivity of this reagent, see Ranu, B. *Synlett* **1993**, 885.

⁹⁰¹ Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Tetrahedron Lett.* **1998**, 39, 5151.

⁹⁰² Ojima, I.; Kogure, T. *Organometallics* **1982**, 1, 1390.

⁹⁰³ Johnson, M.R.; Rickborn, B. *J. Org. Chem.* **1970**, 35, 1041.

⁹⁰⁴ Chaikin, S.W.; Brown, W.G. *J. Am. Chem. Soc.* **1949**, 71, 122.

⁹⁰⁵ Ranu, B.C.; Samanta, S. *Tetrahedron* **2003**, 59, 7901.

When a functional group is selectively attacked in the presence of a different functional group, the reaction is said to be *chemoselective*.⁹⁰⁶ A number of reagents have been found to reduce aldehydes much faster than ketones. Among these⁹⁰⁷ are sodium triacetoxyborohydride⁹⁰⁸ ($\text{NaBH}_4\text{—HCO}_2\text{H}$),⁹⁰⁹ zinc borohydride in THF,⁹¹⁰ a complex of LiAlH_4 and *N*-methyl-2-pyrrolidinone (of particular interest since it is stable in air and to heating),⁹¹¹ and Raney nickel.⁹¹²

Ketones can be chemoselectively reduced in the presence of aldehydes with NaBH_4 in aq EtOH at -15°C in the presence of cerium trichloride (CeCl_3).⁹¹³ The reagent lithium *n*-dihydropyridylaluminum hydride reduces diaryl ketones much better than dialkyl or alkyl aryl ketones.⁹¹⁴ Most other hydrides reduce diaryl ketones more slowly than other types of ketones. Saturated ketones can be reduced in the presence of α,β -unsaturated ketones with $\text{NaBH}_4\text{—}50\% \text{ MeOH—CH}_2\text{Cl}_2$ at -78°C ,⁹¹⁵ and with zinc borohydride.⁹¹⁶

In general, NaBH_4 reduces carbonyl compounds in the order aldehydes $> \alpha,\beta$ -unsaturated aldehydes $>$ ketones $> \alpha,\beta$ -unsaturated ketones, and a carbonyl group of one type can be selectively reduced in the presence of a carbonyl group of a less reactive type.⁹¹⁷ A number of reagents will preferentially reduce the less sterically hindered of two carbonyl compounds, but by the use of Dibal-H in the presence of the Lewis acid methylaluminum bis(2,16-di-*tert*-butyl-4-methylphenoxide), it was possible selectively to reduce the *more hindered* of a mixture of two ketones.⁹¹⁸ It is obvious that reagents can often be found to reduce one kind of carbonyl function in the presence of another.⁹¹⁹ For a discussion of selectivity in reduction reactions (see Sec. 19.B.ii-A). A syn-selective reduction of β -hydroxy ketones was achieved using $(i\text{PrO})_2\text{TiBH}_4$.⁹²⁰ Quinones are reduced to hydroquinones by LiAlH_4 , $\text{SnCl}_2\text{—HCl}$, or sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_4$), as well as by other reducing agents.

The reagent lithium tri-*sec*-butylborohydride [$\text{LiBH}(\text{sec-Bu})_3$, L-Selectride] reduces cyclic and bicyclic ketones in a highly stereoselective manner.⁹²¹ For example, 2-methylcyclohexanone gave *cis*-2-methylcyclohexanol with an isomeric purity $> 99\%$. Both L-Selectride and the potassium salt (K-Selectride) reduce carbonyls in cyclic and acyclic molecules with high diastereoselectivity.⁹²² The more usual reagents (e.g., LiAlH_4 and NaBH_4) reduce relatively

⁹⁰⁶ See Luibrand, R.T.; Taigounov, I.R.; Taigounov, A.A. *J. Org. Chem.* **2001**, 66, 7254.

⁹⁰⁷ See Borbaruah, M.; Barua, N.C.; Sharma, R.P. *Tetrahedron Lett.* **1987**, 28, 5741.

⁹⁰⁸ Gribble, G.W.; Ferguson, D.C. *J. Chem. Soc. Chem. Commun.* **1975**, 535. See also, Nutaitis, C.F.; Gribble, G.W. *Tetrahedron Lett.* **1983**, 24, 4287.

⁹⁰⁹ Blanton, J.R. *Synth. Commun.* **1997**, 27, 2093.

⁹¹⁰ Ranu, B.C.; Chakraborty, R. *Tetrahedron Lett.* **1990**, 31, 7663; See Ranu, B. *Synlett* **1993**, 885.

⁹¹¹ Fuller, J.C.; Stangeland, E.L.; Jackson, T.C.; Singaram, B. *Tetrahedron Lett.* **1994**, 35, 1515. See also, Mogali, S.; Darville, K.; Pratt, L.M. *J. Org. Chem.* **2001**, 66, 2368.

⁹¹² Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* **2000**, 197.

⁹¹³ See Li, K.; Hamann, L.G.; Koreeda, M. *Tetrahedron Lett.* **1992**, 33, 6569.

⁹¹⁴ Lansbury, P.T.; Peterson, J.O. *J. Am. Chem. Soc.* **1962**, 84, 1756.

⁹¹⁵ Ward, D.E.; Rhee, C.K.; Zoghaib, W.M. *Tetrahedron Lett.* **1988**, 29, 517.

⁹¹⁶ Sarkar, D.C.; Das, A.R.; Ranu, B.C. *J. Org. Chem.* **1990**, 55, 5799.

⁹¹⁷ Ward, D.E.; Rhee, C.K. *Can. J. Chem.* **1989**, 67, 1206.

⁹¹⁸ Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, 110, 2650.

⁹¹⁹ For lists, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1089–1092, and references given in Ward, D.E.; Rhee, C.K. *Can. J. Chem.* **1989**, 67, 1206.

⁹²⁰ Ravikumar, K.S.; Sinha, S.; Chandrasekaran, S. *J. Org. Chem.* **1999**, 64, 5841.

⁹²¹ Krishnamurthy, S.; Brown, H.C. *J. Am. Chem. Soc.* **1976**, 98, 3383.

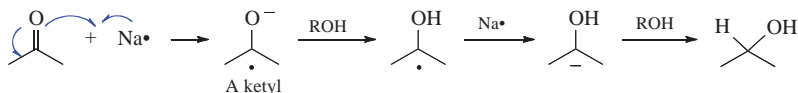
⁹²² K-Selectride: Lawson, E.C.; Zhang, H.-C.; Maryanoff, B.E. *Tetrahedron Lett.* **1999**, 40, 593.

unhindered cyclic ketones either with little or no stereoselectivity⁹²³ or give predominant formation of the more stable isomer (axial attack).⁹²⁴ Reduction of cyclohexanone derivatives with the very hindered $\text{LiAlH}(\text{Cet}_2\text{CMe}_3)_3$ gave primarily the cis-alcohol.⁹²⁵ Cyclohexanones that have a large degree of steric hindrance near the carbonyl group usually give predominant formation of the less stable alcohol, even with LiAlH_4 and NaBH_4 .

Other reagents reduce aldehydes and ketones to alcohols,⁹²⁶ including the following:

1. *Hydrogen and a Catalyst.*⁹²⁷ Common heterogeneous catalysts for carbonyls are Pt and Ru,⁹²⁸ and homogeneous catalysts are commonly used,⁹²⁹ especially for asymmetric hydrogenation (see **A** below). Before the discovery of the metal hydrides, this was one of the most common ways of effecting this reduction, but it suffers from the fact that $\text{C}=\text{C}$, $\text{C}\equiv\text{C}$, $\text{C}=\text{N}$ and $\text{C}\equiv\text{N}$ bonds are often more susceptible to attack than $\text{C}=\text{O}$ bonds.⁹³⁰ For aromatic aldehydes and ketones, reduction to the hydrocarbon (Reaction **19-61**) is a side reaction via hydrogenolysis of the initially produced alcohol (Reaction **19-54**). The mechanism of catalytic hydrogenation of aldehydes and ketones is probably similar to that of reaction **15-11**.⁹³¹
2. *Sodium in Ethanol.*⁹³² This is called the *Bouveault-Blanc procedure* and was more popular for the reduction of carboxylic esters (Reaction **19-38**) than of aldehydes or ketones before the discovery of LiAlH_4 .

For the reaction with sodium in ethanol the following mechanism⁹³³ has been suggested:⁹³⁴



⁹²³ Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* **1983**, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* **1979**, 11, 53; Wigfield, D.C. *Tetrahedron* **1979**, 35, 449; Tramontini, M. *Synthesis* **1982**, 605.

⁹²⁴ See Mukherjee, D.; Wu, Y.; Fronczek, F.R.; Houk, K.N. *J. Am. Chem. Soc.* **1988**, 110, 3328.

⁹²⁵ Boireau, G.; Deberly, A.; Toneva, R. *Synlett* **1993**, 585

⁹²⁶ See Feoktistov, L.G.; Lund, H. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, **1983**, pp. 315–358, 315–326. See also, Coche, L.; Moutet, J. *J. Am. Chem. Soc.* **1987**, 109, 6887.

⁹²⁷ Abdel-Magid, A.F., Ed., *Reductions in Organic Synthesis* American Chemical Society, Washington, DC, **1996**, pp. 31–50; Parker, D. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, **1987**, pp. 979–1047; Tanaka, K. in Cervený, L. *Catalytic Hydrogenation*, Elsevier, NY, **1986**, pp. 79–104; Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, **1985**, pp. 66–77; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, **1967**, pp. 238–290.

⁹²⁸ Hedberg, C.; Källström, K.; Arvidsson, P.I.; Brandt, P.; Andersson, P.G. *J. Am. Chem. Soc.* **2005**, 127, 15083.

⁹²⁹ See Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, **1974**, pp. 65–70; Enthaler, S.; Hagemann, B.; Erre, G.; Junge, K.; Beller, M. *Chemistry: Asian J.* **2006**, 1, 598.

⁹³⁰ See Narasimhan, C.S.; Deshpande, V.M.; Ramnarayan, K. *J. Chem. Soc. Chem. Commun.* **1988**, 99.

⁹³¹ See, however, Pavlenko, N.V. *Russ. Chem. Rev.* **1989**, 58, 453.

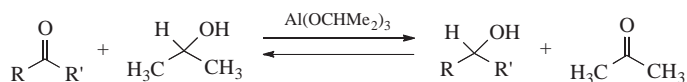
⁹³² See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, pp. 152–160.

⁹³³ Pradhan, S.K. *Tetrahedron* **1986**, 42, 6351; Huffman, J.W. *Acc. Chem. Res.* **1983**, 16, 399. See Rautenstrauch, V. *Tetrahedron* **1988**, 44, 1613; Song, W.M.; Dewald, R.R. *J. Chem. Soc. Perkin Trans. 2*, **1989**, 269; Rassat, A. *Pure Appl. Chem.* **1977**, 49, 1049.

⁹³⁴ House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, p. 151. See, however, Giordano, C.; Perdoncin, G.; Castaldi, G. *Angew. Chem. Int. Ed.* **1985**, 24, 499.

The ketyl intermediate can be isolated.⁹³⁵ Lithium is often a superior metal for alkali metal reductions.⁹³⁶

3. *Other Metal Reductions.* A single carbonyl group of an α -diketone can be reduced to give an α -hydroxy ketone, by heating with Zn powder in aq DMF⁹³⁷ or Zn in methanol in the presence of benzyltriethylammonium chloride.⁹³⁸ Aluminum and NaOH in aq methanol reduces ketones.⁹³⁹ β -Hydroxy ketones are reduced with good antiselectivity using an excess of SmI_2 in water,⁹⁴⁰ and other ketones or aldehydes are reduced with SmI_2 ⁹⁴¹ in aq THF,⁹⁴² or in alcohols.⁹⁴³ Other metals can be used, including FeCl_3/Zn in aq DMF⁹⁴⁴ or Mg in alcohols.⁹⁴⁵ 1,2-Diketones were reduced to the α -hydroxy ketone with TiI_4 in acetonitrile, followed by hydrolysis.⁹⁴⁶ Ammonia and aq TiCl_3 in methanol reduces ketones.⁹⁴⁷
4. *Isopropyl Alcohol and Aluminum Isopropoxide.* This is called the *Meerwein-Ponndorf-Verley reduction*.⁹⁴⁸ It is reversible, and the reverse reaction is known as the *Oppenauer oxidation* (see **19-3**):



The equilibrium is shifted by removal of the acetone by distillation. There is a report of the reduction of benzaldehyde to benzyl alcohol by heating with 2-propanol at 225 °C for 1 day.⁹⁴⁹ The reaction usually takes place under very mild conditions and is highly specific for aldehydes and ketones, so that C=C bonds (including those conjugated with the C=O bonds) and many other functional groups can be present without themselves being reduced.⁹⁵⁰ This includes acetals, so that one of two carbonyl groups in a molecule can be specifically reduced if the other is first converted to an acetal. β -Keto esters, β -diketones, and other ketones and aldehydes with a relatively high enol content do not give this reaction. Zeolites have been used as a medium for this reduction.⁹⁵¹ This reduction can be done catalytically⁹⁵² and an

⁹³⁵ See Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1976**, 98, 5035; **1977**, 99, 6280.

⁹³⁶ Rees, N.V.; Baron, R.; Kershaw, N.M.; Donohoe, T.J.; Compton, R.G. *J. Am. Chem. Soc.* **2008**, 130, 12256.

⁹³⁷ Kreiser, W. *Liebigs Ann. Chem.* **1971**, 745, 164.

⁹³⁸ Kardile, G.B.; Desai, D.G.; Swami, S.S. *Synth. Commun.* **1999**, 29, 2129.

⁹³⁹ Bhar, S.; Guha, S. *Tetrahedron Lett.* **2004**, 45, 3775.

⁹⁴⁰ Keck, G.E.; Wager, C.A.; Sell, T.; Wager, T.T. *J. Org. Chem.* **1999**, 64, 2172.

⁹⁴¹ See Prasad, E.; Flowers II, R.A. *J. Am. Chem. Soc.* **2002**, 124, 6895.

⁹⁴² Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, 43, 7197.

⁹⁴³ Fukuzawa, S.-i.; Nakano, N.; Saitoh, T. *Eur. J. Org. Chem.* **2004**, 2863.

⁹⁴⁴ Sadavarte, V.S.; Swami, S.S.; Desai, D.G. *Synth. Commun.* **1998**, 28, 1139.

⁹⁴⁵ Kim, J.Y.; Kim, H.D.; Seo, M.J.; Kim, H.R.; No, Z.; Ha, D.-C.; Lee, G.H. *Tetrahedron Lett.* **2006**, 47, 9; Chopade, P.R.; Davis, T.A.; Prasad, E.; Flowers, II, R.A. *Org. Lett.* **2004**, 6, 2685.

⁹⁴⁶ Hayakawa, R.; Sahara, T.; Shimizu, M. *Tetrahedron Lett.* **2000**, 41, 7939.

⁹⁴⁷ Clerici, A.; Pastori, N.; Porta, O. *Eur. J. Org. Chem.* **2001**, 2235.

⁹⁴⁸ See Maruoka, K.; Saito, S.; Concepcion, A.B.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, 115, 1183. For a microwave-induced version of this reaction, see Barbry, D.; Torchy, S. *Tetrahedron Lett.* **1997**, 38, 2959.

⁹⁴⁹ Bagnell, L.; Strauss, C.R. *Chem. Commun.* **1999**, 287.

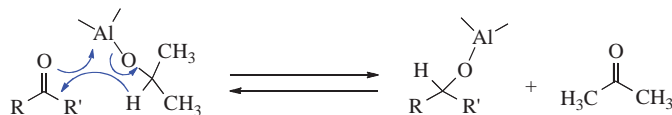
⁹⁵⁰ See Hutton, J. *Synth. Commun.* **1979**, 9, 483; Namy, J.L.; Soupe, J.; Collin, J.; Kagan, H.B. *J. Org. Chem.* **1984**, 49, 2045; Okano, T.; Matsuoka, M.; Konishi, H.; Kiji, J. *Chem. Lett.* **1987**, 181.

⁹⁵¹ Corma, A.; Domine, M.E.; Nemeth, L.; Valencia, S. *J. Am. Chem. Soc.* **2002**, 124, 3194.

⁹⁵² Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Org. Lett.* **2001**, 3, 2391. See Albrecht, M.; Crabtree, R.H.; Mata, J.; Peris, E. *Chem. Commun.* **2002**, 32.

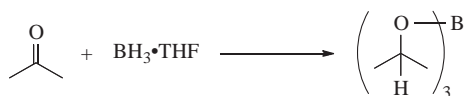
aluminum-free, Zr-zeolite catalyst has been developed.⁹⁵³ Microwave irradiation of a ketone with 2-propanol, KOH, and activated alumina gives good yields of the alcohol.⁹⁵⁴ When the carbonyl substrate has a stereogenic center, the reaction proceeds with good diastereoselectivity.⁹⁵⁵ The use of chiral metal complexes leads to chiral hydrogen transfer.⁹⁵⁶ A combination of 2-propanol with BINOL and AlMe₃ leads to reduction of α -chloroketones to the chlorohydrin with good enantioselectivity.⁹⁵⁷

The *Meerwein-Ponndorf-Verley reaction* usually⁹⁵⁸ involves a cyclic transition state:⁹⁵⁹



but in some cases 2 molar equivalents of aluminum alkoxide are involved: one attacking the carbon and the other the oxygen, a conclusion that stems from the finding that in these cases the reaction was 1.5 order in alkoxide.⁹⁶⁰ The alcohol solvent acts as a hydrogen donor in this reaction.⁹⁶¹ Although, for simplicity, the alkoxide is shown as a monomer, it actually exists as trimers and tetramers, which are the actual reactive species.⁹⁶² Note that supercritical 2-propanol has been used for reduction of ketones, without the need for a catalyst.⁹⁶³

5. *Boranes*. Borane (BH₃) and substituted boranes reduce aldehydes and ketones in a manner similar to their addition to C=C bonds (Reaction **15-16**).⁹⁶⁴ That is, the boron adds to the oxygen and the hydrogen to the carbon:⁹⁶⁵



⁹⁵³ Zhu, Y.; Chuah, G.; Jaenicke, S. *Chem. Commun.* **2003**, 2734.

⁹⁵⁴ Kazemi, F.; Kiasat, A.R. *Synth. Commun.* **2002**, 32, 2255.

⁹⁵⁵ Yin, J.; Huffman, M.A.; Conrad, K.M.; Armstrong, III, J.D. *J. Org. Chem.* **2006**, 71, 840.

⁹⁵⁶ Dong, Z.-R.; Li, Y.-Y.; Chen, J.-S.; Li, B.-Z.; Xing, Y.; Gao, J.-X. *Org. Lett.* **2005**, 7, 1043; Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem. Int. Ed.* **2006**, 45, 3819.

⁹⁵⁷ Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Angew. Chem. Int. Ed.* **2002**, 41, 1020.

⁹⁵⁸ See, however, Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* **1986**, 51, 3593; Yamataka, H.; Hanafusa, T. *Chem. Lett.* **1987**, 643.

⁹⁵⁹ See Warnhoff, E.W.; Reynolds-Warnhoff, P.; Wong, M.Y.H. *J. Am. Chem. Soc.* **1980**, 102, 5956.

⁹⁶⁰ Moulton, W.N.; Van Atta, R.E.; Ruch, R.R. *J. Org. Chem.* **1961**, 26, 290.

⁹⁶¹ Galian, R.E.; Litwinienko, G.; Pérez-Prieto, J.; Ingold, K.U. *J. Am. Chem. Soc.* **2007**, 129, 9280.

⁹⁶² Shiner, Jr., V.J.; Whittaker, D. *J. Am. Chem. Soc.* **1969**, 91, 394.

⁹⁶³ Kamitanaka, T.; Matsuda, T.; Harada, T. *Tetrahedron* **2007**, 63, 1429.

⁹⁶⁴ See Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, **1973**, pp. 324–335. See Cha, J. S.; Moon, S.J.; Park, J.H. *J. Org. Chem.* **2001**, 66, 7514.

⁹⁶⁵ Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* **1960**, 82, 681; Brown, H.C.; Korytnyk, W. *J. Am. Chem. Soc.* **1960**, 82, 3866.

The resulting borate is then hydrolyzed to the alcohol. A variety of alkylboranes can be used for reduction.⁹⁶⁶ Both 9-BBN⁹⁶⁷ (Reaction **15-16**) and $\text{BH}_3\text{—Me}_2\text{S}$ ⁹⁶⁸ reduce only the C=O group of conjugated aldehydes and ketones.⁹⁶⁹ Tributylborane in ionic solvents reduces aldehydes to alcohols.⁹⁷⁰ Enantioselective borane reductions lead to chiral alcohols.⁹⁷¹ Spiroborate esters have been used for enantioselective reduction,⁹⁷² and chiral boronic esters have also been used.⁹⁷³

Alane (AlH_3) derivatives can also be used, including diisobutylaluminum hydride.⁹⁷⁴

6. *Tin Hydrides*. Tributyltin hydride reduces aldehydes to primary alcohols by simply heating in methanol.⁹⁷⁵ A mixture of Bu_3SnH and phenylboronic acid (Reaction **12-28**) reduces aldehydes in dichloromethane.⁹⁷⁶ Reduction of ketones was achieved with Bu_2SnH_2 and a Pd catalyst.⁹⁷⁷ Using triaryl tin hydrides with $\text{BF}_3\cdot\text{OEt}_2$, where aryl is 2,6-diphenylbenzyl, selective reduction of aliphatic aldehydes in the presence of a conjugated aldehyde was achieved.⁹⁷⁸ Tris(trimethylsilyl)methane has been used as a tin-free radical reducing agent.⁹⁷⁹
7. *Cannizzaro Reaction*. In the Cannizzaro reaction (see **19-81**), aldehydes without an α hydrogen are reduced to alcohols.
8. *Silanes*. In the presence of bases, certain silanes can selectively reduce carbonyls.⁹⁸⁰ Transition metal complexes also catalyze hydrosilylation of ketones.⁹⁸¹ Controlling temperature and solvent leads to different ratios of *syn* and *anti* products.⁹⁸² Silanes reduce ketones in the presence of $\text{BF}_3\cdot\text{OEt}_2$.⁹⁸³ Ketones are reduced with Cl_3SiH in the presence of pyrrolidine carbaldehyde⁹⁸⁴ or under

⁹⁶⁶ See Bae, J.W.; Lee, S.H.; Jung, Y.J.; Yoon, C.-O.M.; Yoon, C.M. *Tetrahedron Lett.* **2001**, 42, 2137.

⁹⁶⁷ Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* **1975**, 40, 1864; Lane, C.F. *Aldrichimica Acta* **1976**, 9, 31.

⁹⁶⁸ Mincione, E. *J. Org. Chem.* **1978**, 43, 1829.

⁹⁶⁹ Bartoli, G.; Bosco, M.; Bellucci, M.C.; Daplozzo, R.; Marcantoni, E.; Sambri, L. *Org. Lett.* **2000**, 2, 45.

⁹⁷⁰ Kabalka, G.W.; Malladi, R.R. *Chem. Commun.* **2000**, 2191.

⁹⁷¹ Du, D.-M.; Fang, T.; Xu, J.; Zhang, S.-W. *Org. Lett.* **2006**, 8, 1327; Krzemiński, M.P.; Wojtczak, A. *Tetrahedron Lett.* **2005**, 46, 8299.

⁹⁷² Stepanenko, V.; De Jesús, M.; Correa, W.; Guzmán, I.; Vázquez, C.; de la Cruz, W.; Ortiz-Marciales, M.; Barnes, C.L. *Tetrahedron Lett.* **2007**, 48, 5799.

⁹⁷³ Eagon, S.; Kim, J.; Yan, K.; Haddenham, D.; Singaram, B. *Tetrahedron Lett.* **2007**, 48, 9025.

⁹⁷⁴ Nakamura, S.; Kuroyanagi, M.; Watanabe, Y.; Toru, T. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3143.

⁹⁷⁵ Kamiura, K.; Wada, M. *Tetrahedron Lett.* **1999**, 40, 9059; Adams, C.M.; Schemenaur, J.E. *Synth. Commun.* **1990**, 20, 2359. For a review, see Kuivila, H.G. *Synthesis* **1970**, 499.

⁹⁷⁶ Yu, H.; Wang, B. *Synth. Commun.* **2001**, 31, 2719.

⁹⁷⁷ Kamiya, I.; Ogawa, A. *Tetrahedron Lett.* **2002**, 43, 1701.

⁹⁷⁸ Sasaki, K.; Komatsu, N.; Shiyakawa, S.; Maruoka, K. *Synlett* **2002**, 575.

⁹⁷⁹ Perchyonok, V.T. *Tetrahedron Lett.* **2006**, 47, 5163.

⁹⁸⁰ Ison, E.A.; Trivedi, E.R.; Corbin, R.A.; Abu-Omar, M.M. *J. Am. Chem. Soc.* **2005**, 127, 15374.

⁹⁸¹ For a review, see Díez-González, S.; Nolan, S.P. *Org. Prep. Proceed. Int.* **2007**, 39, 523. See Chen, T.; Liu, X.-G.; Shi, M. *Tetrahedron* **2007**, 63, 4874; Fernandes, A.C.; Fernandes, R.; Romão, C.R.; Royo, B. *Chem. Commun.* **2005**, 213; Comte, V.; Balan, C.; Le Gendre, P.; Moïse, C. *Chem. Commun.* **2007**, 713; Nishiyama, H.; Furuta, A. *Chem. Commun.* **2007**, 760.

⁹⁸² See Yamamoto, Y.; Matsuoaka, K.; Nemoto, H. *J. Am. Chem. Soc.* **1988**, 110, 4475.

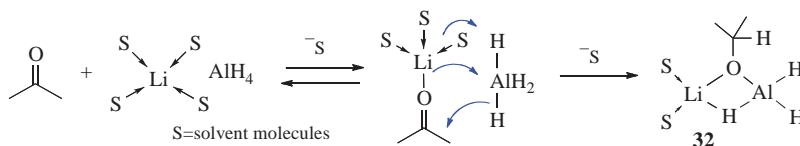
⁹⁸³ Smonou, I. *Tetrahedron Lett.* **1994**, 35, 2071.

⁹⁸⁴ Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, 40, 7507.

photochemical conditions.⁹⁸⁵ Polymethylhydrosiloxane with tetrabutylammonium fluoride reduces α -amino ketones to give the syn amino alcohol.⁹⁸⁶

9. *Ammonium Formates.* Sodium formate and trialkylammonium formates can be used to reduce aldehydes and ketones to the corresponding alcohol. Decanal was reduced to decanol, for example, using sodium formate in *N*-methyl-2-pyrrolidinone as a solvent.⁹⁸⁷ A mixture of formic acid and ethyl magnesium bromide was used to reduce decanal to decanol in 70% yield.⁹⁸⁸ Transfer hydrogenation also occurs with formic acid–triethylamine and a Ru catalyst⁹⁸⁹ in water.⁹⁹⁰
10. *Enzymatic Reductions.* Successful asymmetric reductions (see Section A) have been achieved with biologically derived reducing agents⁹⁹¹ (e.g., baker's yeast),⁹⁹² enzymes from other organisms,⁹⁹³ or with other biocatalysts.⁹⁹⁴ Ionic liquids have been used in conjugation with enzymatic reduction,⁹⁹⁵ and enzymatic reduction has been done in supercritical CO₂.⁹⁹⁶

With most reagents there is an initial attack on the carbon of the carbonyl group by a hydride equivalent (H^-) although with BH_3 ,⁹⁹⁷ the initial attack is on the oxygen. Detailed mechanisms are not known in most cases.⁹⁹⁸ With $LiAlH_4$ or $NaBH_4$, the attacking species is the AlH_4^- (or BH_4^-) ion, which, in effect, transfers H^- to the carbon. The following mechanism has been proposed for $LiAlH_4$.⁹⁹⁹



⁹⁸⁵ Enholm, E.J.; Schulte II, J.P. *J. Org. Chem.* **1999**, *64*, 2610.

⁹⁸⁶ Nadkarni, D.; Hallissey, J.; Mojica, C. *J. Org. Chem.* **2003**, *68*, 594.

⁹⁸⁷ Babler, J.H.; Sarussi, S.J. *J. Org. Chem.* **1981**, *46*, 3367.

⁹⁸⁸ Babler, J.H.; Invergo, B.J. *Tetrahedron Lett.* **1981**, *22*, 621.

⁹⁸⁹ Morris, D.J.; Hayes, A.M.; Wills, M. *J. Org. Chem.* **2006**, *71*, 7035.

⁹⁹⁰ Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3407.

⁹⁹¹ For a review, see Sih, C.J.; Chen, C. *Angew. Chem. Int. Ed.* **1984**, *23*, 570.

⁹⁹² See Wolfson, A.; Dlugy, C.; Tavor, D.; Blumenfeld, J.; Shotland, Y. *Tetrahedron Asymmetry* **2006**, *17*, 2043; Yadav, J.S.; Reddy, G.S.K.K.; Sabitha, G.; Krishna, A.D.; Prasad, A.R.; Rahaman, H.U.R.; Rao, K.V.; Rao, A.B. *Tetrahedron Asymmetry* **2007**, *18*, 717.

⁹⁹³ See Moore, J.C.; Pollard, D.J.; Kosjek, B.; Devine, P.N. *Acc. Chem. Res.* **2007**, *40*, 1412; Ema, T.; Yagasaki, H.; Okita, N.; Takeda, M.; Sakai, T. *Tetrahedron* **2006**, *62*, 6143; Hoyos, P.; Sansottera, G.; Fernández, M.; Molinari, F.; Sinisterra, J.V.; Alcántara, A.R. *Tetrahedron* **2008**, *64*, 7929; Utsukihara, T.; Misumi, O.; Kato, N.; Kuroiwa, T.; Horiuchi, C.A. *Tetrahedron Asymmetry* **2006**, *17*, 1179; Zhu, D.; Malik, H.T.; Hua, L. *Tetrahedron Asymmetry* **2006**, *17*, 3010; Lavandera, I.; Höller, B.; Kern, A.; Ellmer, U.; Glieder, A.; de Wildeman, S.; Kroutil, W. *Tetrahedron Asymmetry* **2008**, *19*, 1954. For enzymatic reduction of thio ketones, see Nielsen, J.K.; Madsen, J.Ø. *Tetrahedron Asymmetry*, **1994**, *5*, 403.

⁹⁹⁴ See Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron Asymmetry* **2003**, *14*, 2659.

⁹⁹⁵ Matsuda, T.; Yamagishi, Y.; Koguchi, S.; Iwai, N.; Kitazume, T. *Tetrahedron Lett.* **2006**, *47*, 4619; Bräutigam, S.; Bringer-Meyer, S.; Weuster-Botz, D. *Tetrahedron Asymmetry* **2007**, *18*, 1883.

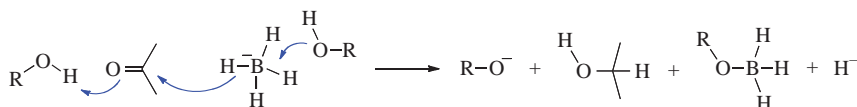
⁹⁹⁶ Matsuda, T.; Marukado, R.; Mukouyama, M.; Harada, T.; Nakamura, K. *Tetrahedron Asymmetry* **2008**, *19*, 2272.

⁹⁹⁷ See Brown, H.C.; Wang, K.K.; Chandrasekharan, J. *J. Am. Chem. Soc.* **1983**, *105*, 2340.

⁹⁹⁸ See Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* **1983**, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* **1979**, *11*, 53; Wigfield, D.C. *Tetrahedron* **1979**, *35*, 449.

⁹⁹⁹ Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* **1976**, *98*, 5524.

Evidence that the cation plays an essential role, at least in some cases, is that when the Li^+ was effectively removed from LiAlH_4 (by the addition of a crown ether), the reaction did not take place.¹⁰⁰⁰ Complex **32** must be hydrolyzed to the alcohol. For NaBH_4 , the Na^+ does not seem to participate in the transition state, but kinetic evidence shows that an OR group from the solvent does participate and remains attached to B.¹⁰⁰¹



Free H^- cannot be the attacking entity in most reductions with boron or aluminum hydrides because the reactions are frequently sensitive to the size of the MH_4^- [or MR_mH_n^- or $\text{M}(\text{OR})_m\text{H}_n^-$ etc.].

The question of whether the initial complex in the LiAlH_4 reduction (**32**, or $\text{H}-\text{C}-\text{OAl}^-\text{H}_3 = \text{33}$) can reduce another carbonyl to give $(\text{H}-\text{C}-\text{O})_2\text{Al}^-\text{H}_2$, and so on has been controversial. It has been shown¹⁰⁰² that this is probably not the case but that, more likely, **33** disproportionates to $(\text{H}-\text{C}-\text{O})_4\text{Al}^-$ and AlH_4^- , which is the only attacking species. Disproportionation has also been reported in the NaBH_4 reaction.¹⁰⁰³

Aluminate (**33**) is essentially LiAlH_4 with one of the hydrogen atoms replaced by an alkoxy group (i.e., LiAlH_3OR). The fact that **33** and other alkoxy derivatives of LiAlH_4 are less reactive than LiAlH_4 itself has led to the use of such compounds as reducing agents that are less reactive and more selective than LiAlH_4 .¹⁰⁰⁴ An example is $\text{LiAlH}(\text{O}-t\text{-Bu})_3$ (Reactions **19-39–19-41**; see also, Table 19.5). As an example of chemoselectivity in this reaction it may be mentioned that $\text{LiAlH}(\text{O}-t\text{-Bu})_3$ has been used to reduce only the keto group in a molecule containing both keto and carboxylic ester groups.¹⁰⁰⁵ However, the use of such reagents is sometimes complicated by the disproportionation mentioned above, which may cause LiAlH_4 to be the active species, even if the reagent is an alkoxy derivative. Another highly selective reagent (reducing aldehydes and ketones, but not other functional groups), which does not disproportionate, is potassium triisopropoxyborohydride.¹⁰⁰⁶

For other reduction reactions of aldehydes and ketones, see **19-61**, **19-76**, and **19-81**.

A. Asymmetric Reduction

Unsymmetrical ketones are prochiral (Sec. 4.M); that is, reduction creates a new stereogenic center:



¹⁰⁰⁰ Pierre, J.; Handel, H. *Tetrahedron Lett.* **1974**, 2317. See also, Loupy, A.; Seyden-Penne, J.; Tchoubar, B. *Tetrahedron Lett.* **1976**, 1677; Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* **1976**, 98, 5524.

¹⁰⁰¹ Wigfield, D.C.; Gowland, F.W. *J. Org. Chem.* **1977**, 42, 1108. See, however, Adams, C.; Gold, V.; Reuben, D. M.E. *J. Chem. Soc. Perkin Trans. 2* **1977**, 1466, 1472; Kayser, M.M.; Eliev, S.; Eisenstein, O. *Tetrahedron Lett.* **1983**, 24, 1015.

¹⁰⁰² Haubenstock, H.; Eliel, E.L. *J. Am. Chem. Soc.* **1962**, 84, 2363; Malmvik, A.; Obenius, U.; Henriksson, U. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1899, 1905.

¹⁰⁰³ Malmvik, A.; Obenius, U.; Henriksson, U. *J. Org. Chem.* **1988**, 53, 221.

¹⁰⁰⁴ For reviews of reductions with alkoxyaluminum hydrides, see Málek, J. *Org. React.* **1988**, 36, 249; **1985**, 34, 1; Málek, J.; Cerny, M. *Synthesis* **1972**, 217.

¹⁰⁰⁵ Levine, S.G.; Eudy, N.H. *J. Org. Chem.* **1970**, 35, 549; Heusler, K.; Wieland, P.; Meystre, C. *Org. Synth.* **V**, 692.

¹⁰⁰⁶ Brown, C.A.; Krishnamurthy, S.; Kim, S.C. *J. Chem. Soc. Chem. Commun.* **1973**, 391.

The relative effectiveness of various reagents for reduction of eight other types of ketone was determined, using several different reducing agents.¹⁰⁰⁷ The ketones examined included heterocyclic, aralkyl, β -keto esters, β -keto acids,¹⁰⁰⁸ and so on.⁹⁹¹ Much effort has been put into finding optically active reducing agents that will produce one enantiomer of the alcohol enantioselectively.¹⁰⁰⁹ Each reagent tends to show a specificity for certain types of ketones.¹⁰¹⁰ Good enantioselectivity is usually obtained with the proper reagent.¹⁰¹¹ Substituents that are remote to the carbonyl group can play a role in facial selectivity of the reduction.¹⁰¹² Asymmetric reduction has been accomplished using bio-reagents (e.g., enzymes, see item 10 above).

Asymmetric reduction with very high enantioselectivity has also been achieved with achiral reducing agents and optically active catalysts.¹⁰¹³ Homogeneous catalytic asymmetric hydrogenation leads to reduction of substrates with high enantioselectivity.¹⁰¹⁴ A typical chiral ligand is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-ruthenium acetate (BINAP, **34**), used with a metal catalysts [e.g., Ru(OAc)₂],¹⁰¹⁵ β -Keto esters are reduced enantioselectively, for example.¹⁰¹⁶ A variety of chiral additives and/or ligands have been used with catalytic hydrogenation reactions. Many functional groups can be tolerated.¹⁰¹⁷ Asymmetric catalytic hydrogenation has been done in ionic liquids.¹⁰¹⁸

¹⁰⁰⁷ Brown, H.C.; Park, W.S.; Cho, B.T.; Ramachandran, P.V. *J. Org. Chem.* **1987**, *52*, 5406.

¹⁰⁰⁸ Wang, Z.; La, B.; Fortunak, J.M.; Meng, X.-J.; Kabalka, G.W. *Tetrahedron Lett.* **1998**, *39*, 5501.

¹⁰⁰⁹ See Singh, V.K. *Synthesis* **1992**, 605; Midland, M.M. *Chem. Rev.* **1989**, *89*, 1553; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, **1986**, pp. 105–130; in Morrison, J.D. *Asymmetric Synthesis*, Academic Press, NY, **1983**, the articles by Midland, M.M. Vol. 2, pp. 45–69, and Grandbois, E.R.; Howard, S.I.; Morrison, J.D. Vol. 2, pp. 71–90; Haubenstock, H. *Top. Stereochem.* **1983**, *14*, 231.

¹⁰¹⁰ For a list of many of these reducing agents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1097–1111.

¹⁰¹¹ See Midland, M.M.; Kazubski, A.; Woodling, R.E. *J. Org. Chem.* **1991**, *56*, 1068.

¹⁰¹² Kaselj, M.; Gonikberg, E.M.; le Noble, W.J. *J. Org. Chem.* **1998**, *63*, 3218.

¹⁰¹³ See Smith, M.B. *Organic Synthesis*, 3rd ed., Wavefunction Inc./Elsevier, Irvine, CA/London, England, **2010**, pp. 391–411.

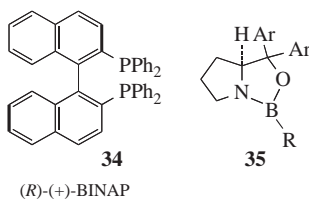
¹⁰¹⁴ See Liang, Y.; Jing, Q.; Li, X.; Shi, L.; Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 7694; Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muñoz, K.; Noyori, R. *J. Am. Chem. Soc.* **2005**, *127*, 8288; Huang, H.; Okuno, T.; Tsuda, K.; Yoshimura, M.; Kitamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 8716; Xie, J.-H.; Zhou, Z.-T.; Kong, W.-L.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1868; Xie, J.-H.; Liu, S.; Huo, X.-H.; Cheng, X.; Duan, H.-F.; Fan, B.-M.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 2867; Truppo, M.D.; Pollard, D.; Devine, P. *Org. Lett.* **2007**, *9*, 335; Ngo, H.L.; Hu, A.; Lin, W. *Tetrahedron Lett.* **2005**, *46*, 595; Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920; Jiang, H.-y.; Yang, C.-f.; Li, C.; Fu, H.-y.; Chen, H.; Li, R.-x.; Li, X.-j. *Angew. Chem. Int. Ed.* **2008**, *47*, 9240; Burk, S.; Franciò, G.; Leitner, W. *Chem. Commun.* **2005**, 3460; Li, W.; Sun, X.; Zhou, L.; Hou, G.; Shichao Yu, S.; Zhang, X. *J. Org. Chem.* **2009**, *74*, 1397; Martins, J., E.D.; Wills, M. *Tetrahedron* **2009**, *65*, 5782; Li, W.; Hou, G.; Wang, C.; Jiang, Y.; Zhang, X. *Chem. Commun.* **2010**, 3979.

¹⁰¹⁵ See Noyori, R. *Science* **1990**, *248*, 1194; Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345; Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* *67*, 20.

¹⁰¹⁶ Taber, D.F.; Silverberg, L.J. *Tetrahedron Lett.* **1991**, *32*, 4227. See also, Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumabayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629.

¹⁰¹⁷ See Sun, L.; Tang, M.; Wang, H.; Wei, D.; Liu, L. *Tetrahedron Asymmetry* **2008**, *19*, 779; Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* **2004**, *6*, 2681; Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626; Sun, Y.; Wan, X.; Guo, M.; Wang, D.; Dong, X.; Pan, Y.; Zhang, Z. *Tetrahedron Asymmetry* **2004**, *15*, 2185. Also see Sandoval, C.A.; Ohkuma, T.; Muñoz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490.

¹⁰¹⁸ Ngo, H.L.; Hu, A.; Lin, W. *Chem. Commun.* **2003**, 1912.



A second approach is reduction with BH_3 —THF or catecholborane,¹⁰¹⁹ using an oxazaborolidine (**35**, $\text{R} = \text{H}$, Me , or $n\text{-Bu}$; $\text{Ar} = \text{Ph}$ or $\beta\text{-naphthyl}$)¹⁰²⁰ or other chiral compounds¹⁰²¹ as a catalyst. Both a polymer-bound oxazaborolidine¹⁰²² and a dendritic chiral catalyst have been used in conjunction with borane,¹⁰²³ as well as other chiral additives can be used.¹⁰²⁴ Chiral sulfonamides have been used as additives.¹⁰²⁵

Lithium aluminum hydride in combination with a chiral diol¹⁰²⁶ or other chiral ligands¹⁰²⁷ leads to enantioselective reduction, often in the presence of a transition metal complex.¹⁰²⁸ Chiral additives have also been used with NaBH_4 .¹⁰²⁹ Examples include $\text{LiBH}_4/\text{NiCl}_2$ and a chiral amino alcohol,¹⁰³⁰ NaBH_4 with chiral Lewis acid complexes,¹⁰³¹ or $\text{NaBH}_4/\text{Me}_3\text{SiCl}$ and a chiral ligand.¹⁰³² A mixture of NaBH_4 and Me_3SiCl with a catalytic amount of a chiral, polymer-bound sulfonamide leads to asymmetric reduction.¹⁰³³

Enantioselective reduction is possible with the other methods mentioned above. Transition metal catalyzed asymmetric transfer hydrogenation is effective for the

¹⁰¹⁹ See Ford, A.; Woodward, S. *Angew. Chem. Int. Ed.* **1999**, 38, 335.

¹⁰²⁰ See Santhi, V.; Rao, J.M. *Tetrahedron Asymmetry* **2000**, 11, 3553; Jones, S.; Atherton, J.C.C. *Tetrahedron Asymmetry* **2000**, 11, 4543; Cho, B.T.; Kim, D.J. *Tetrahedron Asymmetry* **2001**, 12, 2043; Jiang, B.; Feng, Y.; Hang, J.-F. *Tetrahedron Asymmetry* **2001**, 12, 2323; Gilmore, N.J.; Jones, S.; Muldowney, M.P. *Org. Lett.* **2004**, 6, 2805; Huertas, R.E.; Corella, J.A.; Soderquist, J.A. *Tetrahedron Lett.* **2003**, 44, 4435.

¹⁰²¹ See Brunel, J.M.; Legrand, O.; Buono, G. *Eur. J. Org. Chem.* **2000**, 3313; Kawanami, Y.; Murao, S.; Ohga, T.; Kobayashi, N. *Tetrahedron* **2003**, 59, 8411; Basavaiah, D.; Reddy, G.J.; Chandrashekar, V. *Tetrahedron Asymmetry* **2004**, 15, 47; Zhang, Y.-X.; Du, D.-M.; Chen, X.; Lü, S.-F.; Hua, W.-T. *Tetrahedron Asymmetry* **2004**, 15, 177; Lindsay, D.M.; McArthur, D. *Chem. Commun.* **2010**, 2474.

¹⁰²² Price, M.D.; Sui, J.K.; Kurth, M.J.; Schore, N.E. *J. Org. Chem.* **2002**, 67, 8086.

¹⁰²³ Bolm, C.; Derrien, N.; Seger, A. *Chem. Commun.* **1999**, 2087.

¹⁰²⁴ Hu, J.-b.; Zhao, G.; Yang, G.-s.; Ding, Z.-d. *J. Org. Chem.* **2001**, 66, 303; Zhou, H.; Lü, S.; Xie, R.; Chan, A.S. C.; Yang, T.-K. *Tetrahedron Lett.* **2001**, 42, 1107; Basavaiah, D.; Reddy, G.J.; Chandrashekar, V. *Tetrahedron Asymmetry* **2001**, 12, 685.

¹⁰²⁵ Li, G.-Q.; Yan, Z.-Y.; Niu, Y.-N.; Wu, L.-Y.; Wei, H.-L.; Liang, Y.-M. *Tetrahedron Asymmetry* **2008**, 19, 816.

¹⁰²⁶ Ren, Y.; Tian, X.; Sun, K.; Xu, J.; Xu, X.; Lu, S. *Tetrahedron Lett.* **2006**, 47, 463.

¹⁰²⁷ Lange, D.A.; Neudörfl, J.-M.; Goldfuss, B. *Tetrahedron* **2006**, 62, 3704. In an ionic liquid: see Xiao, Y.; Malhotra, S.V. *Tetrahedron Asymmetry* **2006**, 17, 1062.

¹⁰²⁸ For a review, see Daverio, P.; Zanda, M. *Tetrahedron Asymmetry* **2001**, 12, 2225.

¹⁰²⁹ Kim, J.; Singaram, B. *Tetrahedron Lett.* **2006**, 47, 3901.

¹⁰³⁰ Molvinger, K.; Lopez, M.; Court, J. *Tetrahedron Lett.* **1999**, 40, 8375.

¹⁰³¹ Nozaki, K.; Kobori, K.; Uemura, T.; Tsutsumi, T.; Takaya, H.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, 72, 1109.

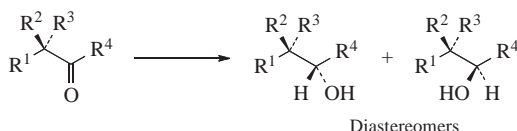
¹⁰³² Jiang, B.; Feng, Y.; Zheng, J. *Tetrahedron Lett.* **2000**, 41, 10281.

¹⁰³³ Zhao, G.; Hu, J.-b.; Qian, Z.-s.; Yin, X.-x. *Tetrahedron Asymmetry* **2002**, 13, 2095.

preparation of chiral alcohols.¹⁰³⁴ Reduction with silanes and transition metal catalysts (e.g., Ru compounds) is also very effective.¹⁰³⁵ Chiral Ru catalysts have been used with triethylammonium formate for the enantioselective reduction.¹⁰³⁶ The transition metal catalyzed hydrosilylation of ketones gives chiral alcohols in the presence of suitable chiral ligands.¹⁰³⁷ Enantioselective reduction was observed with PhSiH₃ and Cu compounds with a chiral ligand,¹⁰³⁸ with a mixture of Ru and Ag catalysts,¹⁰³⁹ or with Mn(dpm)₃ and oxygen (dpm = diphenylmethylene).¹⁰⁴⁰ Enantioselective hydrosilylation is possible using chiral organocatalysts.¹⁰⁴¹ A chiral Sm complex has been used in conjunction with 2-propanol.¹⁰⁴² Chiral mercapto alcohols have also been used for asymmetric reduction.¹⁰⁴³

Enantioselective reduction is usually not possible for aldehydes,¹⁰⁴⁴ since the products are primary alcohols in which the reduced carbon is not chiral. Instead deuterated aldehydes (RCDO) give a chiral product, and these have been reduced enantioselectively with B-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (Alpine-Borane) with almost complete optical purity.¹⁰⁴⁵ Other chiral boranes can be used to reduce aldehydes or ketones.¹⁰⁴⁶

In the above cases, an optically active reducing agent or catalyst interacts with a prochiral substrate. Asymmetric reduction of ketones has also been achieved with an achiral reducing agent, if the ketone is complexed to an optically active transition metal Lewis acid.¹⁰⁴⁷



¹⁰³⁴ Wu, X.; Li, X.; Zanoliti-Gerosa, A.; Pettman, A.; Liu, J.; Mills, A.J.; Xiao, J. *Chemistry: European J.* **2008**, *14*, 2209; Kawasaki, I.; Tsunoda, K.; Tsuji, T.; Yamaguchi, T.; Shibata, H.; Uchida, N.; Yamashita, M.; Ohta, S. *Chem. Commun.* **2005**, 2134; Li, X.; Blacker, J.; Houson, I.; Wu, X.; Xiao, J. *Synlett* **2006**, 1155; Ito, M.; Shibata, Y.; Watanabe, A.; Ikariya, T. *Synlett* **2009**, 1621; Zani, L.; Eriksson, L.; Adolfsson, H. *Eur. J. Org. Chem.* **2008**, 4655.

¹⁰³⁵ Hayashi, T.; Hayashi, C.; Uozumi, Y. *Tetrahedron Asymmetry*, **1995**, *6*, 2503.

¹⁰³⁶ Liu, P.N.; Gu, P.M.; Wang, F.; Tu, Y.Q. *Org. Lett.* **2004**, *6*, 169; Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. *Org. Biomol. Chem.* **2004**, *2*, 1818; Schlatter, A.; Kundu, M.K.; Woggon, W.-D. *Angew. Chem. Int. Ed.* **2004**, *43*, 6731.

¹⁰³⁷ Shaikh, N.S.; Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 2497; Inagaki, T.; Yamada, Y.; Phong, L.T.; Furuta, A.; Ito, J.-i.; Nishiyama, H. *Synlett* **2009**, 253; Ghoshal, A.; Sarkar, A.R.; Manickam, G.; Kumaran, R.S.; Jayashankaran, J. *Synlett* **2010**, 1459.

¹⁰³⁸ Lipshutz, B.H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779.

¹⁰³⁹ Gade, L.H.; César, V.; Bellemin-Laponnaz, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1014.

¹⁰⁴⁰ Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* **2001**, *42*, 6651.

¹⁰⁴¹ Zhou, L.; Wang, Z.; Wei, S.; Sun, J. *Chem. Commun.* **2007**, 2977.

¹⁰⁴² Ohno, K.; Kataoka, Y.; Mashima, K. *Org. Lett.* **2004**, *6*, 4695.

¹⁰⁴³ Yang, T.-K.; Lee, D.-S. *Tetrahedron Asymmetry* **1999**, *10*, 405.

¹⁰⁴⁴ See, however, Li, X.; List, B. *Chem. Commun.* **2007**, 1739. See also, Giacomini, D.; Galletti, P.; Quintavalla, A.; Gucciardo, G.; Paradisi, F. *Chem. Commun.* **2007**, 4038.

¹⁰⁴⁵ Midland, M.M.; Greer, S.; Tramontano, A.; Zderic, S.A. *J. Am. Chem. Soc.* **1979**, *101*, 2352. See also, Midland, M.M.; Zderic, S.A. *J. Am. Chem. Soc.* **1982**, *104*, 525.

¹⁰⁴⁶ Ramachandran, P.V.; Pitre, S.; Brown, H.C. *J. Org. Chem.* **2002**, *67*, 5315. For a discussion of the sources of stereoselectivity, see Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2004**, *69*, 6860.

¹⁰⁴⁷ Dalton, D.M.; Gladysz, J.A. *J. Organomet. Chem.* **1989**, *370*, C17.

There are other stereochemical aspects to the reduction of aldehydes and ketones. If there is a stereogenic center α to the carbonyl group,¹⁰⁴⁸ even an achiral reducing agent can give more of one diastereomer than of the other (a diastereoselective reduction). Such reductions have been carried out with considerable success.¹⁰⁴⁹ In most such cases, *Cram's rule* (Sec. 4.H., category 1) is followed, but exceptions are known.¹⁰⁵⁰

OS I, 90, 304, 554; II, 317, 545, 598; III, 286; IV, 15, 25, 216, 660; V, 175, 294, 595, 692; VI, 215, 769, 887; VII, 129, 215, 241, 402, 417; VIII, 302, 312, 326, 527; IX, 58, 362, 676.

19-37 Reduction of Carboxylic Acids to Alcohols

Dihydro-de-oxo-bisubstitution



Carboxylic acids are easily reduced to primary alcohols by LiAlH_4 .¹⁰⁵¹ The conditions are particularly mild, the reduction proceeding quite well at room temperature. Other hydrides have also been used,¹⁰⁵² but not NaBH_4 (see Table 19.5).¹⁰⁵³ A combination of NaBH_4 and an arylboronic acid (Reaction 12-28) is also effective.¹⁰⁵⁴ A mixture of NaBH_4 , Me_2SO_4 , and $\text{B}(\text{OMe})_3$ is effective for the reduction of hydroxyl-substituted aromatic carboxylic acids.¹⁰⁵⁵ Benzyltriethylammonium borohydride in dichloromethane reduces carboxylic acids to the alcohol.¹⁰⁵⁶ Catalytic hydrogenation is generally ineffective.¹⁰⁵⁷

Borane (BH_3) is particularly good for carboxyl groups (Table 19.4) and permits selective reduction of them in the presence of many other groups (although the reaction with double bonds takes place at about the same rate in ether solvents).¹⁰⁵⁸ For many years, borane was the reagent of choice for this reduction. Borane also reduces carboxylic acid salts.¹⁰⁵⁹ Aluminum hydride reduces COOH groups without affecting carbon-halogen bonds in the same molecule. The reduction has also been carried out with SmI_2 in basic media¹⁰⁶⁰ or aq H_3PO_4 ,¹⁰⁶¹ or simply with SmI_2 in water.¹⁰⁶² A mixture of NaBH_4 and I_2 has been used to reduce amino acids to amino alcohols.¹⁰⁶³

OS III, 60; VII, 221; 530; VIII, 26, 434, 528.

¹⁰⁴⁸ See Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* **1988**, 53, 1021; Evans, D.A.; Chapman, K.T.; Carreira, E.M. *J. Am. Chem. Soc.* **1988**, 110, 3560.

¹⁰⁴⁹ See N6gr6di, M. *Stereoselective Synthesis* VCH, NY, **1986**, pp. 131–148; Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, 17, 338.

¹⁰⁵⁰ See Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* **1988**, 110, 4475.

¹⁰⁵¹ See Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, **1956**, pp. 322–373.

¹⁰⁵² For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1114–1116. Zinc borohydride has also been used; see Narashimhan, S.; Madhavan, S.; Prasad, K.G. *J. Org. Chem.* **1995**, 60, 5314.

¹⁰⁵³ See, however, Fujisawa, T.; Mori, T.; Sato, T. *Chem. Lett.* **1983**, 835.

¹⁰⁵⁴ Tale, R.H.; Patil, K.M.; Dapurkar, S.E. *Tetrahedron Lett.* **2003**, 44, 3427.

¹⁰⁵⁵ Zhou, Y.; Gao, G.; Li, H.; Qu, J. *Tetrahedron Lett.* **2008**, 49, 3260.

¹⁰⁵⁶ Narashimhan, S.; Swarnalakshmi, S.; Balakumar, R. *Synth. Commun.* **2000**, 30, 941.

¹⁰⁵⁷ See Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, **1985**, pp. 78–79.

¹⁰⁵⁸ Brown, H.C.; Stocky, T.P. *J. Am. Chem. Soc.* **1977**, 99, 8218; Chen, M.H.; Kiesten, E.I.S.; Magano, J.; Rodriguez, D.; Sexton, K.E.; Zhang, J.; Lee, H.T. *Org. Prep. Proceed. Int.* **2002**, 34, 665.

¹⁰⁵⁹ Yoon, N.M.; Cho, B.T. *Tetrahedron Lett.* **1982**, 23, 2475.

¹⁰⁶⁰ Kamochi, Y.; Kudo, T. *Bull. Chem. Soc. Jpn.* **1992**, 65, 3049.

¹⁰⁶¹ Kamochi, Y.; Kudo, T. *Tetrahedron* **1992**, 48, 4301.

¹⁰⁶² Kamochi, Y.; Kudo, T. *Chem. Lett.* **1993**, 1495.

¹⁰⁶³ McKennon, M.J.; Meyers, A.I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, 58, 3568.

19-38 Reduction of Carboxylic Esters to Alcohols

Dihydro,hydroxy-de-oxo,alkoxy-tersubstitution



Lithium aluminum hydride reduces carboxylic esters to give two different alcohols, as shown.¹⁰⁶⁴ The reaction is of wide scope and has been used to reduce many esters. Where the interest is in obtaining R'OH, this is a method that is often a working equivalent of "hydrolyzing" esters. Reduction of lactones yields diols.¹⁰⁶⁵ Among the reagents used for this reduction¹⁰⁶⁶ are Dibal-H, lithium triethylborohydride, LiAlH(Ot-Bu)₃,¹⁰⁶⁷ and BH₃—SMe₂ in refluxing THF.¹⁰⁶⁸ Although NaBH₄ reduces phenolic esters, especially those containing electron-withdrawing groups,¹⁰⁶⁹ its reaction with other esters is usually so slow that it is not the reagent of choice, but there are many exceptions.¹⁰⁷⁰ However, it is generally possible to reduce an aldehyde or ketone without reducing an ester function in the same molecule. Note that NaBH₄ reduces esters in the presence of certain compounds (see Table 19.5).¹⁰⁷¹ Note that NaBH₄ in DMF—MeOH reduces aryl carboxylic esters to benzylic alcohols,¹⁰⁷² and NaBH₄—LiCl with microwave irradiation also reduces esters to primary alcohols.¹⁰⁷³

Carboxylic esters can also be reduced to alcohols by hydrogenation over copper chromite catalysts,¹⁰⁷⁴ although high pressures and temperatures are required. Ester functions generally survive low-pressure catalytic hydrogenations, but homogeneous catalytic hydrogenation procedures have been developed.¹⁰⁷⁵ Before the discovery of LiAlH₄, the most common way of carrying out the reaction was with sodium in ethanol, a method known as the *Bouveault–Blanc procedure*.¹⁰⁷⁶ This procedure is still sometimes used where selectivity is necessary (see also, Reactions **19-62**, **19-65**, and **19-59**).

¹⁰⁶⁴ For a review, see Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, **1956**, pp. 391–531.

¹⁰⁶⁵ For a ring size-selective reduction using SmI₂—H₂O, see Duffy, L.A.; Matsubara, H.; Procter, D.J. *J. Am. Chem. Soc.* **2008**, *130*, 1136.

¹⁰⁶⁶ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1116–1120.

¹⁰⁶⁷ Ayers, T.A. *Tetrahedron Lett.* **1999**, *40*, 5467.

¹⁰⁶⁸ Brown, H.C.; Choi, Y.M. *Synthesis* **1981**, 439; Brown, H.C.; Choi, Y.M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.

¹⁰⁶⁹ Takahashi, S.; Cohen, L.A. *J. Org. Chem.* **1970**, *35*, 1505.

¹⁰⁷⁰ For example, see Brown, M.S.; Rapoport, H. *J. Org. Chem.* **1963**, *28*, 3261; Boechat, N.; da Costa, J.C.S.; Mendonca, J.de S.; de Oliveira, P.S.M.; DeSouza, M.V.N. *Tetrahedron Lett.* **2004**, *45*, 6021.

¹⁰⁷¹ See also, Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948; Guida, W.C.; Entreken, E.E.; Guida, W.C. *J. Org. Chem.* **1984**, *49*, 3024.

¹⁰⁷² Zanka, A.; Ohmori, H.; Okamoto, T. *Synlett* **1999**, 1636.

¹⁰⁷³ Feng, J.-C.; Liu, B.; Dai, L.; Yang, X.-L.; Tu, S.-J. *Synth. Commun.* **2001**, *31*, 1875.

¹⁰⁷⁴ For a review, see Adkins, H. *Org. React.* **1954**, *8*, 1.

¹⁰⁷⁵ Zhang, J.; Leitius, G.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1113.

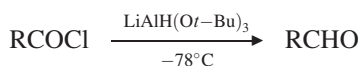
¹⁰⁷⁶ Chablay, E. *Compt. Rend* **1913**, *156*, 1020; Bouveault, L.; Blanc, G. *Bull. Soc. Chim. Fr.* **1904**, *31*, 666; Bouveault, L.; Blanc, G. *Compt. Rend.* **1903**, *136*, 1676. See Bodnar, B.S.; Vogt, P.F. *J. Org. Chem.* **2009**, *74*, 2598.

Silanes (e.g., Ph_2SiH_2), with a catalytic amount of triphenylphosphine and a Rh catalyst reduced esters to primary alcohols.¹⁰⁷⁷ Aliphatic silanes (e.g., EtMe_2SiH) also reduced esters with a Ru catalyst.¹⁰⁷⁸

OS **II**, 154, 325, 372, 468; **III**, 671; **IV**, 834; **VI**, 781; **VII**, 356; **VIII**, 155; **IX**, 251.

19-39 Reduction of Acyl Halides

Hydro-de-halogenation or Dehalogenation



Acyl halides can be reduced to aldehydes¹⁰⁷⁹ by treatment with lithium tri-*tert*-butoxyaluminum hydride in diglyme at -78°C .¹⁰⁸⁰ The R group may be alkyl or aryl and may contain many types of substituents, including NO_2 , CN, and EtOOC groups. The reaction stops at the aldehyde stage because steric hindrance prevents further reduction with this reagent. Acyl halides can also be reduced to aldehydes by hydrogenolysis with Pd on barium sulfate as catalyst in what is called the *Rosenmund reduction*.¹⁰⁸¹ A convenient hydrogenolysis procedure involves Pd on charcoal as the catalyst, with ethyldiisopropylamine as acceptor of the liberated HCl and acetone as the solvent.¹⁰⁸² The reduction of acyl halides to aldehydes has also been carried out¹⁰⁸³ with Bu_3SnH ,¹⁰⁸⁴ an InCl_3 catalyzed reaction using Bu_3SnH ,¹⁰⁸⁵ NaBH_4 in a mixture of DMF and THF,¹⁰⁸⁶ with $\text{Sm}-\text{PBU}_3$,¹⁰⁸⁷ and with formic acid/ NH_4OH .¹⁰⁸⁸ Polymethylhydrosiloxane (PMHS) reduces acid chlorides to aldehydes in the presence of a Pd catalyst.¹⁰⁸⁹ In some of these cases, the mechanisms are free radical.

There are several indirect methods for the conversion of acyl halides to aldehydes, most of them involving prior conversion of the halides to certain types of amides (see Reaction **19-41**). There is also a method in which the COOH group is replaced by a completely different CHO group (Reaction **16-87**).

OS **III**, 551, 627; **VI**, 529, 1007. Also see, OS **III**, 818; **VI**, 312.

¹⁰⁷⁷ Ohta, T.; Kamiya, M.; Kusui, K.; Michibata, T.; Nobutomo, M.; Furukawa, I. *Tetrahedron Lett.* **1999**, 40, 6963.

¹⁰⁷⁸ Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem.* **2002**, 67, 4985.

¹⁰⁷⁹ See Fuson, R.C. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 211–232; Wheeler, O.H. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, **1972**, pp. 231–251.

¹⁰⁸⁰ Cha, J.S.; Brown, H.C. *J. Org. Chem.* **1993**, 58, 4732 and references cited therein.

¹⁰⁸¹ See Rylander, P.N. *Catalytic Hydrogenation Over Platinum Metals*, Academic Press, NY, **1967**, pp. 398–404; Maier, W.F.; Chettle, S.J.; Rai, R.S.; Thomas, G. *J. Am. Chem. Soc.* **1986**, 108, 2608.

¹⁰⁸² Peters, J.A.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1981**, 100, 21. See also, Burgstahler, A.W.; Weigel, L.O.; Shaefer, C.G. *Synthesis* **1976**, 767.

¹⁰⁸³ See Leblanc, J.C.; Moise, C.; Tirouflet, J. *J. Organomet. Chem.* **1985**, 292, 225; Corriu, R.J.P.; Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* **1988**, 29, 1271. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1265–1266.

¹⁰⁸⁴ See Luszytk, J.; Luszytk, E.; Maillard, B.; Ingold, K.U. *J. Am. Chem. Soc.* **1984**, 106, 2923.

¹⁰⁸⁵ Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2000**, 41, 113.

¹⁰⁸⁶ Babler, J.H. *Synth. Commun.* **1982**, 12, 839. See Entwistle, I.D.; Boehm, P.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* **1980**, 27.

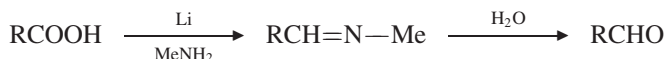
¹⁰⁸⁷ Jia, X.; Liu, X.; Li, J.; Zhao, P.; Zhang, Y. *Tetrahedron Lett.* **2007**, 48, 971.

¹⁰⁸⁸ Shamsuddin, K.M.; Zubairi, Md.O.; Musharraf, M.A. *Tetrahedron Lett.* **1998**, 39, 8153.

¹⁰⁸⁹ Lee, K.; Maleczka Jr., R.E. *Org. Lett.* **2006**, 8, 1887.

19-40 Reduction of Carboxylic Acids, Esters, and Anhydrides to Aldehydes¹⁰⁹⁰**Hydro-de-hydroxylation or Dehydroxylation** (overall transformation)

With most reducing agents, reduction of carboxylic acids generally gives the primary alcohol (Reaction **19-37**) and the isolation of aldehydes is not feasible. However, simple straight-chain carboxylic acids have been reduced to aldehydes¹⁰⁹¹ by treatment with Li in MeNH₂ or NH₃ followed by hydrolysis of the resulting imine,¹⁰⁹² with



with thexylchloro(or bromo)borane-SMe₂¹⁰⁹³ (see Reaction **15-16** for the thexyl group), Me₂N=CHCl⁺ Cl⁻ in pyridine,¹⁰⁹⁴ and with diaminoaluminum hydrides.¹⁰⁹⁵ Benzoic acid derivatives were reduced to benzaldehyde derivatives with NaH₂PO₂ and a diacylperoxide and Pd catalyst.¹⁰⁹⁶ Caproic and isovaleric acids have been reduced to aldehydes in 50% yields or better with Dibal-H (*i*-Bu₂AlH) at -75 to -70 °C.¹⁰⁹⁷

Carboxylic esters have been reduced to aldehydes with Dibal-H at -70 °C, with diaminoaluminum hydrides,¹⁰⁹⁸ and for phenolic esters with LiAlH(*Ot*-Bu)₃ at 0 °C.¹⁰⁹⁹ Pretreatment of the acid with Me₃SiCl followed by reduction with Dibal-H also gives the aldehyde.¹¹⁰⁰ Aldehydes have also been prepared by reducing ethyl thiol esters (RCOSEt) with Et₃SiH and a Pd-C catalyst.¹¹⁰¹ Thioesters have been reduced to the aldehyde with Li metal in THF at -78 °C, followed by quenching with methanol.¹¹⁰²

Anhydrides, both aliphatic and aromatic, as well as mixed anhydrides of carboxylic and carbonic acids, have been reduced to aldehydes in moderate yields with disodium tetracarbonylferrate [Na₂Fe(CO)₄].¹¹⁰³ Heating a carboxylic acid, presumably to form the anhydride, and then reaction with Na/EtOH leads to the aldehyde.¹¹⁰⁴

Acid chlorides are reduced to aldehydes with Bu₃SnH and a Ni catalyst.¹¹⁰⁵

¹⁰⁹⁰ For a review, see Cha, J.S. *Org. Prep. Proced. Int.* **1989**, 21, 451.

¹⁰⁹¹ See Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* **1987**, 28, 3941; Cha, J.S.; Kim, J.E.; Yoon, M.S.; Kim, Y.S. *Tetrahedron Lett.* **1987**, 28, 6231. See also, the lists, in Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1265-1268.

¹⁰⁹² Bedenbaugh, A.O.; Bedenbaugh, J.H.; Bergin, W.A.; Adkins, J.D. *J. Am. Chem. Soc.* **1970**, 92, 5774.

¹⁰⁹³ Chloro - see Brown, H.C.; Cha, J.S.; Yoon, N.M.; Nazer, B. *J. Org. Chem.* **1987**, 52, 5400; Bromo, see Cha, J.S.; Kim, J.E.; Lee, K.W. *J. Org. Chem.* **1987**, 52, 5030.

¹⁰⁹⁴ Fujisawa, T.; Mori, T.; Tsuge, S.; Sato, T. *Tetrahedron Lett.* **1983**, 24, 1543.

¹⁰⁹⁵ Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* **1995**, 27, 95.

¹⁰⁹⁶ Gooßen, L.J.; Ghosh, K. *Chem. Commun.* **2002**, 836.

¹⁰⁹⁷ Zakharkin, L.I.; Sorokina, L.P. *J. Gen. Chem. USSR* **1967**, 37, 525. See Song, J.I.; An, D.K. *Chem. Lett.* **2007**, 36, 886.

¹⁰⁹⁸ Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* **1995**, 27, 95.

¹⁰⁹⁹ Zakharkin, L.I.; Gavrilenko, V.V.; Maslin, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1964**, 867; Weissman, P.M.; Brown, H.C. *J. Org. Chem.* **1966**, 31, 283.

¹¹⁰⁰ Chandrasekhar, S.; Kumar, M.S.; Muralidhar, B. *Tetrahedron Lett.* **1998**, 39, 909.

¹¹⁰¹ Fukuyama, T.; Lin, S.; Li, L. *J. Am. Chem. Soc.* **1990**, 112, 7050.

¹¹⁰² Penn, J.H.; Owens, W.H. *Tetrahedron Lett.* **1992**, 33, 3737.

¹¹⁰³ Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1975**, 48, 2490;

Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Tomi, K.; Takegami, Y. *Tetrahedron Lett.* **1975**, 1063.

¹¹⁰⁴ Shi, Z.; Gu, H. *Synth. Commun.* **1997**, 27, 2701.

¹¹⁰⁵ Malanga, C.; Mannucci, S.; Lardicci, L. *Tetrahedron Lett.* **1997**, 38, 8093.

Also see, Reactions **19-62** and **19-38**.
OS VI, 312; VIII, 241, 498.

19-41 Reduction of Amides to Aldehydes

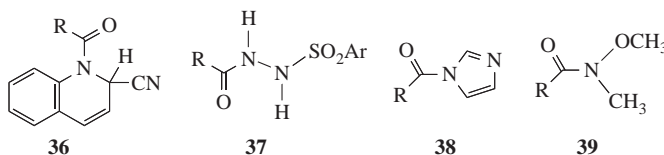
Hydro-de-dialkylamino-substitution



N,N-Disubstituted amides can be reduced to amines with LiAlH_4 (see Reaction **19-64**), but reduction to an aldehyde is possible.¹¹⁰⁶ Keeping the amide in excess gives the aldehyde rather than the amine. Sometimes it is not possible to prevent further reduction and primary alcohols are obtained instead. Other reagents¹¹⁰⁷ that give good yields of aldehydes are Dibal-H,¹¹⁰⁸ $\text{LiAlH}(\text{O}i\text{-Bu})_3$, diaminoaluminum hydrides,¹¹⁰⁹ disiamylborane (see Reaction **15-16** for the disiamyl group),¹¹¹⁰ and $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$.¹¹¹¹

Aldehydes have been prepared from carboxylic acids or acyl halides by first converting them to certain types of amides that are easily reducible. There are several examples:¹¹¹²

1. *Reissert Compounds*.¹¹¹³ Compounds, such as **36**, are prepared from the acyl halide by treatment with quinoline and cyanide ion. Treatment of **36** with sulfuric acid gives the corresponding aldehyde.



2. *Acyl Sulfonylhydrazides*. Compounds, such as **37**, are cleaved with base to give aldehydes. This reaction is known as the *McFadyen-Stevens reduction* and is applicable *only* to aromatic aldehydes or aliphatic aldehydes with no α hydrogen.¹¹¹⁴ Acyl imide ($\text{RCON}=\text{NH}$, see reaction **19-67**) has been proposed as an intermediate in this reaction.¹¹¹⁵
3. *Acyl Imidazoles*. Compounds **38**¹¹¹⁶ can be reduced to aldehydes with LiAlH_4 .

¹¹⁰⁶ Fuson, R.C. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, **1966**, pp. 220–225.

¹¹⁰⁷ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp.1269–1271.

¹¹⁰⁸ Zakharkin, L.I.; Khorlina, I.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1959**, 2046.

¹¹⁰⁹ Muraki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 875.

¹¹¹⁰ Godjoian, G.; Singaram, B. *Tetrahedron Lett.* **1997**, 38, 1717.

¹¹¹¹ White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* **2000**, 122, 11995.

¹¹¹² See Craig, J.C.; Ekwurieb, N.N.; Fu, C.C.; Walker, K.A.M. *Synthesis* **1981**, 303.

¹¹¹³ See Popp, F.D.; Uff, B.C. *Heterocycles* **1985**, 23, 731; Popp, F.D. *Bull. Soc. Chim. Belg.* **1981**, 90, 609; *Adv. Heterocycl. Chem.* **1979**, 24, 187; **1968**, 9, 1. See Bridge, A.W.; Hursthouse, M.B.; Lehmann, C.W.; Lythgoe, D.J.; Newton, C.G. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1839 for isoquinoline Reissert salts.

¹¹¹⁴ Dudman, C.C.; Grice, P.; Reese, C.B. *Tetrahedron Lett.* **1980**, 21, 4645.

¹¹¹⁵ See Cacchi, S.; Paolucci, G. *Gazz. Chem. Ital.* **1974**, 104, 221; Matin, S.B.; Craig, J.C.; Chan, R.P.K. *J. Org. Chem.* **1974**, 39, 2285.

¹¹¹⁶ For a review, see Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* **1968**, 5, 61.

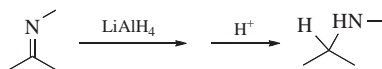
4. *Weinreb Amides*. A *N*-Methoxy-*N*-methyl amide (e.g., **39**) is referred to as a *Weinreb amide*.¹¹¹⁷ Reduction with and excess of LiAlH_4 or Dibal-H leads to the corresponding aldehyde, as does reaction with Cp_2ZrHCl .¹¹¹⁸
5. See also, the *Sonn-Müller Method* (Reaction **19-44**).

OS **VIII**, 68. See OS **IV**, 641, **VI**, 115 for the preparation of Reissert compounds.

C. Attack at Non-Carbonyl Multiple Bonded Heteroatoms

19-42 Reduction of the Carbon–Nitrogen Double Bond (C=N)

C,N-Dihydro-addition



Imines and *Schiff bases*,¹¹¹⁹ hydrazones,¹¹²⁰ and other C=N compounds can be reduced with LiAlH_4 , NaBH_4 ,¹¹²¹ $\text{Na}-\text{EtOH}$, hydrogen and a catalyst, as well as with other reducing agents.¹¹²² Metal-free catalytic hydrogenation is known.¹¹²³ Transfer hydrogenation of imines leads to amines.¹¹²⁴ A mixture of Sm/I_2 ¹¹²⁵ or $\text{In}/\text{NH}_4\text{Cl}$ ¹¹²⁶ also reduces imines. Reduction with Bu_2SnClH in HMPA has been shown to be chemoselective for imines.¹¹²⁷ Iminium salts are reduced by LiAlH_4 to the corresponding amine, although here there is no “addition” to the nitrogen.¹¹²⁸ Silanes¹¹²⁹ with a triarylborane catalyst reduces *N*-sulfonyl imines¹¹³⁰ as does TiI_4 .¹¹³¹ Imines are reduced with samarium bromide in HMPA,¹¹³² 2-propanol with a Ru catalyst,¹¹³³ and with triethylammonium formate with microwave irradiation.¹¹³⁴ Oximes are reduced with hydrogen gas and a catalytic amount of 48% HBr .¹¹³⁵

¹¹¹⁷ Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, 22, 3815; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd Ed. Wiley-Interscience, New Jersey, **2005**, p. 866. See Sibi, M. P. *Org. Prep. Proceed. Int.* **1993**, 25, 15; Mentzel, M.; Hoffmann, H.M.R. *J. Prakt. Chem.* **1997**, 339, 517.

¹¹¹⁸ Spletstoser, J.T.; White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* **2007**, 129, 3408; White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* **2000**, 122, 11995; Wang, J.; Xu, H.; Gao, H.; Su, C.-Y.; Phillips, D.L. *Organometallics* **2010**, 29, 42; Gondi, V.B.; Hagihara, K.; Rawal, V.H. *Chem. Commun.* **2010**, 46, 904.

¹¹¹⁹ See Verdaguer, X.; Lange, U.E.W.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **1998**, 37, 1103.

¹¹²⁰ See Burk, M.J.; Feaster, J.E. *J. Am. Chem. Soc.* **1992**, 114, 6266.

¹¹²¹ Bhattacharyya, S.; Neidigh, K.A.; Avery, M.A.; Williamson, J.S. *Synlett* **1999**, 1781.

¹¹²² See Harada, K. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, **1970**, pp. 276–293; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, **1967**, pp. 123–138.

¹¹²³ Chase, P.A.; Welch, G.C.; Jurca, T.; Stephan, D.W. *Angew. Chem. Int. Ed.* **2007**, 46, 8050.

¹¹²⁴ Zhang, Z.; Schreiner, P.R. *Synlett* **2007**, 1455.

¹¹²⁵ Banik, B.K.; Zegrocka, O.; Banik, I.; Hackfeld, L.; Becker, F.F. *Tetrahedron Lett.* **1999**, 40, 6731.

¹¹²⁶ Banik, B.K.; Hackfeld, L.; Becker, F.F. *Synth. Commun.* **2001**, 31, 1581.

¹¹²⁷ Shibata, I.; Moriuchi-Kawakami, T.; Tanizawa, D.; Suwa, T.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* **1998**, 63, 383.

¹¹²⁸ Paukstelis, J.V.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, **1988**, pp. 275–356.

¹¹²⁹ See Malkov, A.V.; Mariani, A.; MacDougall, K.N.; Kocovsky, P. *Org. Lett.* **2004**, 6, 2253.

¹¹³⁰ Blackwell, J.M.; Sonmor, E.R.; Scoccitti, T.; Piers, W.E. *Org. Lett.* **2000**, 2, 3921.

¹¹³¹ Shimizu, M.; Sahara, T.; Hayakawa, R. *Chem. Lett.* **2001**, 792.

¹¹³² Knettle, B.W.; Flowers II, R.A. *Org. Lett.* **2001**, 3, 2321.

¹¹³³ Samec, J.S.M.; Bäckvall, J.-E. *Chem. Eur. J.* **2002**, 8, 2955.

¹¹³⁴ Moghaddam, F.M.; Khakshoor, O.; Ghaffarzadeh, M. *J. Chem. Res. (S)* **2001**, 525.

¹¹³⁵ Davies, I.W.; Taylor, M.; Marcoux, J.-F.; Matty, L.; Wu, J.; Hughes, D.; Reider, P.J. *Tetrahedron Lett.* **2000**, 41, 8021.

Oximes are generally reduced to amines (Reaction 19-48),¹¹³⁶ but simple reduction to give hydroxylamines can be accomplished with borane¹¹³⁷ or sodium cyanoborohydride.¹¹³⁸ Oxime *O*-ethers are reduced with Bu₃SnH and BF₃·OEt₂.¹¹³⁹ Diazo compounds (ArN=NAr) are reductively cleaved to aniline derivatives with Zn and ammonium formate in methanol.¹¹⁴⁰

Reduction of imines has been carried out enantioselectively.¹¹⁴¹ Catalytic hydrogenation¹¹⁴² with a chiral Ir¹¹⁴³, Re,¹¹⁴⁴ Rh,¹¹⁴⁵ or Pd¹¹⁴⁶ catalyst is effective. Catalytic hydrogenation of iminium salts with a chiral Ru catalyst gives the amine.¹¹⁴⁷ Enantioselective reduction of imines is possible using a mixture of *Escherichia coli* whole cells and H₃N·BH₃.¹¹⁴⁸ *Hantzsch ester* (see Reactions 15-14 and 16-17) reduction of imine-esters, in the presence of a chiral phosphoric acid derivative, leads to chiral amino esters.¹¹⁴⁹ In a related reaction, enamines were reduced by hydrogenation over a chiral Rh catalyst.¹¹⁵⁰

Hydrogenation of oximes with Pd/C and a Ni complex gives the imine, and in the presence of a lipase and ethyl acetate the final product was an acetamide, formed with high enantioselectivity.¹¹⁵¹ Catalytic-transfer hydrogenation of imines leads with a chiral catalyst to chiral amines.¹¹⁵² Conjugated *N*-sulfonyl imines are reduced to the conjugated sulfonamide with good enantioselectivity using a chiral rhodium catalyst in the presence of LiF and PhSnMe₃.¹¹⁵³ Phosphinyl imines, R₂C=N—P(=O)Ar₂, are reduced with high enantioselectivity using a chiral Cu catalyst.¹¹⁵⁴ Silanes (e.g., PhSiH₃) can be used for the reduction of imines, and in the presence of a chiral Ti catalyst the resulting amine was formed with excellent enantioselectivity.¹¹⁵⁵ The enantioselective reduction of aromatic imines is possible using trichlorosilane.¹¹⁵⁶ Enzymatic reduction of imines leads to chiral amines.¹¹⁵⁷

¹¹³⁶ See Bolm, C.; Felder, M. *Synlett* **1994**, 655; Williams, D.R.; Osterhout, M.H.; Reddy, J.P. *Tetrahedron Lett.* **1993**, 34, 3271.

¹¹³⁷ Kawase, M.; Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* **1979**, 643.

¹¹³⁸ See Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* **1979**, 11, 201; Lane, C.F. *Synthesis* **1975**, 135.

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¹¹⁴⁰ Gowda, S.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* **2002**, 43, 1329.

¹¹⁴¹ See Denmark, S.E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, 116, 8797; Fuller, J.C.; Belisle, C.M.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* **1994**, 35, 5389. For a review of asymmetric reductions involving the C=N unit, see Zhu, Q.-C.; Hutchins, R.O. *Org. Prep. Proced. Int.* **1994**, 26, 193.

¹¹⁴² Hou, G.; Gosselin, F.; Li, W.; McWilliams, J.C.; Sun, Y.; Weisel, M.; O'Shea, P.D.; Chen, C.-y.; Davies, I.W.; Zhang, X. *J. Am. Chem. Soc.* **2009**, 131, 9882.

¹¹⁴³ See Li, C.; Wang, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2008**, 130, 14450; Vargas, S.; Rubio, M.; Suárez, A.; Pizzano, A. *Tetrahedron Lett.* **2005**, 46, 2049.

¹¹⁴⁴ Nolin, K.A.; Ahn, R.W.; Toste, F.D. *J. Am. Chem. Soc.* **2005**, 127, 12462.

¹¹⁴⁵ Li, C.; Xiao, J. *J. Am. Chem. Soc.* **2008**, 130, 13208.

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¹¹⁴⁷ Magee, M.P.; Norton, J.R. *J. Am. Chem. Soc.* **2001**, 123, 1778.

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¹¹⁴⁹ Li, G.; Liang, Y.; Antilla, J.C. *J. Am. Chem. Soc.* **2007**, 129, 5830.

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¹¹⁵¹ Choi, Y.K.; Kim, M.J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* **2001**, 3, 4099.

¹¹⁵² Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, 7, 3781.

¹¹⁵³ Hayashi, T.; Ishigedani, M. *Tetrahedron* **2001**, 57, 2589.

¹¹⁵⁴ Lipshutz, B.H.; Shimizu, H. *Angew. Chem. Int. Ed.* **2004**, 43, 2228.

¹¹⁵⁵ Hansen, M.C.; Buchwald, S.L. *Org. Lett.* **2000**, 2, 713.

¹¹⁵⁶ For a review, see Guizzetti, S.; Benaglia, M. *Eur. J. Org. Chem.* **2010**, 5529. See Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, 47, 3751; Malkov, A.V.; Stončius, S.; MacDougall, K.N.; Mariani, A.; McGeoch, G.D.; Kočovský, P. *Tetrahedron* **2006**, 62, 264; Wang, C.; Wu, X.; Zhou, L.; Sun, J. *Chemistry: European J.* **2008**, 14, 8789; Malkov, A.V.; Figlus, M.; Cooke, G.; Caldwell, S.T.; Rabani, G.; Prestly, M.R.; Kočovský, P. *Org. Biomol. Chem.* **2009**, 7, 1878; Malkov, A.V.; Vranková, K.; Sigerson, R.C.; Stončius, S.; Kočovský, P. *Tetrahedron* **2009**, 65, 9481.

¹¹⁵⁷ Vijayananthi, T.; Chadha, A. *Tetrahedron Asymmetry* **2008**, 19, 93.

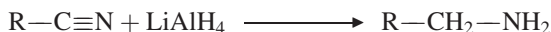
Oxime ethers are reduced with borane and a chiral spiroborate ester catalyst.¹¹⁵⁸

Isocyanates have been catalytically hydrogenated to *N*-substituted formamides: $\text{RNCO} \rightarrow \text{R-NH-CHO}$.¹¹⁵⁹ Isothiocyanates were reduced to thioformamides with SmI_2 in $\text{HMPA}/t\text{-BuOH}$.¹¹⁶⁰

OS **III**, 328, 827; **VI**, 905; **VIII**, 110, 568. Also see, OS **IV**, 283.

19-43 The Reduction of Nitriles to Amines

CC,NN-Tetrahydro-biaddition



Nitriles can be reduced to primary amines with many reducing agents,¹¹⁶¹ including LiAlH_4 , and $\text{BH}_3\cdot\text{SMe}_2$.¹¹⁶² The reagent NaBH_4 does not generally reduce nitriles except in alcoholic solvents with a catalyst (e.g., CoCl_2 ,¹¹⁶³ NiCl_2 ,¹¹⁶⁴ or Raney nickel).¹¹⁶⁵ Lithium dimethylaminoborohydride ($\text{LiBH}_3\text{NMe}_2$) reduces aryl nitriles to the corresponding benzylamines.¹¹⁶⁶

The reduction of nitriles is of wide scope and has been applied to many nitriles. Catalytic hydrogenation converts nitriles to primary amines,¹¹⁶⁷ but secondary amines $[(\text{RCH}_2)_2\text{NH}]$ are often side products.¹¹⁶⁸ These can be avoided by adding a compound (e.g., acetic anhydride), which removes the primary amine as soon as it is formed,¹¹⁶⁹ or by the use of excess ammonia to drive the equilibria backward.¹¹⁷⁰ Sponge nickel¹¹⁷¹ or nickel on silica gel¹¹⁷² have been used for the catalytic hydrogenation of aryl nitriles to amines.

Attempts to stop with the addition with only 1 equiv of hydrogen, have failed; that is, to convert the nitrile to an imine, except where the imine is subsequently hydrolyzed (Reaction **19-44**).

¹¹⁵⁸ Chu, Y.; Shan, Z.; Liu, D.; Sun, N. *J. Org. Chem.* **2006**, *71*, 3998; Huang, K.; Merced, F.G.; Ortiz-Marciales, M.; Meléndez, H.J.; Correa, W.; De Jesús, M. *J. Org. Chem.* **2008**, *73*, 4017.

¹¹⁵⁹ Howell, H.G. *Synth. Commun.* **1983**, *13*, 635.

¹¹⁶⁰ Park, H.S.; Lee, I.S.; Kim, Y.H. *Chem. Commun.* **1996**, 1805.

¹¹⁶¹ See Rabinovitz, M. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, pp. 307–340; Enthaler, S.; Addis, D.; Junge, K.; Erre, G.; Beller, M. *Chemistry: European J.* **2008**, *14*, 9491. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 875–878.

¹¹⁶² See Brown, H.C.; Choi, Y.M.; Narasimhan, S. *Synthesis* **1981**, 605.

¹¹⁶³ Satoh, T.; Suzuki, S. *Tetrahedron Lett.* **1969**, 4555. For a discussion of the mechanism, see Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801.

¹¹⁶⁴ Khurana, J.M.; Kukreja, G. *Synth. Commun.* **2002**, *32*, 1265.

¹¹⁶⁵ Egli, R.A. *Helv. Chim. Acta* **1970**, *53*, 47.

¹¹⁶⁶ Thomas, S.; Collins, C.J.; Cuzens, J.R.; Spieciarich, D.; Goralski, C.T.; Singaram, B. *J. Org. Chem.* **2001**, *66*, 1999.

¹¹⁶⁷ See Reguillo, R.; Grellier, M.; Vautravers, N.; Vendier, L.; Sabo-Etienne, S. *J. Am. Chem. Soc.* **2010**, *132*, 7854.

¹¹⁶⁸ See Galán, A.; de Mendoza, J.; Prados, P.; Rojo, J.; Echavarren, A.M. *J. Org. Chem.* **1991**, *56*, 452.

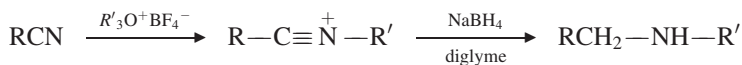
¹¹⁶⁹ See Gould, F.E.; Johnson, G.S.; Ferris, A.F. *J. Org. Chem.* **1960**, *25*, 1658.

¹¹⁷⁰ For example, see Freifelder, M. *J. Am. Chem. Soc.* **1960**, *82*, 2386.

¹¹⁷¹ Tanaka, K.; Nagasawa, M.; Kasuga, Y.; Sakamura, H.; Takuma, Y.; Iwatani, K. *Tetrahedron Lett.* **1999**, *40*, 5885.

¹¹⁷² Takamizawa, S.; Wakasa, N.; Fuchikami, T. *Synlett* **2001**, 1623.

N-Alkyltrinitilium ions are reduced to secondary amines by NaBH₄.¹¹⁷³



Since nitrilium salts can be prepared by treatment of nitriles with trialkyloxonium salts (see Reaction 16-8), this is a method for the conversion of nitriles to secondary amines.

Note that the related compounds, the isocyanides (R—N⁺≡CO[−], also called isocyanides) have been reduced to *N*-methyamines with LiAlH₄, as well as with other reducing agents.

OS III, 229, 358, 720; VI, 223.

19-44 The Reduction of Nitriles to Aldehydes

Hydro,oxy-de-nitrilo-tersubstitution



There are two principal methods for the reduction of nitriles to aldehydes.¹¹⁷⁴ In one of these, known as the *Stephen reduction*, the nitrile is treated with HCl to form an iminium salt (40). Subsequent reduction of (40) with anhydrous SnCl₂ gives RCH=NH, which precipitates as a complex with SnCl₄ and is then hydrolyzed (Reaction 16-2) to the aldehyde. The *Stephen reduction* is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons.¹¹⁷⁵ It is also possible to prepare 40 in a different way, by treating ArCONHPh with PCl₅, which can then be converted to the aldehyde. This is known as the *Sonn-Müller method*. Aqueous formic acid in the presence of PtO₂, followed by treatment with aqueous acid converts aryl nitriles to aryl aldehydes.¹¹⁷⁶

The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 molar equivalent of hydrogen and subsequent hydrolysis, *in situ*, of the resulting imine (which is undoubtedly coordinated to the metal). This reaction has been carried out with LiAlH₄, LiAlH(OEt)₃,¹¹⁷⁷ LiAlH(NR₂)₃,¹¹⁷⁸ and Dibal-H.¹¹⁷⁹ The metal hydride method is useful for aliphatic and aromatic nitriles.

OS III, 626, 818; VI, 631.

¹¹⁷³ Borch, R.F. *Chem. Commun.* **1968**, 442.

¹¹⁷⁴ Rabinovitz, M. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, **1970**, p. 307. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1271–1272.

¹¹⁷⁵ Zil'berman, E.N.; Pyralova, P.S. *J. Gen. Chem. USSR* **1963**, 33, 3348.

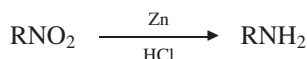
¹¹⁷⁶ Xi, F.; Kamal, F.; Schenerman, M.A. *Tetrahedron Lett.* **2002**, 43, 1395.

¹¹⁷⁷ Brown, H.C.; Shoaf, C.J. *J. Am. Chem. Soc.* **1964**, 86, 1079. For a review of reductions with this and related reagents, see Málek, J. *Org. React.* **1988**, 36, 249, see pp. 287–289, 438–448.

¹¹⁷⁸ Cha, J.S.; Lee, S.E.; Lee, H.S. *Org. Prep. Proceed. Int.* **1992**, 24, 331. Also see, Cha, J.S.; Jeoung, M.K.; Kim, J.M.; Kwon, O.O.; Lee, J.C. *Org. Prep. Proceed. Int.* **1994**, 26, 583.

¹¹⁷⁹ Marshall, J.A.; Andersen, N.H.; Schlicher, J.W. *J. Org. Chem.* **1970**, 35, 858.

19-45 Reduction of Nitro Compounds to Amines



Both aliphatic¹¹⁸⁰ and aromatic nitro compounds can be reduced to amines, although the reaction has been applied much more often to aromatic nitro compounds, owing to their greater availability. Many reducing agents have been used to reduce aromatic nitro compounds, the most common being Zn, Sn, or Fe (or sometimes other metals) and acid, and catalytic hydrogenation.¹¹⁸¹ Chemoselective catalytic hydrogenation of nitro compounds is possible.¹¹⁸² Transfer hydrogenation is used to reduce nitro compounds.¹¹⁸³ Indium metal in aq ethanol with ammonium chloride¹¹⁸⁴ or with water in aq THF¹¹⁸⁵ also reduces aromatic nitro compounds to the corresponding aniline derivative. Indium metal in methanol, with acetic anhydride and acetic acid, converts aromatic nitro compounds to the acetanilide.¹¹⁸⁶ Both samarium metal in methanol with ultrasound,¹¹⁸⁷ and a mixture of SmI₂–water and an amine reduce nitro compounds.¹¹⁸⁸ Alternative reduction methods use ultrasound with Al(Hg) in aq THF¹¹⁸⁹ or with stannous chloride in an ionic liquid.¹¹⁹⁰ Some other reagents used¹¹⁹¹ were Et₃SiH/RhCl(PPh)₃,¹¹⁹² AlH₃–AlCl₃, formic acid and Pd–C,¹¹⁹³ or formic acid with Raney nickel in methanol.¹¹⁹⁴ The reaction with sulfides or polysulfides is called the *Zinin reduction*.¹¹⁹⁵ Amines are also the products when nitro compounds, both alkyl and aryl, are reduced with HCOONH₄–Pd–C.¹¹⁹⁶ Many other functional groups (e.g., COOH, COOR, CN, amide) are not affected by this reagent (although ketones are reduced, see Reaction 19-33). With optically active alkyl substrates this method gives retention of configuration.¹¹⁹⁷

¹¹⁸⁰ See Ioffe, S.L.; Tartakovskii, V.A.; Novikov, S.S. *Russ. Chem. Rev.* **1966**, 35, 19.

¹¹⁸¹ For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, **1985**, pp. 104–116, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, **1967**, pp. 168–202. See Deshpande, R.M.; Mahajan, A.N.; Diwakar, M.M.; Ozarde, P.S.; Chaudhari, R.V. *J. Org. Chem.* **2004**, 69, 4835.

¹¹⁸² Takasaki, M.; Motoyama, Y.; Higashi, K.; Yoon, S.-H.; Mochida, I.; Nagashima, H. *Org. Lett.* **2008**, 10, 1601. See also Gelder, E.A.; Jackson, S.D.; Lok, C.M. *Chem. Commun.* **2005**, 522; Chen, Y.; Wang, C.; Liu, H.; Qiu, J.; Bao, X. *Chem. Commun.* **2005**, 5298.

¹¹⁸³ Soltani, O.; Ariger, M.A.; Carreira, E.M. *Org. Lett.* **2009**, 11, 4196.

¹¹⁸⁴ Banik, B.K.; Suhendra, M.; Banik, I.; Becker, F.F. *Synth. Commun.* **2000**, 30, 3745.

¹¹⁸⁵ Lee, J.G.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Kang, Y.; Cho, Y.S. *Synthesis* **2001**, 81.

¹¹⁸⁶ Kim, B.H.; Han, R.; Piao, F.; Jun, Y.M.; Baik, W.; Lee, B.M. *Tetrahedron Lett.* **2003**, 44, 77.

¹¹⁸⁷ Basu, M.K.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* **2000**, 41, 5603.

¹¹⁸⁸ Ankner, T.; Hilmersson, G. *Tetrahedron Lett.* **2007**, 48, 5707.

¹¹⁸⁹ Fitch, R.W.; Luzzio, F.A. *Tetrahedron Lett.* **1994**, 35, 6013.

¹¹⁹⁰ Rai, G.; Jeong, J.M.; Lee, Y.-S.; Kim, H.W.; Lee, D.S.; Chung, J.-K.; Lee, M.C. *Tetrahedron Lett.* **2005**, 46, 3987.

¹¹⁹¹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 821–828.

¹¹⁹² Brinkman, H.R. *Synth. Commun.* **1996**, 26, 973.

¹¹⁹³ Entwistle, I.D.; Jackson, A.E.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* **1977**, 443. See also, Terpko, M.O.; Heck, R.F. *J. Org. Chem.* **1980**, 45, 4992; Babler, J.H.; Sarussi, S.J. *Synth. Commun.* **1981**, 11, 925.

¹¹⁹⁴ Gowda, D.C.; Gowda, A.S.P.; Baba, A.R.; Gowda, S. *Synth. Commun.* **2000**, 30, 2889.

¹¹⁹⁵ For a review of the Zinin reduction, see Porter, H.K. *Org. React.* **1973**, 20, 455.

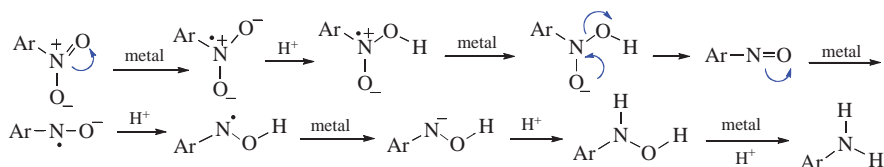
¹¹⁹⁶ Ram, S.; Ehrenkauffer, R.E. *Tetrahedron Lett.* **1984**, 25, 3415; Abiraj, K.; Srinivasa, G.R.; Gowda, D.C. *Synth. Commun.* **2005**, 35, 223.

¹¹⁹⁷ Barrett, A.G.M.; Spilling, C.D. *Tetrahedron Lett.* **1988**, 29, 5733.

Lithium aluminum hydride reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (Reaction **19-80**). Most metal hydrides, including NaBH_4 and BH_3 , do not reduce nitro groups at all, although both aliphatic and aromatic nitro compounds have been reduced to amines with NaBH_4 and various catalysts (e.g., NiCl_2 or CoCl_2 ¹¹⁹⁸ and ZrCl_4).¹¹⁹⁹ Borohydride exchange resin (BER) in the presence of $\text{Ni}(\text{OAc})_2$, however, gives the amine.¹²⁰⁰ Treatment of aromatic nitro compounds with NaBH_4 alone has resulted in reduction of the *ring* to a cyclohexane ring with the nitro group still intact¹²⁰¹ or in cleavage of the nitro group from the ring.¹²⁰² With $(\text{NH}_4)_2\text{S}$ or other sulfides or polysulfides it is often possible to reduce just one of two or three nitro groups on an aromatic ring or on two different rings in one molecule.¹²⁰³ Bakers yeast reduces aromatic nitro compounds to aniline derivatives.¹²⁰⁴ A combination of $\text{NaH}_2\text{PO}_2/\text{FeSO}_4$ with microwave irradiation reduces aromatic nitro compounds to aniline derivatives.¹²⁰⁵ Hydrazine on alumina, with FeCl_3 and microwave irradiation, accomplishes this reduction.¹²⁰⁶ Hydrazine–formic acid with Raney nickel in methanol reduces aromatic nitro compounds.¹²⁰⁷ Heating aromatic nitro compounds with 57% HI reduces the nitro group to the amino group.¹²⁰⁸

With some reducing agents, especially with aromatic nitro compounds, the reduction can be stopped at an intermediate stage, and hydroxylamines (Reaction **19-46**), hydrazobenzenes, azobenzenes (Reaction **19-80**), and azoxybenzenes (Reaction **19-79**) can be obtained in this manner. However, nitroso compounds, which are often postulated as intermediates, are too reactive to be isolated, if indeed they are intermediates. Reduction by metals in mineral acids cannot be stopped, but always produces the amine.

The mechanisms of these reductions have not been much studied, although it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates. Both of these types of compounds give amines when exposed to most of these reducing agents (Reaction **19-47**), and hydroxylamines can be isolated (Reaction **19-46**). With metals and acid the following path has been suggested¹²⁰⁹:



¹¹⁹⁸ See He, Y.; Zhao, H.; Pan, X.; Wang, S. *Synth. Commun.* **1989**, *19*, 3047 and references cited therein.

¹¹⁹⁹ Chary, K.P.; Ram, S.R.; Iyengar, D.S. *Synlett* **2000**, 683.

¹²⁰⁰ Yoon, N.M.; Choi, J. *Synlett* **1993**, 135.

¹²⁰¹ Severin, T.; Schmitz, R. *Chem. Ber.* **1962**, *95*, 1417; Severin, T.; Adam, M. *Chem. Ber.* **1963**, *96*, 448.

¹²⁰² Kaplan, L.A. *J. Am. Chem. Soc.* **1964**, *86*, 740. See also, Swanwick, M.G.; Waters, W.A. *Chem. Commun.* **1970**, 63.

¹²⁰³ See Ono, A.; Terasaki, S.; Tsuruoka, Y. *Chem. Ind. (London)* **1983**, 477; Ayyangar, N.R.; Kalkote, U.R.; Lugad, A.G.; Nikrad, P.V.; Sharma, V.K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3159.

¹²⁰⁴ Baik, W.; Han, J.L.; Lee, K.C.; Lee, N.H.; Kim, B.H.; Hahn, J.-T. *Tetrahedron Lett.* **1994**, *35*, 3965.

¹²⁰⁵ Meshram, H.M.; Ganesh, Y.S.S.; Sekhar, K.C.; Yadav, J.S. *Synlett* **2000**, 993.

¹²⁰⁶ Vass, A.; Dudás, J.; Tóth, J.; Varma, R.S. *Tetrahedron Lett.* **2001**, *42*, 5347.

¹²⁰⁷ Gowda, S.; Gowda, D.C. *Tetrahedron* **2002**, *58*, 2211.

¹²⁰⁸ Kumar, J.S.D.; Ho, M.M.; Toyokuni, T. *Tetrahedron Lett.* **2001**, *42*, 5601.

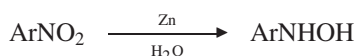
¹²⁰⁹ House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, **1972**, p. 211.

Certain aromatic nitroso compounds (Ar—NO) can be obtained in good yields by irradiation of the corresponding nitro compounds in 0.1 M aq KCN with UV light.¹²¹⁰ The reaction has also been performed electrochemically.¹²¹¹ When nitro compounds are treated with most reducing agents, nitroso compounds are either not formed or react further under the reaction conditions and cannot be isolated.

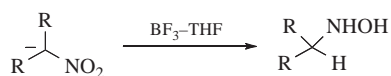
Reductive alkylation of aromatic nitro compounds is possible. The reaction of nitrobenzene with allylic or benzyl halides in the presence of an excess of tin metal in methanol, leads to the *N,N*-diallyl or dibenzyl aniline.¹²¹² A similar reaction occurs with nitrobenzene, allyl bromide, and In metal in aq acetonitrile.¹²¹³

OS **I**, 52, 240, 455, 485; **II**, 130, 160, 175, 254, 447, 471, 501, 617; **III**, 56, 59, 63, 69, 73, 82, 86, 239, 242, 453; **IV**, 31, 357; **V**, 30, 346, 552, 567, 829, 1067, 1130; **81**, 188.

19-46 Reduction of Nitro Compounds to Hydroxylamines



When aromatic nitro compounds are reduced with zinc and water under neutral conditions,¹²¹⁴ hydroxylamines are formed. Among other reagents used for this purpose have been SmI₂,¹²¹⁵ N₂H₄—Rh—C,¹²¹⁶ and KBH₄/BiCl₃.¹²¹⁷ Borane in THF reduces aliphatic nitro enolate anions to hydroxylamines¹²¹⁸:

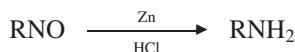


Nitro compounds have been reduced electrochemically, to hydroxylamines, as well as to other products.¹²¹⁹

OS **I**, 445; **III**, 668; **IV**, 148; **VI**, 803; **VIII**, 16.

19-47 Reduction of Nitroso Compounds and Hydroxylamines to Amines

N-Dihydro-de-oxo-bisubstitution



¹²¹⁰ Petersen, W.C.; Letsinger, R.L. *Tetrahedron Lett.* **1971**, 2197; Vink, J.A.J.; Cornelisse, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1971**, 90, 1333.

¹²¹¹ Lamoureux, C.; Moinet, C. *Bull. Soc. Chim. Fr.* **1988**, 59.

¹²¹² Bieber, L.W.; da Costa, R.C.; da Silva, M.F. *Tetrahedron Lett.* **2000**, 41, 4827.

¹²¹³ Kang, K.H.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Chung, B.Y.; Cho, Y.S. *Synth. Commun.* **2001**, 31, 2277.

¹²¹⁴ See Entwistle, I.D.; Gilkerson, T.; Johnstone, R.A.W.; Telford, R.P. *Tetrahedron* **1978**, 34, 213.

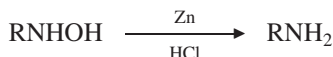
¹²¹⁵ Kende, A.S.; Mendoza, J.S. *Tetrahedron Lett.* **1991**, 32, 1699.

¹²¹⁶ Oxley, P.W.; Adger, B.M.; Sasse, M.J.; Forth, M.A. *Org. Synth.* **67**, 187.

¹²¹⁷ Ren, P.D.-D.; Pan, X.-W.; Jin, Q.-H.; Yao, Z.-P. *Synth. Commun.* **1997**, 27, 3497.

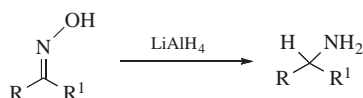
¹²¹⁸ Feuer, H.; Bartlett, R.S.; Vincent, Jr., B.F.; Anderson, R.S. *J. Org. Chem.* **1965**, 31, 2880.

¹²¹⁹ See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, **1989**, pp. 188–198; Lund, H. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, **1983**, pp. 285–313.

N-Hydro-de-hydroxylation or N-Dehydroxylation

Nitroso compounds and hydroxylamines can be reduced to amines by the same reagents that reduce nitro compounds (Reaction 19-45). Reaction with CuCl, and then phenylboronic acid (Reaction 12-28), also reduces nitroso compounds to the amine.¹²²⁰ A hydroxylamine can be reduced to the amine with CS₂ in acetonitrile.¹²²¹ Indium metal in EtOH/aq NH₄Cl reduces hydroxylamines to the amine.¹²²² *N*-Nitroso compounds are similarly reduced to hydrazines (R₂N—NO → R₂N—NH₂).¹²²³

OS I, 511; II, 33, 202, 211, 418; III, 91; IV, 247. See also, OS VIII, 93.

19-48 Reduction of Oximes to Primary Amines or Aziridines

Both aldoximes and ketoximes can be reduced to primary amines with LiAlH₄. The reaction is slower than similar reduction of ketones, so that, for example, PhCOCH=NOH gave 34% PhCHOHCH=NOH.¹²²⁴ Among other reducing agents that give this reduction¹²²⁵ are zinc and acetic acid, BH₃,¹²²⁶ NaBH₃CN—TiCl₃,¹²²⁷ PMHS with Pd-C,¹²²⁸ and sodium and an alcohol.¹²²⁹ Catalytic hydrogenation is also effective.¹²³⁰ Reduction of oximes with In metal in acetic anhydride/acetic acid–THF leads to the acetamide.¹²³¹

The reduction has been performed enantioselectively with Baker's yeast¹²³² and with Ph₂SiH₂ and an optically active Rh complex catalyst.¹²³³ Oxime *O*-ethers are reduced to the amine with modest enantioselectivity using a chiral boron compound.¹²³⁴

¹²²⁰ Yu, Y.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* **2004**, 6, 2631.

¹²²¹ Schwartz, M.A.; Gu, J.; Hu, X. *Tetrahedron Lett.* **1992**, 33, 1687.

¹²²² Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, 5, 1773.

¹²²³ See Lunn, G.; Sansone, E.B.; Keefer, L.K. *J. Org. Chem.* **1984**, 49, 3470.

¹²²⁴ Felkin, H. *C.R. Acad. Sci.* **1950**, 230, 304.

¹²²⁵ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 845–846.

¹²²⁶ Feuer, H.; Braunstein, D.M. *J. Org. Chem.* **1969**, 34, 1817.

¹²²⁷ Leeds, J.P.; Kirst, H.A. *Synth. Commun.* **1988**, 18, 777.

¹²²⁸ Chandrasekhar, S.; Reddy, M.V.; Chandraiah, L. *Synlett* **2000**, 1351.

¹²²⁹ See Sugden, J.K.; Patel, J.J.B. *Chem. Ind. (London)* **1972**, 683.

¹²³⁰ See Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, **1967**, pp. 139–159.

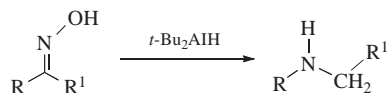
¹²³¹ Harrison, J.R.; Moody, C.J.; Pitts, M.R. *Synlett* **2000**, 1601.

¹²³² Gibbs, D.E.; Barnes, D. *Tetrahedron Lett.* **1990**, 31, 5555.

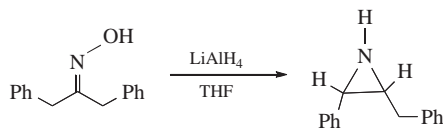
¹²³³ Brunner, H.; Becker, R.; Gauder, S. *Organometallics* **1986**, 5, 739; Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.* **2001**, 2360.

¹²³⁴ Fontaine, E.; Namane, C.; Meneyrol, J.; Geslin, M.; Serva, L.; Russey, E.; Tissandié, S.; Maftouh, M.; Roger, P. *Tetrahedron Asymmetry* **2001**, 12, 2185; Huang, X.; Ortiz-Marciales, M.; Huang, K.; Stepanenko, V.; Merced, F.G.; Ayala, A.M.; Correa, W.; De Jesús, M. *Org. Lett.* **2007**, 9, 1793.

When the reducing agent is Dibal-H, the product is a secondary amine, arising from a rearrangement¹²³⁵:



With certain oximes (e.g., those of the type $\text{ArCH}_2\text{CR}=\text{NOH}$), treatment with LiAlH_4 gives aziridines,¹²³⁶ for example,

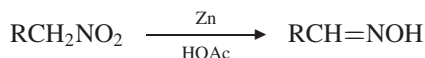


Hydrazones, arylhydrazones, and semicarbazones can also be reduced to amines with various reducing agents, including $\text{Zn}-\text{HCl}$ and H_2 and Raney nickel.

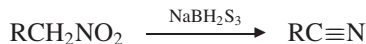
Oximes have been reduced in a different way, to give imines ($\text{RR}'\text{C}=\text{NOH} \rightarrow \text{RR}'\text{C}=\text{NH}$), which are generally unstable, but which can be trapped to give useful products. Among reagents used for this purpose have been $\text{Bu}_3\text{P}-\text{SPh}_2$ ¹²³⁷ and $\text{Ru}_3(\text{CO})_{12}$.¹²³⁸ Oximes can also be reduced to hydroxylamines (Reaction 19-42). Nitrones have been reduced to imines using $\text{AlCl}_3 \cdot 6 \text{H}_2\text{O}/\text{KI}$ followed by $\text{Na}_2\text{S}_2\text{O}_3-\text{H}_2\text{O}$.¹²³⁹

OS II, 318; III, 513; V, 32, 83, 373, 376.

19-49 Reduction of Aliphatic Nitro Compounds to Oximes or Nitriles



Nitro compounds that contain an α hydrogen can be reduced to oximes with zinc dust in acetic acid¹²⁴⁰ or with other reagents, among them CS_2-NEt_3 ,¹²⁴¹ CrCl_2 ,¹²⁴² and (for α -nitro sulfones) NaNO_2 .¹²⁴³ α -Nitro alkenes have been converted to oximes ($-\text{C}=\text{C}-\text{NO}_2 \rightarrow -\text{CH}-\text{C}=\text{NOH}$) with sodium hypophosphite, In with aq. $\text{NH}_4\text{Cl}/\text{MeOH}$,¹²⁴⁴ and with $\text{Pb}-\text{HOAc}-\text{DMF}$, as well as with certain other reagents.¹²⁴⁵



¹²³⁵ Sasatani, S.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, 24, 4711.

¹²³⁶ For a review, see Kotera, K.; Kitahonoki, K. *Org. Prep. Proced.* **1969**, 1, 305. See Tatchell, A.R. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1294; Ferrero, L.; Rouillard, M.; Decouzon, M.; Azzaro, M. *Tetrahedron Lett.* **1974**, 131; Diab, Y.; Laurent, A.; Mison, P. *Tetrahedron Lett.* **1974**, 1605.

¹²³⁷ Barton, D.H.R.; Motherwell, W.B.; Simon, E.S.; Zard, S.Z. *J. Chem. Soc. Chem. Commun.* **1984**, 337.

¹²³⁸ Akazome, M.; Tsuji, Y.; Watanabe, Y. *Chem. Lett.* **1990**, 635.

¹²³⁹ Boruah, M.; Konwar, D. *Synlett* **2001**, 795.

¹²⁴⁰ Johnson, K.; Degering, E.F. *J. Am. Chem. Soc.* **1939**, 61, 3194.

¹²⁴¹ Albanese, D.; Landini, D.; Penso, M. *Synthesis* **1990**, 333.

¹²⁴² Hanson, J.R. *Synthesis* **1974**, 1, pp. 7-8.

¹²⁴³ Zeilstra, J.J.; Engberts, J.B.F.N. *Synthesis* **1974**, 49.

¹²⁴⁴ Yadav, J.S.; Subba Reddy, B.V.; Srinivas, R.; Ramalingam, T. *Synlett* **2000**, 1447.

¹²⁴⁵ See Kabalka, G.W.; Pace, E.D.; Wadgaonkar, P.P. *Synth. Commun.* **1990**, 20, 2453; Sera, A.; Yamauchi, H.; Yamada, H.; Itoh, K. *Synlett* **1990**, 477.

Primary aliphatic nitro compounds can be reduced to aliphatic nitriles with $t\text{-BuN}\equiv\text{C}/\text{BuN}=\text{C}=\text{O}$.¹²⁴⁶ Secondary compounds give mostly ketones (e.g., nitrocyclohexane gave 45% cyclohexanone, 30% cyclohexanone oxime, and 19% *N*-cyclohexylhydroxylamine). Tertiary aliphatic nitro compounds do not react with this reagent (see also, Reaction 19-45).

OS IV, 932.

19-50 Reduction of Azides to Primary Amines

N-Dihydro-de-diazo-bisubstitution



Azides are easily reduced to primary amines by LiAlH_4 , as well as by a number of other reducing agents,¹²⁴⁷ including NaBH_4 , $\text{NaBH}_4/\text{LiCl}$,¹²⁴⁸ $\text{NaBH}_4/\text{CoCl}_2/\text{H}_2\text{O}$,¹²⁴⁹ $\text{NaBH}_4/\text{ZrCl}_4$,¹²⁵⁰ H_2 and a catalyst, Mg or Ca in MeOH,¹²⁵¹ Sm/NiCl_2 ,¹²⁵² Sm/I_2 ,¹²⁵³ CeCl_3 ,¹²⁵⁴ $\text{Zn}/\text{NH}_4\text{Cl}/\text{aq EtOH}$,¹²⁵⁵ baker's yeast,¹²⁵⁶ and In metal in EtOH.¹²⁵⁷ Triethylsilane has been used for the radical reduction of azides to amines.¹²⁵⁸

Reaction with PPh_3 leads to a phosphazide ($\text{Ph}_3\text{P}=\text{N}-\text{N}=\text{N}-\text{R}$), which loses nitrogen in what is called the *Staudinger reaction*¹²⁵⁹: a method to prepare phosphazo compounds, but in this case leads to reduction. Alkylation is possible, and the reaction of an alkyl azide with PMe_3 , and then an excess of iodomethane, leads to the *N*-methylated amine.¹²⁶⁰ The reaction is diastereoselective.¹²⁶¹ Chiral *N*-heterocyclic carbenes catalyze the *Staudinger reaction* of ketenes with imines to form β -lactam derivatives.¹²⁶² This reaction, combined with $\text{RX} \rightarrow \text{RN}_3$ (10-43), is an important way of converting alkyl halides (RX) to primary amines (RNH_2); in some cases the two procedures have been

¹²⁴⁶ El Kaim, L.; Gacon, A. *Tetrahedron Lett.* **1997**, 38, 3391.

¹²⁴⁷ For a review, see Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* **1988**, 88, 297, see pp. 321–327. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 815–820; Rolla, F. *J. Org. Chem.* **1982**, 47, 4327.

¹²⁴⁸ Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* **2000**, 30, 4495.

¹²⁴⁹ Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* **2000**, 646.

¹²⁵⁰ Chary, K.P.; Ram, S.R.; Salahuddin, S.; Iyengar, D.S. *Synth. Commun.* **2000**, 30, 3559.

¹²⁵¹ Maiti, S.N.; Spevak, P.; Narendar Reddy, A.V. *Synth. Commun.* **1988**, 18, 1201.

¹²⁵² Wu, H.; Chen, R.; Zhang, Y. *Synth. Commun.* **2002**, 32, 189.

¹²⁵³ Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett.* **1997**, 38, 1065.

¹²⁵⁴ Bartoli, G.; Di Antonio, G.; Giovannini, R.; Giuli, S.; Lanari, S.; Paoletti, M.; Marcantoni, E. *J. Org. Chem.* **2008**, 73, 1919.

¹²⁵⁵ Lin, W.; Zhang, X.; He, Z.; Jin, Y.; Gong, L.; Mi, A. *Synth. Commun.* **2002**, 32, 3279.

¹²⁵⁶ Kamal, A.; Damayanthi, Y.; Reddy, B.S.N.; Lakminarayana, B.; Reddy, B.S.P. *Chem. Commun.* **1997**, 1015; Baruah, M.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synlett* **1996**, 1193.

¹²⁵⁷ Reddy, G.V.; Rao, G.V.; Iyengar, D.S. *Tetrahedron Lett.* **1999**, 40, 3937.

¹²⁵⁸ Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2006**, 71, 5822.

¹²⁵⁹ Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, 2, 635. See Golobov, Y.G.; Zhmurova, I.N.; Kasukhin, L.F. *Tetrahedron* **1981**, 37, 437; Tian, W.Q.; Wang, Y.A. *J. Org. Chem.* **2004**, 69, 4299; Lin, F.L.; Hoyt, H.M.; van Halbeek, H.; Bergman, R.G.; Bertozzi, C.R. *J. Am. Chem. Soc.* **2005**, 127, 2686. For a modification that leads to β -lactams, see Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, 128, 6060.

¹²⁶⁰ Kato, H.; Ohmori, K.; Suzuki, K. *Synlett* **2001**, 1003.

¹²⁶¹ Hu, L.; Wang, Y.; Li, B.; Du, D.-M.; Xu, J. *Tetrahedron* **2007**, 63, 9387.

¹²⁶² Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, 10, 277.

combined into one laboratory step.¹²⁶³ Sulfonyl azides (RSO_2N_3) have been reduced to sulfonamides (RSO_2NH_2) by irradiation in isopropyl alcohol¹²⁶⁴ and with NaH .¹²⁶⁵
OS V, 586; VII, 433.

19-51 Reduction of Miscellaneous Nitrogen Compounds

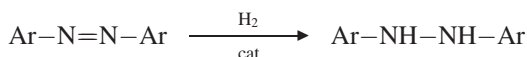
Isocyanate-methylamine transformation



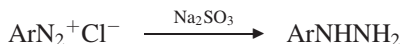
Isothiocyanate-methylamine transformation



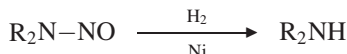
N,N-Dihydro-addition



Diazonium-arylhydrazone reduction



N-Hydro-de-nitroso-substitution



Isocyanates and isothiocyanates are reduced to methylamines on treatment with LiAlH_4 . Azo compounds are not usually reduced by LiAlH_4 ,¹²⁶⁶ (indeed these are the products from LiAlH_4 reduction of nitro compounds, Reaction 19-80), but they can be reduced to hydrazo compounds by catalytic hydrogenation or with diimide¹²⁶⁷ (see Reaction 15-11). Diazonium salts are reduced to hydrazines by sodium sulfite. This reaction probably has a nucleophilic mechanism.¹²⁶⁸ The initial product is a salt of hydrazinesulfonic acid, which is converted to the hydrazine by acid treatment. Diazonium salts can also be reduced to arenes (Reaction 19-69). *N*-Nitrosoamines can be denitrosated to secondary amines by a number of reducing agents, including H_2 and a catalyst,¹²⁶⁹ $\text{BF}_3\text{--THF--NaHCO}_3$,¹²⁷⁰ and $\text{NaBH}_4\text{--TiCl}_4$,¹²⁷¹ as well as by hydrolysis.¹²⁷²

¹²⁶³ See Koziara, A.; Osowska-Pacewicz, K.; Zawadzki, S.; Zwierzak, A. **1987**, 487. The Reactions **10-48**, **10-43**, and **19-50** have also been accomplished in one laboratory step: Koziara, A. *J. Chem. Res. (S)* **1989**, 296.

¹²⁶⁴ Reagen, M.T.; Nickon, A. *J. Am. Chem. Soc.* **1968**, 90, 4096.

¹²⁶⁵ Lee, Y.; Closson, W.D. *Tetrahedron Lett.* **1974**, 381.

¹²⁶⁶ See Newbold, B.T. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, **1975**, pp. 601, 604–614.

¹²⁶⁷ See Ioffe, B.V.; Sergeeva, Z.I.; Dumpis, Yu.Ya. *J. Org. Chem. USSR* **1969**, 5, 1683.

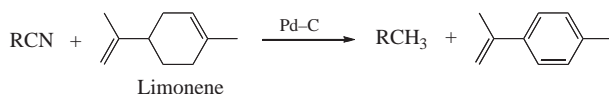
¹²⁶⁸ Huisgen, R.; Lux, R. *Chem. Ber.* **1960**, 93, 540.

¹²⁶⁹ Enders, D.; Hassel, T.; Pieter, R.; Renger, B.; Seebach, D. *Synthesis* **1976**, 548.

¹²⁷⁰ Jeyaraman, R.; Ravindran, T. *Tetrahedron Lett.* **1990**, 31, 2787.

¹²⁷¹ Kano, S.; Tanaka, Y.; Sugino, E.; Shibuya, S.; Hibino, S. *Synthesis* **1980**, 741.

¹²⁷² Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* **1971**, 40, 34, pp. 41–42.



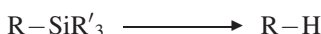
A cyano group can be reduced to a methyl group by treatment with a terpene (e.g., limonene), which acts as reducing agent in the presence of Pd-charcoal.¹²⁷³ Hydrogen gas (H_2) is also effective,¹²⁷⁴ although higher temperatures are required. The R group may be alkyl or aryl.

Aryl nitro compounds are reduced to diaryl hydrazines with Al-KOH in methanol.¹²⁷⁵ OS I, 442; III, 475. Also see, OS V, 43.

D. Reactions in which a Heteroatom Is Removed from the Substrate

19-52 Reduction of Silanes to Methylene Compounds

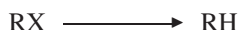
Si-Hydrogen-uncoupling



In certain cases, the C-Si bond of silanes can be converted to C-H. α -Silyl esters are reduced to esters with mercuric acetate and tetrabutylammonium fluoride, for example.¹²⁷⁶

19-53 Reduction of Alkyl Halides

Hydro-de-halogenation or Dehalogenation



This type of reduction can be accomplished with many reducing agents.¹²⁷⁷ A powerful but highly useful reagent (LiAlH_4)¹²⁷⁸ reduces almost all types of alkyl halide, including vinylic, bridgehead, and cyclopropyl halides.¹²⁷⁹ Reduction with lithium aluminum deuteride serves to introduce deuterium into organic compounds. An even more powerful reducing agent, lithium triethylborohydride (LiEt_3BH ; Super hydride), rapidly reduces primary, secondary, allylic, benzylic, and neopentyl halides, but not tertiary (these give elimination) or aryl halides.¹²⁸⁰ A complex formed from lithium trimethoxyaluminum hydride [$\text{LiAlH}(\text{OMe})_3$] and CuI is another powerful reagent, which reduces primary, secondary, tertiary, allylic, vinylic, aryl, and neopentyl halides.¹²⁸¹ Sodium borohydride (NaBH_4) is a milder reducing agent that reduces primary, secondary, and some tertiary¹²⁸²

¹²⁷³ Kindler, K.; Lührs, K. *Chem. Ber.* **1966**, 99, 227; *Liebigs Ann. Chem.* **1967**, 707, 26.

¹²⁷⁴ See also, Brown, G.R.; Foubister, A.J. *Synthesis* **1982**, 1036.

¹²⁷⁵ Khurana, J.M.; Singh, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1893.

¹²⁷⁶ Poliskie, G.M.; Mader, M.M.; van Well, R. *Tetrahedron Lett.* **1999**, 40, 589.

¹²⁷⁷ See Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, **1984**, pp. 62-67, 181; Pinder, A.R. *Synthesis* **1980**, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 29-39.

¹²⁷⁸ See Pizey, J.S. *Synthetic reagents*, Vol. 1, Wiley, NY, **1974**, pp. 101-294; Seyden-Penne, J. *Reductions by the Almino- and Borohydrides*, VCH, NY, **1991**; Hajós, A. *Complex Hydrides*, Elsevier, NY, **1979**.

¹²⁷⁹ Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* **1982**, 47, 276.

¹²⁸⁰ Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* **1980**, 45, 849; **1983**, 48, 3085.

¹²⁸¹ Masamune, S.; Bates, G.S.; Georgiou, P.E. *J. Am. Chem. Soc.* **1974**, 96, 3686.

¹²⁸² Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* **1971**, 36, 1568.

halides in good yield, in a dipolar aprotic solvent (e.g., Me₂SO, DMF, or sulfolane)¹²⁸³ at room temperature or above without affecting other functional groups that would be reduced by LiAlH₄ (e.g., CO₂H, CO₂R, CN).¹²⁸⁴ A mixture of NaBH₄ and InCl₃ efficiently reduces secondary bromides.¹²⁸⁵ Borohydride exchange resin is also an effective reducing agent in the presence of metal catalysts [e.g., Ni(OAc)₂].¹²⁸⁶

Other reducing agents¹²⁸⁷ include Zn (with acid or base), SnCl₂, and Et₃SiH in the presence of an AlCl₃,¹²⁸⁸ and also an Ir¹²⁸⁹ or In¹²⁹⁰ catalyst. Diethyl phosphonate–Et₃N,¹²⁹¹ phosphorus tris(dimethylamide) [(Me₂N)₃P],¹²⁹² and organotin hydrides (R_nSnH_{4-n})¹²⁹³ (chiefly Bu₃SnH) usually used in conjunction with a radical-initiator (e.g., AIBN),¹²⁹⁴ or with transition metal salts (e.g., InCl₃).¹²⁹⁵ A water-soluble organotin hydride has been developed [(MeOCH₂CH₂OCH₂CH₂CH₂)₃SnH], which reduces alkyl halides.¹²⁹⁶ Raney nickel in 2-propanol reduces primary iodides in the presence of a lactone moiety.¹²⁹⁷ Aluminum amalgam efficiently reduced an iodohydrin to the alcohol.¹²⁹⁸

Reduction, especially of bromides and iodides, can also be effected by catalytic hydrogenation.¹²⁹⁹ Raney nickel by itself can reduce alkyl halides.¹³⁰⁰ Homogeneous, chiral transition metal complexes can be used for the asymmetric hydrogenation of halides.¹³⁰¹

Alkali metals (e.g., Li¹³⁰² or Na¹³⁰³ in *t*-BuOH or THF) are good reducing agents for the removal of all halogen atoms in a polyhalo compound (including vinylic, allylic, geminal, and even bridgehead halogens). Zinc and ammonium chloride in alcohol facilitates

¹²⁸³ Hutchins, R.O.; Kandasamy, D.; Dux III, F.; Maryanoff, C.A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259.

¹²⁸⁴ See Bergbreiter, D.E.; Blanton, J.R. *J. Org. Chem.* **1987**, *52*, 472.

¹²⁸⁵ Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906.

¹²⁸⁶ Yoon, N.M.; Lee, H.J.; Ahn, J.H.; Choi, J. *J. Org. Chem.* **1994**, *59*, 4687.

¹²⁸⁷ See Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *J. Chem. Soc. Perkin Trans. 1* **1991**, 103; Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, **1984**, pp. 62–67, 181; Pinder, A.R. *Synthesis* **1980**, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 29–39.

¹²⁸⁸ Doyle, M.P.; McOsker, C.C.; West, C.T. *J. Org. Chem.* **1976**, *41*, 1393; Parnes, Z.N.; Romanova, V.S.; Vol'pin, M.E. *J. Org. Chem. USSR* **1988**, *24*, 254.

¹²⁸⁹ Yang, J.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 12656.

¹²⁹⁰ Miura, K.; Tomita, M.; Yamada, Y.; Hosomi, A. *J. Org. Chem.* **2007**, *72*, 787.

¹²⁹¹ Hirao, T.; Kohno, S.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1881.

¹²⁹² Downie, I.M.; Lee, J.B. *Tetrahedron Lett.* **1968**, 4951.

¹²⁹³ Seyferth, D.; Yamazaki, H.; Alleston, D.L. *J. Org. Chem.* **1963**, *28*, 703. For a novel trialkyltin hydride, see Gastaldi, S.; Stein, D. *Tetrahedron Lett.* **2002**, *43*, 4309.

¹²⁹⁴ See Neumann, W.P. *Synthesis* **1987**, 665; Kuivila, H.G. *Synthesis* **1970**, 499, *Acc. Chem. Res.* **1968**, *1*, 299; Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O.; Tsuji, J. *Tetrahedron Lett.* **1996**, *37*, 6759.

¹²⁹⁵ Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4981.

¹²⁹⁶ Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2957.

¹²⁹⁷ Mebane, R.C.; Grimes, K.D.; Jenkins, S.R.; Deardorff, J.D.; Gross, B.H. *Synth. Commun.* **2002**, *32*, 2049.

¹²⁹⁸ Wang, Y.-C.; Yan, T.-H. *Chem. Commun.* **2000**, 545.

¹²⁹⁹ Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, **1985**; Kantam, M.L.; Rahman, A.; Bandyopadhyay, T.; Haritha, Y. *Synth. Commun.* **1999**, *29*, 691. See Ye, P.; Gellman, A.J. *J. Am. Chem. Soc.* **2008**, *130*, 8518.

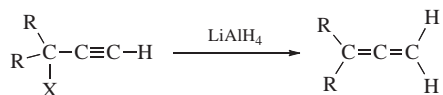
¹³⁰⁰ See Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* **2001**, 493.

¹³⁰¹ Ohkuma, T.; Tsutsumi, K.; Utsumi, N.; Arai, N.; Noyori, R.; Murata, K. *Org. Lett.* **2007**, *9*, 255.

¹³⁰² See Fieser, L.F.; Sachs, D.H. *J. Org. Chem.* **1964**, *29*, 1113; Berkowitz, D.B. *Synthesis* **1990**, 649.

¹³⁰³ See Gassman, P.G.; Aue, D.H.; Patton, D.S. *J. Am. Chem. Soc.* **1968**, *90*, 7271; Gassman, P.G.; Marshall, J.L. *Org. Synth.* **V**, 424.

dehalogenation with microwave irradiation.¹³⁰⁴ Nickel boride facilitates debromination.¹³⁰⁵ Propargylic halides can often be reduced with allylic rearrangement to give allenes.¹³⁰⁶



The choice of a reducing agent usually depends on what other functional groups are present since each reducing agent reduces certain groups and not others. This type of selectivity is called *chemoselectivity*. A chemoselective reagent is one that reacts with one functional group (e.g., halide), but not another (e.g., C=O). For example, there are several reagents that reduce only the halogen of α -halo ketones, leaving the carbonyl group intact.¹³⁰⁷ Among them are decaborane with 10% Pd/C,¹³⁰⁸ Bi in aq THF¹³⁰⁹ or In metal in water,¹³¹⁰ and *i*-Bu₂AlH–SnCl₂.¹³¹¹ Ionic liquids promote the selective debromination of α -bromo ketones.¹³¹² Debromination is also induced by indium metal in a carboxylic acid.¹³¹³ In a similar chemoselective reaction, the halogen in α -haloimines has been reduced with SnCl₂/MeOH without reducing the C=N bond.¹³¹⁴

Tertiary alkyl, benzylic, and allylic halides are reduced by NaBH₃CN–SnCl₂¹³¹⁵, but do not react with primary or secondary alkyl or aryl halides. Sodium cyanoborohydride (NaBH₃CN) in HMPA is another highly selective reagent, in this case for primary and secondary iodo and bromo groups.¹³¹⁶ Most of the reducing agents mentioned reduce chlorides, bromides, and iodides, but organotin hydrides also reduce fluorides.¹³¹⁷ See Section 19.B.ii-A for a discussion of selectivity in reduction reactions.

Alkyl halides, including fluorides and polyhalides, can be reduced with Mg and a secondary or tertiary alcohol (most often 2-propanol).¹³¹⁸ This is actually an example of the occurrence in one step of the sequence:



More often the process is carried out in two separate steps (Reactions 12-36 and 12-22).

¹³⁰⁴ Li, J.; Ye, D.; Liu, H.; Luo, X.; Jiang, H. *Synth. Commun.* **2008**, 38, 567.

¹³⁰⁵ Khurana, J.M.; Kandpal, B.M.; Kukreja, G.; Sharma, P. *Can. J. Chem.* **2006**, 84, 1019.

¹³⁰⁶ See Claesson, A.; Olsson, L. *J. Am. Chem. Soc.* **1979**, 101, 7302.

¹³⁰⁷ See Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, 29, 163.

¹³⁰⁸ Lee, S.H.; Jung, Y.J.; Cho, Y.J.; Yoon, C.-O.M.; Hwang, H.-J.; Yoon, C.M. *Synth. Commun.* **2001**, 31, 2251.

¹³⁰⁹ Ren, P.-D.; Hin, Q.-H.; Yao, Z.-P. *Synth. Commun.* **1997**, 27, 2577.

¹³¹⁰ Park, L.; Keum, G.; Kang, S.B.; Kim, K.S.; Kim, Y. *J. Chem. Soc. Perkin Trans. 1* **2000**, 4462.

¹³¹¹ Oriyama, T.; Mukaiyama, T. *Chem. Lett.* **1984**, 2069.

¹³¹² Ranu, B.C.; Chattopadhyay, K.; Jana, R. *Tetrahedron* **2007**, 63, 155.

¹³¹³ Lee, S.H.; Cho, M.Y.; Nam, M.H.; Park, Y.S.; Yoo, B.W.; Lee, C.-W.; Yoon, C.M. *Synth. Commun.* **2005**, 35, 1335.

¹³¹⁴ Aelterman, W.; Eeckhaut, A.; De Kimpe, N. *Synlett* **2000**, 1283.

¹³¹⁵ Kim, S.; Ko, J.S. *Synth. Commun.* **1985**, 15, 603.

¹³¹⁶ Hutchins, R.O.; Kandasamy, D.; Maryanoff, C.A.; Masilamani, D.; Maryanoff, B.E. *J. Org. Chem.* **1977**, 42, 82.

¹³¹⁷ See Ohsawa, T.; Takagaki, T.; Haneda, A.; Oishi, T. *Tetrahedron Lett.* **1981**, 22, 2583. See also, Brandänge, S.; Dahlman, O.; Ölund, J. *Acta Chem. Scand. Ser. B* **1983**, 37, 141.

¹³¹⁸ Bryce-Smith, D.; Wakefield, B.J.; Blues, E.T. *Proc. Chem. Soc.* **1963**, 219.

Vinyl halides can be reduced to the corresponding alkene in some cases.¹³¹⁹ When vinyl dibromides (e.g., $\text{RCH}=\text{CBr}_2$) are treated with $(\text{MeO})_2\text{P}(=\text{O})\text{H}$ and triethylamine, for example, the product is the vinyl bromide ($\text{RCH}=\text{HBr}$).¹³²⁰ Indium metal in ethanol accomplishes the same transformation.¹³²¹ Similar reduction occurs when vinyl diiodides are treated with $\text{Zn}-\text{Cu}$ in acetic acid.¹³²²

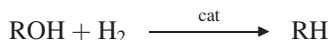
With LiAlH_4 and most other metallic hydrides, the mechanism usually consists of simple nucleophilic substitution with attack by hydride ion equivalents. The mechanism is $\text{S}_{\text{N}}2$ rather than $\text{S}_{\text{N}}1$, since primary halides react better than secondary or tertiary (tertiary generally give alkenes or do not react at all) and since *Walden inversion* has been demonstrated. However, rearrangements found in the reduction of bicyclic tosylates with LiAlH_4 indicate that the $\text{S}_{\text{N}}1$ mechanism can take place.¹³²³ There is evidence that LiAlH_4 and other metal hydrides can also reduce halides by an SET mechanism,¹³²⁴ especially those (e.g., vinylic,¹³²⁵ cyclopropyl,¹³²⁶ or bridgehead halides) that are resistant to nucleophilic substitution. Reduction of halides by NaBH_4 in 80% aq diglyme¹³²⁷ and by BH_3 in nitromethane¹³²⁸ takes place by an $\text{S}_{\text{N}}1$ mechanism. It is known that NaBH_4 in sulfolane reduces tertiary halides possessing a β hydrogen by an elimination–addition mechanism.¹³²⁹

The mechanism for reduction of alkyl halides is not always nucleophilic substitution. For example, reductions with organotin hydrides generally¹³³⁰ take place by free radical mechanisms,¹³³¹ as do those with $\text{Fe}(\text{CO})_5$.

OS I, 357, 358, 548; II, 320, 393; V, 424; VI, 142, 376, 731; VIII, 82. See also, OS VIII, 583.

19-54 Reduction of Alcohols¹³³²

Hydro-de-hydroxylation or Dehydroxylation



The hydroxyl groups of most alcohols can seldom be cleaved by catalytic hydrogenation and alcohols are often used as solvents for hydrogenation of other compounds. However, benzyl-type alcohols undergo the reaction readily and have often been reduced.¹³³³ Diaryl

¹³¹⁹ See Curran, D.P. *Synthesis* **1988**, 417, 489.

¹³²⁰ Abbas S.; Hayes, C.J.; Worden, S. *Tetrahedron Lett.* **2000**, 41, 3215.

¹³²¹ Ranu, B.C.; Samanta, S.; Guchhait, S.K. *J. Org. Chem.* **2001**, 66, 4102.

¹³²² Kdota, I.; Ueno, H.; Ohno, A.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, 44, 8645.

¹³²³ See Kraus, W.; Chassin, C. *Tetrahedron Lett.* **1970**, 1443. See Omoto, M.; Kato, N.; Sogon, T.; Mori, A. *Tetrahedron Lett.* **2001**, 42, 939.

¹³²⁴ Ashby, E.C.; Deshpande, A.K. *J. Org. Chem.* **1994**, 59, 3798. See however Park, S.; Chung, S.; Newcomb, M. *J. Org. Chem.* **1987**, 52, 3275.

¹³²⁵ Chung, S. *J. Org. Chem.* **1980**, 45, 3513.

¹³²⁶ Hatem, J.; Waegell, B. *Tetrahedron* **1990**, 46, 2789.

¹³²⁷ Bell, H.M.; Brown, H.C. *J. Am. Chem. Soc.* **1966**, 88, 1473.

¹³²⁸ Matsumura, S.; Tokura, N. *Tetrahedron Lett.* **1969**, 363.

¹³²⁹ Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* **1971**, 36, 1568.

¹³³⁰ For an exception, see Carey, F.A.; Tramper, H.S. *Tetrahedron Lett.* **1969**, 1645.

¹³³¹ Tanner, D.D.; Singh, H.K. *J. Org. Chem.* **1986**, 51, 5182.

¹³³² For a review, see Müller, P. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, **1980**, pp. 515–522.

¹³³³ See Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, **1985**, pp. 157–163, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, **1967**, pp. 449–468. For a review of the stereochemistry of hydrogenolysis, see Klabunovskii, E.I. *Russ. Chem. Rev.* **1966**, 35, 546.

and triarylcarbinols are similarly easy to reduce with $\text{LiAlH}_4\text{--AlCl}_3$,¹³³⁴ with NaBH_4 in F_3CCOOH ,¹³³⁵ and with iodine, water, and red phosphorus (OS I, 224). Other reagents have been used,¹³³⁶ including $\text{Me}_3\text{SiCl--NaI}$,¹³³⁷ $\text{Et}_3\text{SiH--BF}_3$,¹³³⁸ $\text{SmI}_2\text{--THF--HMPA}$,¹³³⁹ and Sn/HCl . The reduction of secondary alcohols was accomplished using Ph_2SiClH and InCl_3 .¹³⁴⁰ 1,3-Diols are especially susceptible to hydrogenolysis. Tertiary alcohols can be reduced by catalytic hydrogenolysis when the catalyst is Raney nickel.¹³⁴¹ Allylic alcohols (and ethers and acetates) can be reduced (often with accompanying allylic rearrangement) with Zn amalgam and HCl, as well as with certain other reagents.¹³⁴² Reagents that reduce the OH group of α -hydroxy ketones without affecting the C=O group include red phosphorus-iodine,¹³⁴³ and Me_3SiI .¹³⁴⁴

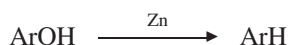
Alcohols can also be reduced indirectly by conversion to a sulfonate and reduction of that compound (Reaction 19-57). The two reactions can be carried out without isolation of the sulfonate if the alcohol is treated with pyridine- SO_3 in THF, followed by LiAlH_4 .¹³⁴⁵ Another indirect reduction that can be done in one step involves treatment of the alcohol (primary, secondary, or benzylic) with NaI, Zn, and Me_3SiCl .¹³⁴⁶ In this case, the alcohol is first converted to the iodide, which is reduced. For other indirect reductions of OH, see Reaction 19-59.

The mechanisms of most alcohol reductions are obscure.¹³⁴⁷ Hydrogenolysis of benzyl alcohols can give inversion or retention of configuration, depending on the catalyst.¹³⁴⁸ The mechanism of electroreduction of allylic alcohols in acidic aqueous media has been examined.¹³⁴⁹

OS I, 224; IV, 25, 218, 482; V, 339; VI, 769.

19-55 Reduction of Phenolic and Other Hydroxyaryl Compounds

Hydro-de-hydroxylation or Dehydroxylation, and so on



¹³³⁴ Avendaño, C.; de Diego, C.; Elguero, J. *Monatsh. Chem.* **1990**, 121, 649.

¹³³⁵ See Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* **1985**, 17, 317. Also see, Nutaitis, C.F.; Bernardo, J.E. *Synth. Commun.* **1990**, 20, 487.

¹³³⁶ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 44-46.

¹³³⁷ Cain, G.A.; Holler, E.R. *Chem. Commun.* **2001**, 1168.

¹³³⁸ Orfanopoulos, M.; Smonou, I. *Synth. Commun.* **1988**, 18, 833; Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* **1988**, 29, 5793; Wustrow, D.J.; Smith, III, W.J.; Wise, L.D. *Tetrahedron Lett.* **1994**, 35, 61.

¹³³⁹ Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, 30, 2945.

¹³⁴⁰ Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, 66, 7741.

¹³⁴¹ Krafft, M.E.; Crooks, III, W.J. *J. Org. Chem.* **1988**, 53, 432. For another catalyst, see Parnes, Z.N.; Shaapuni, D.Kh.; Kalinkin, M.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1974**, 23, 1592.

¹³⁴² See Elphimoff-Felkin, I.; Sarda, P. *Org. Synth.* **VI**, 769; *Tetrahedron* **1977**, 33, 511. For another reagent, see Lee, J.; Alper, H. *Tetrahedron Lett.* **1990**, 31, 4101.

¹³⁴³ Ho, T.L.; Wong, C.M. *Synthesis* **1975**, 161.

¹³⁴⁴ Ho, T.L. *Synth. Commun.* **1979**, 9, 665.

¹³⁴⁵ Corey, E.J.; Achiwa, K. *J. Org. Chem.* **1969**, 34, 3667.

¹³⁴⁶ Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* **1981**, 32.

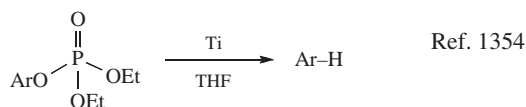
¹³⁴⁷ See Garbisch, Jr., E.W.; Schreader, L.; Frankel, J.J. *J. Am. Chem. Soc.* **1967**, 89, 4233; Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* **1970**, 43, 2143.

¹³⁴⁸ Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* **1970**, 43, 2143.

¹³⁴⁹ Shukun, H.; Yougun, S.; Jindong, Z.; Jian, S. *J. Org. Chem.* **2001**, 66, 4487.

Oxygenated compounds (e.g., phenols, phenolic esters, and ethers) can be reduced.¹³⁵⁰ Phenols can be reduced by distillation over zinc dust or with HI and red phosphorus, but these methods are quite poor and are seldom feasible. Catalytic hydrogenation has also been used, but the corresponding cyclohexanol (see Reaction **15-13**) is a side product.¹³⁵¹

Much better results have been obtained by conversion of phenols to certain esters or ethers and reduction of the latter:



With a Pd–C catalyst, phenol derivatives are deoxygenated using Mg and MeO in the presence of ammonium acetate.¹³⁵⁵ Palladium-on-carbon also mediated hydrodeoxygenation of phenol derivatives in the presence of diethylamine.¹³⁵⁶

OS VI, 150. See also, OS VII, 476.

19-56 Replacement of Alkoxy by Hydrogen

Hydro-de-alkoxylation or Dealkoxylation



Simple ethers are not normally cleaved by reducing agents, although such cleavage has sometimes been reported¹³⁵⁷ [e.g., THF treated with $\text{LiAlH}_4\text{--AlCl}_3$ ¹³⁵⁸ or with a mixture of $\text{LiAlH}(\text{O}t\text{-Bu})_3$ and Et_3B ¹³⁵⁹ gave 1-butanol; the latter reagent also cleaves methyl alkyl ethers].¹³⁶⁰ Certain types of ethers can be cleaved quite well by reducing agents.¹³⁶¹

¹³⁵⁰ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 44–52ff.

¹³⁵¹ Shuikin, N.I.; Erivanskaya, L.A. *Russ. Chem. Rev.* **1960**, 29, 309, see pp. 313–315. See also, Bagnell, L.J.; Jeffery, E.A. *Aust. J. Chem.* **1981**, 34, 697.

¹³⁵² Cacchi, S.; Ciattini, P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, 27, 5541. See also, Cabri, W.; De Bernardinis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* **1990**, 55, 350.

¹³⁵³ Wang, F.; Chiba, K.; Tada, M. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1897.

¹³⁵⁴ Welch, S.C.; Walters, M.E. *J. Org. Chem.* **1978**, 43, 4797. See also, Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* **1973**, 38, 2314.

¹³⁵⁵ Sajiki, H.; Mori, A.; Mizusaki, T.; Ikawa, T.; Maegawa, T.; Hirota, K. *Org. Lett.* **2006**, 8, 987.

¹³⁵⁶ Mori, A.; Mizusaki, T.; Ikawa, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* **2007**, 63, 1270.

¹³⁵⁷ Ranu, B.C.; Bhar, S. *Org. Prep. Proceed. Int.* **1996**, 28, 371.

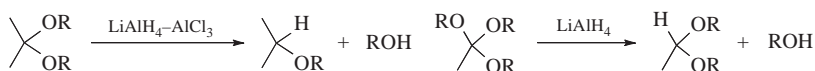
¹³⁵⁸ Bailey, W.J.; Marktscheffel, F. *J. Org. Chem.* **1960**, 25, 1797.

¹³⁵⁹ Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* **1979**, 44, 3678.

¹³⁶⁰ For a review of ether reduction, see Müller, P. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, **1980**, pp. 522–528.

¹³⁶¹ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1013–1019.

Among these are allyl aryl,¹³⁶² vinyl aryl,¹³⁶³ benzylic ethers,^{1333,1364} and anisole¹³⁶⁵ (for epoxides, see Reaction 19-35). 7-Oxobicyclo[2.2.1]heptanes can be reductively cleaved with Dibal-H and nickel catalysts.¹³⁶⁶ α -Methoxy ketones are demethoxylated ($\text{O}=\text{C}-\text{COMe} \rightarrow \text{O}=\text{C}-\text{CH}$) with SmI_2 .¹³⁶⁷



Acetals and ketals are resistant to LiAlH_4 and similar hydrides, and carbonyl groups are often converted to acetals or ketals for protection (Reaction 16-5). However, a combination of LiAlH_4 and AlCl_3 ¹³⁶⁸ does reduce acetals and ketals, removing one group, as shown above.¹³⁶⁹ The actual reducing agents in this case are primarily chloroaluminum hydride (AlH_2Cl) and dichloroaluminum hydride (AlHCl_2), which are formed from the reagents.¹³⁷⁰ This conversion can also be accomplished with Dibal-H,¹³⁷¹ as well as with other reagents.¹³⁷² Ortho esters are easily reduced to acetals by LiAlH_4 alone, offering a route to aldehydes, which are easily prepared by hydrolysis of the acetals (Reaction 10-6). Mixed ketals $[\text{R}(\text{OMe})\text{OR}']$ can be demethoxylated (to give RHOR') with $\text{Bn}_3\text{SnCl}/\text{NaCH}_2\text{BH}_3$ in the presence of AIBN.¹³⁷³

OS III, 693; IV, 798; V, 303. Also see, OS III, 742; VII, 386.

19-57 Reduction of Tosylates and Similar Compounds

Hydro-de-sulfonyloxy-substitution



Tosylates and other sulfonates can be reduced¹³⁷⁴ with LiAlH_4 ,¹³⁷⁵ with NaBH_4 in a dipolar aprotic solvent,¹³⁷⁶ with LiEt_3BH , with $i\text{-Bu}_2\text{AlH}$ (Dibal-H),¹³⁷⁷ or with $\text{Bu}_3\text{SnH}-\text{NaI}$.¹³⁷⁸ The Ni catalyzed reduction of aryl tosylates proceeds in the presence

¹³⁶² Rao, G.V.; Reddy, D.S.; Mohan, G.H.; Iyengar, D.S. *Synth. Commun.* **2000**, 30, 3565.

¹³⁶³ Tweedie, V.L.; Barron B.G. *J. Org. Chem.* **1960**, 25, 2023. See also, Hutchins, R.O.; Learn, K. *J. Org. Chem.* **1982**, 47, 4380.

¹³⁶⁴ Shi, L.; Xia, W.J.; Zhang, F.M.; Tu, Y.Q. *Synlett* **2002**, 1505. See also, Olivero, S.; Duñach, E. *Tetrahedron Lett.* **1997**, 38, 6193.

¹³⁶⁵ Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* **1994**, 35, 8727.

¹³⁶⁶ Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, 117, 532.

¹³⁶⁷ Mikami, K.; Yamaoka, M.; Yoshida, A. *Synlett* **1998**, 607.

¹³⁶⁸ See Rerick, M.N. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, **1968**, pp. 1–94.

¹³⁶⁹ Eliel, E.L.; Badding, V.G.; Rerick, M.N. *J. Am. Chem. Soc.* **1962**, 84, 2371.

¹³⁷⁰ Ashby, E.C.; Prather, J. *J. Am. Chem. Soc.* **1966**, 88, 729; Diner, U.E.; Davis, H.A.; Brown, R.K. *Can. J. Chem.* **1967**, 45, 207.

¹³⁷¹ See Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

¹³⁷² See Hojo, M.; Ushioda, N.; Hosomi, A. *Tetrahedron Lett.* **2004**, 45, 4499; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 931–942.

¹³⁷³ Srikrishna, A.; Viswajanani, R. *Synlett* **1995**, 95.

¹³⁷⁴ For a list of substrate types and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 46–52.

¹³⁷⁵ See Goodenough, K.M.; Moran, W.J.; Raubo, P.; Harrity, J.P.A. *J. Org. Chem.* **2005**, 70, 207.

¹³⁷⁶ Hutchins, R.O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.* **1969**, 3495.

¹³⁷⁷ Janssen, C.G.M.; Hendriks, A.H.M.; Godefroi, E.F. *Recl. Trav. Chim. Pays-Bas* **1984**, 103, 220.

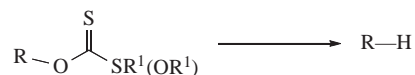
¹³⁷⁸ Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett.* **1983**, 795.

of borane hydrides.¹³⁷⁹ The scope of the reaction seems to be similar to that of **19-53**. When the reagent is LiAlH_4 , alkyl tosylates are reduced more rapidly than iodides or bromides if the solvent is Et_2O , but the order is reversed in diglyme.¹³⁸⁰ The reactivity difference is great enough so that a tosylate function can be reduced in the presence of a halide and vice versa.

OS VI, 376, 762; VIII, 126. See also, OS VII, 66.

19-58 Hydrogenolysis of esters (Barton–McCombie Reaction)

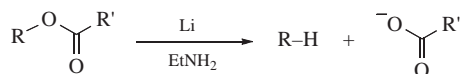
Hydro-de-thioacetoxylation



Alcohols can readily be converted to carbonate and thiocarbonate derivatives. Under radical conditions,¹³⁸¹ using AIBN (Sec. 14.A.i) and Bu_3SnH , the carbonate or thiocarbonate unit is reduced and replaced with hydrogen. The overall process is reduction of the ROH unit to RH and is called the *Barton–McCombie reaction*.¹³⁸² Both $\text{PhSiH}_3/\text{AIBN}$ ¹³⁸³ and $\text{PhSiH}_2-\text{BET}_3\cdot\text{O}_2$ can be used.¹³⁸⁴ This reaction can be catalytic in Bu_3SnH .¹³⁸⁵ Variations include reduction of ROCSNHPH derivatives using $\text{Ph}_3\text{SiH}/\text{BET}_3$.¹³⁸⁶ Another variation used water as the hydrogen atom source when BMe_3 was used.¹³⁸⁷ Tetrabutylammonium peroxydisulfate and formate ion has been used.¹³⁸⁸

19-59 Reductive Cleavage of Carboxylic Esters

Hydro-de-acyloxylation or Deacyloxylation



The alkyl group (R) of certain carboxylic esters can be reduced to RH ¹³⁸⁹ by treatment with lithium in ethylamine.¹³⁹⁰ The reaction is successful when R is a tertiary or a sterically

¹³⁷⁹ Kogan, V. *Tetrahedron Lett.* **2006**, 47, 7515.

¹³⁸⁰ Krishnamurthy, S. *J. Org. Chem.* **1980**, 45, 2550.

¹³⁸¹ Barton, D.H.R.; Jaszberenyi, J.Cs.; Tang, D. *Tetrahedron Lett.* **1993**, 34, 3381.

¹³⁸² See Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, 105, 4059; Lopez, R.M.; Hays, D.S.; Fu, G.C. *J. Am. Chem. Soc.* **1997**, 119, 6949; *The Merck Index*, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, **2006**, p ONR-6; Mundy, B.P.; Ellerd, M.G.; Favalaro, Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd Ed. Wiley-Interscience, New Jersey, **2005**, pp. 68–69.

¹³⁸³ Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* **1993**, 49, 2793.

¹³⁸⁴ Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* **1993**, 49, 7193.

¹³⁸⁵ Lopez, R.M.; Hays, D.S.; Fu, G.C. *J. Am. Chem. Soc.* **1997**, 119, 6949.

¹³⁸⁶ Oba, M.; Nishiyama, K. *Tetrahedron* **1994**, 50, 10193.

¹³⁸⁷ Spiegel, D.A.; Wiberg, K.B.; Schacherer, L.N.; Medeiros, M.R.; Wood, J.L. *J. Am. Chem. Soc.* **2005**, 127, 12513.

¹³⁸⁸ Park, H.S.; Lee, H.Y.; Kim, Y.H. *Org. Lett.* **2005**, 7, 3187.

¹³⁸⁹ See Hartwig, W. *Tetrahedron* **1983**, 39, 2609.

¹³⁹⁰ Barrett, A.G.M.; Godfrey, C.R.A.; Hollinshead, D.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; Joukhadar, L.; McGhie, J.F.; Misra, S.C. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1501. See Garst, M.E.; Dolby, L.J.; Esfandiari, S.; Fedoruk, N.A.; Chamberlain, N.C.; Avey, A.A. *J. Org. Chem.* **2000**, 65, 7098.

hindered secondary alkyl group. A free radical mechanism is likely.¹³⁹¹ Similar reduction, also by a free radical mechanism, has been reported with sodium in HMPA-*t*-BuOH.¹³⁹² In the latter case, tertiary R groups give high yields of RH, but primary and secondary R are converted to a mixture of RH and ROH. Both of these methods provide an indirect method of accomplishing Reaction 19-54 for tertiary R.¹³⁹³ The same thing can be done for primary and secondary R by treating alkyl chloroformates (ROCOCl) with tri-*n*-propylsilane in the presence of *tert*-butylperoxide¹³⁹⁴ and by treating thiono ethers [ROC(=S)W, where W can be OAr or other groups] with Ph₂SiH₂¹³⁹⁵ or Ph₃SiH¹³⁹⁶ and a free radical initiator. Allylic acetates can be reduced with NaBH₄ and a Pd complex,¹³⁹⁷ and with SmI₂-Pd(0).¹³⁹⁸ For other carboxylic ester reductions, see Reactions 19-62, 19-38, and 19-65.

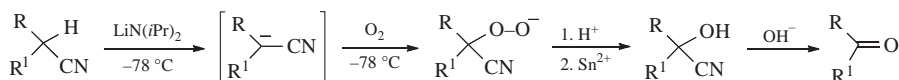
Note that acid chlorides can be reduced (R-COCl → R-H) using (Me₃Si)₃SiH/AIBN.¹³⁹⁹

OS VII, 139.

19-60 Reduction of Hydroperoxides and Peroxides



Hydroperoxides can be reduced to alcohols with LiAlH₄ or Ph₃P¹⁴⁰⁰ or by catalytic hydrogenation. This functional group is very susceptible to catalytic hydrogenation, as shown by the fact that a double bond may be present in the same molecule without being reduced.¹⁴⁰¹



The reaction is an important step in a method for the oxidative decyanation of nitriles containing an α hydrogen.¹⁴⁰² The nitrile is first converted to the α-hydroperoxy nitrile by treatment with base at -78 °C followed by O₂. The hydroperoxy nitrile is then reduced to the cyanohydrin, which is cleaved (the reverse of Reaction 16-52) to the corresponding ketone. The method is not successful for the preparation of aldehydes (R' = H).

¹³⁹¹ Barrett, A.G.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; McGhie, J.F. *J. Chem. Soc. Chem. Commun.* **1979**, 1173.

¹³⁹² Deshayes, H.; Pete, J. *Can. J. Chem.* **1984**, 62, 2063.

¹³⁹³ Also see, Barton, D.H.R.; Crich, D. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1603.

¹³⁹⁴ Jackson, R.A.; Malek, F. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1207.

¹³⁹⁵ See Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.C. *Tetrahedron Lett.* **1990**, 31, 4681, and references cited therein. For similar methods, see Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1990**, 63, 2578; Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *Tetrahedron Lett.* **1990**, 31, 5093.

¹³⁹⁶ Oba, M.; Nishiyama, K. *Synthesis* **1994**, 624.

¹³⁹⁷ Hutchins, R.O.; Learn, K.; Fulton, R.P. *Tetrahedron Lett.* **1980**, 21, 27. See also, Ipaktschi, J. *Chem. Ber.* **1984**, 117, 3320.

¹³⁹⁸ Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, 27, 601, 5237. See also, Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, 30, 2945.

¹³⁹⁹ Ballestri, M.; Chatgililoglu, C.; Cardi, N.; Sommazzi, A. *Tetrahedron Lett.* **1992**, 33, 1787.

¹⁴⁰⁰ See Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, **1979**, pp. 318-320.

¹⁴⁰¹ Rebeller, M.; Clément, G. *Bull. Soc. Chim. Fr.* **1964**, 1302.

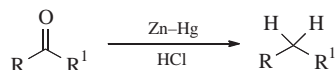
¹⁴⁰² Freerksen, R.W.; Selikson, S.J.; Wroble, R.R.; Kyler, K.S.; Watt, D.S. *J. Org. Chem.* **1983**, 48, 4087.

Peroxides are cleaved to 2 molar equivalents of alcohols by LiAlH_4 , Mg/MeOH ,¹⁴⁰³ or by catalytic hydrogenation. Peroxides can be reduced to ethers with P(OEt)_3 .¹⁴⁰⁴ In a similar reaction, disulfides (RSSR') can be converted to sulfides RSR' by treatment with tris(diethylamino)phosphine $[(\text{Et}_2\text{N})_3\text{P}]$.¹⁴⁰⁵

OS VI, 130.

19-61 Reduction of Carbonyl to Methylene in Aldehydes and Ketones

Dihydro-de-oxo-bisubstitution



There are various ways of reducing the C=O group of aldehydes and ketones to CH_2 .¹⁴⁰⁶ Two old but still popular methods are the *Clemmensen reduction*¹⁴⁰⁷ and the *Wolff-Kishner reduction*. The *Clemmensen reduction* consists of heating the aldehyde or ketone with zinc amalgam and aq HCl .¹⁴⁰⁸ Ketones are reduced more often than aldehydes. In the *Wolff-Kishner reduction*,¹⁴⁰⁹ the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). The *Huang-Minlon modification*¹⁴¹⁰ of the *Wolff-Kishner reduction*, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. A microwave-assisted *Huang-Minlon* procedure has been reported.¹⁴¹¹ The reaction can be carried out under more moderate conditions (room temperature) in DMSO with potassium *tert*-butoxide as base.¹⁴¹² A new modification of the reduction treats a ketone with hydrazine in toluene with microwave irradiation, and subsequent reaction with KOH with microwave irradiation completes the *Wolff-Kishner reduction*.¹⁴¹³ The *Wolff-Kishner reduction* can also be applied to the semicarbazones of aldehydes or ketones.

The *Clemmensen reduction* is usually easier to perform, but it fails for acid-sensitive and high-molecular-weight substrates. For these cases, the *Wolff-Kishner reduction* is quite useful. For high-molecular-weight substrates, a modified *Clemmensen reduction*, using activated zinc and gaseous HCl in an organic solvent (e.g., as ether or acetic anhydride) has proved successful.¹⁴¹⁴ The *Clemmensen* and *Wolff-Kishner reductions* are complementary, since the former uses acidic and the latter basic conditions.

¹⁴⁰³ Dai, P.; Dussault, P.H.; Trullinger, T.K. *J. Org. Chem.* **2004**, 69, 2851.

¹⁴⁰⁴ Horner, L.; Jurgeleit, W. *Liebigs Ann. Chem.* **1955**, 591, 138. See also, Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, **1979**, pp. 320–322.

¹⁴⁰⁵ Harpp, D.N.; Gleason, J.G. *J. Am. Chem. Soc.* **1971**, 93, 2437. For another method, see Comasseto, J.V.; Lang, E.S.; Ferreira, J.T.B.; Simonelli, F.; Correi, V.R. *J. Organomet. Chem.* **1987**, 334, 329.

¹⁴⁰⁶ See Reusch, W. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, **1968**, pp. 171–211.

¹⁴⁰⁷ See, however, Bailey, K.E.; Davis, B.R. *Aust. J. Chem.* **1995**, 48, 1827. Also see, Rosnati, V. *Tetrahedron Lett.* **1992**, 33, 4791.

¹⁴⁰⁸ See Vedejs, E. *Org. React.* **1975**, 22, 401. For a discussion of experimental conditions, see Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, **1967**, pp. 1287–1289.

¹⁴⁰⁹ See Todd, D. *Org. React.* **1948**, 4, 378.

¹⁴¹⁰ Huang-Minlon *J. Am. Chem. Soc.* **1946**, 68, 2487; **1949**, 71, 3301.

¹⁴¹¹ Jaisankar, P.; Pal, B.; Giri, V.S. *Synth. Commun.* **2002**, 32, 2569.

¹⁴¹² Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc.* **1962**, 84, 1734.

¹⁴¹³ Gadhwal, S.; Baruah, M.; Sandhu, J.S. *Synlett* **1999**, 1573.

¹⁴¹⁴ Toda, M.; Hayashi, M.; Hirata, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1972**, 45, 264.

Both methods are fairly specific for aldehydes and ketones and can be carried out with many other functional groups present. However, certain types of aldehydes and ketones do not give normal reduction products. Under *Clemmensen* conditions,¹⁴¹⁵ α -hydroxy ketones give either ketones (hydrogenolysis of the OH, Reaction **19-54**) or alkenes, and 1,3-diones usually undergo rearrangement (e.g., $\text{MeCOCH}_2\text{COMe} \rightarrow \text{MeCOCHMe}_2$).¹⁴¹⁶ Neither method is suitable for α,β -unsaturated ketones, which give pyrazolines¹⁴¹⁷ under *Wolff-Kishner* conditions. Under *Clemmensen* conditions, both groups of these molecules may be reduced or if only one group is reduced, it is the C=C bond.¹⁴¹⁸ Sterically hindered ketones are resistant to both the *Clemmensen* and *Huang-Minlon* procedures, but can be reduced by vigorous treatment with anhydrous hydrazine.¹⁴¹⁹ In the *Clemmensen reduction*, pinacols (Reaction **19-76**) are often side products.

Other reagents have also been used to reduce the C=O of aldehydes and ketones to CH_2 .¹⁴²⁰ Among these are Me_3SiCl followed by $\text{Et}_3\text{SiH/TiCl}_4$,¹⁴²¹ Ni(OAc)_2 on borohydride exchange resin,¹⁴²² Et_3SiH on pyridinium poly(hydrogen fluoride) (PPHF),¹⁴²³ and, for aryl ketones (ArCOR and ArCOAr), NaBH_3CN in THF-aq HCl,¹⁴²⁴ Ni-Al in H_2O ,¹⁴²⁵ $\text{HCOONH}_4\text{-Pd-C}$,¹⁴²⁶ or trialkylsilanes in F_3CCOOH .¹⁴²⁷ Hydrogenation with a heterogeneous Cu-silica catalyst has been used.¹⁴²⁸ Silanes (e.g., Et_3SiH) and a triarylborane catalyst reduce aliphatic aldehydes to methyl, $-\text{CHO} \rightarrow -\text{CH}_3$.¹⁴²⁹ Zinc oxide/triethylsilane has been used,¹⁴³⁰ and also titanocene dichloride [$(\text{C}_5\text{H}_5)_2\text{TiCl}_2$].¹⁴³¹ Most of these reagents also reduce aryl aldehydes (ArCHO) to methylbenzenes (ArCH_3).¹⁴³² One carbonyl group of 1,2-diketones can be selectively reduced by H_2S with an amine catalyst¹⁴³³ or by HI in refluxing acetic acid.¹⁴³⁴ One carbonyl group of quinones (e.g., **41**), can be reduced with Cu and H_2SO_4 or with Sn and HCl.¹⁴³⁵ One carbonyl group of 1,3-diketones was selectively reduced by catalytic hydrogenolysis.¹⁴³⁶

¹⁴¹⁵ See Buchanan, J.G.S.; Woodgate, P.D. *Q. Rev. Chem. Soc.* **1969**, 23, 522.

¹⁴¹⁶ Galton, S.A.; Kalafer, M.; Beringer, F.M. *J. Org. Chem.* **1970**, 35, 1.

¹⁴¹⁷ Pyrazolines can be converted to cyclopropanes; see Reaction **17-34**.

¹⁴¹⁸ See, however, Banerjee, A.K.; Álvarez, J.; Santana, M.; Carrasco, M.C. *Tetrahedron* **1986**, 42, 6615.

¹⁴¹⁹ Barton, D.H.R.; Ives, D.A.J.; Thomas, B.R. *J. Chem. Soc.* **1955**, 2056.

¹⁴²⁰ For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 61–66.

¹⁴²¹ Yato, M.; Homma, K.; Ishida, A. *Heterocycles* **1995**, 41, 17.

¹⁴²² Bandgar, B.P.; Nikat, S.M.; Wadgaonkar, P.P. *Synth. Commun.* **1995**, 25, 863.

¹⁴²³ Olah, G.A.; Wang, Q.; Prakash, G.K.S. *Synlett* **1992**, 647.

¹⁴²⁴ Pashkovsky, F.S.; Lokot, I.P.; Lakhvich, F.A. *Synlett* **2001**, 1391.

¹⁴²⁵ Ishimoto, K.; Mitoma, Y.; Negashima, S.; Tashiro, H.; Prakash, G.K.S.; Olah, G.A.; Tahshiro, M. *Chem. Commun.* **2003**, 514.

¹⁴²⁶ Ram, S.; Spicer, L.D. *Tetrahedron Lett.* **1988**, 29, 3741.

¹⁴²⁷ West, C.T.; Donnelly, S.J.; Kooistra, D.A.; Doyle, M.P. *J. Org. Chem.* **1973**, 38, 2675. See also, Olah, G.A.; Arvanaghi, M.; Ohannesian, L. *Synthesis* **1986**, 770.

¹⁴²⁸ Zaccheria, F.; Ravasio, N.; Ercoli, M.; Allegrini, P. *Tetrahedron Lett.* **2005**, 46, 7743.

¹⁴²⁹ Gevorgyan, V.; Rubin, M.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* **2001**, 66, 1672.

¹⁴³⁰ Li, Z.; Deng, G.; Li, Y.-C. *Synlett* **2008**, 3053.

¹⁴³¹ van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* **1974**, 96, 5290.

¹⁴³² See Zahalka, H.A.; Alper, H. *Organometallics* **1986**, 5, 1909.

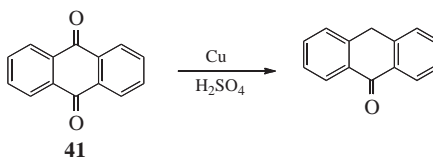
¹⁴³³ Mayer, R.; Hiller, G.; Nitzsche, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* **1963**, 2, 370.

¹⁴³⁴ Reusch, W.; LeMahieu, R. *J. Am. Chem. Soc.* **1964**, 86, 3068.

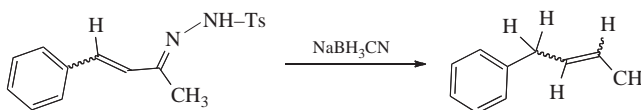
¹⁴³⁵ Meyer, K.H. *Org. Synth.* **I**, 60; Macleod, L.C.; Allen, C.F.H. *Org. Synth.* **II**, 62.

¹⁴³⁶ Cormier, R.A.; McCauley, M.D. *Synth. Commun.* **1988**, 18, 675.

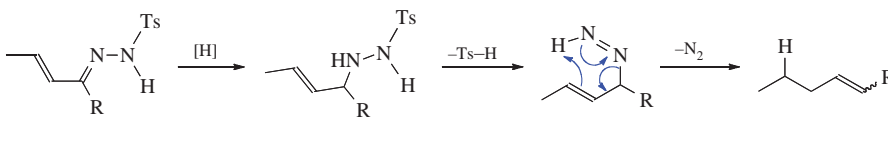
Simply heating a ketone in supercritical 2-propanol reduces the ketone to the methylene compound.¹⁴³⁷



An indirect method of accomplishing the reaction is reduction of tosylhydrazones ($R_2C=N-NHTs$) to R_2CH_2 with $NaBH_4$, BH_3 , catecholborane, bis(benzyloxy)borane, or $NaBH_3CN$. The reduction of α,β -unsaturated tosylhydrazones with $NaBH_3CN$, with $NaBH_4-HOAc$, or with catecholborane proceeds with migration of the double bond to the position formerly occupied by the carbonyl carbon, even if this removes the double bond from conjugation with an aromatic ring,¹⁴³⁸ for example,

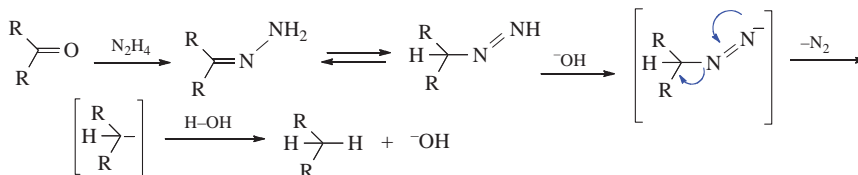


A cyclic mechanism is apparently involved:



Another indirect method is conversion of the aldehyde or ketone to a dithioacetal or ketal, and desulfurization using Raney nickel or another reagent (Reaction 14-27).

The first step in the mechanism¹⁴³⁹ of the *Wolff-Kishner reduction* consists of formation of the hydrazone (**16-14**). It is this species that undergoes reduction in the presence of base, most likely in the following manner:



¹⁴³⁷ Hatano, B.; Tagaya, H. *Tetrahedron Lett.* **2003**, 44, 6331.

¹⁴³⁸ Hutchins, R.O.; Natale, N.R. *J. Org. Chem.* **1978**, 43, 2299; Greene, A.E. *Tetrahedron Lett.* **1979**, 63.

¹⁴³⁹ Szmant, H.H. *Angew. Chem. Int. Ed.* **1968**, 7, 120. Also see Taber, D.F.; Stachel, S.J. *Tetrahedron Lett.* **1992**, 33, 903.

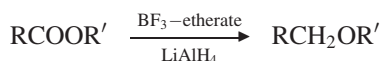
Not much is known about the mechanism of the *Clemmensen reduction*. Several mechanisms have been proposed,¹⁴⁴⁰ including one going through a zinc–carbene intermediate.¹⁴⁴¹ One thing reasonably certain is that the corresponding alcohol is not an intermediate, since alcohols prepared in other ways fail to give the reaction. Note that the alcohol is not an intermediate in the *Wolff–Kishner reduction* either.

It is interesting to see that amines can be deaminated to give the corresponding methylene compounds with low-valent titanium (TiCl₃/Li/THF).¹⁴⁴²

OS I, 60; II, 62, 499; III, 410, 444, 513, 786; IV, 203, 510; V, 533, 747; VI, 62, 293, 919; VII, 393. Also see, OS IV, 218; VII, 18.

19-62 Reduction of Carboxylic Esters to Ethers

Dihydro-de-oxo-bisubstitution



Carboxylic esters and lactones have been reduced to ethers, although 2 molar equivalents of alcohol are more commonly obtained (Reaction 19-38). Reduction to ethers has been accomplished with a reagent prepared from BF₃–etherate and either LiAlH₄, LiBH₄, or NaBH₄,¹⁴⁴³ with trichlorosilane and UV light,¹⁴⁴⁴ and with catalytic hydrogenation. The reaction with the BF₃ reagent apparently succeeds with secondary R', but not with primary R', which give 19-38. Acyloxy groups are reduced by cleavage of the C–C=O bond, R(Ar)COO–C → C–H) with an excess of Ph₂SiH₂ and di-*tert*-butyl peroxide.¹⁴⁴⁵ Esters are reduced to ethers using Et₃SiH and TiCl₄,¹⁴⁴⁶ BF₃,¹⁴⁴⁷ In(III) compounds,¹⁴⁴⁸ or FeCl₃.¹⁴⁴⁹ Lactones are converted to cyclic ethers¹⁴⁵⁰ by treatment with Cp₂TiCl₂ followed by Et₃SiH on Amberlyst 15.¹⁴⁵¹

Thiono esters (RCSOR') can be reduced to ethers (RCH₂OR') with Raney nickel (Reaction 14-27).¹⁴⁵² Reaction of thio esters (e.g., C–OC(=O)Ph) with Ph₂SiH₂ and Ph₃SnH with BEt₃, followed by AIBN (Sec. 14.A.i) leads to reduction of the C=S unit to give an ether.¹⁴⁵³ Since the thiono esters can be prepared from carboxylic esters (Reaction 16-11), this provides an indirect method for the conversion of carboxylic esters to ethers. Thiol esters (RCOSR') have been reduced to thioethers (RCH₂SR').¹⁴⁵⁴

See also, Reactions 19-65 and 19-59.

¹⁴⁴⁰ See Di Vona, M.L.; Rosnati, V. *J. Org. Chem.* **1991**, 56, 4269.

¹⁴⁴¹ Burdon, J.; Price, R.C. *J. Chem. Soc. Chem. Commun.* **1986**, 893.

¹⁴⁴² Talukdar, S.; Banerji, A. *Synth. Commun.* **1996**, 26, 1051.

¹⁴⁴³ Ager, D.J.; Sutherland, I.O. *J. Chem. Soc. Chem. Commun.* **1982**, 248. See also, Dias, J.R.; Pettit, G.R. *J. Org. Chem.* **1971**, 36, 3485.

¹⁴⁴⁴ Baldwin, S.W.; Haut, S.A. *J. Org. Chem.* **1975**, 40, 3885. See also, Kraus, G.A.; Frazier, K.A.; Roth, B.D.; Taschner, M.J.; Neuenschwander, K. *J. Org. Chem.* **1981**, 46, 2417.

¹⁴⁴⁵ Kim, J.-G.; Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* **2004**, 45, 3031.

¹⁴⁴⁶ Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* **2001**, 57, 5353.

¹⁴⁴⁷ Morra, N.A.; Pagenkopf, B.L. *Synthesis* **2008**, 511.

¹⁴⁴⁸ Sakai, N.; Moriya, T.; Fujii, K.; Konakahara, T. *Synthesis* **2008**, 3533.

¹⁴⁴⁹ Iwanami, K.; Seo, H.; Tobita, Y.; Oriyama, T. *Synthesis* **2005**, 183.

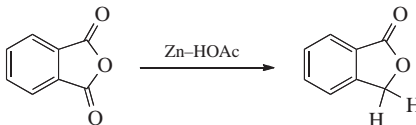
¹⁴⁵⁰ See Pettit, G.R.; Kasturi, T.R.; Green, B.; Knight, J.C. *J. Org. Chem.* **1961**, 26, 4773; Edward, J.T.; Ferland, J.M. *Chem. Ind. (London)* **1964**, 975.

¹⁴⁵¹ Hansen, M.C.; Verdaguer, X.; Buchwald, S.L. *J. Org. Chem.* **1998**, 63, 2360.

¹⁴⁵² Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* **1981**, 46, 831.

¹⁴⁵³ Jang, D.O.; Song, S.H. *Synlett* **2000**, 811; Jang, D.O.; Song, S.H.; Cho, D.H. *Tetrahedron* **1999**, 55, 3479.

¹⁴⁵⁴ Eliel, E.L.; Daignault, R.A. *J. Org. Chem.* **1964**, 29, 1630; Bublit, D.E. *J. Org. Chem.* **1967**, 32, 1630.

19-63 Reduction of Cyclic Anhydrides to Lactones and Acid Derivatives to Alcohols**Dihydro-de-oxo-bisubstitution**

Cyclic anhydrides are reduced with Zn–HOAc to give lactones, and also with hydrogen and Pt or $\text{RuCl}_2(\text{Ph}_3\text{P})_3$,¹⁴⁵⁵ with NaBH_4 .¹⁴⁵⁶ With cyclic anhydrides the reaction with LiAlH_4 can be controlled to give either diols or lactones,¹⁴⁵⁷ although diols are the more usual product. A BINOL– LiAlH_4 –EtOH complex, however, gives smooth reduction to the lactone.¹⁴⁵⁸ With some reagents the reaction can be accomplished regioselectively; that is, only a specific one of the two C=O groups of an unsymmetrical anhydride is reduced.¹⁴⁵⁹ Open-chain anhydrides either are not reduced at all (e.g., with LiAlH_4 or NaBH_4) or give 2 molar equivalents of alcohol. The NaBH_4 in THF, with dropwise addition of methanol, reduces open-chain anhydrides to 1 equiv of primary alcohol and 1 equiv of carboxylic acid.¹⁴⁶⁰

Acyl halides are reduced¹⁴⁶¹ to alcohols by LiAlH_4 or NaBH_4 , as well as by other metal hydrides (Table 19.4), but not by borane.

In general, reduction of amides to alcohols is difficult. More commonly the amide is reduced to an amine. An exception uses LiH_2NBH_3 to give the alcohol.¹⁴⁶² Reduction with sodium metal in propanol also gives the alcohol.¹⁴⁶³ Acyl imidazoles are also reduced to the corresponding alcohol with NaBH_4 in aq HCl.¹⁴⁶⁴

There are no *Organic Syntheses* references, but see OS II, 526, for a related reaction. See OS VI, 482 for reduction to alcohols and OS IV, 271 for reduction of acyl halides.

19-64 Reduction of Amides to Amines**Dihydro-deoxo-bisubstitution**

A useful reagent is LiAlH_4 , although the reaction is more difficult than the reduction of most other functional groups. Other groups are often reduced without disturbing an amide function. Although NaBH_4 by itself does not reduce amides, it does so in the presence

¹⁴⁵⁵ Morand, P.; Kayser, M.M. *J. Chem. Soc. Chem. Commun.* **1976**, 314. See also, Hara, Y.; Wada, K. *Chem. Lett.* **1991**, 553.

¹⁴⁵⁶ Bailey, D.M.; Johnson, R.E. *J. Org. Chem.* **1970**, 35, 3574.

¹⁴⁵⁷ Bloomfield, J.J.; Lee, S.L. *J. Org. Chem.* **1967**, 32, 3919.

¹⁴⁵⁸ Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.* **1993**, 34, 1167.

¹⁴⁵⁹ See Soucy, C.; Favreau, D.; Kayser, M.M. *J. Org. Chem.* **1987**, 52, 129.

¹⁴⁶⁰ Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis* **1987**, 647.

¹⁴⁶¹ See Wheeler, O.H. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, **1972**, pp. 231–251. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 1263–1264.

¹⁴⁶² Myers, A.G.; Yang, B.H.; Kopecky, D.J. *Tetrahedron Lett.* **1996**, 37, 3623.

¹⁴⁶³ Moody, H.M.; Kaptein, B.; Broxterman, Q.B.; Boesten, W.H.J.; Kamphuis, J. *Tetrahedron Lett.* **1994**, 35, 1777.

¹⁴⁶⁴ Sharma, R.; Voynov, G.H.; Ovaska, T.V.; Marquez, V.E. *Synlett* **1995**, 839.

of certain other reagents¹⁴⁶⁵ including iodine.¹⁴⁶⁶ Lithium borohydride reduces acetamides.¹⁴⁶⁷ Substituted amides can be reduced with these powerful reagents, and secondary amides are reduced to secondary amine and tertiary amides to tertiary amines. Borane¹⁴⁶⁸ and sodium in 1-propanol¹⁴⁶⁹ are good reducing agents for all three types of amides. Lithium triethylborohydride produces the alcohol with most *N,N*-disubstituted amides, but not with unsubstituted or *N*-substituted amides.¹⁴⁷⁰ Sodium (dimethylamino)borohydride reduces unsubstituted and disubstituted, but not monosubstituted amides.¹⁴⁷¹

Amides can be reduced¹⁴⁷² to amines by catalytic hydrogenation,¹⁴⁷³ but high temperatures and pressures are usually required. Another reagent that reduces disubstituted amides to amines is trichlorosilane.¹⁴⁷⁴ Other silanes (e.g., Et₃SiH) in the presence of a Re¹⁴⁷⁵ Pt,¹⁴⁷⁶ In,¹⁴⁷⁷ Zn,¹⁴⁷⁸ or Ru,¹⁴⁷⁹ catalyst, reduce amides to amines. Electrolytic reduction of carbamates to give an amine are possible.¹⁴⁸⁰

Hantzsch esters (see Reactions **15-14** and **16-17**) have been used for metal-free reduction of amides to amines.¹⁴⁸¹

With some RCONR₂, LiAlH₄ causes cleavage, and the aldehyde (Reaction **10-41**) or alcohol is obtained. Lactams are reduced to cyclic amines in high yields with LiAlH₄, although cleavage sometimes occurs here too. A mixture of LiBHet₃/Et₃SiH is also effective.¹⁴⁸² Lactams are also reduced to cyclic amines with 9-BBN¹⁴⁸³ (Reaction **15-16**) or LiBH₃NMe₂.¹⁴⁸⁴

Imides are generally reduced on both sides,¹⁴⁸⁵ although it is sometimes possible to stop with just one. Both cyclic and acyclic imides have been reduced in this manner, although with acyclic imides cleavage is often obtained.¹⁴⁸⁶

¹⁴⁶⁵ See Wann, S.R.; Thorsen, P.T.; Kreevoy, M.M. *J. Org. Chem.* **1981**, *46*, 2579; Mandal, S.B.; Giri, V.S.; Pakrashi, S.C. *Synthesis* **1987**, 1128; Akabori, S.; Takanohashi, Y. *Chem. Lett.* **1990**, 251.

¹⁴⁶⁶ Prasad, A.S.B.; Kanth, J.V.B.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623.

¹⁴⁶⁷ Tanaka, H.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 4417.

¹⁴⁶⁸ See Bonnat, M.; Hercourt, A.; Le Corre, M. *Synth. Commun.* **1991**, *21*, 1579.

¹⁴⁶⁹ Bhandari, K.; Sharma, V.L.; Chatterjee, S.K. *Chem. Ind. (London)* **1990**, 547.

¹⁴⁷⁰ Brown, H.C.; Kim, S.C. *Synthesis* **1977**, 635.

¹⁴⁷¹ Hutchins, R.O.; Learn, K.; El-Telbany, F.; Stercho, Y.P. *J. Org. Chem.* **1984**, *49*, 2438.

¹⁴⁷² See Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, **1970**, pp. 795–801; Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, **1956**, p. 544. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 869–872.

¹⁴⁷³ Aoun, R.; Renaud, J.-L.; Dixneuf, P.H.; Bruneau, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2021; Magro, A.A.N.; Eastham, G.R.; Cole-Hamilton, D.J. *Chem. Commun.* **2007**, 3154.

¹⁴⁷⁴ Nagata, Y.; Dohmaru, T.; Tsurugi, J. *Chem. Lett.* **1972**, 989. See also, Benkeser, R.A.; Li, G.S.; Mozden, E.C. *J. Organomet. Chem.* **1979**, *178*, 21.

¹⁴⁷⁵ Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.* **2001**, *42*, 1945.

¹⁴⁷⁶ Hanada, S.; Motoyama, Y.; Nagashima, H. *Tetrahedron Lett.* **2006**, *47*, 6173.

¹⁴⁷⁷ Sakai, N.; Fujii, K.; Konakahara, T. *Tetrahedron Lett.* **2008**, *49*, 6873.

¹⁴⁷⁸ Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 1770.

¹⁴⁷⁹ Hanada, S.; Ishida, T.; Motoyama, Y.; Nagashima, H. *J. Org. Chem.* **2007**, *72*, 7551.

¹⁴⁸⁰ Franco, D.; Duñach, E. *Tetrahedron Lett.* **2000**, *41*, 7333.

¹⁴⁸¹ Barbe, G.; Charette, A.B. *J. Am. Chem. Soc.* **2008**, *130*, 18.

¹⁴⁸² Pedregal, C.; Ezquerro, J.; Escribano, A.; Carreño, M.C.; García Ruano, J.L.G. *Tetrahedron Lett.* **1994**, *35*, 2053.

¹⁴⁸³ Collins, C.J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* **1999**, *40*, 3673.

¹⁴⁸⁴ Flaniken, J.M.; Collins, C.J.; Lanz, M.; Singaram, B. *Org. Lett.* **1999**, *1*, 799.

¹⁴⁸⁵ See Akula, M.R.; Kabalka, G.W. *Org. Prep. Proceed. Int.* **1999**, *31*, 214.

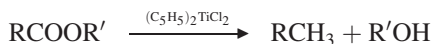
¹⁴⁸⁶ Witkop, B.; Patrick, J.B. *J. Am. Chem. Soc.* **1952**, *74*, 3861.

Note that imides can be reduced to hydroxy lactams using different reagents, including NaBH_4 .¹⁴⁸⁷

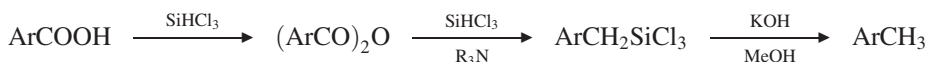
OS IV, 339, 354, 564; VI, 382; VII, 41.

19-65 Reduction of Carboxylic Acids and Esters to Alkanes

Trihydro-de-alkoxy,oxo-tersubstitution, and so on



The reagent titanocene dichloride reduces carboxylic esters in a different manner from that of Reactions **19-59**, **19-62**, or **19-38**. The products are the alkane RCH_3 and the alcohol $\text{R}'\text{OH}$. The mechanism probably involves an alkene intermediate. Aromatic acids can be reduced to methylbenzenes by a procedure involving refluxing first with trichlorosilane in MeCN, then with tripropylamine added, and finally with KOH and MeOH (after removal of the MeCN).¹⁴⁸⁸ The following sequence has been suggested¹⁴⁸⁸:



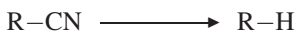
Esters of aromatic acids are not reduced by this procedure, so an aromatic COOH group can be reduced in the presence of a COOR' group.¹⁴⁸⁹ However, it is also possible to reduce aromatic ester groups, by a variation of the trichlorosilane procedure.¹⁴⁹⁰ Both *o*- and *p*-hydroxybenzoic acids and their esters have been reduced to cresols ($\text{HOC}_6\text{H}_4\text{CH}_3$) with sodium bis(2-methoxyethoxy)aluminum hydride $[\text{NaAlH}_2(\text{OC}_2\text{H}_4\text{OMe})_2, \text{Red-Al}]$.¹⁴⁹¹ Heating a 2-pyridylbenzyl ester with ammonium formate and a Ru catalyst leads to reduction of the CH_3COO unit to the alkane.¹⁴⁹²

Carboxylic acids can also be converted to alkanes, indirectly,¹⁴⁹³ by reduction of the corresponding tosylhydrazides (RCONHNH_2) with LiAlH_4 or borane.¹⁴⁹⁴

OS VI, 747.

19-66 Hydrogenolysis of Nitriles

Hydro-de-cyanation



This transformation is not common, but given the proliferation of nitriles in organic chemistry, it is potentially quite useful. In the presence of mercuric compounds, tertiary nitriles can be reduced to the hydrocarbon with sodium cyanoborohydride.¹⁴⁹⁵

¹⁴⁸⁷ See Issa, F.; Fischer, J.; Turner, P.; Coster, M.J. *J. Org. Chem.* **2006**, *71*, 4703.

¹⁴⁸⁸ Benkeser, R.A.; Foley, K.M.; Gaul, J.M.; Li, G.S. *J. Am. Chem. Soc.* **1970**, *92*, 3232.

¹⁴⁸⁹ Benkeser, R.A.; Ehler, D.F. *J. Org. Chem.* **1973**, *38*, 3660.

¹⁴⁹⁰ Benkeser, R.A.; Mozden, E.C.; Muth, C.L. *J. Org. Chem.* **1979**, *44*, 2185.

¹⁴⁹¹ Cerny, M.; Málek, J. *Collect. Czech. Chem. Commun.* **1970**, *35*, 2030.

¹⁴⁹² Chatani, N.; Tatamidani, H.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 4849.

¹⁴⁹³ See Le Deit, H.; Cron S.; Le Corre, M. *Tetrahedron Lett.* **1991**, *32*, 2759.

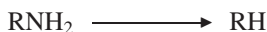
¹⁴⁹⁴ Attanasi, O.; Caglioti, L.; Gasparrini, F.; Misiti, D. *Tetrahedron* **1975**, *31*, 341, and references cited therein.

¹⁴⁹⁵ Sassaman, M.B. *Tetrahedron* **1996**, *52*, 10835.

gem-Dinitriles can be reduced to the corresponding mono-nitrile with SmI_2 .¹⁴⁹⁶ Hydro-silanes facilitate reductive cleavage of nitriles in the presence of a Rh catalyst.¹⁴⁹⁷

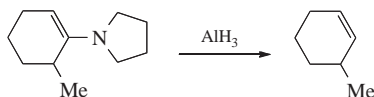
19-67 Reduction of the C–N Bond

Hydro-de-amination or Deamination



Benzylic amines are particularly susceptible to hydrogenolysis by catalytic hydrogenation¹⁴⁹⁸ or dissolving metal reduction.¹⁴⁹⁹ Note that the *Wolff–Kishner reduction* in Reaction 19-61 involved formation of a hydrazone and deprotonation by base that led to loss of nitrogen and reduction. Ceric ammonium nitrate in aq acetonitrile has also been shown to reductively cleave the *N*-benzyl group.¹⁵⁰⁰ Primary amines have been reduced to RH with hydroxylamine-*O*-sulfonic acid and aq NaOH to give the hydrocarbon, nitrogen gas, and the sulfate anion.¹⁵⁰¹ It is postulated that $\text{R}-\text{N}=\text{N}-\text{H}$ is an intermediate that decomposes to the carbocation. An indirect means of achieving the same result is the conversion of the primary amine to the sulfonamide ($\text{RNHSO}_2\text{R}'$) (Reaction 16-102) and subsequent treatment with $\text{NH}_2\text{OSO}_2\text{OH}$ ¹⁵⁰² or NaOH, and then NH_2Cl .¹⁵⁰³ Tosylaziridines derived from terminal alkenes are reduced to the corresponding primary tosylamine with polymethylhydrosiloxane/Pd-C.¹⁵⁰⁴ Aziridines can be reduced in the same way as epoxides (Reaction 19-35).

Other indirect methods involve reduction of *N,N*-ditosylates (Sec. 10.G.iii) with NaBH_4 in HMPA¹⁵⁰⁵ and modifications of the *Katritzky pyrylium–pyridinium method*.¹⁵⁰⁶ Allylic and benzylic amines¹³³³ can be reduced by catalytic hydrogenolysis. Aziridines can be reductively opened with SmI_2 ¹⁵⁰⁷ or with Bu_3SnH and AIBN.¹⁵⁰⁸ The C–N bond of enamines is reductively cleaved to give an alkene with alane (AlH_3)¹⁵⁰⁹:



and with 9-BBN (Reaction 15-16) or borane methyl sulfide (BMS).¹⁵¹⁰ Since enamines can be prepared from ketones (Reaction 16-13), this is a way of converting ketones to alkenes.

¹⁴⁹⁶ Kang, H.-Y.; Hong, W.S.; Cho, Y.S.; Koh, H.Y. *Tetrahedron Lett.* **1995**, 36, 7661.

¹⁴⁹⁷ Tobisu, M.; Nakamura, R.; Kita, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, 131, 3174.

¹⁴⁹⁸ Hartung, W.H.; Simonoff, R. *Org. React.* **1953**, 7, 263.

¹⁴⁹⁹ du Vigneaud, V.; Behrens, O.K. *J. Biol. Chem.* **1937**, 117, 27.

¹⁵⁰⁰ Bull, S.D.; Davies, S.G.; Fenton, G.; Mulvaney, A.W.; Prasad, R.S.; Smith, A.D. *J. Chem. Soc. Perkin Trans. I* **2000**, 3765.

¹⁵⁰¹ Doldouras, G.A.; Kollonitsch, J. *J. Am. Chem. Soc.* **1978**, 100, 341.

¹⁵⁰² Nickon, A.; Hill, R.H. *J. Am. Chem. Soc.* **1964**, 86, 1152.

¹⁵⁰³ Guzic, Jr., F.S.; Wei, D. *J. Org. Chem.* **1992**, 57, 3772.

¹⁵⁰⁴ Chandrasekhar, S.; Ahmed, M. *Tetrahedron Lett.* **1999**, 40, 9325.

¹⁵⁰⁵ Hutchins, R.O.; Cistone, F.; Goldsmith, B.; Heuman, P. *J. Org. Chem.* **1975**, 40, 2018.

¹⁵⁰⁶ See Katritzky, A.R.; Bravo-Borja, S.; El-Mowafy, A.M.; Lopez-Rodriguez, G. *J. Chem. Soc. Perkin Trans. I* **1984**, 1671.

¹⁵⁰⁷ Molander, G.A.; Stengel, P.J. *Tetrahedron* **1997**, 53, 8887.

¹⁵⁰⁸ Schwan, A.L.; Refvik, M.D. *Tetrahedron Lett.* **1993**, 34, 4901.

¹⁵⁰⁹ Coulter, J.M.; Lewis, J.W.; Lynch, P.P. *Tetrahedron* **1968**, 24, 4489.

¹⁵¹⁰ Singaram, B.; Goralski, C.T.; Rangaishenvi, M.V.; Brown, H.C. *J. Am. Chem. Soc.* **1989**, 111, 384.

In the latter case, BMS gives retention of configuration [an (*E*)-isomer gives the (*E*)-product], while 9-BBN gives the other isomer.¹⁵¹⁰ Diazo ketones are reduced to methyl ketones by HI: $\text{RCOCHN}_2 + \text{HI} \rightarrow \text{RCOCH}_3$.¹⁵¹¹

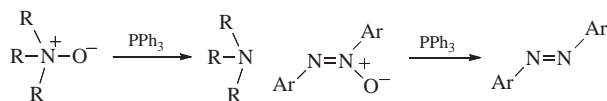
Quaternary ammonium salts can be cleaved with LiAlH_4 , $\text{R}_4\text{N}^+ + \text{LiAlH}_4 \rightarrow \text{R}_3\text{N} + \text{R}^-$, as can quaternary phosphonium salts (R_4P^+). Other reducing agents have also been used (e.g., lithium triethylborohydride, which preferentially cleaves methyl groups,¹⁵¹² and Na in liquid ammonia). When quaternary salts are reduced with $\text{Na}(\text{Hg})$ in water, the reaction is known as the *Emde reduction*. However, this reagent is not applicable to the cleavage of ammonium salts with four *saturated* alkyl groups.

Nitro compounds (RNO_2) can be reduced to RH ¹⁵¹³ by sodium methylmercaptide (CH_3SNa) in an aprotic solvent¹⁵¹⁴ or by Bu_3SnH .¹⁵¹⁵ Both reactions have free radical mechanisms.¹⁵¹⁶ Tertiary nitro compounds can be reduced to RH by NaHTe .¹⁵¹⁷ The nitro group of aromatic nitro compounds has been removed with sodium borohydride.¹⁵¹⁸ Reduction of the C–N bond on aromatic amines with Li metal in THF generates the aryl compounds.¹⁵¹⁹ Sodium nitrite, sodium bisulfite in EtOH/water/acetic acid does a similar reduction.¹⁵²⁰ Conversion of the aniline derivative to the methanesulfonamide and subsequent treatment with NaH and NH_2Cl gives the same result.¹⁵²¹ The Bu_3SnH reagent also reduces isocyanides (RNC , prepared from RNH_2 by formylation followed by Reaction 17-31) to RH ,¹⁵²² a reaction that can also be accomplished with Li or Na in liquid NH_3 ,¹⁵²³ or with K and a crown ether in toluene.¹⁵²⁴ α -Nitro ketones can be reduced to ketones with $\text{Na}_2\text{S}_2\text{O}_4\text{--Et}_3\text{SiH}$ in $\text{HMPA--H}_2\text{O}$.¹⁵²⁵

OS III, 148; IV, 508; VIII, 152.

19-68 Reduction of Amine Oxides and Azoxy Compounds

N-Oxygen-detachment



¹⁵¹¹ For example, see Pojer, P.M.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* **1968**, 21, 1375.

¹⁵¹² Cooke, Jr., M.P.; Parلمان, R.M. *J. Org. Chem.* **1975**, 40, 531.

¹⁵¹³ See Fessard, T.C.; Motoyoshi, H.; Carreira, E.M. *Angew. Chem. Int. Ed.* **2007**, 46, 2078.

¹⁵¹⁴ Kornblum, N.; Carlson, S.C.; Smith, R.G. *J. Am. Chem. Soc.* **1979**, 101, 647; Kornblum, N.; Widmer, J.; Carlson, S.C. *J. Am. Chem. Soc.* **1979**, 101, 658.

¹⁵¹⁵ See Ono, N. in Feuer, H.; Nielsen, A.T. *Nitro Compounds: Recent Advances in Synthesis and Chemistry*, VCH, NY, **1990**, pp. 1–135, 1–45; Rosini, G.; Ballini, R. *Synthesis* **1988**, 833, see pp. 835–837; Ono, N.; Kaji, A. *Synthesis* **1986**, 693. See Kamimura, A.; Ono, N. *Bull. Chem. Soc. Jpn.* **1988**, 61, 3629.

¹⁵¹⁶ Tanner, D.D.; Harrison, D.J.; Chen, J.; Kharrat, A.; Wayner, D.D.M.; Griller, D.; McPhee, D.J. *J. Org. Chem.* **1990**, 55, 3321; Bowman, W.R.; Crosby, D.; Westlake, P.J. *J. Chem. Soc. Perkin Trans. 2* **1991**, 73.

¹⁵¹⁷ Suzuki, H.; Takaoka, K.; Osuka, A. *Bull. Chem. Soc. Jpn.* **1985**, 58, 1067.

¹⁵¹⁸ See Kniel, P. *Helv. Chim. Acta* **1968**, 51, 371. For another method, see Ono, N.; Tamura, R.; Kaji, A. *J. Am. Chem. Soc.* **1983**, 105, 4017.

¹⁵¹⁹ Azzena, U.; Dessanti, F.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* **1999**, 40, 8291.

¹⁵²⁰ Geoffroy, O.J.; Morinelli, T.A.; Meier, G.B. *Tetrahedron Lett.* **2001**, 42, 5367.

¹⁵²¹ Wang, Y.; Guzic Jr., F.S. *J. Org. Chem.* **2001**, 66, 8293.

¹⁵²² Barton, D.H.R.; Bringmann, G.; Motherwell, W.B. *Synthesis* **1980**, 68.

¹⁵²³ See Yadav, J.S.; Reddy, P.S.; Joshi, B.V. *Tetrahedron Lett.* **1988**, 44, 7243.

¹⁵²⁴ Ohsawa, T.; Mitsuda, N.; Nezu, J.; Oishi, T. *Tetrahedron Lett.* **1989**, 30, 845.

¹⁵²⁵ Kamimura, A.; Kurata, K.; Ono, N. *Tetrahedron Lett.* **1989**, 30, 4819.

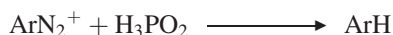
Amine oxides¹⁵²⁶ and azoxy compounds (both alkyl and aryl)¹⁵²⁷ can be reduced practically quantitatively with triphenylphosphine.¹⁵²⁸ Other reducing agents have also been used, including LiAlH_4 , $\text{NaBH}_4/\text{LiCl}$,¹⁵²⁹ $\text{H}_2\text{-Ni}$, PCl_3 , $\text{Ga/H}_2\text{O}$,¹⁵³⁰ or In/TiCl_4 .¹⁵³¹ Indium metal with aq ammonium chloride in methanol gives good yields of pyridine from pyridine *N*-oxide.¹⁵³² Similar results are obtained using ammonium formate and Raney nickel¹⁵³³ or zinc.¹⁵³⁴ Sodium in ethanol, in a sealed tube, reduces pyridine *N*-oxide to pyridine.¹⁵³⁵ Similar reduction was accomplished with Mo(CO)_6 in ethanol.¹⁵³⁶ Indium (III) chloride has been used for the reduction of quinoline *N*-oxide to quinoline.¹⁵³⁷ Nitrile oxides¹⁵³⁸ ($\text{R-C}\equiv\text{N}^+-\text{O}^-$) can be reduced to nitriles with trialkylphosphines,¹⁵³⁹ and isocyanates (RNCO) to isocyanides (RNC) with $\text{Cl}_3\text{SiH-Et}_3\text{N}$.¹⁵⁴⁰

Analogous to amino *N*-oxides, phosphine oxides ($\text{R}_3\text{P=O}$) are reduced to phosphines (R_3P). Treatment of a phosphine oxide with MeOTf followed by reduced with LiAlH_4 ¹⁵⁴¹ or Dibal-H¹⁵⁴² gives the phosphine. Chiral phosphine oxides are reduced to the phosphine with excellent enantioselectivity using PPh_3 and Cl_3SiH .¹⁵⁴³

OS IV, 166. See also, OS VIII, 57.

19-69 Replacement of the Diazonium Group by Hydrogen

Dediazoniation or Hydro-de-diazoniation



Reduction of a diazonium group (*dediazoniation*) provides an indirect method for the removal of an amino group from an aromatic ring.¹⁵⁴⁴ A common method uses hypophosphorous acid (H_3PO_2), although many other reducing agents¹⁵⁴⁵ have been used,

¹⁵²⁶ See Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, **1991**, pp. 120–134; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, **1971**, pp. 166–231.

¹⁵²⁷ See Newbold, B.T. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, **1975**, pp. 602–603, 614–624.

¹⁵²⁸ See Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, **1979**, pp. 295–350.

¹⁵²⁹ Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* **2000**, *30*, 3511.

¹⁵³⁰ Han, J.H.; Choi, K.I.; Kim, J.H.; Yoo, B.W. *Synth. Commun.* **2004**, *34*, 3197.

¹⁵³¹ Yoo, B.W.; Choi, K.H.; Choi, K.I.; Kim, J.H. *Synth. Commun.* **2003**, *33*, 4185.

¹⁵³² Yadav, J.S.; Reddy, B.V.S.; Reddy, M.M. *Tetrahedron Lett.* **2000**, *41*, 2663.

¹⁵³³ Balicki, R.; Maciejewski, G. *Synth. Commun.* **2002**, *32*, 1681.

¹⁵³⁴ Balicki, R.; Cybulski, M.; Maciejewski, G. *Synth. Commun.* **2003**, *33*, 4137.

¹⁵³⁵ Bjørsvik, H.-R.; Gambarotti, C.; Jensen, V.R.; González, R.R. *J. Org. Chem.* **2005**, *70*, 3218.

¹⁵³⁶ Yoo, B.W.; Choi, J.W.; Yoon, C.M. *Tetrahedron Lett.* **2006**, *47*, 125.

¹⁵³⁷ Ilias, Md.; Barman, D.C.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* **2002**, *43*, 1877.

¹⁵³⁸ See Torsell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, **1988**, pp. 55–74; Grundmann, C. *Fortschr. Chem. Forsch.* **1966**, *7*, 62.

¹⁵³⁹ Grundmann, C.; Frommelt, H.D. *J. Org. Chem.* **1965**, *30*, 2077.

¹⁵⁴⁰ Baldwin, J.E.; Derome, A.E.; Riordan, P.D. *Tetrahedron* **1983**, *39*, 2989.

¹⁵⁴¹ Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3*, 87.

¹⁵⁴² Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C.H. *Org. Lett.* **2005**, *7*, 4277.

¹⁵⁴³ Wu, H.-C.; Yu, J.-Q.; Spencer, J.B. *Org. Lett.* **2004**, *6*, 4675.

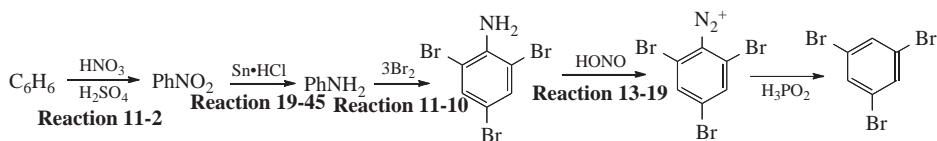
¹⁵⁴⁴ See Zollinger, H. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, **1983**, pp. 603–669.

¹⁵⁴⁵ For lists of some of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 39–41; Tröndlin, F.; Rüchardt, C. *Chem. Ber.* **1977**, *110*, 2494.

including HMPA,¹⁵⁴⁶ thiophenol,¹⁵⁴⁷ and sodium stannite (Na_2SnO_2). Ethanol was the earliest reagent used, and it frequently gives good yields, but ethers (ArOEt) are often side products. When H_3PO_2 is used, 5–15 molar equivalents of this reagent are required per molar equivalent of substrate. Diazonium salts can be reduced in nonaqueous media by several methods, including treatment with Bu_3SnH or Et_3SiH in ethers or MeCN ¹⁵⁴⁸ and by isolation as the BF_4^- salt and reduction of this with NaBH_4 in DMF.¹⁵⁴⁹ Aromatic amines can be deaminated ($\text{ArNH}_2 \rightarrow \text{ArH}$) in one laboratory step by treatment with an alkyl nitrite in DMF¹⁵⁵⁰ or boiling THF.¹⁵⁵¹ The corresponding diazonium salt is an intermediate.

Not many investigations of the mechanism have been carried out. It is generally assumed that the reaction of diazonium salts with ethanol to produce ethers takes place by an ionic ($\text{S}_{\text{N}}1$) mechanism while the reduction to ArH proceeds by a free radical process.¹⁵⁵² The reduction with H_3PO_2 is also believed to have a free radical mechanism.¹⁵⁵³ In the reduction with NaBH_4 , an aryldiazene intermediate ($\text{ArN}=\text{NH}$) has been demonstrated,¹⁵⁵⁴ arising from nucleophilic attack by BH_4^- on the β nitrogen. Such diazenes can be obtained as moderately stable (half-life of several hours) species in solution.¹⁵⁵⁵ It is not entirely clear how the aryldiazene decomposes, but there are indications that either the aryl radical (AR^\bullet) or the corresponding anion (Ar^-) may be involved.¹⁵⁵⁶

The dediazonation reaction is used for functionalization of aromatic rings, to remove an amino group after it has been used to direct one or more other groups to ortho and para positions. For example, the compound 1,3,5-tribromobenzene cannot be prepared by direct bromination of benzene because the bromo group is ortho–para directing; however, this compound is easily prepared by the following sequence:



Many other compounds that would otherwise be difficult to prepare are easily synthesized with the aid of the dediazonation reaction.

Unwanted dediazonation can be suppressed by using hexasulfonated calix[6]arenes (see Sec. 3.C.ii).¹⁵⁵⁷

OS I, 133, 415; II, 353, 592; III, 295; IV, 947; VI, 334.

¹⁵⁴⁶ Shono, T.; Matsumura, Y.; Tsubata, K. *Chem. Lett.* **1979**, 1051.

¹⁵⁴⁷ See Korzeniowski, S.H.; Blum, L.; Gokel, G.W. *J. Org. Chem.* **1977**, 42, 1469.

¹⁵⁴⁸ Nakayama, J.; Yoshida, M.; Simamura, O. *Tetrahedron* **1970**, 26, 4609.

¹⁵⁴⁹ Hendrickson, J.B. *J. Am. Chem. Soc.* **1961**, 83, 1251. See also, Threadgill, M.D.; Gledhill, A.P. *J. Chem. Soc. Perkin Trans. 1* **1986**, 873.

¹⁵⁵⁰ Doyle, M.P.; Dellaria, Jr., J.F.; Siegfried, B.; Bishop, S.W. *J. Org. Chem.* **1977**, 42, 3494.

¹⁵⁵¹ Cadogan, J.I.G.; Molina, G.A. *J. Chem. Soc. Perkin Trans. 1* **1973**, 541.

¹⁵⁵² See Broxton, T.J.; Bunnett, J.F.; Paik, C.H. *J. Org. Chem.* **1977**, 42, 643.

¹⁵⁵³ See Levit, A.F.; Kiprianova, L.A.; Gragerov, I.P. *J. Org. Chem. USSR* **1975**, 11, 2395.

¹⁵⁵⁴ König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* **1972**, 11, 45.

¹⁵⁵⁵ Smith III, M.R.; Hillhouse, G.L. *J. Am. Chem. Soc.* **1988**, 110, 4066.

¹⁵⁵⁶ See König, E.; Musso, H.; Záhorszky, U.I.; König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* **1972**, 11, 45; Broxton, T.J.; McLeish, M.J. *Aust. J. Chem.* **1983**, 36, 1031.

¹⁵⁵⁷ Shinkai, S.; Mori, S.; Araki, K.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1987**, 60, 3679.

19-70 Desulfurization

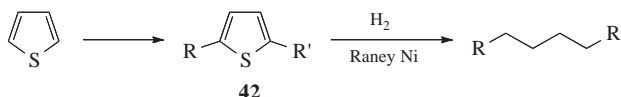
Hydro-de-thio-substitution, and so on



Thiols and thioethers,¹⁵⁵⁸ both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.¹⁵⁵⁹ The hydrogen is usually not applied externally, since Raney nickel typically contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, including disulfides, thiono esters,¹⁵⁶⁰ thioamides, sulfoxides, and thioacetals.¹⁵⁶¹ Reduction of thioacetals is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see Reaction 19-61), and it can also give the alkene if a hydrogen atom is present.¹⁵⁶² In most of the examples given, R can also be aryl. Other reagents¹⁵⁶³ have also been used.¹⁵⁶⁴ Reductive cleavage of sulfones and sulfonamides occurs with organobases [e.g., bis(imidazolylidenes)].¹⁵⁶⁵

Lithium aluminum hydride reduces most sulfur compounds with cleavage of the C–S bond, including thiols.¹⁵⁶⁶ Thioesters can be reduced with Ni_2B (from $\text{NiBr}_2/\text{NaBH}_4$).¹⁵⁶⁷ β -Ketosulfones are reduced with $\text{TiCl}_4\text{--Zn}$ ¹⁵⁶⁸ or $\text{TiCl}_4\text{--Sm}$.¹⁵⁶⁹

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene to **42**, followed by reduction to give the alkane.



Thiophenes can also be desulfurized to alkenes ($\text{RCH}_2\text{CH=CHCH}_2\text{R}'$ from **42**) with a nickel boride catalyst prepared from NiCl_2 and NaBH_4 in CH_3OH .¹⁵⁷⁰ Only one SR group of a dithioacetal is reduced by treatment with borane–pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of AlCl_3 .¹⁵⁷¹ Phenyl selenides (RSePh) can be reduced to RH with

¹⁵⁵⁸ For a review of the reduction of thioethers, see Block, E. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, **1980**, pp. 585–600.

¹⁵⁵⁹ For reviews, see Belen'kii, L.I. in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, **1990**, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* **1962**, 12, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* **1962**, 62, 347.

¹⁵⁶⁰ See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* **1981**, 46, 831.

¹⁵⁶¹ See Nakata, D.; Kusaka, C.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* **2001**, 42, 415.

¹⁵⁶² Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* **1963**, 28, 1443.

¹⁵⁶³ For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 53–60. See Luh, T.; Ni, Z. *Synthesis* **1990**, 89; Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* **1989**, 54, 4848.

¹⁵⁶⁴ See Ikeshita, K.-i.; Kihara, N.; Ogawa, A. *Tetrahedron Lett.* **2005**, 46, 8773.

¹⁵⁶⁵ Schoenebeck, F.; Murphy, J.A.; Zhou, S.-z.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. J. *Am. Chem. Soc.* **2007**, 129, 13368.

¹⁵⁶⁶ Smith, M.B.; Wolinsky, J. *J. Chem. Soc. Perkin Trans. 2* **1998**, 1431.

¹⁵⁶⁷ Back, T.G.; Baron D.L.; Yang, K. *J. Org. Chem.* **1993**, 58, 2407.

¹⁵⁶⁸ Guo, H.; Ye, S.; Wang, J.; Zhang, Y. *J. Chem. Res. (S)* **1997**, 114.

¹⁵⁶⁹ Wang, J.; Zhang, Y. *Synth. Commun.* **1996**, 26, 1931.

¹⁵⁷⁰ Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* **1972**, 2, 415.

¹⁵⁷¹ Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* **1984**, 609.

Ph_3SnH ¹⁵⁷² and with nickel boride.¹⁵⁷³ Cleavage of the C–Se bond can also be achieved with SmI_2 .¹⁵⁷⁴

The exact mechanism of the Raney nickel reactions is still in doubt, although they are probably of the free radical type.¹⁵⁷⁵ It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds; that is the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the alkenes and the failure to isolate any potential sulfur-containing intermediates.¹⁵⁷⁶

OS IV, 638; V, 419; VI, 109, 581, 601. See also, OS VII, 124, 476.

19-71 Reduction of Sulfonyl Halides and Sulfonic Acids to Thiols or Disulfides



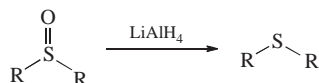
Thiols can be prepared by the reduction of sulfonyl halides¹⁵⁷⁷ with LiAlH_4 . Usually, the reaction is carried out on aromatic sulfonyl chlorides. Zinc and acetic acid, and HI, also give the reduction. Sulfonic acids have been reduced to thiols with a mixture of triphenylphosphine and either I_2 or a diaryl disulfide.¹⁵⁷⁸ For the reduction of sulfonyl chlorides to sulfinic acids, see Reaction 16-104.

Disulfides (RSSR) can also be produced.¹⁵⁷⁹ Other sulfonic acid derivatives can be converted to disulfides. Esters (e.g., PhSAc) are converted to disulfides (PhS-SPh) with Clayan and microwave irradiation.¹⁵⁸⁰ Thiobenzoate derivatives (PhSBz) are similarly converted to PhS-SPh with SmI_2 .¹⁵⁸¹ In a similar manner, $\text{RS-SO}_3\text{Na}$ is converted to RS-SR when heated with Sm metal in water.¹⁵⁸²

OS I, 504; IV, 695; V, 843.

19-72 Reduction of Sulfoxides and Sulfones

S-Oxygen-detachment



¹⁵⁷² Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc. Chem. Commun.* **1978**, 41.

¹⁵⁷³ Back, T.G. *J. Chem. Soc. Chem. Commun.* **1984**, 1417.

¹⁵⁷⁴ Ogawa, A.; Ohya, S.; Doi, M.; Sumino, Y.; Sonoda, N.; Hirao, T. *Tetrahedron Lett.* **1998**, 39, 6341.

¹⁵⁷⁵ For a review, see Bonner, W.A.; Grimm, R.A. in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, NY, **1966**, pp. 35–71, 410–413. Also see Friend, C.M.; Roberts, J.T. *Acc. Chem. Res.* **1988**, 21, 394.

¹⁵⁷⁶ Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* **1962**, 40, 941.

¹⁵⁷⁷ See Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, **1974**, pp. 216–220.

¹⁵⁷⁸ Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* **1983**, 56, 3802; **1984**, 57, 232.

¹⁵⁷⁹ See Narayana, C.; Padmanabhan, S.; Kabalka, G.W. *Synlett* **1991**, 125.

¹⁵⁸⁰ Meshram, H.M.; Bandyopadhyay, A.; Reddy, G.S.; Yadav, J.S. *Synth. Commun.* **1999**, 29, 2705.

¹⁵⁸¹ Yoo, B.W.; Baek, H.S.; Keum, S.R.; Yoon, C.M.; Nam, G.S.; Kim, S.H.; Kim, J.H. *Synth. Commun.* **2000**, 30, 4317.

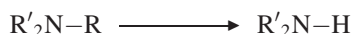
¹⁵⁸² Wang, L.; Li, P.; Zhou, L. *Tetrahedron Lett.* **2002**, 43, 8141.

Sulfoxides can be reduced to sulfides by many reagents,¹⁵⁸³ including LiAlH_4 , HI , Bu_3SnH ,¹⁵⁸⁴ $\text{H}_2\text{—Pd—C}$,¹⁵⁸⁵ $\text{NaBH}_4\text{—NiCl}_2$,¹⁵⁸⁶ NaBH_4/I_2 ,¹⁵⁸⁷ catecholborane,¹⁵⁸⁸ BH_3 with a Mo catalyst,¹⁵⁸⁹ a Mo/In system,¹⁵⁹⁰ Ti compounds,¹⁵⁹¹ and Sm/methanolic NH_4Cl with ultrasound.¹⁵⁹² Sulfoxides are deoxygenated by treatment with 2,4-diphenyl-1,3-diselenadiphosphetane-2,4-diselenide.¹⁵⁹³ Sulfones, however, are usually more difficult to reduce, but they have been reduced to sulfides with Dibal-H.¹⁵⁹⁴ A less general reagent is LiAlH_4 , which reduces some sulfones to sulfides, but not others.¹⁵⁹⁵ Both sulfoxides and sulfones can be reduced by heating with sulfur, which is oxidized to SO_2 , although the reaction with sulfoxides proceeds at a lower temperature. It has been shown by using substrate labeled with ^{35}S that sulfoxides simply give up the oxygen to the sulfur, but that the reaction with sulfones is more complex, since $\sim 75\%$ of the original radioactivity of the sulfone is lost.¹⁵⁹⁶ This indicates that most of the sulfur in the sulfide product comes in this case from the *reagent*. There is no direct general method for the reduction of sulfones to sulfoxides, but an indirect method has been reported.¹⁵⁹⁷ Selenoxides can be reduced to selenides with a number of reagents.¹⁵⁹⁸

OS IX, 446

E. Reduction with Cleavage

19-73 de-Alkylation of Amines and Amides



Certain amines can be dealkylated, usually under reductive conditions. Both *N*-allyl amines and *N,N*-dialkyl allyl amines, are converted to the corresponding amine, $\text{R}_2\text{N—H}$, with Dibal-H/ NiCl_2dppp [$\text{dppp} = 1, 3\text{-bis(diphenylphosphino)propane}$],¹⁵⁹⁹ and with $\text{Pd}(\text{dba})_2\text{dppb}$ [$\text{dppb} = 1, 4\text{-bis(diphenylphosphino)butane}$].¹⁶⁰⁰ A mixture of TiCl_3 and

¹⁵⁸³ See Kukushkin, V.Yu. *Russ. Chem. Rev.* **1990**, 59, 844; Madesclaire, M. *Tetrahedron* **1988**, 44, 6537; Drabowicz, J.; Togo, H.; Mikolajczyk, M.; Oae, S. *Org. Prep. Proced. Int.* **1984**, 16, 171; Drabowicz, J.; Numata, T.; Oae, S. *Org. Prep. Proced. Int.* **1977**, 9, 63. See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**.

¹⁵⁸⁴ Kozuka, S.; Furumai, S.; Akasaka, T.; Oae, S. *Chem. Ind. (London)* **1974**, 496.

¹⁵⁸⁵ Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Synthesis* **1975**, 385.

¹⁵⁸⁶ Khurana, J.M.; Ray, A.; Singh, S. *Tetrahedron Lett.* **1998**, 39, 3829.

¹⁵⁸⁷ Karimi, B.; Zareyee, D. *Synthesis* **2003**, 335.

¹⁵⁸⁸ Harrison, D.J.; Tam, N.C.; Vogels, C.M.; Langler, R.F.; Baker, R.T.; Decken, A.; Westcott, S.A. *Tetrahedron Lett.* **2004**, 45, 8493.

¹⁵⁸⁹ Fernandes, A.C.; Romão, C.C. *Tetrahedron Lett.* **2007**, 48, 9176.

¹⁵⁹⁰ Yoo, B.W.; Song, M.S.; Park, M.C. *Synth. Commun.* **2007**, 37, 3089.

¹⁵⁹¹ See Yoo, B.W.; Choi, K.H.; Kim, D.Y.; Choi, K.I.; Kim, J.H. *Synth. Commun.* **2003**, 33, 53.

¹⁵⁹² Yadav, J.S.; Subba Reddy, B.V.; Srinivas, C.; Srihari, P. *Synlett* **2001**, 854.

¹⁵⁹³ Hua, G.; Woollins, J.D. *Tetrahedron Lett.* **2007**, 48, 3677.

¹⁵⁹⁴ Gardner, J.N.; Kaiser, S.; Krubiner, A.; Lucas, H. *Can. J. Chem.* **1973**, 51, 1419.

¹⁵⁹⁵ See Weber, W.P.; Stromquist, P.; Ito, T.I. *Tetrahedron Lett.* **1974**, 2595.

¹⁵⁹⁶ Kiso, S.; Oae, S. *Bull. Chem. Soc. Jpn.* **1967**, 40, 1722. See also, Oae, S.; Nakai, M.; Tsuchida, Y.; Furukawa, N. *Bull. Chem. Soc. Jpn.* **1971**, 44, 445.

¹⁵⁹⁷ Still, I.W.J.; Ablenas, F.J. *J. Org. Chem.* **1983**, 48, 1617.

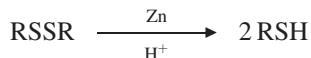
¹⁵⁹⁸ See Denis, J.N.; Krief, A. *J. Chem. Soc. Chem. Commun.* **1980**, 544.

¹⁵⁹⁹ Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1998**, 39, 4679.

¹⁶⁰⁰ Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.-P. *Bull. Soc. Chim. Fr.* **1995**, 132, 1157; Lemaire-Audoire, S.; Savignac, M.; Genêt, J.-P.; Bernard, J.-M. *Tetrahedron Lett.* **1995**, 36, 1267.

19-75 Reduction of Disulfides to Thiols

S-Hydrogen-uncoupling



Disulfides can be reduced to thiols by mild reducing agents¹⁶¹⁸ (e.g., Zn and dilute acid, In and $\text{NH}_4\text{Cl}/\text{EtOH}$,¹⁶¹⁹ or Ph_3P and H_2O).¹⁶²⁰ The reaction can also be accomplished simply by heating with alkali.¹⁶²¹ Among other reagents used have been LiAlH_4 , $\text{NaBH}_4/\text{ZrCl}_4$,¹⁶²² Mg/MeOH ,¹⁶²³ and hydrazine or substituted hydrazines.¹⁶²⁴

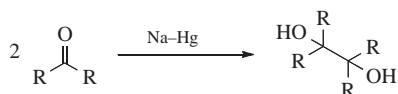
Aryl diselenides are similarly cleaved to selenols (ArSeH) with Cp_2TiH followed by $\text{Ph}_2\text{I}^+\text{X}^-$.¹⁶²⁵

OS II, 580. Also see, OS IV, 295.

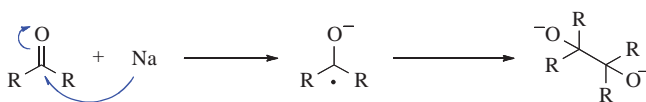
F. Reductive Coupling

19-76 Bimolecular Reduction of Aldehydes and Ketones to 1,2-Diols and Imines to 1,2-Diamines

2/O-Hydrogen-coupling and 2/N-Hydrogen-coupling



1,2-Diols (pinacols) can be synthesized by reduction of aldehydes and ketones with active metals (e.g., Na, Mg, or Al).¹⁶²⁶ Aromatic ketones give better yields than aliphatic ones. The use of a Mg-MgI_2 mixture has been called the *Gomberg-Bachmann pinacol synthesis*.¹⁶²⁷ As with a number of other reactions involving Na, there is a direct electron transfer that converts the ketone or aldehyde to a ketyl, which dimerizes.



¹⁶¹⁸ See Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, **1974**, pp. 220–229.

¹⁶¹⁹ Reddy, G.V.S.; Rao, G.V.; Iyengar, D.S. *Synth. Commun.* **2000**, 30, 859.

¹⁶²⁰ Overman, L.E.; Smoot, J.; Overman, J.D. *Synthesis* **1974**, 59.

¹⁶²¹ See Danehy, J.P.; Hunter, W.E. *J. Org. Chem.* **1967**, 32, 2047.

¹⁶²² Chary, K.P.; Rajaram, S.; Iyengar, D.S. *Synth. Commun.* **2000**, 30, 3905.

¹⁶²³ Sridhar, M.; Vadivel, S.K.; Bhalerao, U.T. *Synth. Commun.* **1997**, 27, 1347.

¹⁶²⁴ Maiti, S.N.; Spevak, P.; Singh, M.P.; Micetich, R.G.; Narender Reddy, A.V. *Synth. Commun.* **1988**, 18, 575.

¹⁶²⁵ Huang, X.; Wu, L.-L.; Xu, X.-H. *Synth. Commun.* **2001**, 31, 1871.

¹⁶²⁶ See Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc. Perkin Trans. 1* **1988**, 1729. Also see Bian, Y.-J.; Liu, S.-M.; Li, J.-T.; Li, T.-S. *Synth. Commun.* **2002**, 32, 1169.

¹⁶²⁷ Gomberg, M.; Bachmann, W.E. *J. Am. Chem. Soc.* **1927**, 49, 236; *The Merck Index*, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, **2006**, p ONR-74; Mundy, B.P.; Ellerd, M.G.; Favaloro, Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd Ed. Wiley-Interscience, New Jersey, **2005**, pp. 512–513. See Wang, J.-S.; Li, J.-T.; Lin, Z.-P.; Li, T.-S. *Synth. Commun.* **2005**, 35, 1419; Wang, S.-X.; Wang, K.; Li, J.-T. *Synth. Commun.* **2005**, 35, 2387; Li, J.-T.; Chen, Y.-X.; Li, T.-S. *Synth. Commun.* **2005**, 35, 2831.

Other reagents have been used,¹⁶²⁸ including Sm,¹⁶²⁹ SmI₂,¹⁶³⁰ Pr,¹⁶³¹ Yb,¹⁶³² In with ultrasound,¹⁶³³ InCl₃ catalyst with Mg,¹⁶³⁴ InCl₃/Al in H₂O,¹⁶³⁵ Al/TiCl₃,¹⁶³⁶ VCl₃/Zn in H₂O,¹⁶³⁷ activated Mn,¹⁶³⁸ Zn,¹⁶³⁹ and a low-valent Ti reagent¹⁶⁴⁰ (see Reaction 19-76). Unsymmetrical coupling between two different ketones has been accomplished using TiCl₃ in aqueous solution,¹⁶⁴¹ and coupling of two different aldehydes has been achieved by the use of a V complex.¹⁶⁴² Two aldehydes have also been coupled using Mg in water.¹⁶⁴³ Coupling leads to a mixture of *syn*- and *anti*-diols. "Syn-selective" reagents are Cp₂TiCl₂/Mn,¹⁶⁴⁴ TiCl₄/Bu₄I,¹⁶⁴⁵ TiI₄,¹⁶⁴⁶ and NbCl₅.¹⁶⁴⁷ "Anti-selective" coupling reactions are also known: Ti-salen,¹⁶⁴⁸ Mg with a NiCl₂ catalyst,¹⁶⁴⁹ and Sm/SmCl₃.¹⁶⁵⁰ Aryl aldehydes are coupled to give the bis(trimethylsilyl) ether using Mn, Me₃SiCl and Cp₂TiCl₂.¹⁶⁵¹

Stereoselective pinacol coupling reactions are well known.¹⁶⁵² Chiral additives with pinacol couplings lead to formation of a diol with moderate to good enantioselectivity.¹⁶⁵³ A crossed-pinacol coupling was reported using Et₂Zn and with a BINOL catalyst gave good enantioselectivity.¹⁶⁵⁴ Enantioselective coupling was reported using a chiral salen-Mo

¹⁶²⁸ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp.1111–1114.

¹⁶²⁹ Héllion, F.; Lannou, M.-I.; Namy, J.-L. *Tetrahedron Lett.* **2003**, *44*, 5507. See Banik, B.K.; Banik, I.; Aounallah, N.; Castillo, M. *Tetrahedron Lett.* **2005**, *46*, 7065.

¹⁶³⁰ Aspinall, H.C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *7*, 1919.

¹⁶³¹ Drapo, J.R.; Priefer, R. *Synth. Commun.* **2009**, *39*, 85.

¹⁶³² Hou, Z.; Takamine, K.; Fujiwara, Y.; Taniguchi, K. *Chem. Lett.* **1987**, 2061.

¹⁶³³ Lim, H.J.; Keum, G.; Kang, S.B.; Chung, B.Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 4367.

¹⁶³⁴ Mori, K.; Ohtaka, S.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1497.

¹⁶³⁵ Wang, C.; Pan, Y.; Wu, A. *Tetrahedron* **2007**, *63*, 429.

¹⁶³⁶ Li, J.-T.; Lin, Z.-P.; Qi, N.; Li, T.-S. *Synth. Commun.* **2004**, *34*, 4339.

¹⁶³⁷ Xu, X.; Hirao, T. *J. Org. Chem.* **2005**, *70*, 8594.

¹⁶³⁸ Rieke, R.D.; Kim, S.-H. *J. Org. Chem.* **1998**, *63*, 5235. See Groth, U.; Jeske, M. *Synlett* **2001**, 129.

¹⁶³⁹ Hekmatshoar, R.; Yavari, I.; Beheshtiha, Y.S.; Heravi, M.M. *Monat. Chem.* **2001**, *132*, 689.

¹⁶⁴⁰ For a discussion of the mechanism, see Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem. Soc.* **2001**, *123*, 1503. See Duan, X.-F.; Feng, J.-X.; Zi, G.-F.; Zhang, Z.-B. *Synthesis* **2009**, 277. Also see Li, T.; Cui, W.; Liu, J.; Zhao, J.; Wang, Z. *Chem. Commun.* **2000**, 139; Kagayama, A.; Igarashi, K.; Mukaiyama, T. *Can. J. Chem.* **2000**, *78*, 657.

¹⁶⁴¹ Clerici, A.; Porta, O. *J. Org. Chem.* **1982**, *47*, 2852; *Tetrahedron* **1983**, *39*, 1239. See Delair, P.; Luche, J. J. *Chem. Soc. Chem. Commun.* **1989**, 398; Takahara, P.M.; Freudenberger, J.H.; Konradi, A.W.; Pedersen, S.F. *Tetrahedron Lett.* **1989**, *30*, 7177.

¹⁶⁴² Freudenberger, J.H.; Konradi, A.W.; Pedersen, S.F. *J. Am. Chem. Soc.* **1989**, *111*, 8014.

¹⁶⁴³ Zhang, W.-C.; Li, C.-J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3131.

¹⁶⁴⁴ Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 2673. Also see, Barden, M.C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484; Gansäuer, A. *Chem. Commun.* **1997**, 457; Gansäuer, A. *Synlett* **1997**, 363.

¹⁶⁴⁵ Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, *65*, 5066.

¹⁶⁴⁶ Hayakawa, R.; Shimizu, M. *Chem. Lett.* **2000**, 724. For a syn-selective coupling with conjugated aldehydes see Shimizu, M.; Goto, H.; Hayakawa, R. *Org. Lett.* **2002**, *4*, 4097.

¹⁶⁴⁷ Szymoniak, J.; Besançon, J.; Moïse, C. *Tetrahedron* **1994**, *50*, 2841.

¹⁶⁴⁸ Chatterjee, A.; Bennur, T.H.; Joshi, N.N. *J. Org. Chem.* **2003**, *68*, 5668.

¹⁶⁴⁹ Shi, L.; Fan, C.-A.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M. *Tetrahedron* **2004**, *60*, 2851. See also Luanphai-sarnnont, T.; Ndubaku, C.O.; Jamison, T.F. *Org. Lett.* **2005**, *7*, 2937.

¹⁶⁵⁰ Matsukawa, S.; Hinakubo, Y. *Org. Lett.* **2003**, *5*, 1221.

¹⁶⁵¹ Dunlap, M.S.; Nicholas, K.M. *Synth. Commun.* **1999**, *29*, 1097.

¹⁶⁵² For a review, see Chatterjee, A.; Joshi, N.N. *Tetrahedron* **2006**, *62*, 12137.

¹⁶⁵³ Enders, D.; Ullrich, E.C. *Tetrahedron Asymmetry* **2000**, *11*, 3861.

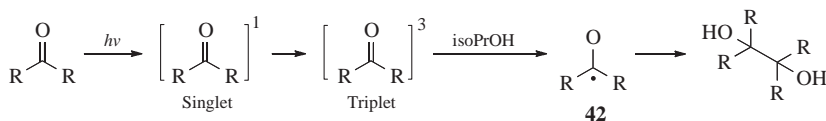
¹⁶⁵⁴ Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169.

complex.¹⁶⁵⁵ A combination of Mg and Me₃SiCl was also used to effect a crossed-pinacol.¹⁶⁵⁶ Chiral metal complexes in conjunction with a metal leads to diol formation with good enantioselectivity.¹⁶⁵⁷

Intramolecular pinacol coupling reactions are known, giving cyclic 1,2-diols.¹⁶⁵⁸ Dialdehydes have been cyclized by reaction with TiCl₃ to give cyclic 1,2-diols in good yield.¹⁶⁵⁹

A variation of the pinacol coupling treats acyl nitriles with In metal and ultrasound to give a 1,2-diketone.¹⁶⁶⁰ Another variation couples acetals to give 1,2-diols.¹⁶⁶¹

The photochemical dimerization of ketones to 1,2-diols is one of the most common photochemical reactions.¹⁶⁶² The substrate, which is usually a diaryl or aryl alkyl ketone, is irradiated with UV light in the presence of a hydrogen donor (e.g., isopropyl alcohol, toluene, or an amine).¹⁶⁶³ In the case of benzophenone, irradiated in the presence of 2-propanol, the ketone molecule initially undergoes $n \rightarrow \pi^*$ excitation, and the singlet species thus formed crosses to the T_1 state with a very high efficiency.



The T_1 species abstracts hydrogen from the alcohol (Sec. 7.A.vii, category 4) and then dimerizes. The $i\text{PrO}^\bullet$ radical, which is formed by this process, reacts by atom transfer of H^\bullet to another molecule of ground-state benzophenone, producing acetone and another molecule of **51**. This mechanism¹⁶⁶⁴ predicts that the quantum yield for the disappearance of benzophenone should be 2, since each quantum of light results in the conversion of 2 equiv of benzophenone to **42**. Under favorable experimental conditions, the observed quantum yield does approach 2. Benzophenone abstracts hydrogen with very high efficiency. Other aromatic ketones are dimerized with lower quantum yields, and some (e.g., *p*-aminobenzophenone, *o*-methylacetophenone) cannot be dimerized at all in 2-propanol (although *p*-aminobenzophenone, e.g., can be dimerized in cyclohexane¹⁶⁶⁵). The reaction has also been carried out electrochemically.¹⁶⁶⁶

¹⁶⁵⁵ Yang, H.; Wang, H.; Zhu, C. *J. Org. Chem.* **2007**, 72, 10029.

¹⁶⁵⁶ Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yonemura, K.; Nishiguchi, I. *Tetrahedron Lett.* **2004**, 45, 3869.

¹⁶⁵⁷ See Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, 126, 13198.

¹⁶⁵⁸ See Handa, S.; Kachala, M.S.; Lowe, S.R. *Tetrahedron Lett.* **2004**, 45, 253.

¹⁶⁵⁹ McMurry, J.E.; Siemers, N.O. *Tetrahedron Lett.* **1993**, 34, 7891. See Raw, A.S.; Pedersen, S.F. *J. Org. Chem.* **1991**, 56, 830; Chiara, J.L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, 32, 1125.

¹⁶⁶⁰ Baek, H.S.; Lee, S.J.; Yoo, B.W.; Ko, J.J.; Kim, S.H.; Kim, J.H. *Tetrahedron Lett.* **2000**, 41, 8097.

¹⁶⁶¹ Studer, A.; Curran, D.P. *Synlett* **1996**, 255.

¹⁶⁶² See Schönberg, A. *Preparative Organic Photochemistry*; Springer, NY, **1968**, pp. 203–217; Neckers, D.C. *Mechanistic Organic Photochemistry*, Reinhold, NY, **1967**, pp. 163–177; Calvert, J.G.; Pitts, Jr., J.N. *Photochemistry*, Wiley, NY, **1966**, pp. 532–536; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, **1978**, pp. 363–385; Kan, R.O. *Organic Photochemistry*, McGraw-Hill, NY, **1966**, pp. 222–229.

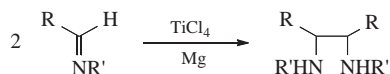
¹⁶⁶³ See Cohen, S.G.; Parola, A.; Parsons, Jr., G.H. *Chem. Rev.* **1973**, 73, 141.

¹⁶⁶⁴ See Huyser, E.S.; Neckers, D.C. *J. Am. Chem. Soc.* **1963**, 85, 3641.

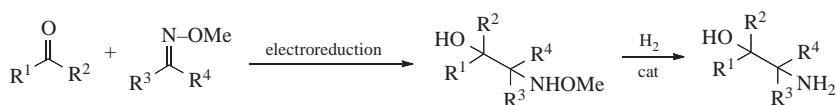
¹⁶⁶⁵ Porter, G.; Suppan, P. *Proc. Chem. Soc.* **1964**, 191.

¹⁶⁶⁶ Elinson, M.N.; Feducovich, S.K.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron* **2000**, 56, 9999. See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, **1989**, pp. 174–180; Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, **1984**, pp. 137–140; Baizer, M.M.; Petrovich, J.P. *Prog. Phys. Org. Chem.* **1970**, 7, 189; Baizer, M.M. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, **1983**, pp. 639–689.

A coupling reaction similar to pinacol coupling has been used with imines, which dimerize to give 1,2-diamines. A number of reagents have been used, including treatment with $\text{TiCl}_4\text{-Mg}$,¹⁶⁶⁷ In/aq EtOH ,¹⁶⁶⁸ Zn/aq NaOH ,¹⁶⁶⁹ or SmI_2 .¹⁶⁷⁰



When electroreduction was used, it was possible to obtain cross-products by coupling a ketone to an *O*-methyl oxime¹⁶⁷¹: *O*-Methyl oxime ethers are coupled to give 1,2-diamines using Zn and TiCl_4 .¹⁶⁷² Aldehydes are converted to 1,2-diamines by treatment with TMS_2NH , NaH , and Li metal in 5 M LiClO_4 in ether, with sonication.¹⁶⁷³ Aldehydes are coupled with *N*-sulfinyl imines to give *N*-sulfinyl amino alcohols in the presence of SmI_2 .¹⁶⁷⁴ Hemiaminals are coupled to give 1,2-diamines with TiI_4/Zn .¹⁶⁷⁵ Amides are converted to 1,2-diamines with Cp_2TiF_2 and PhMeSiH_2 .¹⁶⁷⁶ Samarium(II) iodide was used to couple iminium salts, giving the 1,2-diamine.¹⁶⁷⁷ Ketones can be treated with Yb , and then an imine to give amino alcohols.¹⁶⁷⁸

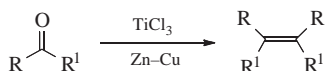


The *N*-methoxyamino alcohol could then be reduced to the amino alcohol.¹⁶⁷¹ A photochemical coupling has also been reported.¹⁶⁷⁹ A variation of this reaction treats an imine with Yb in THF/HMPA , and then an aldehyde to give a 1,2-bis(imine).¹⁶⁸⁰

OS I, 459; II, 71; X, 312; 81, 26.

19-77 Bimolecular Reduction of Aldehydes or Ketones to Alkenes

De-oxygen-coupling



Aldehydes and ketones, both aromatic and aliphatic (including cyclic ketones), can be converted in high yields to dimeric alkenes by treatment with low valent Ti ,¹⁶⁸¹ initially

¹⁶⁶⁷ See Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 873, 875.

¹⁶⁶⁸ Kalyanam, N.; Rao, G.V. *Tetrahedron Lett.* **1993**, 34, 1647.

¹⁶⁶⁹ Dutta, M.P.; Baruah, B.; Boruah, A.; Prajapati, D.; Sandu, J.S. *Synlett* **1998**, 857.

¹⁶⁷⁰ Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, 6, 4747.

¹⁶⁷¹ Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* **1991**, 32, 525.

¹⁶⁷² Kise, N.; Ueda, N. *Tetrahedron Lett.* **2001**, 42, 2365.

¹⁶⁷³ Mojtahedi, M.M.; Saidi, M.R.; Shirzi, J.S.; Bolourtchian, M. *Synth. Commun.* **2001**, 31, 3587.

¹⁶⁷⁴ Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, 127, 11956.

¹⁶⁷⁵ Yoshimura, N.; Mukaiyama, T. *Chem. Lett.* **2001**, 1334.

¹⁶⁷⁶ Selvakumar, K.; Harrod, J.F. *Angew. Chem. Int. Ed.* **2001**, 40, 2129.

¹⁶⁷⁷ Kim, M.; Knettle, B.W.; Dahlén, A.; Hilmersson, G.; Flowers III, R.A. *Tetrahedron* **2003**, 59, 10397.

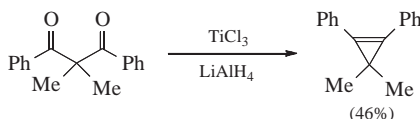
¹⁶⁷⁸ Su, W.; Yang, B. *Synth. Commun.* **2003**, 33, 2613.

¹⁶⁷⁹ Ortega, M.; Rodríguez, M.A.; Campos, P.J. *Tetrahedron* **2004**, 60, 6475.

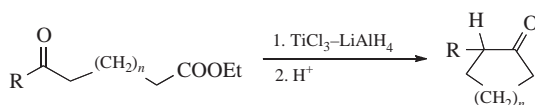
¹⁶⁸⁰ Jin, W.; Makioka, Y.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2001**, 66, 514.

¹⁶⁸¹ See Rele, S.; Chattopadhyay, S.; Nayak, S.K. *Tetrahedron Lett.* **2001**, 42, 9093.

generated with TiCl_3 and a Zn–Cu couple.¹⁶⁸² This is called the *McMurry reaction*.¹⁶⁸³ The reagent produced in this way is called a *low-valent titanium reagent*, and the reaction has also been accomplished¹⁶⁸⁴ with low-valent Ti reagents prepared in other ways, for example, from Mg and a TiCl_3 –THF complex;¹⁶⁸⁵ from TiCl_4 and Zn or Mg;¹⁶⁸⁶ from TiCl_3 and LiAlH_4 ;¹⁶⁸⁷ and from TiCl_3 and K or Li;¹⁶⁸⁸ and with certain compounds prepared from WCl_6 and either lithium, lithium iodide, LiAlH_4 , or an organolithium¹⁶⁸⁹ (see Reaction 17–18). Microwave irradiation has been used to facilitate the coupling.¹⁶⁹⁰ The reaction has been used to convert dialdehydes and diketones to cycloalkenes.¹⁶⁹¹ Rings of 3–16 and 22 members have been closed in this way, for example,¹⁶⁹²



The same reaction on a keto ester gives a cycloalkanone.¹⁶⁹³



Indoles have been prepared from *o*-acyl amides with $\text{Ti}(\text{powder})$ and Me_3SiCl ¹⁶⁹⁴ or with TiCl_3 – C_8K .¹⁶⁹⁵ Benzofurans have been prepared by a closely related reaction.¹⁶⁹⁶

Unsymmetrical alkenes can be prepared from a mixture of two ketones in a cross-coupling reaction, if one is in excess.¹⁶⁹⁷ An aldehyde and a ketone were cross-coupled using $\text{Yb}(\text{OTf})_3$, for example.¹⁶⁹⁸ The mechanism consists of initial coupling of two radical

¹⁶⁸² McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* **1978**, *43*, 3255. For an optimized procedure, see McMurry, J.E.; Lectka, T.; Rico, J.G. *J. Org. Chem.* **1989**, *54*, 3748.

¹⁶⁸³ See McMurry, J.E. *Chem. Rev.* **1989**, *89*, 1513; *Acc. Chem. Res.* **1983**, *16*, 405; Lenoir, D. *Synthesis* **1989**, 883; Betschart, C.; Seebach, D. *Chimia* **1989**, *43*, 39; Lai, Y. *Org. Prep. Proceed. Int.* **1980**, *12*, 363. For related reviews, see Kahn, B.E.; Rieke, R.D. *Chem. Rev.* **1988**, *88*, 733; Pons, J.; Santelli, M. *Tetrahedron* **1988**, *44*, 4295. See Duan, X.-F.; Zeng, J.; Lü, J.-W.; Zhang, Z.-B. *J. Org. Chem.* **2006**, *71*, 9873.

¹⁶⁸⁴ For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, **1999**, pp. 305–308.

¹⁶⁸⁵ Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147.

¹⁶⁸⁶ Carroll, A.R.; Taylor, W.C. *Aust. J. Chem.* **1990**, *43*, 1439.

¹⁶⁸⁷ Dams, R.; Malinowski, M.; Geise, H.J. *Bull. Soc. Chim. Belg.* **1982**, *91*, 149, 311; Bottino, F.A.; Finocchiaro, P.; Libertini, E.; Reale, A.; Recca, A. *J. Chem. Soc. Perkin Trans. 2* **1982**, 77. This reagent has been reported to give capricious results; see McMurry, J.E.; Fleming, M.P. *J. Org. Chem.* **1976**, *41*, 896.

¹⁶⁸⁸ Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* **2001**, *66*, 2990.

¹⁶⁸⁹ Dams, R.; Malinowski, M.; Geise, H.J. *Bull. Soc. Chim. Belg.* **1982**, *19*, 149, 311. See also, Chisholm, M.H.; Klang, J.A. *J. Am. Chem. Soc.* **1989**, *111*, 2324.

¹⁶⁹⁰ Stühr-Hansen, N. *Tetrahedron Lett.* **2005**, *46*, 5491.

¹⁶⁹¹ McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* **1978**, *43*, 3255.

¹⁶⁹² Baumstark, A.L.; McCloskey, C.J.; Witt, K.E. *J. Org. Chem.* **1978**, *43*, 3609.

¹⁶⁹³ McMurry, J.E.; Miller, D.D. *J. Am. Chem. Soc.* **1983**, *105*, 1660.

¹⁶⁹⁴ Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468.

¹⁶⁹⁵ Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215.

¹⁶⁹⁶ Fürstner, A.; Jumbam, D.N. *Tetrahedron* **1992**, *48*, 5991.

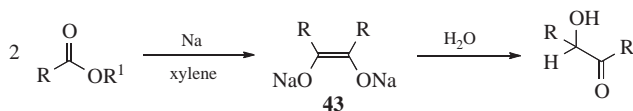
¹⁶⁹⁷ See Chisholm, M.H.; Klang, J.A. *J. Am. Chem. Soc.* **1989**, *111*, 2324.

¹⁶⁹⁸ Curini, M.; Epifano, F.; Maltese, F.; Marcotullio, M.C. *Eur. J. Org. Chem.* **2003**, 1631.

species to give a 1,2-dioxygen compound (a titanium pinacolate), which is then deoxygenated.¹⁶⁹⁹

OS VII, 1.

19-78 Acyloin Ester Condensation



When carboxylic esters are heated with sodium in refluxing ether or benzene, a bimolecular reduction takes place, and the product is an α -hydroxy ketone (called an acyloin).¹⁷⁰⁰ The reaction, called the *acyloin ester condensation* (or just *acyloin condensation*),¹⁷⁰¹ is quite successful when R is alkyl. Acyloins with long chains have been prepared in this way (e.g., R = C₁₇H₃₅), but for high-molecular-weight esters, toluene or xylene is used as the solvent. Modifications to this procedure have been reported, including an ultrasound-promoted acyloin condensation in ether,¹⁷⁰² which improved the yields of four-, five-, and six-membered rings, and Olah's procedure, which was also done in ether.¹⁷⁰³

The acyloin condensation has been used with great success, in boiling xylene, to prepare cyclic acyloins from diesters.¹⁷⁰⁴ The yields are 50–60% for the preparation of 6- and 7-membered rings, 30–40% for 8- and 19-membered, and 60–95% for rings of 10–20 members. Even larger rings have been closed in this manner. Indeed, this is one of the best ways of closing rings of 10 members or more. The reaction has been used to close 4-membered rings,¹⁷⁰⁵ although this is generally unsuccessful. For larger rings, the presence of double or triple bonds does not interfere.¹⁷⁰⁶ Even a benzene ring can be present, and many paracyclopentane derivatives (**44**) with $n=9$ or more have been synthesized in this manner.¹⁷⁰⁷

Yields in the acyloin condensation can be improved by running the reaction in the presence of chlorotrimethylsilane (Me₃SiCl), in which case the dianion (**43**) is converted to the bis (silyl) enol ether (**45**), which can be isolated and subsequently hydrolyzed to the acyloin with aq acid.¹⁷⁰⁸ This is now the standard way to conduct the acyloin condensation. Among other things, this method inhibits the *Dieckmann condensation*¹⁷⁰⁹ (Reaction **16-85**), which otherwise competes with the acyloin condensation when a five-, six-, or seven-membered ring can be closed (note that the ring formed by a *Dieckmann condensation* is

¹⁶⁹⁹ Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H.Y. *J. Org. Chem.* **1982**, 47, 248. See Villiers, C.; Ephritikhine, M. *Angew. Chem., Int. Ed.* **1997**, 36, 2380; Stahl, M.; Pindur, U.; Frenking, G. *Angew. Chem. Int. Ed.* **1997**, 36, 2234.

¹⁷⁰⁰ See Bloomfield, J.J.; Owsley, D.C.; Nelke, J.M. *Org. React.* **1976**, 23, 259. For a list of reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, pp. 1313–1315.

¹⁷⁰¹ Also see Daynard, T.S.; Eby, P.S.; Hutchinson, J.H. *Can. J. Chem.* **1993**, 71, 1022.

¹⁷⁰² Fadel, A.; Canet, J.-L.; Salaün, J. *Synlett* **1990**, 89.

¹⁷⁰³ Olah, G.A.; Wu, A. *Synthesis* **1991**, 1177.

¹⁷⁰⁴ See Finley, K.T. *Chem. Rev.* **1964**, 64, 573.

¹⁷⁰⁵ Bloomfield, J.J.; Irelan, J.R.S. *J. Org. Chem.* **1966**, 31, 2017.

¹⁷⁰⁶ Cram, D.J.; Gaston, L.K. *J. Am. Chem. Soc.* **1960**, 82, 6386.

¹⁷⁰⁷ For a review, see Cram, D.J. *Rec. Chem. Prog.* **1959**, 20, 71.

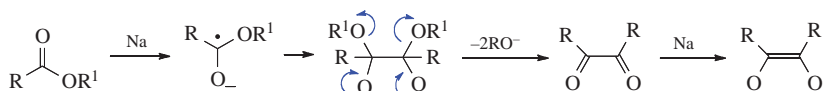
¹⁷⁰⁸ Schräpler, U.; Rühlmann, K. *Chem. Ber.* **1964**, 97, 1383. See Rühlmann, K. *Synthesis* **1971**, 236.

¹⁷⁰⁹ Bloomfield, J.J. *Tetrahedron Lett.* **1968**, 591.

always one carbon atom smaller than that formed by an acyloin condensation of the same substrate). The Me_3SiCl method is especially good for the closing of four-membered rings.¹⁷¹⁰



The mechanism is usually presumed to have a diketone (RCOCOR) as an intermediate,¹⁷¹¹ since small amounts of it are usually isolated as side products, and when it is resistant to reduction (e.g., $t\text{-Bu-COCO-}t\text{-Bu}$), it is the major product. A possible sequence (analogous to that of Reaction 19-76) is



A large surface area for the Na is usually required for good results in this coupling, consistent with a surface reaction. In order to account for the ready formation of large rings, which means that the two ends of the chain must approach each other even though this is conformationally unfavorable for long chains, it may be postulated that the two ends become attached to nearby sites on the surface¹⁷¹² of the Na. Although high dilution techniques are not always necessary, effective stirring (high-speed stirrer at 2000–2500 rpm) is usually required to generate “sodium sand”. Highly pure Na gives poorer results because the presence of a small percentage of K is important. Up to 50% potassium (1 : 1 Na/K)¹⁷¹³ has been used in acyloin condensations.

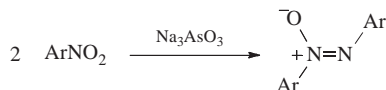
In a related reaction, aromatic carboxylic acids were condensed to α -diketones ($2\text{ArCOOH} \rightarrow \text{ArCOCOAr}$) on treatment with excess Li in dry THF in the presence of ultrasound.¹⁷¹⁴

The acyloin condensation was used in an ingenious manner to prepare the first reported catenane (see Sec. 3.D).¹⁷¹⁵ This synthesis of a catenane produced only a small yield and relied on chance for threading the molecules before ring closure.

OS II, 114; IV, 840; VI, 167.

19-79 Reduction of Nitro to Azoxy Compounds

Nitro-azoxy reductive transformation



¹⁷¹⁰ Bloomfield, J.J.; Martin, R.A.; Nelke, J.M. *J. Chem. Soc. Chem. Commun.* **1972**, 96.

¹⁷¹¹ Another mechanism has been proposed: Bloomfield, J.J.; Owsley, D.C.; Ainsworth, C.; Robertson, R.E. *J. Org. Chem.* **1975**, 40, 393.

¹⁷¹² For the preparation of high-surface sodium, see Makosza, M.; Grela, K. *Synlett* **1997**, 267.

¹⁷¹³ Vogel, I.A. *A Textbook of Practical Organic Chemistry*, 3rd ed, Wiley, NY, **1966**, p. 856.

¹⁷¹⁴ Karaman, R.; Fry, J.L. *Tetrahedron Lett.* **1989**, 30, 6267.

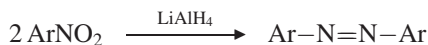
¹⁷¹⁵ For reviews of the synthesis of catenanes, see Sauvage, J. *Acc. Chem. Res.* **1990**, 23, 319; *Nouv. J. Chim.* **1985**, 9, 299; Dietrich-Buchecker, C.O.; Sauvage, J. *Chem. Rev.* **1987**, 87, 795.

Azoxy compounds can be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide, NaTeH,¹⁷¹⁶ and glucose. The most probable mechanism with most reagents is that one molecule of nitro compound is reduced to a nitroso compound and another to a hydroxylamine (Reaction 19-46), and these combine (Reaction 12-51). The combination step is rapid compared to the reduction process.¹⁷¹⁷ Nitroso compounds can be reduced to azoxy compounds with triethylphosphite or triphenylphosphine¹⁷¹⁸ or with an alkaline aqueous solution of an alcohol.¹⁷¹⁹

OS II, 57.

19-80 Reduction of Nitro to Azo Compounds

N-De-bisoxxygen-coupling



Nitro compounds can be reduced to azo compounds with various reducing agents, of which LiAlH₄ and Zn and alkali are the most common. A combination of triethylammonium formate and lead in methanol is also effective.¹⁷²⁰ With many of these reagents, slight differences in conditions can lead either to the azo or azoxy (Reaction 19-79) compound. By analogy to Reaction 19-79, this reaction may be looked on as a combination of ArN=O and ArNH₂ (13-24). However, when the reducing agent was NaBH₄,¹⁷²¹ it was shown that azoxy compounds were intermediates. Nitroso compounds can be reduced to azo compounds with LiAlH₄. Dicarborane, with a catalytic amount of acetic acid, reduces aromatic nitro compounds to the amine.¹⁷²²

Nitro compounds can be further reduced to hydrazo compounds with Zn and sodium hydroxide, with hydrazine hydrate and Raney nickel,¹⁷²³ or with LiAlH₄ mixed with a metal chloride (e.g., TiCl₄ or VCl₃).¹⁷²⁴ The reduction has also been accomplished electrochemically.

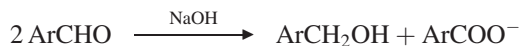
OS III, 103.

G. Reactions in which an Organic Substrate Is Both Oxidized and Reduced

Some reactions that belong in this category have been considered in earlier chapters. Among these are the *Tollens' condensation* (Reaction 16-43), the *benzil-benzilic acid rearrangement* (Reaction 18-6), and the *Wallach rearrangement* (Reaction 18-43).

19-81 The Cannizzaro Reaction

Cannizzaro Aldehyde Disproportionation



¹⁷¹⁶ Osuka, A.; Shimizu, H.; Suzuki, H. *Chem. Lett.* **1983**, 1373. See Ohe, K.; Uemura, S.; Sugita, N.; Masuda, H.; Taga, T. *J. Org. Chem.* **1989**, *54*, 4169.

¹⁷¹⁷ Ogata, Y.; Mibae, J. *J. Org. Chem.* **1962**, *27*, 2048.

¹⁷¹⁸ Bunyan, P.J.; Cadogan, J.I.G. *J. Chem. Soc.* **1963**, 42.

¹⁷¹⁹ See Hutton, J.; Waters, W.A. *J. Chem. Soc. B* **1968**, 191. See also, Porta, F.; Pizzotti, M.; Cenini, S. *J. Organomet. Chem.* **1981**, *222*, 279.

¹⁷²⁰ Srinavasa, G.R.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* **2003**, *44*, 5835.

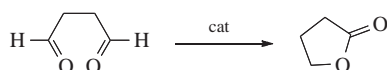
¹⁷²¹ Hutchins, R.O.; Lamson, D.W.; Rufa, L.; Milewski, C.; Maryanoff, B. *J. Org. Chem.* **1971**, *36*, 803.

¹⁷²² Bae, J.W.; Cho, Y.J.; Lee, S.H.; Yoon, C.M. *Tetrahedron Lett.* **2000**, *41*, 175.

¹⁷²³ Furst, A.; Moore, R.E. *J. Am. Chem. Soc.* **1957**, *79*, 5492.

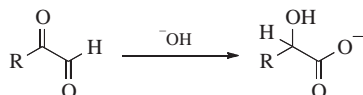
¹⁷²⁴ Olah, G.A. *J. Am. Chem. Soc.* **1959**, *81*, 3165.

Aromatic aldehydes, and aliphatic ones with no α hydrogen, give the *Cannizzaro reaction* when treated with NaOH or other strong bases.¹⁷²⁵ Reaction with triethylamine and MgBr₂ gave a room temperature *Cannizzaro reaction*.¹⁷²⁶ The reaction is mediated by organobases.¹⁷²⁷ In this reaction, one molecule of aldehyde oxidizes another to the acid and is itself reduced to the primary alcohol. Aldehydes with an α hydrogen do not give the reaction, because when these compounds are treated with base, the aldol reaction (**16-34**) is much faster.¹⁷²⁸ Normally, the best yield of acid or alcohol is 50% each, but this can be altered in certain cases. Solvent-free reactions are known.¹⁷²⁹ On the other hand, high yields of alcohol can be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde.¹⁷³⁰ In this case, the formaldehyde reduces the aldehyde to alcohol and is itself oxidized to formic acid. In such a case, where the oxidant aldehyde differs from the reductant aldehyde, the reaction is called the *crossed-Cannizzaro reaction*.¹⁷³¹ The *Tollens' condensation* (Reaction **16-43**) includes a *crossed-Cannizzaro reaction* as its last step. A *Cannizzaro reaction* with 1,4-dialdehydes (note that α -hydrogen atoms are present here) and a Rh catalyst gives ring closure, for example,¹⁷³²



The product is the lactone derived from the hydroxy acid that would result from a normal *Cannizzaro reaction*. Chiral additives have been used, but with bis(oxazolidine) derivatives, the reaction proceeded with poor enantioselectivity.¹⁷³³

α -Keto aldehydes give internal *Cannizzaro reactions*.¹⁷³⁴:



This product is also obtained on alkaline hydrolysis of compounds of the formula RCOCHX₂. Similar reactions have been performed on α -keto acetals¹⁷³⁵ and γ -keto aldehydes.

The mechanism¹⁷³⁶ of the *Cannizzaro reaction*¹⁷³⁷ involves a hydride shift (an example of mechanism type 2, Sec. 19.A). First OH^- adds to the C=O to give **46**, which may lose a proton in the basic solution to give the diion (**47**).

¹⁷²⁵ See Geissman, T.A. *Org. React.* **1944**, 2, 94.

¹⁷²⁶ Abaee, M.S.; Sharifi, R.; Mojtahedi, M.M. *Org. Lett.* **2005**, 7, 5893.

¹⁷²⁷ Basavaiah, D.; Sharada, D.S.; Veerendhar, A. *Tetrahedron Lett.* **2006**, 47, 5771.

¹⁷²⁸ An exception is cyclopropanecarboxaldehyde: van der Maeden, F.P.B.; Steinberg, H.; de Boer, T.J. *Recl. Trav. Chim. Pays-Bas* **1972**, 91, 221.

¹⁷²⁹ Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* **2001**, 42, 7983.

¹⁷³⁰ See Thakuria, J.A.; Baruah, M.; Sandhu, J.S. *Chem. Lett.* **1999**, 995.

¹⁷³¹ See Reddy, B.V.S.; Srinivas, R.; Yadav, J.S.; Ramalingam, T. *Synth. Commun.* **2002**, 32, 219.

¹⁷³² Bergens, S.H.; Fairlie, D.P.; Bosnich, B. *Organometallics* **1990**, 9, 566.

¹⁷³³ Russell, A.E.; Miller, S.P.; Morken, J.P. *J. Org. Chem.* **2000**, 65, 8381.

¹⁷³⁴ Russell, G.A.; Mikol, G.J. *J. Am. Chem. Soc.* **1966**, 88, 6498; Prey, V.; Berbdk, H.; Steinbauer, E. *Monatsh. Chem.* **1960**, 91, 1196; **1962**, 93, 237.

¹⁷³⁵ Thompson, J.E. *J. Org. Chem.* **1967**, 32, 3947.

¹⁷³⁶ See Ashby, E.C.; Coleman, III, D.T.; Gamasa, M.P. *J. Org. Chem.* **1987**, 52, 4079; Fuentes, A.; Marinas, J.M.; Sinisterra, J.V. *Tetrahedron Lett.* **1987**, 28, 2947.

¹⁷³⁷ See Swain, C.G.; Powell, A.L.; Sheppard, W.A.; Morgan, C.R. *J. Am. Chem. Soc.* **1979**, 101, 3576; Watt, C.I. *F. Adv. Phys. Org. Chem.* **1988**, 24, 57, pp. 81–86.

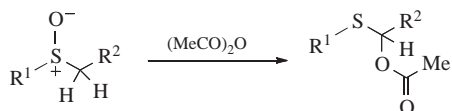
aldehydes, by disodium tetracarbonylferrate $[\text{Na}_2\text{Fe}(\text{CO})_4]$.¹⁷⁴⁸ Both CaO (noted above) and SrO have been used as catalysts.¹⁷⁴⁹ A bis(phenylenedioxy) bis(aluminum) catalyst has been used to convert aliphatic aldehydes to the corresponding ester.¹⁷⁵⁰ The bis $\text{Al}(\text{O}-i\text{Pr})_2$ derivative of catechol has also been used as a catalyst.¹⁷⁵¹

A *Tishchenko–aldol transfer reaction* was reported using β -hydroxy ketones and an aldehydes with an AlMe_3 catalyst, giving a monoacyl diol.¹⁷⁵²

OS I, 104.

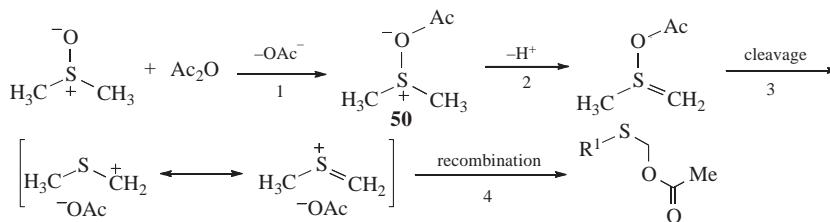
19-83 The Pummerer Rearrangement¹⁷⁵³

Pummerer methyl sulfoxide rearrangement



When sulfoxides bearing an α hydrogen are treated with acetic anhydride, the product is an α -acetoxy sulfide. This is one example of the *Pummerer rearrangement*,¹⁷⁵⁴ in which the sulfur is reduced while an adjacent carbon is oxidized.¹⁷⁵⁵ The product is readily hydrolyzed (Reaction 10-6) to the aldehyde (R_2CHO).¹⁷⁵⁶ Besides acetic anhydride, other anhydrides and acyl halides give similar products. Inorganic acids (e.g., HCl), also give the reaction, and $\text{RSOCH}_2\text{R}'$ can be converted to $\text{RSCHCIR}'$ in this way. Sulfoxides can also be converted to α -halo sulfides¹⁷⁵⁷ by other reagents, including sulfonyl chloride, NBS, and NCS. Enantioselective *Pummerer rearrangements* are known.¹⁷⁵⁸ Uncatalyzed thermal rearrangements are also known.¹⁷⁵⁹

The following 4-step mechanism has been proposed for the reaction between acetic anhydride and DMSO¹⁷⁶⁰:



¹⁷⁴⁸ Yamashita, A.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1976**, 49, 3597.

¹⁷⁴⁹ Seki, T.; Akutsu, K.; Hattori, H. *Chem. Commun.* **2001**, 1000.

¹⁷⁵⁰ Ooi, T.; Miura, T.; Takaya, K.; Maruoka, K. *Tetrahedron Lett.* **1999**, 40, 7695.

¹⁷⁵¹ Simpura, I.; Jevlainen, V. *Tetrahedron* **2001**, 57, 9867.

¹⁷⁵² Simpura, I.; Nevalainen, V. *Tetrahedron Lett.* **2001**, 42, 3905; Cavazzini, M.; Pozzi, G.; Quici, S.; Maillard, D.; Sinou, D. *Chem. Commun.* **2001**, 1220.

¹⁷⁵³ See Bur, S.K.; Padwa, A. *Chem. Rev.* **2004**, 104, 2401.

¹⁷⁵⁴ For a review, see Feldman, K.S. *Tetrahedron* **2006**, 62, 5003. Also see Smith, L.H.S.; Coote, S.C.; Sneddon, H.F.; Procter, D.J. *Angew. Chem. Int. Ed.* **2010**, 49, 5832.

¹⁷⁵⁵ See De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, 40, 157; Warren, S. *Chem. Ind. (London)* **1980**, 824; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**, pp. 154–162.

¹⁷⁵⁶ See Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, 881.

¹⁷⁵⁷ See Dilworth, B.M.; McKerver, M.A. *Tetrahedron* **1986**, 42, 3731.

¹⁷⁵⁸ Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K. *Tetrahedron Lett.* **1995**, 36, 115;

Kita, Y.; Shibata, N.; Fukui, S.; Fujita, S. *Tetrahedron Lett.* **1994**, 35, 9733.

¹⁷⁵⁹ Wladislaw, B.; Marzorati, L.; Biaggio, F.C. *J. Org. Chem.* **1993**, 58, 6132.

¹⁷⁶⁰ See Kita, Y.; Shibata, N.; Yoshida, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* **1994**, 35, 2569.

For DMSO and acetic anhydride, step 4 is intermolecular, as shown by ^{18}O isotopic labeling studies.¹⁷⁶¹ With other substrates, however, step 4 can be inter- or intramolecular, depending on the structure of the sulfoxide.¹⁷⁶² Depending on the substrate and reagent, any of the first three steps can be rate determining. In the case of Me_2SO treated with $(\text{F}_3\text{CCO})_2\text{O}$, the intermediate corresponding to **50**¹⁷⁶³ could be isolated at low temperature, and on warming gave the expected product.¹⁷⁶⁴ There is also an abundance of other evidence for this mechanism.¹⁷⁶⁵

A *sila-Pummerer rearrangement* has been reported.¹⁷⁶⁶

19-84 The Willgerodt Reaction

Willgerodt carbonyl transformation



In the *Willgerodt reaction*, a straight- or branched-chain aryl alkyl ketone is converted to the amide and/or the ammonium salt of the acid by heating with ammonium polysulfide.¹⁷⁶⁷ The carbonyl group of the product is always at the end of the chain. Thus $\text{ArCOCH}_2\text{CH}_3$ gives the amide and the salt of $\text{ArCH}_2\text{CH}_2\text{CO}_2\text{H}$ and $\text{ArCOCH}_2\text{CH}_2\text{CH}_3$ gives derivatives of $\text{ArCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$. However, yields sharply decrease with increasing length of chain. The reaction has also been carried out on vinylic and ethynyl aromatic compounds and on aliphatic ketones, but yields are usually lower in these cases. Unlike the *Pummerer rearrangement* (Reaction 19-83), which involves transposition of an oxygen from S to C, the *Willgerodt reaction* involves oxygen migration and oxidation of the organic species. The use of sulfur and a dry primary or secondary amine (or ammonia), as the reagent is called the *Kindler modification* of the *Willgerodt reaction*.¹⁷⁶⁸ The product in this case is $\text{Ar}(\text{CH}_2)_n\text{CSNR}_2$,¹⁷⁶⁹ which can be hydrolyzed to the acid. Particularly good results are obtained with morpholine as the amine. For volatile amines, the HCl salts can be used instead, with NaOAc in DMF at 100°C .¹⁷⁷⁰ Dimethylamine has also been used in the form of dimethylammonium dimethylcarbamate ($\text{Me}_2\text{NCOO}^-\text{Me}_2\text{NH}_2^+$).¹⁷⁷¹ The *Kindler modification* has also been applied to aliphatic ketones.¹⁷⁷² Thioamides have been prepared from ketones in a base-catalyzed reaction.¹⁷⁷³

¹⁷⁶¹ Oae, S.; Kitao, T.; Kawamura, S.; Kitaoka, Y. *Tetrahedron* **1963**, 19, 817.

¹⁷⁶² See Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, 56, 266; Oae, S.; Itoh, O.; Numata, T.; Yoshimura, T. *Bull. Chem. Soc. Jpn.* **1983**, 56, 270.

¹⁷⁶³ See Marino, J.P. *Top. Sulfur Chem.* **1976**, 1, 1.

¹⁷⁶⁴ Sharma, A.K.; Swern, D. *Tetrahedron Lett.* **1974**, 1503.

¹⁷⁶⁵ See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, **1978**, pp. 154–156; Oae, S.; Numata, T. *Isot. Org. Chem.* **1980**, 5, 45, p. 48; Wolfe, S.; Kazmaier, P.M. *Can. J. Chem.* **1979**, 57, 2388, 2397; Russell, G.A.; Mikol, G.J. *Mech. Mol. Migr.* **1968**, 1, 157.

¹⁷⁶⁶ Kirpichenko, S.V.; Suslova, E.N.; Albanov, A.I.; Shainyan, B.A. *Tetrahedron Lett.* **1999**, 40, 185.

¹⁷⁶⁷ For a review, see Brown, E.V. *Synthesis* **1975**, 358.

¹⁷⁶⁸ See Mayer, R. in Oae, S. *The Organic Chemistry of Sulfur*, Plenum, NY, **1977**, pp. 58–63; Lundstedt, T.; Carlson, R.; Shabana, R. *Acta Chem. Scand. Ser. B* **1987**, 41, 157, and other papers in this series. See also, Kanyonyo, M.R.; Gozzo, A.; Lambert, D.M.; Lesieur, D.; Poupaert, J.H. *Bull. Soc. Chim. Belg.* **1997**, 106, 39.

¹⁷⁶⁹ See Asinger, F.; Offermanns, H. *Angew. Chem. Int. Ed.* **1967**, 6, 907.

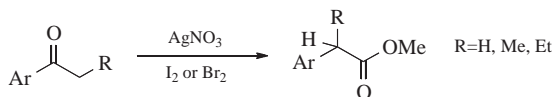
¹⁷⁷⁰ Amupitan, J.O. *Synthesis* **1983**, 730.

¹⁷⁷¹ Schroth, W.; Andersch, J. *Synthesis* **1989**, 202.

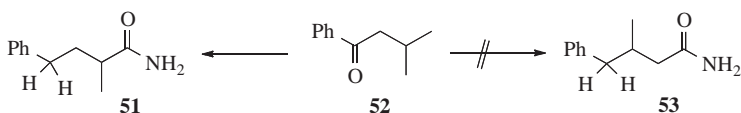
¹⁷⁷² See Dutron-Woitrin, F.; Merényi, R.; Viehe, H.G. *Synthesis* **1985**, 77.

¹⁷⁷³ For a review, see Poupaert, J.H.; Bouinidane, K.; Renard, M.; Lambert, D.; Isa, M. *Org. Prep. Proceed. Int.* **2001**, 33, 335.

Alkyl aryl ketones can be converted to arylacetic acid derivatives in an entirely different manner. The reaction consists of treatment of the substrate with silver nitrate and I_2 or Br_2 .¹⁷⁷⁴



The mechanism of the *Willgerodt reaction* is not completely known, but some conceivable mechanisms can be excluded. Thus, one might suppose that the alkyl group becomes completely detached from the ring, and then attacks it with its other end. However, this possibility is ruled out by experiments, such as the following: When isobutyl phenyl ketone (**51**) is subjected to the *Willgerodt reaction*, the product is **52**, not **53**, which would arise if the end carbon of the ketone became bonded to the ring in the product¹⁷⁷⁵:



This also excludes a cyclic-intermediate mechanism similar to that of the *Claisen rearrangement* (Reaction 18-33). Another important fact is that the reaction is successful for singly branched side chains (e.g., **52**), but not for doubly branched side chains, as in PhCOCMe_3 .¹⁷⁷⁵ Still another piece of evidence is that compounds oxygenated along the chain give the same products; thus $\text{PhCOCH}_2\text{CH}_3$, PhCH_2COMe , and $\text{PhCH}_2\text{CH}_2\text{CHO}$ all give $\text{PhCH}_2\text{CH}_2\text{CONH}_2$.¹⁷⁷⁶ All these facts point to a mechanism consisting of consecutive oxidations and reductions along the chain, although just what form these take is not certain. Initial reduction to the hydrocarbon can be ruled out, since alkylbenzenes do not give the reaction. In certain cases, imines¹⁷⁷⁷ or enamines¹⁷⁷⁸ have been isolated from primary and secondary amines, respectively, and these have been shown to give the normal products, leading to the suggestion that they may be reaction intermediates.

¹⁷⁷⁴ Higgins, S.D.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* **1982**, 235. See also, Higgins, S.D.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* **1983**, 1483.

¹⁷⁷⁵ King, J.A.; McMillan, F.H. *J. Am. Chem. Soc.* **1946**, 68, 632.

¹⁷⁷⁶ See Asinger, F.; Saus, A.; Mayer, A. *Monatsh. Chem.* **1967**, 98, 825.

¹⁷⁷⁷ Asinger, F.; Halcour, K. *Monatsh. Chem.* **1964**, 95, 24. See also, Nakova, E.P.; Tolkachev, O.N.; Evstigneeva, R.P. *J. Org. Chem. USSR* **1975**, 11, 2660.

¹⁷⁷⁸ Mayer, R. in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, **1967**, pp. 229–232.

The Literature of Organic Chemistry

All discoveries in the laboratory must be published somewhere if the information is to be made available to the scientific community. A new experimental result that is not published is useless, insofar as it benefits the entire chemical world. Traditionally, the total body of chemical knowledge (called *the literature*) is located on the combined shelves of all the chemical libraries in the world. Nowadays, books remain on library shelves, but many, if not most, chemical journals are available online. As e-books become increasingly available, however, books will be available online or for personal electronic reading devices. Anyone who wishes to learn the answer to a chemical question will access the chemical literature, both books and original articles in journals. The expressions “is known”, “has been done”, and so on, usually means “has been published”. The contents of the scientific literature may appear formidably large, but the process of extracting information from the literature of organic chemistry is usually manageable. Appendix A examines both the print literature of organic chemistry¹ and, within reasonable limits, electronic forms of the literature.

It is quite clear that the literature can be divided into two broad categories: primary sources and secondary sources. A *primary source* publishes the original results of laboratory investigations, usually in scientific journals. Indeed, the two chief kinds of primary source are journals and patents. Books, indexes, and other publications that cover material that has previously been published in primary sources are called *secondary sources*. Electronic search engines that use primary sources as a database are also considered to be secondary sources. It is because of the excellence of the secondary sources in organic chemistry (especially *Chemical Abstracts*, *SciFinder*) that literature searching is comparatively straightforward.

¹ See Williams, S. *College Teaching* **2005**, 53, 137 Kennedy, M.M. *Educational Researcher* **2007**, 36, 139; Available at www.chemistryguide.org; Gallagher, G.J.; Adams, D.L. *J. Chem. Educ.* **2002**, 79, 1368. Also see Wolman, Y. *Chemical Information*, 2nd ed., Wiley, NY, **1988**; Maizell, R.E. *How to Find Chemical Information*, 2nd ed., Wiley, NY, **1987**; Mellon, M.G. *Chemical Publications*, 5th ed., McGraw-Hill, NY, **1982**; Skolnik, H. *The Literature Matrix of Chemistry*, Wiley, NY, **1982**; Antony, A. *Guide to Basic Information Sources in Chemistry*, Jeffrey Norton Publishers, NY, **1979**; Bottle, R.T. *Use of the Chemical Literature*, Butterworth, London, **1979**; Woodburn, H.M. *Using the Chemical Literature*, Marcel Dekker, NY, **1974**. For a three-part article on the literature of organic chemistry, see Hancock, J.E.H. *J. Chem. Educ.* **1968**, 45, 193, 260, 336.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.
Michael B. Smith.

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A. PRIMARY SOURCES

A.i. Journals

For well over 100 years, nearly all new work in organic chemistry (except for that disclosed in patents) has been published in journals. There are many journals that publish chemical papers, in many countries and in many languages. Nowadays, a high percentage of the journals are published in English, but not all. Some print papers cover all fields of science; some are restricted to chemistry; some to organic chemistry; and some are still more specialized. As noted above, many journals are now available in electronic form.² The actual article is usually offered as an html file, or a PDF file, often with links to the cited references. The vast majority of important papers in “pure” organic chemistry (as opposed to “applied”) are published in relatively few journals, perhaps 50 or fewer. The concept of “pure” organic chemistry is not as useful nowadays because organic chemistry is important in many areas, and multidisciplinary research often includes organic chemistry. Literature that is important to an organic chemist is found in journals and patents that focus on bioorganic, organometallic, materials science, polymer science, separation science, medicinal chemistry, pharmaceutical sciences, and medicine to name a few. The reader is therefore cautioned that the journals listed in this section have organic chemistry as their primary focus, but are by no means the only sources of information concerning organic chemistry. The literature is vast and many journals are published weekly and some semimonthly.

Ordinary papers, usually referred to as full papers, usually include full experimental details, either as part of the paper itself or as accompanying supplemental information. Such details are the mainstay of modern research, providing a guide to what has been done, and the experimental details allow one to repeat that work. With the increase in the volume of chemical literature, and especially with the proliferation of electronic journals, and as noted above, many journals now place full experimental details into “Supplemental Information”. For journals published by the American Chemical Society, a URL link is provided for each article that contains the supplemental information: experiential details, spectral data, visual reproductions of spectral data, X-ray crystallographic data, and so on. Other publishers offer similar links. Once a paper is accepted, the online version (e.g., American Chemical Society ASAP papers) can be found before the print version or the full electronic version that contains the page numbers appear.

In addition to full papers, there are two other types of publications in which original work is reported: *notes* and *communications*. A note is a brief paper, often without a summary (nearly all papers are published with summaries or abstracts prepared by the author). Otherwise, a note is similar to a paper.³ Some journals specialize in publishing only notes. Communications (also called *letters*) are also brief and are usually without summaries (some journals now publish summaries along with their communications), and there are journals that publish only communications or letters.

Communications differ from notes and papers in three respects:

1. They are brief, not because the work is of small scope, but because they are condensed. Usually they include only the most important experimental details or none at all.

² For examples of the contents of an academic electronic library see <http://lib.uconn.edu/> or <http://www.chem.ox.ac.uk/cheminfo/ejournals.html>. Also see eJournal Locator.

³ In some journals, notes are called “short communications”, an unfortunate practice, because they are not communications as that term is defined in this text.

2. They are often of immediate significance. Journals that publish communications make every effort to have them appear as soon as possible after they are received. With modern computer technology, communications can often be published in a matter of weeks.
3. Communications are preliminary reports, and the material in them may be republished as papers at a later date, in contrast to the material in papers and notes, which cannot be republished.

Although chemical publications are published in many languages, the vast majority of important papers in organic chemistry are published in English. For example, six prominent European journals (*Chemische Berichte*, *Liebigs Annalen der Chemie*, *Bulletin de la Société Chimique de France*, *Bulletin des Sociétés Chimique Belges*, *Recueil des Travaux Chimiques des Pays-Bas*, and *Gazzetta Chimica Italiana*) were discontinued. In their place is the *European Journal of Organic Chemistry*, published in English. Most of the articles published in other languages have summaries printed in English also. Important papers were published in German and French for >200 years, and these are generally not available in translation, so that the organic chemist was required to have at least a reading knowledge of these languages. Before ~1920, more than one-half of the important chemical papers were in these languages. In recent years, however, fewer papers in French or German have appeared without an English translation. Of course, a reading knowledge of French and German (especially German) is critical for the older literature. It must be realized that the original literature is never obsolete. With the rise of China in the scientific community, journals are published in Chinese, and there are journals and important chemical discoveries published in Japanese. Work by Chinese and Japanese scientists regularly appears in English-language journals. Secondary sources become superseded or outdated, but nineteenth century journals with primary literature are found in most chemical libraries and are still consulted. Table A.1 presents a list of important current journals that publish original papers⁴ and communications in organic chemistry. Some of them also publish review articles, book reviews, and other material. In 1999, the *Journal of Organic Chemistry* stopped publishing communications, and these are now published in *Organic Letters*.

For some years, the American Chemical Society journals, including *J. Am. Chem. Soc.* and *J. Org. Chem.*, provided supplementary material for some of their papers on microfilm or microfiche. As noted above, this material is now available online, and for older literature from the Microforms and Back Issues Office at the ACS Washington office, either on microfiche, or as a photocopy. These practices have not yet succeeded in substantially reducing the total volume of the world's primary chemical literature since many new journals have appeared, and the yearly page count for most journals has doubled or tripled.

A.ii. Patents

In many countries, including the United States, it is possible to patent a new compound or a new method for making a known compound (either laboratory or industrial procedures). It comes as a surprise to many to learn that a substantial proportion of the patents granted (perhaps 20–30%) have been chemical patents. Chemical patents are part of the chemical literature, and both U.S. and foreign patents were regularly abstracted by *Chemical Abstracts* and now *SciFinder*. In addition to learning about the contents of patents

⁴ In Table A.1, notes are counted as papers.

TABLE A.1 A List of the More Important *Current Journals*^a

No.	Name	Papers or Communications	Issues per Year
1	Angewandte Chemie (1887) ^b	C ^c	12
2	Angewandte Chemie International Edition (1962) ^b	C ^c	48
3	Australian Journal of Chemistry (1948)	P	12
4	Bioorganic Chemistry (1971)	P ^b	4
5	Bioorganic & Medicinal Chemistry Letters (1991)	C	12
6	Bulletin of the Chemical Society of Japan (1926)	P	12
7	Canadian Journal of Chemistry (1929)	P,C	12
8	Carbohydrate Research (1965)	P,C	22
9	Chemistry, a European Journal (1995)	P	24
10	Chemistry, an Asian Journal (2006)	P	24
11	Chemistry and Industry (London) (1923)	C	24
12	Chemistry Letters (1972)	C	12
13	Chimia (1947)	C ^b	12
14	ChemPlusChem	New	
15	Doklady Chemistry (1922) ^b	C	12
17.	European Journal of Organic Chemistry (1998)	P	12
18	Helvetica Chimica Acta (1918)	P	8
19	Heteroatom Chemistry (1990)	P	6
20	Heterocycles (1973)	C ^b	12
21	Indian Journal of Chemistry (Section B)	P	12
22	International Journal of chemical Kinetics (1969)	P	12
23	Israel Journal of Chemistry (1963)	P ^d	4
23	Journal of the American Chemical Society (1879)	P,C	52
25	Journal of Carbohydrate Chemistry (1981)	P,C	6
26	Journal of Chemical Research, Synopses (1977)	P	12
27	Chemical Communications (1965)	C	24
28	Journal of Combinatorial Chemistry (2000)	P,C	6
29.	Journal of Computational Chemistry (1979)	P	16
30	Journal of Fluorine Chemistry (1971)	P,C	12
31	Journal of Heterocyclic Chemistry (1964)	P,C	12
32	Journal of the Indian Chemical Society (1924)	P	12
33	Journal of Lipid Research (1959)	P	12
34	Journal of Medicinal Chemistry (1958)	P,C	12
35	Journal of Molecular Structure (1967)	P,C	16
36	Journal of Organometallic Chemistry (1963)	P,C	48
37	Journal of Organic Chemistry (1936)	P,C	26
38	Journal of Photochemistry and Photobiology, A: Chemistry (1972)	P	12
39	Journal of Physical Organic Chemistry (1988)	P	12
40	Journal of Polymer Science Part A (1962)	P	24
41	Journal für Praktische Chemie (1834)	P	6
42	Macromolecules (1968)	P,C	26
43	Liebigs Annalen der Chemie (1832)	P	12
44	Mendeleev Communications (1991)	C	8
45	Monatshefte für Chemie (1870)	P	12
46	New Journal of Chemistry (1977) ^d	P	11
47	Organometallics (1982)	P,C	12
48	Organic and Biomolecular Chemistry (2003)	P	24

49	Organic Letters (1999)	C	12
50	Organic Mass Spectrometry (1968)	PC	12
51	Organic Preparations and Procedures International (1969)	P ^b	6
52	Organic Process Research & Development (1997)	P	6
53	Photochemistry and Photobiology (1962)	P ^b	12
54	Polish Journal of Chemistry (1921) ^c	PC	12
55	Pure and Applied Chemistry (1960)	f	12
56	Research on Chemical Intermediates (1973) ^g	P ^b	6
57	Russian Journal of Organic Chemistry (1984)	P,C	12
58	Sulfur Letters (1982)	C	6
59	Synlett (1989)	C ^b	12
60	Synthetic Communications (1971)	C	22
61	Synthesis (1969)	P ^b	12
62	Tetrahedron (1958)	P ^b	52
63	Tetrahedron: Asymmetry (1990)	PC	12
64	Tetrahedron Letters (1959)	C	52

^aThese journals currently publish original papers in organic chemistry, listed in alphabetical order of *Chemical Abstracts* abbreviations, which are indicated in boldface. Also given are the year of founding, number of issues per year as of 2012, and whether the journal primarily publishes papers (P), communications (C), or both.

^bSee Ref. 5.

^cSee Ref. 6.

^dSee Ref. 7.

^eSee Ref. 8.

^fSee Ref. 9.

^gSee Ref. 10.

from this source, chemists may consult the *Official Gazette* of the U.S. Patent Office, which, published weekly and available in many libraries, lists titles of all patents issued that week. Bound volumes of all U.S. patents are kept in a number of large libraries, including the New York Public Library, which also has an extensive collection of foreign patents. Photocopies of any U.S. patent and most foreign patents were obtained at low cost from the U.S. Patent and Trademark Office, Washington, DC, 20231. Many patents can now be obtained online as well or are available as PDF files. Patents are also available via SciFinder (formerly, CAS online).

Although patents are often very useful to the laboratory chemist, and no literature search is complete that neglects relevant patents, as a rule they are not as reliable as papers. There are two reasons for this finding:

1. It is in the interest of the inventor to claim as much as possible. The patent may show, for example, that a reaction was actually carried with ethanol and with 1-propanol, but will claim all primary alcohols, and perhaps even secondary and tertiary alcohols, glycols, and phenols. An investigator repeating the reaction on an alcohol that the inventor did not use may find that the reaction gives no yield at all.

⁵ These journals are available in English translation.

⁶ These journals also publish review articles regularly.

⁷ Each issue of this journal is devoted to a specific topic.

⁸ Before 1978 this journal was called *Roczniki Chemii*.

⁹ *Pure Appl. Chem.* publishes IUPAC reports and lectures given at IUPAC meetings.

¹⁰ Before 1989 this journal was called *Reviews of Chemical Intermediates*.

In general, it is safest to duplicate the actual examples given, of which most chemical patents contain one or more.

2. Although legally a patent gives an inventor a monopoly, any alleged infringements must be protected in court, and this may cost a good deal of money. Therefore some patents are written so that certain essential details are concealed or entirely omitted. A patent is supposed to be a full disclosure, but patent attorneys are generally skilled in the art of writing patents, and procedures given are not always sufficient to duplicate the results.

Fortunately, the above statements do not apply to all chemical patents: many make full disclosures and claim only what was actually done. It must also be pointed out that it is not always possible to duplicate the work reported in every paper in a journal due to the use of proprietary catalysts or equipment not available to the public. It is not uncommon to literally purchase the world's supply of a key ingredient. Note, however, that some work is not published or patented but rather maintained within the company as a trade secret. Such work is not, of course, available to the public.

B. SECONDARY SOURCES

Journal articles and patents contain virtually all of the original work in organic chemistry. However, if this were all, if there were no indexes, abstracts, review articles, and other secondary sources, the literature would be unusable, because it is so vast that no one could hope to find anything in particular. Fortunately, the secondary sources are excellent. There are various kinds and the classification shown here is somewhat arbitrary.

B.i. Listings of Titles

The profusion of original papers is so great that publications that list the titles of current papers find much use. Such lists are primarily methods of alerting the chemist to useful papers published in journals that are not normally read. This approach using print versions containing lists or journals and articles is used sparingly nowadays. Most journals are available online with useful search engines, and most have the original papers, with supplemental material, as html and PDF¹¹ documents. The PDF document can be downloaded to the searcher's desktop, sometimes for a fee, shipped to other scientists electronically, and is most convenient. *Chemical Abstracts* was available online as *CAS OnLine*, but this service has been supplanted by *SciFinder* (see Appendix A.D.iii). University libraries and companies pay the appropriate fees, so access to the journals is usually quite easy if one is affiliated with these organizations. Search engines allow one to quickly scan an enormous amount of literature from office or home. In addition, most browsers have online searching capabilities via various search engines, and simply typing in an author, a topic, a chemical, or a few keywords can lead to important articles or information. "Google[®] searching"¹² is commonly employed for a "quick and dirty" search, but one is strongly urged to use one of the established scientific search engines for a proper search.

¹¹ Adobe Acrobat files.

¹² Available at www.google.com/

The more important online technology will be discussed below. However, some other resources¹³ include Specialty Citation Indexes Science Citation Index ExpandedTM, Web of Science[®], Science Citation Index[®], ISI ProceedingsSM, Reaction Citation IndexTM, and the Derwent Innovations IndexSM. The discussion will begin with the older print versions for chemical searches.

A print-version “title” publication covering the whole of chemistry is *Current Contents Physical, Chemical & Earth Sciences*,¹⁴ which began in 1967 and appears weekly, contains the contents pages of all issues of about 800 journals in chemistry, physics, earth sciences, mathematics, and allied sciences. Each issue contains an index of important words taken from the titles of the papers listed in that issue, and an author index, which, however, lists only the first-named author of each paper. The author’s address is also given, so that one may write for reprints. An online service is available called *Current Contents Connect*[®] is a multidisciplinary Web resource providing access to complete bibliographic information from >8000 of the world’s leading scholarly journals and >2000 books.¹⁵

Chemical titles is a similar publication produced by the Chemical Abstracts Service (CAS). SciFinder described below allows one to search a variety of databases, including journal titles.

B.ii. Abstracts

Listings of titles are valuable, as far as they go, but they do not tell what is in the paper, beyond the implications carried by the titles. Most current journals contain a graphic abstract, as well as a title and a brief print description of the research. The graphical abstract is extremely useful for scanning the literature presented in a journal, and both the print and graphical abstracts are available online for most journals.

From the earliest days of organic chemistry, abstracts of papers have been widely available, often as sections of journals whose principal interests lay elsewhere.¹⁶ At the present time there are only two publications entirely devoted to abstracts covering the whole field of chemistry. One of these, *Referativnyi Zhurnal, Khimiya*, which began in 1953, is published in Russian and is chiefly of interest to Russian-speaking chemists. The other is *Chemical Abstracts*, which was published until 2010. Abstracts are now available online via *SciFinder*. Although out of print, knowledge of Chemical Abstracts is important to properly do a literature search that includes older literature. *Chemical Abstracts* appeared weekly and printed abstracts in English of virtually every paper containing original work in pure or applied chemistry published anywhere in the world.¹⁷ More than 18,000 journals were covered, in many languages. In addition, *CA* published abstracts of every patent of chemical interest from 18 countries, as well as many patents from additional countries. The abstracts currently appeared in 80 sections, with sections 21–34 devoted to organic chemistry, under such headings as Alicyclic Compounds, Alkaloids, Physical Organic Chemistry, Heterocyclic Compounds (One Heteroatom),

¹³ See <http://scientific.thomson.com/products/categories/citation/>

¹⁴ Title pages of organic chemistry journals are also carried by *Current Contents Life Sciences*, which is a similar publication covering biochemistry and medicine.

¹⁵ Available at <http://scientific.thomson.com/products/ccc/>

¹⁶ For example, *Chem. Ind. (London)* publishes abstracts of papers that appear in other journals. In the past, journals, such as *J. Am. Chem. Soc.*, *J. Chem. Soc.*, and *Ber.* also did so.

¹⁷ For a guide to the use of *CA*, see Schulz, H. *From CA to CAS ONLINE*; VCH: NY, 1988.

and so on. Each abstract of a paper had a heading that gave (1) the abstract number;¹⁸ (2) the title of the paper; (3) the authors' names as given in the paper; (4) the authors' address; (5) the abbreviated name of the journal (see Table A.1);¹⁹ (6) the year, volume, issue, and page numbers; and (7) the language of the paper. In earlier years *CA* gave the language only if it differed from the language of the journal title. Abstracts of patents showed the abstract number, title, inventor and company (if any), patent number, patent class number, date patent issued, country of priority, patent application number, date patent applied for, and number of pages in the patent. The body of the abstract contained a concise summary of the information in the paper. For many common journals, the author's summary (if there is one) was used in *CA* as it appeared in the original paper, with perhaps some editing and additional information. Each issue of *CA* contained an author index, a patent index, and an index of keywords taken from the titles and the texts or contexts of the abstracts. The patent index listed all patents in order of number. The same compound or method is often patented in several countries. *Chemical Abstracts* abstracted only the first patent, but listed the patent numbers of the duplicated patents in the patent index along with all previous patent numbers that correspond to it. Before 1981 there were separate Patent Number Indexes and Patent Concordances (the latter began in 1963).

At the end of each section of *CA* a list of cross-references to related papers in other sections is given.

Chemical Abstracts is useful as a repository of chemical information, a place for finding out what was done in the past. This value stems from the excellent indexes, which enable the chemist in most cases to ascertain quickly where information is located. From the time of its founding in 1907 until 1961, *CA* published annual indexes. After 1962 there were two volumes published each year, and a separate index is issued for each volume. Each volume contained an index of subjects, authors, formulas, and patent numbers. Beginning in 1972, the subject index was issued in two parts, a chemical substance index and a general subject index, which included all entries that are not the names of single chemical substances. However, the indexes to each volume were essentially superseded by each collective index. The first collective indexes were 10-year (decennial) indexes, but the volume of information made 5-year indexes necessary since 1956. Collective indexes so far published are shown in Table A.2.

As noted above, the print form of Chemical Abstracts has been superseded by SciFinder (see Appendix A.D.iii)

Beginning with the Eighth collective index period, *CA* has published an *Index Guide*. This publication gave structural formulas and/or alternate names for thousands of compounds, as well as many other cross-references. It was designed to help the user efficiently and rapidly to find *CA* references to subjects of interest in the general subject, formula, and chemical substance indexes. Each collective index contained its own *Index Guide*. The *Index Guide* was necessary because the *CA* general subject index was a "controlled index", meaning it restricted its entries only to certain terms.

For example, anyone looking for the term "refraction" in the printed general subject index will not find it. The *Index Guide* included this term, and directed the reader to "Electromagnetic wave, refraction of", "Sound and ultrasound, refraction of", and other terms, all of which were found in the general subject index. Similarly, the chemical substance index usually listed a compound only under one name - the approved *CA* name.

¹⁸ Began in 1967. See Appendix A.B.ii.

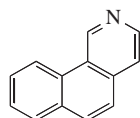
¹⁹ These abbreviations are changed from time to time. Therefore the reader may notice inconsistencies.

TABLE A.2 CA Collective Indexes So Far Published

Collective Index	Subject General Subject	Chemical Substance	Author	Formula	Patents
1	1907–1916		1907–1916		
2	1917–1926		1917–1926		1907–1936
3	1927–1936		1927–1936	1920–1946	
4	1937–1946		1937–1946		1937–1946
5	1947–1956		1947–1956	1947–1956	1947–1956
6	1957–1961		1957–1961	1957–1961	1957–1961
7	1962–1966		1962–1966	1962–1966	1962–1966
8	1967–1971		1967–1971	1967–1971	1967–1971
9	1972–1976	1972–1976	1972–1976	1972–1976	1972–1976
10	1977–1981	1977–1981	1977–1981	1977–1981	1977–1981
11	1982–1986	1982–1986	1982–1986	1982–1986	1982–1986
12	1987–1991	1987–1991	1987–1991	1987–1991	1987–1991
13	1992–1996	1992–1996	1992–1996	1992–1996	1992–1996
14	1997–2001	1997–2001	1997–2001	1997–2001	1997–2001
15	2002–2006	2002–2006	2002–2006	2002–2006	2002–2006

Trivial and other names were found in the *Index Guide*. For example, the term “methyl carbonate” is not in the chemical substance index, but the *Index Guide* does have this term, and directs the reader to the chemical substance index under the headings “carbonic acid, esters, dimethyl ester” (for Me_2CO_3) and “carbonic acid, esters, monomethyl ester” (for MeHCO_3). Furthermore, the *Index Guide* gives terms related to the chosen term, helping users to broaden a search. For example, one who looks for “Atomic orbital” in the *Index Guide* will find the terms “Energy Level”, “Molecular orbital”, “Atomic integral”, and “Exchange, quantum mechanical, integrals for”, all of which are controlled index terms.

Each index (annual, semiannual, or collective) also provided an index of ring systems. This valuable index enables the user to ascertain immediately if any ring system appears in the corresponding subject or chemical substance index and under what names. For example, someone wishing to determine whether any compounds



Benz(h)isoquinoline

containing the benz(h)isoquinoline ring system are reported in the 1982–1986 collective index would locate, under the heading “3-ring systems”, the listing **6, 6, 6** (since the compound has three rings of six-members each), and would find the sublisting $\text{C}_5\text{N}-\text{C}_6-\text{C}_6$ (since one ring contains five carbons and a nitrogen while the others are all-carbon), under which is listed the name benz(h)isoquinoline, as well as the names of 30 other systems $\text{C}_5\text{N}-\text{C}_6-\text{C}_6$. A search of the chemical substance index under these names will give all references to these ring systems that appeared in *CA* from 1982 to 1986.

Nowadays, the drawing tools of *SciFinder* (sec. Appendix A.D.iii) are used to draw this structure, and then perform the search.

Before 1967, *CA* used a two-column page, with each column separately numbered. A row of letters from *a* to *h* appeared down the center of the page for the guidance of the user. Thus an entry 7337*b* refers to the *b* section of column 7337. In early years, superscript numbers (e.g., 4327⁵) were used in a similar manner. In very early years, these numbers were not printed on the page at all, though they are given in the decennial indexes, so that the user must mentally divide the page into nine parts. Beginning with 1967, abstracts are individually numbered and column numbers are discarded. Therefore, beginning with 1967, index entries give abstract number rather than column number. The abstract numbers are followed by a letter that serves as a check character to prevent miscopying errors in computer handling. To use the *CA* general subject, chemical substance, and formula indexes intelligently requires practice, and the student should become familiar with representative volumes of these indexes and with the introductory sections to them, as well as with the *Index Guides*.

In the *CA* formula indexes, formulas were listed in order of (1) number of carbon atoms; (2) number of hydrogen atoms; (3) other elements in alphabetic order. Thus, all C₃ compounds are listed before any C₄ compound; all C₅H₇ compounds before any C₅H₈ compound; C₇H₁₁Br before C₇H₁₁N; C₉H₆N₄S before C₉H₆O, and so on. Deuterium and tritium are represented by D and T and treated alphabetically (e.g., C₂H₅DO after C₂H₅Cl and before C₂H₅F or C₂H₆).

Since 1965, *CA* has assigned a Registry Number²⁰ to each unique chemical substance. This is a number of the form [766-51-8] that remains invariant, no matter what names are used in the literature. More than 64 million numbers have already been assigned and thousands are added each week. Registry Numbers are primarily for computer use, but chemical suppliers use CAS registry numbers to identify chemicals that are available for sale.

There were a number of earlier abstracting publications now defunct. The most important are *Chemisches Zentralblatt* and *British Abstracts*. These publications are still valuable because they began before *CA* and can therefore supply abstracts for papers that appeared before 1907. Furthermore, even for papers published after 1907, *Zentralblatt* and *British Abstracts* are often more detailed. *Zentralblatt* was published, under various names, from 1830 to 1969.²¹ *British Abstracts* was a separate publication from 1926 to 1953, but earlier abstracts from this source are available in the *Journal of the Chemical Society* from 1871 to 1925.

B.iii. Beilstein

This publication has been so important to organic chemistry that it deserves a section by itself. Beilstein's *Handbuch der Organischen Chemie*, usually referred to as *Beilstein*, lists all the known organic compounds reported in the literature during its period of coverage. The print version will be described first, as it is particularly important for older literature.

For each compound in *Beilstein*, the following data are given: all names; the molecular formula; the structural formula; all methods of preparation (briefly, e.g., "by refluxing 1-butanol with NaBr and sulfuric acid"); physical constants (melting point, refractive index, etc.); other physical properties; chemical properties including reactions; occurrence in nature (i.e., which species it was isolated from); biological properties, if any; derivatives

²⁰ See <http://www.cas.org/expertise/cascontent/registry/regsyst.html>

²¹ An "obituary" of *Zentralblatt* by Weiske, C., gives its history and statistical data about its abstracts and indexes, and was published in the April 1973 issue of *Chem. Ber.* (pp. I–XVI).

with melting points; analytical data, and any other information that has been reported in the literature.²² Equally important, for every piece of information, a reference is given to the original literature. Furthermore, the data in Beilstein have been critically evaluated. That is, all information is carefully researched and documented, and duplicate and erroneous results are eliminated. Some compounds are discussed in two or three lines and others require several pages.

The print editions are invaluable for searching older literature, but even today provide valuable data for many compounds used every day. A discussion of using *Beilstein* is therefore essential.

The first three editions of Beilstein are obsolete. The fourth edition (*vierte Auflage*) covers the literature from its beginnings through 1909. This edition, called *das Hauptwerk*, consists of 27 volumes. The compounds are arranged in order of a system too elaborate to discuss fully here.²³ The compounds are divided into three divisions that are further subdivided into “systems”:

Division	Volumes	System Numbers
I. Acyclic Compounds	1–4	1–499
II Carbocyclic Compounds	5–16	450–2359
III. Heterocyclic Compounds	17–27	2360–4720

Das Hauptwerk is still the basis of Beilstein and has not been superseded. The later literature is covered by supplements that have been arranged to parallel *das Hauptwerk*. The same system is used, so that the compounds are treated in the same order. The first supplement (*erstes Ergänzungswerk*) covers 1910–1919; the second supplement (*zweites Ergänzungswerk*) covers 1920–1929; the third supplement (*drittes Ergänzungswerk*) covers 1930–1949; the fourth supplement (*viertes Ergänzungswerk*) covers 1950–1959, and the fifth supplement covers 1960–1979. Like *das Hauptwerk*, each supplement contains 27 volumes,²⁴ except that supplements 3 and 4 are combined for Vols. 17–27, so that for these volumes the combined third and fourth supplement covers the years 1930–1959. Each supplement has been divided into volumes in the same way as *das Hauptwerk*, and, for example, compounds found in Vol. 3, system number 199 of *das Hauptwerk* will also be found in Vol. 3, system number 199 of each supplement. To make cross-referencing even easier, each supplement gives, for each compound, the page numbers at which the same compound can be found in the earlier books. Thus, on page 554 of Vol. 6 of the fourth supplement, under the listing phenetole are found the symbols (H 140; E I 80; E II 142; E III 545) indicating that earlier information on phenetole is given on page 140 of Vol. 6 of *das Hauptwerk*, on page 80 of the first, page 142 of the second, and

²² For a discussion of how data are processed for inclusion in Beilstein, see Luckenbach, R.; Ecker, R.; Sunkel, J. *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 841 [*Angew. Chem.* 93, 876].

²³ For descriptions of the Beilstein system and directions for using it, see Sunkel, J.; Hoffmann, E.; Luckenbach, R. *J. Chem. Educ.* **1981**, 58, 982; Luckenbach, R. *CHEMTECH* **1979**, 612. The Beilstein Institute has also published two English language guides to the system. One, available free, is *How to Use Beilstein*, Beilstein Institute, Frankfurt/Main, **1979**. The other is by Weissbach, O. *A Manual for the Use of Beilstein's Handbuch der Organischen Chemie*, Springer, NY, **1976**. An older work, which many students will find easier to follow, is by Huntress, E.H. *A Brief Introduction to the Use of Beilstein's Handbuch der Organischen Chemie*, 2nd ed., Wiley, NY, **1938**.

²⁴ In some cases, to keep the system parallel and to avoid books that are too big or too small, volumes are issued in two or more parts, and, in other cases, two volumes are bound as one.

page 545 of the third supplement. Furthermore, each page of the supplements contains, at the top center, the corresponding page numbers of *das Hauptwerk*. Since the same systematic order is followed in all six series, location of a compound in any one series gives its location in the other five. If a compound is found, for example, in Vol. 5 of *das Hauptwerk*, one has but to note the page number and scan Vol. 5 of each supplement until that number appears in the top center of the page (the same number often covers several pages). Of course, many compounds are found in only one, two, three, four, or five of the series, since no work may have been published on that compound during a particular period covered.

From *das Hauptwerk* to the fourth supplement, Beilstein is in German, but it is not difficult to read since most of the words are the names of compounds (a Beilstein German–English Dictionary, available free from the publisher, is in many libraries). For the fifth supplement (covering 1960–1979), which is in English, publication of Division III began before the earlier divisions. Volumes 17–22 (totaling 70 separate parts exclusive of index volumes) of this supplement have been published, as well as a combined index for volumes 17–19. This index covers only the fifth supplement. The subject portion of this index, which lists compound names only, gives these names in English.

Volumes 28 and 29 of Beilstein are subject and formula indexes, respectively. The most recent complete edition of these volumes is part of the second supplement and covers only *das Hauptwerk* and the first two supplements (though complete indexes covering *das Hauptwerk* and the first four supplements have been announced to appear in the next few years). For Vol. 1, there is a cumulative subject and a cumulative formula index, which combine *das Hauptwerk* and the first four supplements.²⁵ Similar index volumes, covering all four supplements, have been issued for the other volumes, 2–27. Some of these are combined (e.g., 2–3, 12–14, and 23–25). For English-speaking chemists (and probably for many German-speaking chemists) the formula indexes are more convenient. Of course (except for the fifth supplement indexes), one must still know some German, because most formula listings contain the names of many isomers. If a compound is found only in *das Hauptwerk*, the index listing is merely the volume and page numbers (e.g., **1**, 501). Roman numbers are used to indicate the supplements (e.g., **26**, 15, **I** 5, **II** 7). Thus the subject and formula indexes lead at once to locations in *das Hauptwerk* and the first four supplements. The Beilstein formula indexes are constructed the same way as the *CA* indexes (Appendix A.B.ii).

There is also a fourth division of Beilstein (systems 4721–4877) that covers natural products of uncertain structure: rubbers, sugars, and so on. These are treated in Vols. 30 and 31, which do not go beyond 1935 and that are covered in the collective indexes. These volumes will not be updated. All such compounds are now included in the regular Beilstein volumes.

In recent years, Beilstein was available online, with the useful search engine *CrossFire*. However, this database is now incorporated into *Reaxys* (see Appendix A.D.vi).

B.iv. Tables of Information

In addition to Beilstein, there are many other print reference works in organic chemistry that are essentially compilations of data. These books are very useful and often save the

²⁵ Most page number entries in the combined indexes contain a letter (e.g., CHBr₂Cl 67f, **II** 33a, **III** 87d, **IV**, 81). These letters tell where on the page to find the compound and are useful because the names given in the index are not necessarily those used in the earlier series. The letter “a” means the compound is the first on its page, “b” is the second, and so on. No letters are given for the fourth supplement.

research worker a great deal of time. In this section, we discuss some of the more important of such works.

1. The sixth edition of *Heilbron's Dictionary of Organic Compounds*, J. Buckingham, Ed., 9 vols., Chapman and Hall, London, **1996**, contains brief listings of >150,000 organic compounds, giving names, structural formulas, physical properties, and derivatives, with references. For many entries, additional data concerning occurrence, biological activity, and toxicity hazard information are also given. The arrangement is alphabetical. The dictionary contains indexes of names, formulas, heteroatoms, and CA Registry Numbers. Annual supplements, with cumulative indexes, have appeared since 1983. A similar work, devoted to organometallic compounds, is the 2nd edition of the *Dictionary of Organometallic Compounds*, 6 vols. in its 5th supplement, published by Chapman and Hall in **1989**. Another, *Dictionary of Steroids*, 2 vols., 1991, is also published by Chapman and Hall.
2. A multivolume compendium of physical data is *Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik, und Technik*, 6th ed., by H. Landolt and R. Börnstein, Springer, Berlin, 1950. There is also a "New Series", for which the volumes are given the English title *Numerical Data and Functional Relationships in Science and Technology*, as well as the German title. This compendium, which is not yet complete, lists a great deal of data, some of which are of interest to organic chemists (e.g., indexes of refraction, heats of combustion, optical rotations, and spectral data). Literature references are given for all data.
3. *The Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL (called the "rubber handbook"), which is revised annually (92nd ed., 2011–2012), is a valuable repository of data quickly found. For organic chemists an important table is *Physical Constants of Organic Compounds*, which lists names, formulas, color, solubility, and physical properties of thousands of compounds. However, there are many other useful tables. A similar work is *Lange's Handbook of Chemistry*, 16th ed., McGraw-Hill, New York, 2004. Another such handbook, but restricted to data of interest to organic chemists, is *Dean's Handbook of Organic Chemistry*, 2nd ed., McGraw-Hill, New York, 2003. This book also contains a long table of *Physical Constants of Organic Compounds*, and has much other information including tables of thermodynamic properties, spectral peaks, pK_a values, bond distances, and dipole moments.
4. A list of most of the known natural compounds (e.g., terpenes, alkaloids, carbohydrates) to which structures have been assigned, along with structural formulas, melting points, optical rotations, and references, is provided in T.K. Devon and A.J. Scott, *Handbook of Naturally Occurring Compounds*, 3 vols., Academic Press, New York, **1972**.
5. R.R. Dreisbach, *Physical Properties of Chemical Compounds*, Advances in Chemistry Series Nos. 15, 22, 29, American Chemical Society, Washington, 1955–1961 lists many physical properties of >1000 organic compounds.
6. Physical properties of thousands of organometallic compounds, with references, are collected in five large compendia: the *Dictionary of Organometallic Compounds*, mentioned under item 1, above; M. Dub, *Organometallic Compounds*, 2nd ed., 3 vols. with supplements and index, Springer, New York, 1966–1975; N. Hagihara, M. Kumada, and R. Okawara, *Handbook of Organometallic Compounds*,

- W.A. Benjamin, New York, **1968**; and H.C. Kaufman, *Handbook of Organometallic Compounds*, Van Nostrand, Princeton, NJ, **1961**; *Comprehensive Organometallic Chemistry II*, 14 vols, Pergamon, 1995.
7. The *Merck Index*, 14th ed., Merck and Company, Rahway, NJ, **2006** is a good source of information about chemicals of medicinal importance. Many drugs are given three types of name: chemical *name* (which is the name an organic chemist would give it; of course, there may well be more than one); *generic name*, which must be placed on all containers of the drug; and *trade names*, which are different for each company that markets the drug. For example, the generic name for 1-(4-chlorobenzhydryl)-4-methylpiperazine is chlorcyclazine. Among the trade names for this drug, which is an antihistamine, are Trihistan, Perazyl, and Alergicide. The *Merck Index* is especially valuable because it gives all known names of all three types for each compound and the names are cross-indexed. Also given, for each compound, are the structural formula, *CA* preferred name and Registry Number, physical properties, medicinal and other uses, toxicity indications, and references to methods of synthesis. There are indexes of formulas and Registry Numbers, and miscellaneous tables. The “*Merck Index*” also includes a lengthy list of organic name reactions, with references.
 8. There are two publications that list properties of azeotropic mixtures. J. Timmermans, *The Physico-chemical Constants of Binary Systems in Concentrated Solutions*, 4 vols., Interscience, New York, **1959–1960**, is by far the more comprehensive. The other is *Azeotropic Data*, 2 vols., Advances in Chemistry Series No. 6 and No. 35, American chemical Society, Washington, **1952, 1962**.
 9. Thousands of dipole moments, with references, are collected in V.A.L. McClellan, *Tables of Experimental Dipole Moments*, Vol. 1, W.H. Freeman, San Francisco, CA, **1963**; Vol. 2, Rahara Enterprises, El Cerrita, CA, **1974**.
 10. *Tables of Interatomic Distances and Configurations in Molecules and Ions*, London Chemical Society Special publication no. 11, **1958**, and its supplement, Special publication no. 18, **1965**, include bond distances and angles for hundreds of compounds, along with references.
 11. The *Ring Systems Handbook*, published in 1988 by the chemical Abstracts Service, provides the names and formulas of ring and cage systems that have been published in *CA*. The ring systems are listed under a system essentially the same as that used for the *CA* index of ring systems (sec. Appendix A.B.i, A.B.ii). Each entry gives the *CA* index name and Registry Number for that ring system. In many cases a *CA* reference is also given. There is a separate Formula Index (for the parent ring systems) and a *Ring Name Index*. Cumulative supplements are issued twice a year. The *Ring Systems Handbook* supersedes earlier publications called *The Parent Compound Handbook* and *The Ring Index*.
 12. The Sadtler Research Laboratories published large collections of IR, UV, NMR, and other spectra, in loose-leaf form. Indexes are available.
 13. Infrared, UV, NMR, Raman, and mass spectral data, as well as melting-point, boiling-point, solubility, density, and other data for >30,000 organic compounds are collected in the *CRC Handbook of Data on Organic Compounds*, 2nd ed., 9 vols., CRC Press, Boca Raton, FL, 1988, edited by R.C. Weast and J.G. Grasselli. It differs from the Sadtler collection in that the data are given in tabular form (lists of peaks)

rather than reproduction of the actual spectra, but this book has the advantage that all the spectral and physical data for a given compound appear at one place. References are given to the Sadtler and other collections of spectra. Volumes 7–9 contain indexes of spectral peaks for IR, UV, NMR, ^{13}C NMR, mass, and Raman spectra, as well as indexes of other names, molecular formulas, molecular weights, and physical constants. Annual updates began appearing in 1990 (the first one is called volume 10).

14. The *Aldrich Library of Infrared Spectra*, 3rd ed., Aldrich Chemical Company, Milwaukee, WI, **1981**, by Pouchert contains >12,000 IR spectra so arranged that the user could readily see the change that takes place in a given spectrum when a slight change is made in the structure of a molecule. The same company also publishes the *Aldrich Library of FT-IR Spectra* and the *Aldrich Library of NMR Spectra*, both also by C. Pouchert. A similar volume, which has IR and Raman spectra of ~1000 compounds, is *Raman/Infrared Atlas of Organic Compounds*, 2nd ed., VCH, New York, **1989**, by B. Schrader.
15. An extensive list of visible and uv peaks is given in *Organic Electronic Spectral Data*, Wiley, New York. Twenty-six volumes have appeared so far, covering the literature through 1984.
16. A collection of 500 ^{13}C NMR spectra is found in L.F. Johnson and W.C. Jankowski, *Carbon-13 NMR Spectra*, Wiley, New York, **1972**.

C. REVIEWS

A review article is an intensive survey of a rather narrow field. For example, the titles of some recent reviews are “Metathesis of Alkanes and Related Reactions”²⁶, “Potassium Organo-trifluoroborates: New Perspectives in Organic Synthesis”²⁷, and “Asymmetric Addition of Allylic Nucleophiles to Imino Compounds”.²⁸ A good review article is of enormous value, because it is a thorough survey of all the work done in the field under discussion. Review articles are printed in review journals and in certain books. The most important review journals in organic chemistry (though most are not exclusively devoted to organic chemistry) are shown in Table A.3. Some of the journals listed in Table A.1, for example, *Chemical Reviews*, *Accounts of Chemical Research*, and *Synlett*, *Tetrahedron*, *Synthesis*, *Organic Preparations and Procedures International*, and *J. Organomet. Chem.* also publish occasional review articles. As with other journals, journals that contain reviews are available online.

There are several open-ended serial publications that are similar in content to the review journals but are published irregularly (seldom more often than once a year) and are hardbound. Some of these publish reviews in all fields of chemistry; some cover only organic chemistry; some specialize further. The coverage is indicated by the titles. Table A.4 shows some of the more important such publications, with CA abbreviations.

Another publication is the *Index of Reviews in Organic Chemistry*, compiled by Lewis, Chemical Society, London, a classified listing of review articles. The first volume, published in 1971, lists reviews from ~1960 (in some cases much earlier) to ~1970 in alphabetical

²⁶ Basset, J.-M.; Copret, C.; Soulivong, D.; Taoufik, M.; Cazat, J.T. *Acc. Chem. Res.* **2010**, 43, 323.

²⁷ Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, 108, 288.

²⁸ Ding, H.; Friestad, G.K. *Synthesis* **2005**, 2815.

TABLE A.3 Review Journals, with Year of Founding and Issues per Year

Journal	Issues
Accounts of Chemical Research (1968)	12
Aldrichimica Acta (1968)	4
Angewandte Chemie (1888)	12
and its English Translation: Angewandte Chemie, International Edition (1962)	12
Chemical Reviews (1924)	8
Chemical Society Reviews (1947) ^a	4
Heterocycles (1973)	12
Natural Product Reports (1984)	6
Organic Preparations and Procedures International (1969)	6
Soviet Scientific Reviews, Section B, Chemistry Reviews (1979) Irreg.	
Sulfur Reports (1980)	6
Synlett (1989)	12
Synthesis (1969)	12
Tetrahedron (1958)	52
Topics in Current Chemistry (1949) ^b	Irreg.
Uspekhi Khimii (1932)	12
and its English translation: Russian chemical Reviews (1960)	12

^aSee Ref. 29.^bSee Ref. 30.

TABLE A.4 Irregularly Published Serial Publications

Advances in Carbocation Chemistry
Advances in Carbohydrate Chemistry and Biochemistry
Advances in Catalysis
Advances in Cycloaddition
Advances in Free Radical Chemistry
Advances in Heterocyclic Chemistry
Advances in Metal-Organic Chemistry
Advances in Molecular Modeling
Advances in Organometallic Chemistry
Advances in Oxygenated Processes
Advances in Photochemistry
Advances in Physical Organic Chemistry
Advances in Protein Chemistry
Advances in Theoretically Interesting Molecules
Fluorine Chemistry Reviews
Fortschritte der Chemie Organischer Naturstoffe
Isotopes in Organic Chemistry
Molecular Structure and Energetics
Organic Photochemistry
Organometallic Reactions
Organic Reactions
Organic Synthesis: Theory and Applications

²⁹ Successor to *Quarterly Reviews* (abbreviated as *Q. Rev., Chem. Soc.*).³⁰ Formerly called *Fortschritte der Chemischen Forschung*.

Progress in Heterocyclic Chemistry
Progress in Macrocyclic Chemistry
Progress in Physical Organic Chemistry
Reactive Intermediates (Plenum)
Reactive Intermediates (Wiley)
Survey of Progress in Chemistry
Topics in Physical Organometallic Chemistry
Topics in Stereochemistry

order of topic. Thus four reviews are listed under “Knoevenagel condensation”, five under “Inclusion compounds”, and one under “Vinyl ketones”. There is no index. A second volume (1977) covers the literature to 1976. Annual or biannual supplements appeared from 1979 until the publication was terminated in 1985. Classified lists of review articles on organometallic chemistry are found in articles by Smith and Walton³¹ and by Bruce.³² A similar list for heterocyclic chemistry is found in articles by A. Katritzky and others.³³ See also the discussion of the *Index of Scientific Reviews* in Appendix A.D.iv.

C.i. Annual Reviews

The review articles discussed in Table A.3 are each devoted to a narrow topic covering the work done in that area over a period of years. An annual review is a publication that covers a broad area but limits the period covered, usually to 1 or 2 years.

1. The oldest annual review publication still publishing is *Annual Reports on the Progress of Chemistry*, published by the Royal Society of Chemistry (formerly the chemical Society), which began in 1905 and which covers the whole field of chemistry. Since 1967 it has been divided into sections. Organic chemistry is found in Section B.
2. Because the number of papers in chemistry has become so large, the Royal Society of Chemistry publishes annual-review-type volumes of smaller scope, called *Specialist Periodical Reports*. Among those of interest to organic chemists are *Carbohydrate Chemistry* (Vol. 22 covers 1988); *Photochemistry* (Vol. 21 covers 1988–1989); and *General and Synthetic Methods* (Vol. 12 covers 1987).
3. *Organic Reaction Mechanisms*, published by Wiley, New York, is an annual survey that covers the latest developments in the field of mechanisms. The first volume, covering 1965, appeared in 1966.
4. There are two annual reviews devoted to progress in organic synthesis. Theilheimer, *Synthetic Methods of Organic Chemistry*, S. Karger, Verlag, Basel, is an annual compilation, beginning in 1946, of new methods for the synthesis of organic compounds, arranged according to a system based on bond closing and bond breaking reactions. Equations, brief procedures, yields, and literature references are given. Volume 44 was issued in 1990. Volumes 3 and 4 are available only in

³¹ Smith, J.D.; Walton, D.R.M. *Adv. Organomet. Chem.* **1975**, *13*, 453.

³² Bruce, M.I. *Adv. Organomet. Chem.* **1972**, *10*, 273, **1973**, *11*, 447, **1974**, *12*, 380.

³³ Belen'kii, L.I. *Adv. Heterocycl. Chem.* **1988**, *44*, 269; Katritzky, A.R.; Jones, P.M. *Adv. Heterocycl. Chem.* **1979**, *25*, 303; Katritzky, A.R.; Weeds, S.M. *Adv. Heterocycl. Chem.* **1966**, *7*, 225.

German, but all the rest are in English. There is an index to each volume. Cumulative indexes appear in every fifth volume. Beginning with vol. 8, each volume includes a short summary of trends in synthetic organic chemistry. A more recent series is *Annual Reports in Organic Synthesis*, Academic Press, New York, which has covered the literature of each year since 1970. Equations are listed with yields and references according to a fairly simple system.

C.ii. Awareness Services

Besides the annual reviews and the title and abstract services previously mentioned, there exist a number of publications designed to keep readers aware of new developments in organic chemistry or in specific areas of it.

1. *Chemtracts: Organic Chemistry* is a bimonthly Periodical, begun in 1988, that prints abstracts of certain recently published papers (those that the editors consider most important), with commentaries on these papers by distinguished organic chemists. Important current research in bioorganic, organometallic, synthesis, physical-organic and theoretical chemistry, and pharmaceutical/medicinal chemistry is covered in each issue, giving readers updates on the newest trends and developments in organic chemistry by summarizing and commenting on current and past research.
2. The Institute for Scientific Information (ISI), besides publishing *Current Contents* (sec. Appendix A.B.i) and the *Science Citation Index* (sec. Appendix A.B.i), also publishes *Index Chemicus* (formerly called *Current Abstracts of Chemistry and Index Chemicus*). This publication, begun in 1960 and appearing weekly, is devoted to printing structural formulas of all new compounds appearing in >100 journals, along with equations to show how they were synthesized and an author's summary of the work. Each issue contains five indexes: author, journal, biological activity, labeled compounds, and intermediates that were not isolated. These indexes are cumulated annually.
3. Theilheimer and the *Annual Reports on Organic Synthesis*, mentioned in the previous section, list new synthetic methods once a year. There are several publications that do this monthly. Among these are *Current Chemical Reactions* (begun in 1979 and published by ISI), *Journal of Synthetic Methods* (begun in 1975 and published by Derwent publications), and *Methods in Organic Synthesis*, begun in 1984 and published by the Royal Society of Chemistry. *Methods in Organic Synthesis* also lists books and review articles pertaining to organic synthesis.
4. *Natural Product Updates*, a monthly publication begun in 1987 and published by the Royal Society of Chemistry, lists recent results in the chemistry of natural products, along with structural formulas. It covers new compounds, structure determinations, new properties and total syntheses, among other topics.

C.iii. General Treatises

There are a number of large-scale multivolume treatises that cover the whole field of organic chemistry or large areas of it.

1. *Rodd's Chemistry of Carbon Compounds*, edited by S. Coffey, Elsevier, Amsterdam, is a treatise consisting of five main volumes, each of which contains several

parts. Publication began in 1964 and is not yet complete. The organization is not greatly different from most textbooks, but the coverage is much broader and deeper. Supplements to many of the volumes have appeared. An earlier edition, called *Chemistry of Carbon Compounds*, edited by E.H. Rodd, was published in 10 parts from 1951 to 1962.

2. Houben–Weyl's *Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, is a major treatise in German devoted to laboratory methods. The fourth edition, which was begun in 1952 and consists of 20 volumes, most of them in several parts, is edited by E. Muller. The series includes supplementary volumes. The first four volumes contain general laboratory methods, analytical methods, physical methods, and general chemical methods. The later volumes are devoted to the synthesis of specific types of compounds (hydrocarbons, oxygen compounds, nitrogen compounds, etc.). Beginning in 1990 parts of the series have appeared in English.
3. *Comprehensive Organic Chemistry*, Pergamon, Elmsford, NY, **1979**, is a six-volume treatise on the synthesis and reactions of organic compounds. The first three volumes cover the various functional groups, Vol. 4, heterocyclic compounds, and Vol. 5, biological compounds (e.g., proteins, carbohydrates, and lipids). Probably the most useful volume is Vol. 6, which contains formula, subject, and author indexes, as well as indexes of reactions and reagents. The last two of these not only refer to pages within the treatise, but directly give references to review articles and original papers. Several similar treatises, including the nine-volume *Comprehensive Organometallic Chemistry* (1982), the eight-volume *Comprehensive Heterocyclic Chemistry* (1984), and the six-volume *Comprehensive Medicinal Chemistry* (1989) are also published by Pergamon. The indexes to these works also include references.
4. A major treatise devoted to experimental methods of chemistry is *Techniques of Chemistry*, edited first by A. Weissberger and then by J.K.M. Saunders, Wiley, New York. This publication, which began in 1970, so far consists of 21 volumes, most of them in several parts, covering such topics as electrochemical and spectral methods, kinetic methods, photochromism, and organic solvents. *Techniques of Chemistry* is a successor to an earlier series, called *Techniques of Organic Chemistry*, which appeared in 14 volumes, some of them in more than one edition, from 1945 to 1969.
5. *Comprehensive Chemical Kinetics*, edited by C.H. Bamford and C.F.H. Tipper, **1969**, Elsevier, Amsterdam, is a multivolume treatise covering the area of reaction kinetics. Six of these volumes (not all published at the time of writing) deal with the kinetics and mechanisms of organic reactions in a thorough and comprehensive manner.
6. Three multivolume treatises that cover specific areas are R.C. Elderfield, *Heterocyclic Compounds*, Wiley, New York, **1950**; R.H.F. Manske and H.L. Holmes, *The Alkaloids*, Academic Press, New York, **1950**; and J.L. Simonson, L.N. Owen, D.H. R. Barton, and W.C.J. Ross, *The Terpenes*, Cambridge University Press, London, 1947–1957.
7. *Encyclopedia of Reagents for Organic Synthesis*, edited by L. Paquette, Wiley, New York, was published in 1995. It is an 8 volume, alphabetic listing of reagents used in organic chemistry with descriptions of the preparation, use and chemistry, with references. Each reagent was researched by organic chemists active in research, who contributed to the total publication.

This latter work is available online as **eEROS**. The *Encyclopedia of Reagents for Organic Synthesis*, e-EROS, provides updated information on ~3800 reagents with a database of close to 50,000 reactions. Each reagent entry includes properties (e.g., physical data, solubility, form supplied in, purification, and preparative methods); examples of use in reactions; and literature references. Search options include: name, CAS number, structure and reaction.

8. *Comprehensive Organic Synthesis*, edited by B.M. Trost and I. Fleming, Pergamon, was published in 1991. It is a 9 volume compilation.
9. *Comprehensive Organic Functional Group Transformations*, edited by A.R. Katritzky, O. Meth-Cohn, and C.W. Rees, Pergamon, was published in 1995. It is a 7 volume compilation.

C.iv. Monographs and Treatises on Specific Areas

There are many books devoted to organic chemistry that provide a thorough coverage of a specific area. Many of these are essentially very long review articles, differing from ordinary review articles only in size and scope. Some are comprised of a series of articles, edited by an organic chemist for a specific area of research. Some of the books are by a single author, and others have chapters by different authors. All, however, are carefully planned to cover a specific area. Many of these books have been referred to in footnotes in appropriate places in this book. There have been several series of monographs, one of which is worth special mention: *The Chemistry of Functional Groups*, under the general editorship of Z. Rappoport (S. Patai was the original editor), published by Wiley, New York. Each volume deals with the preparation, reactions, and physical and chemical properties of compounds containing a given functional group. There are >130 volumes in the series, covering functional groups have appeared so far, including books on alkenes, cyano compounds, amines, carboxylic acids and esters, quinones, and so far. Since 2003, the series has appeared both in print and online.

C.v. Textbooks

There are many excellent textbooks in the field of organic chemistry. We restrict ourselves to listing only a few of those published, mostly since 1985. Some of these are first-year texts and some are advanced (advanced texts generally give references; first-year texts do not, though they may give general bibliographies, suggestions for further reading, etc.); some cover the whole field, and others cover reactions, structure, and/or mechanism only. All the books listed here are not only good textbooks and the advanced books are valuable reference books for graduate students and practicing chemists.

Bruckner, *Advanced Organic Chemistry: Reaction Mechanisms*, Academic Press, **2001**.

Bruice, *Organic Chemistry*, 6th ed., Prentice-Hall, NJ, **2010**.

Carey, *Organic Chemistry*, 8th ed., McGraw-Hill, New York, **2010**.

Carey and Sundberg, *Advanced Organic Chemistry: Structure and Mechanisms (Part A)*, 4th ed., Springer, **2004**.

Carey and Sundberg, *Advanced Organic Chemistry: Structure and Mechanisms (Part B)*, 4th ed., Springer, **2001**.

- Carruthers and Coldham, *Some Modern Methods of Organic Synthesis*, 4th ed., Cambridge University Press, Cambridge, **2004**.
- Ege, *Organic Chemistry: Structure and Reactivity*, 5th ed., D.C. Houghton Mifflin, Boston **2003**.
- Fox and Whitesell, *Organic Chemistry*, 3rd ed, Jones and Bartlett, Sudbury, MA, **2004**.
- Grossman *The Art of Writing Reasonable Organic Reaction Mechanisms*, 2nd ed, Springer, **2005**.
- House, *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, New York, **1972**.
- Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, **1969**.
- Isaacs, *Physical Organic Chemistry*, Wiley, New York, **1987**.
- Jones, *Organic Chemistry*, 4th ed. W.W. Norton, New York, **2009**.
- Klein, *Organic Chemistry*, Wiley, New York, **2011**.
- Loudon, *Organic Chemistry*, 5th ed., Oxford University Press, **2009**.
- Lowry and Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, New York, **1987**.
- McMurry, *Organic Chemistry*, 8th ed., Brooks/Cole, Monterey CA, **2012**.
- Maskill, *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford, **1985**.
- Mundy, Ellerd and Favaloro, Jr. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed, Wiley, **2005**.
- Ritchie, *Physical Organic Chemistry*, 2nd ed., Marcel Dekker, New York, **1989**.
- Solomons and Fryhle, *Organic Chemistry*, 10th ed., Wiley, New York, **2011**.
- Smith, *Organic Synthesis*, 3rd ed. Wavefunction Inc. and Elsevier, New York/London, **2010**.
- Smith, *Organic Chemistry: An Acid–Base Approach*, CRC Press, Boca Raton, FL, **2011**.
- Streitwieser, Heathcock and Kosower, *Introductory Organic Chemistry*, 4th ed., Prentice Hall, **1998**.
- Sykes, *A Guidebook to Mechanism in Organic Chemistry*, 6th ed., Longmans Scientific and Technical, Essex, **1986**.
- Vollhardt and Schore, *Organic Chemistry*, 6th ed., W.H. Freeman, New York, **2010**.
- Wade, *Organic Chemistry*, 7th ed., Prentice-Hall, Upper Saddle River, NJ, **2009**.

C.vi. Other Books

In this section, we mention several books that do not fit conveniently into the previous categories. All but the last have to do with laboratory synthesis.

1. *Organic Syntheses*, published by Wiley, New York is a collection of procedures for the preparation of specific compounds. *Organic Syntheses* is currently available online.³⁴ The thin annual volumes have appeared each year since 1921. For the first

³⁴ Available at <http://www.orgsyn.org/>

59 volumes, the procedures for each 10- (or 9-) year period are collected in cumulative volumes. Beginning with Vol. 60, the cumulative volumes cover 5-year periods. The cumulative volumes published so far are

Annual Volumes	Collective Volumes
1–9	I
10–19	II
20–29	III
30–39	IV
40–49	V
50–59	VI
60–64	VII
65–69	VIII
70–74	IX
75–80	X
81–84	XI

The advantage of the procedures in *Organic Syntheses*, compared with those found in original journals, is that these procedures are *tested*. Each preparation is carried out first by its author and then by a member of the *Organic Syntheses* editorial board, and only if the yield is essentially duplicated is the procedure published. While it is possible to repeat most procedures given in journals, this is not always the case. All *Organic Syntheses* preparations are noted in Beilstein and in *CA*. In order to locate a given reaction in *Organic Syntheses*, the reader may use the OS references given in the present volume (through OS 69); the indexes in *Organic Syntheses* itself; R. Shriner and R. Shriner, “*Organic Syntheses* Collective Volumes **I, II, III, IV, V** Cumulative Indices”, Wiley, New York, **1976**, or S. Sugawara and S. Nakai, “Reaction Index of *Organic Syntheses*”, Wiley, New York, **1967** (through OS 45). Another book classifies virtually all the reactions in *Organic Syntheses* (collective vols. **I–VII** and annual vols. 65–68) into 11 categories: annulation, rearrangement, oxidation, reduction, addition, elimination, substitution, C—C bond formation, cleavage, protection/deprotection, and miscellaneous. This is *Organic Syntheses: Reaction Guide*, by D. Liotta and M. Volmer, published by Wiley, New York, in **1991**. Some of the categories are subdivided further, and some reactions are listed in more than one category. What is given under each entry are the equation, the volume, and page reference to *Organic Syntheses*.

2. Volume 1 of *Reagents for Organic Synthesis*, by L. Fieser and M. Fieser, Wiley, New York, **1967**, is a 1457–page volume that discusses, in separate sections, some 1120 reagents and catalysts. It tells how each reagent is used in organic synthesis (with references) and, for each, tells which companies sell it, or how to prepare it, or both. The listing is alphabetical. There are now a total of 25 volumes published as of 2009, which continue the format of Vol. 1 and add more recent material. A cumulative index for Vols. 1–12, by J. Smith and M. Fieser, was published in **1990**. A cumulative index for volumes 1–22 was published in **2005**, by M.B. Smith. The series included volumes 1–18 with Mary Fieser.

After the death of Mary Fieser, the series was resumed by T.-L. Ho and now includes volumes 19–25.

3. *Comprehensive Organic Transformations*, 2nd ed. by R.C. Larock, Wiley-VCH, New York, **1999**, has been frequently referred to in footnotes in Part 2 of this book. This compendium is devoted to listings of methods for the conversion of one functional group into another, and covers the literature through 1987. It is divided into nine sections covering the preparation of alkanes and arenes, alkenes, alkynes, halides, amines, ethers, alcohols and phenols, aldehydes and ketones, and nitriles, carboxylic acids and derivatives. Within each section are given many methods for synthesizing the given type of compound, arranged in a logical system. A schematic equation is given for each method, and then a list of references (without author names, to save space) for locating examples of the use of that method. When different reagents are used for the same functional group transformation, the particular reagent is shown for each reference. There is a 164 page index of group transformations. The 2nd edition has only recently been published and is *not* referenced in this edition, and a CD-ROM version is now available.
4. *Survey of Organic Synthesis*, by C.A. Buehler and D.E. Pearson, Wiley, New York, 2 vols., **1970**, **1977**, discusses hundreds of reactions used to prepare the principal types of organic compounds. The arrangement is by chapters, each covering a functional group (ketones, acyl halides, amines, etc.). Each reaction is thoroughly discussed and brief synthetic procedures are given. There are many references.
5. A similar publication is S. Sandler and W. Karo, *Organic Functional Group Preparations*, 2nd ed., 3 vols., Academic Press, New York, 1983–1989. This publication covers more functional groups than Buehler and Pearson.
6. *Compendium of Organic Synthetic Methods*, Wiley, New York, contains equations describing the preparation of thousands of monofunctional and difunctional compounds with references. Twelve volumes have been published so far (Vols. 1–2, edited by I.T. Harrison and S. Harrison; Vol. 3, edited by L. Hegedus and L.G. Wade, Jr.; Vol. 4–5, edited by L.G. Wade, Jr.; Vols. 6–12, edited by M.B. Smith). Volume 13 will appear in 2014.
7. *The Vocabulary of Organic Chemistry*, by M. Orchin, F. Kaplan, R.S. Macomber, R. M. Wilson, and H. Zimmer, Wiley, New York, **1980**, presents definitions of >1000 terms used in many branches of organic chemistry, including stereochemistry, thermodynamics, wave mechanics, natural products, and fossil fuels. There are also lists of classes of organic compounds, types of mechanism, and name reactions (with mechanisms). The arrangement is topical rather than alphabetical, but there is a good index. *Compendium of Chemical Terminology*, by V. Gold, K.L. Loening, A. D. McNaught, and P. Sehmi (the “Gold book”), published by Blackwell Scientific Publications, Oxford, in **1987**, is an official IUPAC list of definitions of terms in several areas of chemistry, including organic.

D. LITERATURE SEARCHING

Until recently, searching the chemical literature meant looking only at printed materials (some of which might be on microfilm or microfiche). Now, however, virtually all of the literature can be searched online. Whether the search is online or uses only the printed material, there are two basic types of search, (1) searches for information about one or more specific compounds or classes of compounds, and (2)

other types of searches. First, we will discuss searches using only printed materials, and then online searching.³⁵

D.i. Literature Searching Using Printed Materials

Searching for Specific Compounds. Organic chemists often need to know if a compound has ever been prepared and if so, how, and/or they may be seeking a melting point, an ir spectrum, or some other property. Someone who wants all the information that has ever been published on any compound begins by consulting the formula indexes in Beilstein (sec. Appendix A.B.iii). At this time there are two ways to do this. (1) The formula index to the second supplement (Vol. 29, see Appendix A.B.iii) will quickly show whether the compound is mentioned in the literature through 1929. If it is there, the searcher turns to the pages indicated, where all methods used to prepare the compound are given, as well as all physical properties, with references. Use of the page heading method described in Appendix A.B.iii will then show the locations, if any, in the third and later supplements. (2) If one has an idea what volume of Beilstein the compound is in (and the tables of contents at the front of the volumes may help), one may search the cumulative index for that volume. If not sure, one may consult several indexes. One of these two procedures will locate all compounds mentioned in the literature through 1959. If the compound is heterocyclic, it may be in the fifth supplement. If it is in Vols. 17–19 (or in a later volume whose index has been published), the corresponding indexes may be consulted. If not, the page heading method will find it, if it was reported before 1960.³⁶ There is a way by which all of the above can be avoided. At this point, the investigator will know (1) all information published through 1959 or 1979,³⁵ or (2) that the compound is not mentioned in the literature through 1959 or 1979.³⁷ In some cases, scrutiny of Beilstein will be sufficient, perhaps if only a boiling point or a refractive index is required. In other cases, especially where specific laboratory directions are needed, the investigator will have to turn to the original papers.

To carry the search to more recent articles, the chemist turned to the collective formula indexes of *Chemical Abstracts* and such later collective indexes as have appeared; and the semiannual indexes thereafter. *However, such searches now would use SciFinder.*

If the compound has not been reported, the investigator will know that. Indeed, this is perhaps the most important consideration when considering a new area of research. It should be pointed out that for common compounds (benzene, ether, acetone, etc.), trivial mentions in the literature are not indexed (so they will not be found by this procedure), only significant ones. Thus, if acetone is converted to another compound, an index entry will be found, but not if it is used as a solvent or an eluant in a common procedure.

³⁵ For a monograph that covers both online searching and searching using printed materials, see Wiggins, G. *Chemical Information Sources*, McGraw-Hill, NY, **1991**.

³⁶ Compounds newly reported in the fifth supplement that are in a volume whose index has not yet been published will not be found by this procedure. To find them in Beilstein, it is necessary to know something about the system, but they may also be found by consulting *SciFinder*.

³⁷ For those heterocyclic compounds that would naturally belong to a volume for which the fifth supplement has been published.

While online searching is extraordinarily powerful, it should be pointed out that there are two problems with computer searches. First of all, far too many “hits” may be returned. For example, a 2011 research topic search (see Appendix A.D.iii) of the topic “macrolactones from hydroxy acids” gave the results:

Research Topic Candidates	References
159 references were found containing the two concepts “macrolactones” and “hydroxy acids” closely associated with one another	159
474 references were found where the two concepts “macrolactones” and “hydroxy acids” were present anywhere in the reference	474
35157 references were found containing the concept “macrolactones”	35157
193323 references were found containing the concept “hydroxy acids”	193323

Clearly, only examining the first few hundred references is practical. The search can, and must be refined. Depending on the scope of the search, this fact can be a limitation. The second problem relates to the search words used (the keywords). If they are too broad, little useful information is returned. If the keywords are too narrow in scope, many useful references may be missed. The point of these two cautions is to take care in choosing keywords. On the other hand, using many related keywords and doing multiple searches is very easy using SciFinder, and is probably a good strategy.

Often, all the information one needs about a compound will be found in one of the handbooks (Appendix A.C.i), in the *Dictionary of Organic Compounds* (Appendix A.C.i), or in one of the other compendia listed in this chapter, most of which give references to the original literature.

Other Searches. There is no definite procedure for making other literature searches using only printed materials. Any chemist who wishes to learn all that is known about the mechanism of the reaction between aldehydes and HCN, or which compounds of the general formula Ar_3CR have been prepared, or which are the best catalysts for *Friedel–Crafts acylation* of naphthalene derivatives with anhydrides, or where the group $-\text{C}(\text{NH}_2)=\text{N}-$ absorbs in the IR, is dependent on ingenuity and knowledge of the literature. If a specific piece of information is needed, it may be possible to find it in one of the compendia mentioned previously. If the topic is more general, the best procedure is often to begin by consulting one or more monographs, treatises, or textbooks that will give general background information and often provide references to review articles and original papers. In many cases this is sufficient, but when a complete search is required, it is necessary to consult the *CA* subject and/or chemical substance indexes, and also *SciFinder*, where the ingenuity of the investigator is most required, for now it must be decided which words to look under. This statement relates to the keyword used for a computer search, as indicated above. If one is interested in the mechanism of the reaction between aldehydes and HCN, one might look under “aldehydes”, or “hydrogen cyanide”, or even under “acetaldehyde” or “benzaldehyde”, and so on, but then the search is likely to prove long. A better choice in this case would be “cyanohydrin”, since these are the normal products and references there would be fewer. It would be a waste of time to look under “mechanism”. In any case, many of the abstracts would not prove helpful. If it is necessary to search before 1907

(and even before 1920, since *CA* was not very complete from 1907 to ~1920), recourse may be made to *Chemisches Zentralblatt* and the abstracts in the *Journal of the Chemical Society*.

D.ii. Literature Searching Online²⁰

Most of the *Chemical Abstracts* literature can be accessed online via *CAS*, using *SciFinder* in Appendix A.D.iii, the largest and most current database of chemical substance information in the world. *CAS* is located in Columbus, Ohio and is a division of the American Chemical Society. *CAS* can be contacted at Chemical Abstracts Service, 2540 Olentangy River Road, P.O. Box 3012, Columbus, Ohio 43210 (e-mail: help@cas.org). *CAS* is a team of scientists who provide digital information environment for scientific research and discovery. *CAS* provides pathways to published research in the world's journal and patent literature back to the beginning of the 20th century. Since 1907, *CAS* has indexed and summarized chemistry-related articles from >40,000 scientific journals, in addition to patents, conference proceedings and other documents pertinent to chemistry, life sciences, and many other fields. Through the printed *CA* (*Chemical Abstracts*), *CA* on CD, *STN*, the *CAS* files distributed through licensed vendors, the *SciFinder* and *SciFinder Scholar* desktop research tools, and the *STN Easy* or *STN* on the Web services, data produced by *CAS* is accessible to virtually any scientific researcher worldwide in industry, governmental research institutions, and academia.

Substance identification is a special strength of *CAS*. It is widely known as the *CAS Registry*, the largest substance identification system in existence. When a chemical substance, newly encountered in the literature, is processed by *CAS*, its molecular structure diagram, systematic chemical name, molecular formula, and other identifying information are added to the Registry and it is assigned a unique *CAS Registry* Number.

The *CAS REGISTRY* mostly covers substances identified from the scientific literature from 1957 to the present with some classes (fluorine- and silicon-containing compounds) going back to the early 1900s. An important piece of information that assists in such a search is the *CAS* registry number. Each substance in *REGISTRY* is identified by a unique numeric identifier called a *CAS Registry Number*.³⁸ "The *CAS Registry* number is a unique number assigned to a chemical by the Chemical Abstracts Service."³⁹ A fairly large collection of *CAS* numbers, with links to safety data for many chemicals, can be found at the listing of chemicals by *CAS* number at the Safety Home Page of the Physical and Theoretical Chemistry Laboratory at Oxford University".⁴⁰ The *CAS Registry Number* is a unique numeric identifier that designates only one substance, has no chemical significance, and is a link to finding information about a specific chemical substance. A *CAS Registry Number* includes up to 9 digits that are separated into 3 groups by hyphens. The first part of the number, starting from the left, has up to 6 digits; the second part has 2 digits. The final part consists of a single check digit.⁴¹

Online searching means using a computer terminal to search a *database*. Although databases in chemistry are available from several organizations, *STN International* (The

³⁸ Available at <http://www.cas.org/EO/regsys.html>

³⁹ Available at <http://www.cas.org/>

⁴⁰ Available at <http://ptcl.chem.ox.ac.uk/MSDS/glossary/casnumber.html>

⁴¹ Available at <http://www.cas.org/EO/checkdig.html>

Scientific & Technical Information Network) is important because it is comprehensive and available in many countries. STN has dozens of databases, including many that cover chemistry and chemical engineering. To access these databases a chemistry department, a library, or an individual subscribes to STN (for a nominal fee), and receives code numbers that will permit access to the system, usually via a desktop computer.

D.iii. SciFinder—the CAS database⁴²

Tutorials are available to help use Sci-Finder.⁴³ SciFinder can search a research topic⁴⁴ or a compound can be searched by structure⁴⁵ The search engine is known as STN Express with Discover!⁴⁶ and can easily and efficiently search >200 scientific and technical databases online through STN[®].⁴⁷ The Analysis Edition of STN Express with Discover! allows one to search, analyze, visualize, and discover sci-tech information by the ability to create a table for substance analysis that identifies the common substructure for an answer set of structurally related substances: Group related author/inventor names and company names for better analysis and visualization results; Analyze and tabulate data from single- or multi-file search results, and create a data table and 3D chart; Save an answer set from databases (e.g., CAPLUS, PCTFULL, and USPATFULL) with the Save for STN AnaVist Wizard, and then import and open it in STN[®] AnaVistTM; Create an interactive spreadsheet from all or only hit CAS Registry Numbers and their corresponding CAS Roles through the CAS Registry Number[®]; Upload lengthy genetic sequences automatically for searching in DGENE and PCTGEN via the Upload Query Wizard. STN Express was developed in collaboration with Hampden Data Services.

To illustrate how STN is used, an online tutorial is available.⁴⁸ A few online windows from a *SciFinder* search are provided to illustrate how searches can be done. This presentation is by no means complete or intended as an alternative to the actual tutorial. Indeed, one could *not* use *SciFinder* properly after simply reading this discussion. The intent is to illustrate some features that are available and to present an overview of the use of this important tool.

Using *SciFinder*[®], a search can be done in one of several different ways. Searches can be done by research topic, by substances, or by reactions. The latter two searches use drawing tools that are part of *SciFinder*. An example is shown of a search done by research topic:⁴⁹ The example shown in Fig. A.3. shows a search for intramolecular hydroamination of aminoalkenes. To begin, click Explore by research topic and enter the appropriate information.

It is possible to use filters (see Fig. A.1) in order to refine the search by year, document type (journal, patent, review, etc.), author or company. A window is returned that contain references categorized by their relationship to the search phrase, as shown in Fig. A.2. One simply checks those reference lists that appear closest to those of interest.

⁴² Available at <http://www.cas.org/>

⁴³ Available at <http://www.cas.org/SCIFINDER/SCHOLAR/interact/>

⁴⁴ Available at <http://www.cas.org/SCIFINDER/SCHOLAR/page2a.html>

⁴⁵ Available at <http://www.cas.org/SCIFINDER/SCHOLAR/scholstruc.html>

⁴⁶ Available at <http://www.cas.org/ONLINE/STN/discover.html>

⁴⁷ Available at <http://www.cas.org/stn.html>

⁴⁸ Available at <http://www.cas.org/ONLINE/STN/expressmac.pdf>

⁴⁹ Available at <http://www.cas.org/SCIFINDER/topic.html>

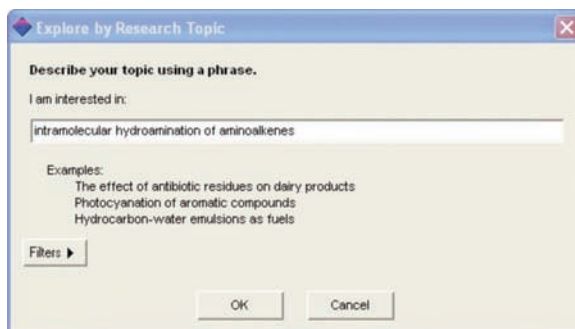


FIG. A.1. Explore by research topic.

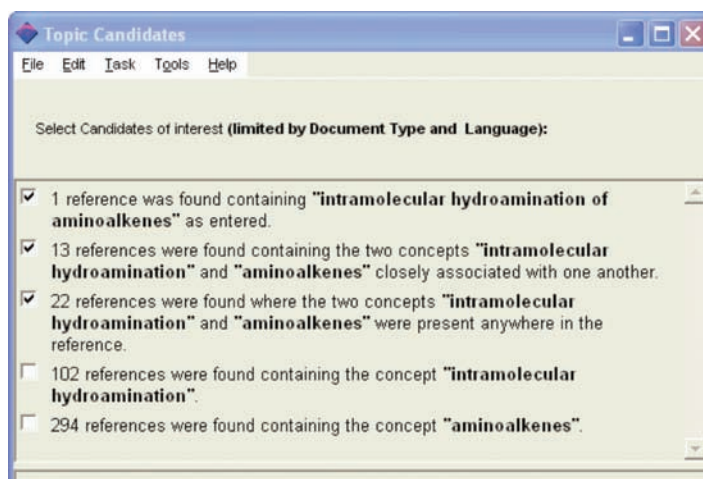


FIG. A.2. Selection of candidates of interest for search by research topic.

After clicking on “get references,” a screen is returned (Fig. A.3) that has the original references, as shown in the window. One is given the option of refining this list further, and for each reference, most browsers allow viewing the abstract or the full references as an HTML or a PDF file. However, your library must have paid the appropriate fees so the journal and volumes of interest are available online. Otherwise, interlibrary loan or direct ordering of the article may be necessary.

Other examples of typical searches allowed by SciFinder include search by author's name,⁵⁰ as with the example of Professor K. Barry Sharpless shown in Fig. A.4. Search by structure is also possible,⁵¹ such as the example shown in Fig. A.5, using SciFinder drawing tools. Once a structure is drawn, SciFinder searches to find matches based on that structure. The drawing tools can be used to show a reaction, and reaction information is returned, as shown in Fig. A.6. Ultimately, journal article and/or patents are returned that provide direct access to the literature of interest.

⁵⁰ Available at <http://www.cas.org/SCIFINDER/author.html>

⁵¹ Available at <http://www.cas.org/SCIFINDER/structure.html>

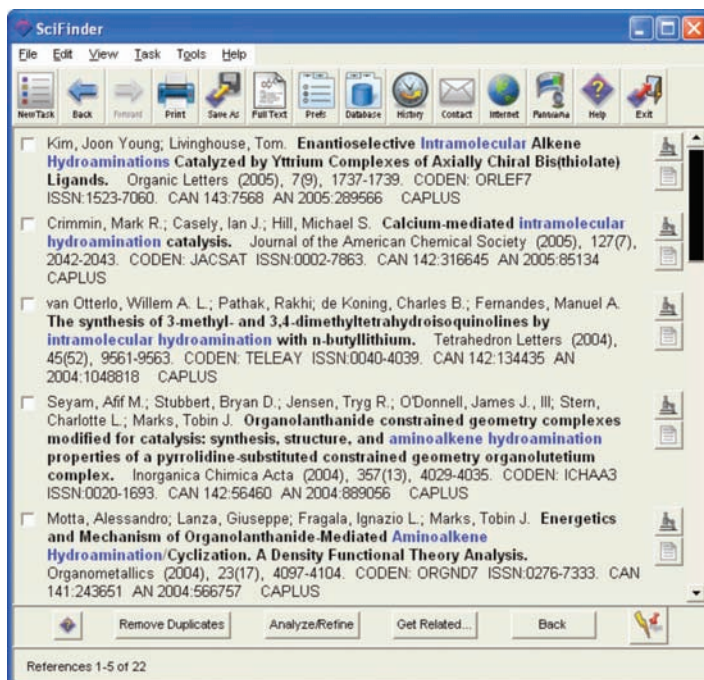


FIG. A.3. Original literature references returned for search by research topic.

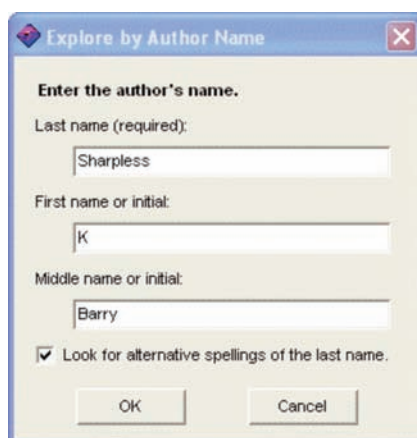


FIG. A.4. Screen shot for beginning a search by author.

D.iv. Science Citation Index

As seen in the SciFinder search tutorials, it is possible to track papers that have cited a particular article or author. A publication that can greatly facilitate literature searching is *Science Citation Index*(SCI), begun in 1961. This publication, which is quite different from any other mentioned in this chapter, gives a list of all papers in a given year that have cited a

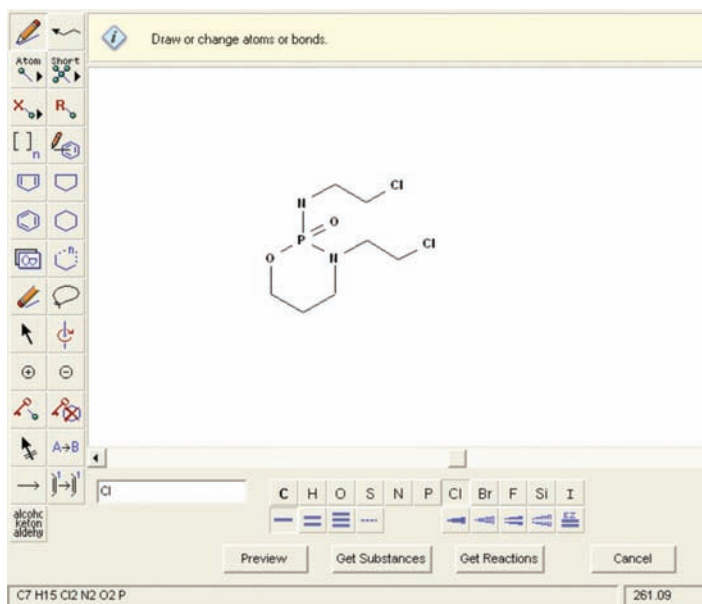


FIG. A.5. Screen shot for beginning a search by structure, using the drawing tools.

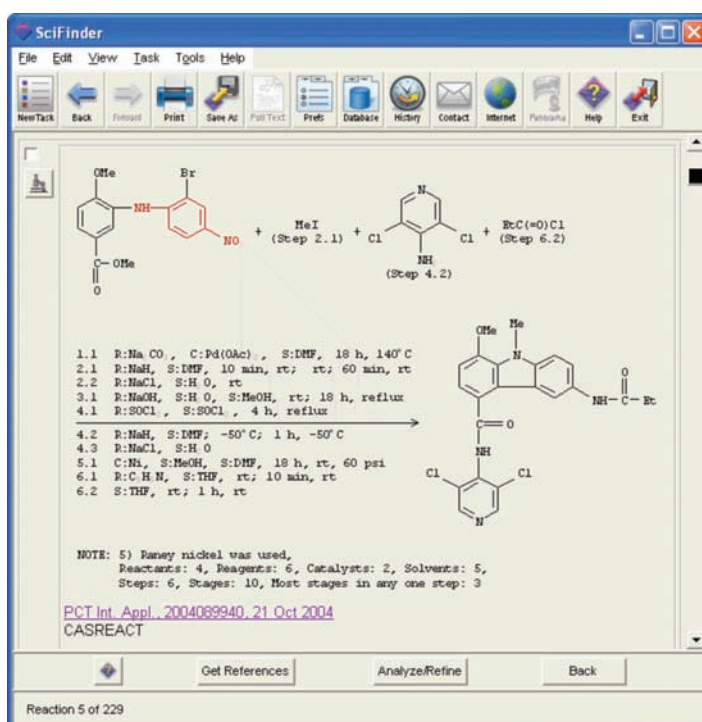


FIG. A.6. Screen shot of results for a search by reaction, using the drawing tools.

given paper, patent, or book. Its utility lies in the fact that it enables the user to search *forward* from a given paper or patent, rather than backward, as is usually the case. For example, suppose a chemist is familiar with a paper by W.P. Jencks and M. Gilchrist (*J. Am. Chem. Soc.*, **1968**, 90, 2622) entitled "Nonlinear Structure–Reactivity Correlations. The Reactivity of Nucleophilic Reagents toward Esters". The chemist is easily able to begin a search for earlier papers by using references supplied in this paper and can then go further backward with the aid of references in those papers, and so on. But for obvious reasons the paper itself supplies no way to locate *later* papers. *Science Citation Index* is designed to make up for this gap. The citation index of *SCI* lists all papers, patents, or books cited in a given year or 2-month period (by first author only) and then gives a list of papers that have done the citing. The index is published bimonthly and cumulated annually. For example, column 43901 of the 1989 citation index shows that the Jencks paper mentioned above was cited as a footnote in 16 papers published in 1989. It is reasonable to assume that most of the papers that cited the Jencks paper were on closely related subjects. For each of the 16 papers are listed the first author, journal abbreviation, volume and page numbers, and year. In a similar manner, if one consulted *SCI* for all the years from 1968 to date, one would have a complete list of papers that cited that paper. One could obviously broaden the search by then consulting *SCI* (from 1989 on) for papers that cited these 16 papers, and so on. Papers, patents, or books listed (e.g., in the 1989 *SCI*) may go back many years (e.g., papers published by A. Einstein in 1905 and 1906 are included). The only requirement is that a paper published in 1989 (or late 1988) has mentioned the earlier paper in a footnote. The arrangement of cited papers or books is alphabetical by cited first author and then by cited year. Cited patents are listed in a separate table, in order of patent number, though the inventor and country are also given.

SCI covers ~3200 journals in the physical and biological sciences, as well as in medicine, agriculture, and technology. In addition to the citation index, each bimonthly and annual *SCI* also includes three other indexes. One of these, called *Source Index*, is similar to the *CA* author index. It lists the titles, journal abbreviations, volume, issue, page numbers, and year of all papers published by a given author during that 2-month period or year. All authors are listed; not just first authors. The second, called the *Corporate Index*, lists all publications that have been published from a given institution during that period, by first author. Thus, the corporate index for 1989 lists 63 papers by 45 different first authors emanating from the Department of Chemistry of Rutgers University, New Brunswick, NJ. The main section of the corporate index (the Geographic Section) lists institutions by country or (for the US) by state. There is also an Organization Section, which lists the names of institutions alphabetically, and for each gives the location, so it can be found in the geographic section. The third index included in *SCI* is the *Permuterm*⁵²*Subject Index*. This index alphabetically lists every significant word in the titles of all papers published in that year or bimonthly period, paired with all other significant words in the same title. Thus, for example, a title with seven significant words appears at 42 separate places in the index. Each of the seven words appears six times as the main word, each time paired with a different word as the cword. The user is then led to the *Source Index*, where the full reference is given. *Science Citation Index* is also available online (though not through STN) and on CD-ROM discs. A version of *SCI* that is restricted to chemistry but also includes searchable abstracts, is available only in the CD-ROM format.

⁵² Registered trade name.

The publishers of *SCI* also produce another publication, called *Index to Scientific Reviews* that appears semiannually. This publication, which began in 1974, is very similar to *SCI*, but confines itself to listing citations to review articles. The citations come from ~2500 journals in the same general areas as are covered by *SCI*. The review articles cited appeared in ~215 review journals and books, as well as in those journals that publish occasional review articles. Like *SCI*, the *Index to Scientific Reviews* contains citation, source, corporate, and Permuterm indexes. It also contains a “Research Front Specialty Index”, which classifies reviews by subject.

D.v. How to Locate Journal Articles

Having obtained a reference from various sources or searches, one often needs to consult the original journal (patents are discussed in Appendix A.A.ii). The first step is to ascertain the full name of the journal, since it is the abbreviation that is generally given. Of course, everyone should be familiar with the abbreviations of the very important journals (*J. Org. Chem.*, *Chem. Ber.*, etc.), but references are often found to journals whose titles are not at all familiar (e.g., *K. Skogs Lantbruksakad. Tidskr.* or *Nauchn. Tr. Mosk. Lesotekh. Inst.*). In such cases, one consults the *Chemical Abstracts Service Source Index* (CASSI), 1989 edition, which contains the names of all the journals covered by *CA* from 1907 to 1989 (even those no longer published), with the most recent abbreviations in bold print. *Chemical Abstracts Service Source Index* also lists journals covered by *Chemisches Zentralblatt* and its predecessors from 1830 to 1969, and journals cited in Beilstein before 1907. The journals are listed in alphabetical order of the *abbreviations*, not of the titles. Journal title changes have not been infrequent, and *CASSI* also contains all former names, with cross-references to the current names. Quarterly supplements, cumulated annually, to *CASSI* have appeared since 1990 listing new journals and recent changes in journal titles. Note that while many publications use the *CA* abbreviations, not all do. Usage will vary from country to country, and even from journal to journal within a country. Furthermore, the *CA* abbreviations have changed from time to time. This latter point is particularly important when doing keywords searches. Using a structure search in SciFinder may get around this problem.

Once the complete title is known, the journal can easily be obtained if it is in the library customarily used by the chemist, or if that journal is available in electronic form. If not, one must use another library. The next step is to find out which libraries carry the journal and *CASSI* answers this question too, since it carries a list of some 360 libraries in the United States and other countries. *For each journal it tells which of these libraries carries it*, and furthermore, if the holdings are incomplete, which volumes of that journal are carried by each library. However, most libraries have an inter-library loan service that will provide access to such journal articles. It may be possible to visit the closest library personally and *CASSI* also includes lists of journal publishers, sales agents, and document depositories. Photocopies of most documents cited in *CA* can be obtained from chemical Abstracts Document Delivery Service, Customer Services, 2540 Olentangy River Road, Columbus OH, 43210, USA. Orders for documents can be placed by mail, telephone, Telex, fax, or online through STN or other services.

These latter comments are largely out of date given the online status of most journals. As mentioned above, PDF files of an article can be downloaded, or they can be read directly via the HTML file using any current browser. The reader is encouraged to contact the library person in your establishment that is responsible for chemical literature and to learn which online services are available through your local library.

D.vi. REAXYS®⁵³

Launched in 2009, “Reaxys was created through the merger of the existing *CrossFire* databases (Appendix A.B.iii.) into a single database with a new and intuitive user interface. Reaxys is a fully integrated content source providing in-depth coverage of inorganic, organic, and organometallic small molecule chemistries excerpted from appropriate journal and patent literature”.⁵⁴ Reaxys is available online with drawing tools that allows entry of a structure, or multiple structures as part of a reaction. Once the structure is drawn, Reaxys offers several options for the search:

Reaxys is a unique workflow solution for research chemists providing in depth coverage of inorganic, organic, and organometallic small molecule chemistries. The database consists of chemical compounds and related factual properties; chemical reaction and synthesis information; related bibliographic data, all of which have been excerpted from a carefully selected list of journals and patents: The latter is sourced from carefully selected patent classes and patent offices. This content is delivered through a web-based interface, designed for chemists, with powerful functionality that delivers the content in a flexible and intuitive way and helps a chemist with his/her major information tasks.

At the heart of Reaxys is the concept of “Chemistry as the organizing principle”. This means that the chemical compound or reaction is central to the way in which the data is organized in the database. This is fundamentally different from bibliographic databases in which a journal or patent record is at the center. This chemically focused approach allows all data from multiple sources to be combined together in one de duplicated record for a given compound or reaction (i.e., a single compound or reaction can have multiple source citations, whereas a bibliographic database will have one record per published item, so the same compound or reaction may be found in multiple records).

The value of Reaxys to organic chemists may be understood best in relation to the synthesis of compounds, which is at the core of organic chemistry. Devising new routes to unique and artificial scaffolds requires the skills of planning and executing multistep syntheses and having a toolbox of methodologies at one’s disposal. However, even the best conceived synthesis plans may require modifications, fine-tuning or entire rerouting, and chemists are faced with the daily challenge of choosing the right combination of reagents and building blocks for a whole set of problems: Which building blocks are optimal? In which sequence should they be assembled? Which reactions accomplish the task best? The Reaxys synthesis planning tool has been designed to make these choices as painless as possible using information and data from the journal and patent literature to investigate a number of possible alternative synthetic routes.

As an example, searching for papers that have reported direct arylation of indoles at the C-3 position. Construct a graphical search query (using one of the common graphical chemical structure editors, e.g., ChemDraw), with GH on indole nitrogen and also at the 5- and 6-positions of indole. The screen in Fig. A.7. shows the entry information required for the search. This query, retrieved 164 reactions from 45 citations (search results obtained in February 2012):

⁵³ Available at <https://www.reaxys.com/info/>

⁵⁴ Available at [Reaxys_whitepaper_2011_whatsinReaxys.pdf](#)

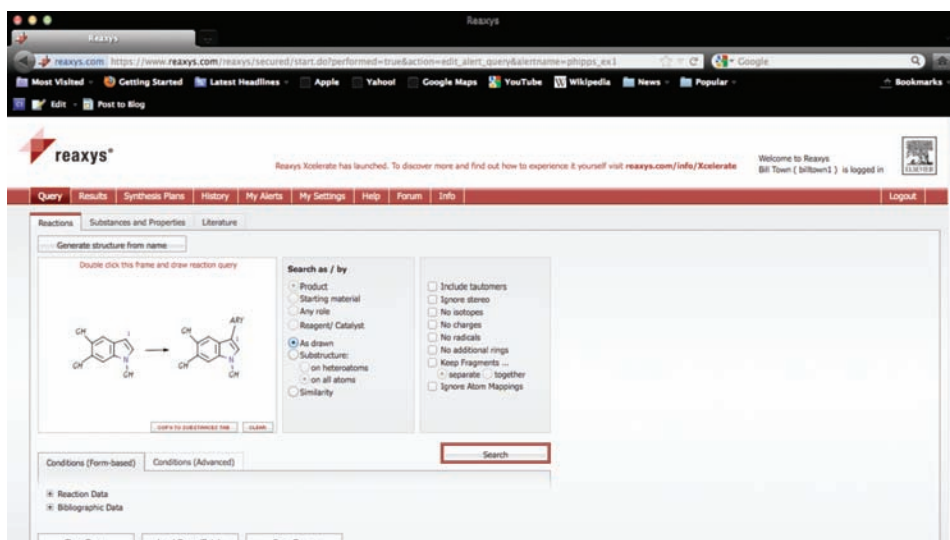


FIG. A.7. Search for direct arylation of indoles at C-3.

The Reaxys Version used in the above example is Application version: 1.0.9619; Content last updated: February 2012; Reactions: 31.681.788; Substances: 20.286.045; Citations: 4.504.504. Figure A.8 shows details for one of the reactions returned for this search. Also shown on this screen are various parameters that are available to search for this example. The original publication from which the reaction was taken is readily available.

It is also possible to expand the literature review by viewing the details of any recent articles that cite articles of interest. This is easily achieved by clicking on the 'view citing

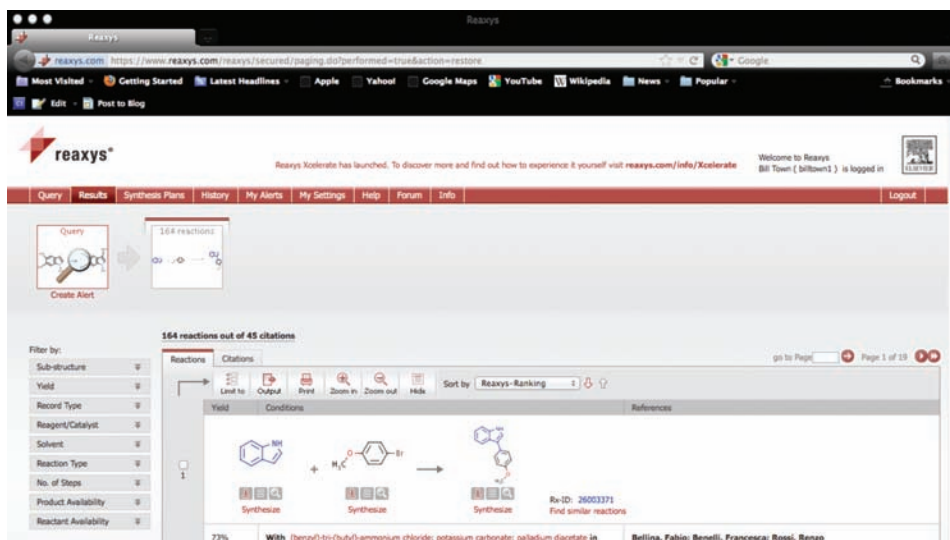


FIG. A.8. One reaction returned for this search.

Reaxys Xcelerate has launched. To discover more and find out how to experience it yourself visit reaxys.com/info/Xcelerate

Welcome to Reaxys
Bill Town (b1town1) is logged in

Query Results Synthesis Plans History My Alerts My Settings Help Forum Info Logout

164 reactions out of 45 citations

Filter by:

- Sub-structure
- Yield
- Record Type
- Reagent/Catalyst
- Solvent
- Reaction Type
- No. of Steps
- Product Availability
- Reactant Availability

Reactions Citations

go to Page: Page 1 of 5

Title of the Document	Authors	Year	Source	Times cited
1,3,6-SUBSTITUTED INDOLE DERIVATIVES HAVING INHIBITORY ACTIVITY FOR PROTEIN KINASE	Korea Institute of Science and Technology	2011	Patent: US2011/46370 A1, 2011 ; Patent Family: US2011/46370 A1; Full Text	

a. Title/Abstract
1,3,6-SUBSTITUTED INDOLE DERIVATIVES HAVING INHIBITORY ACTIVITY FOR PROTEIN KINASE
 Disclosed are a 1,3,6-substituted indole compound having inhibitory activity for protein kinase, a pharmaceutically acceptable thereof, and a pharmaceutical composition for prevention and treatment of diseases caused by abnormal cell growth including the compound as an active ingredient. Since the novel indole compound exhibits superior inhibitory activity for various protein kinases involved in growth factor signal transduction, it is useful as a novel for prevention or treatment of diseases caused by abnormal cell growth.

FIG. A.9. Papers that cited the work in Fig. A.8.

articles' hyperlink. The reaction shown in Fig. A.8 was cited in the patent literature and also in the *Journal of Organic Chemistry*, as shown in Fig. A.9. In this manner, relevant, more recent articles may be identified and explored using citation data from Scopus. A few of such citations are shown in Fig. A.10.

The synthesis planning tool allows a more in depth investigation. The Reaxys synthesis tool makes it easy to add more steps to the synthesis plan by searching the journal and patent literature for reactions designed to prepare the precursor molecules in any reaction step. Figure A.11 illustrates how a synthesis of a target that is consistent with the original

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Welcome to Reaxys
Bill Town (b1town1) is logged in

Query Results Synthesis Plans History My Alerts My Settings Help Forum Info Logout

164 reactions 13 citations

13 citations

Please note: there are no filters available for this data set in Reaxys. Please switch to Scopus for more analytical features for bibliographic data.

Cited article: Lapointe, David; Markiewicz, Thomas; Whipp, Christopher J.; Toderian, Amy; Fagnou, Keith (2011) *Journal of Organic Chemistry*, 76, # 3 pp. 749 - 759

go to Page: Page 1 of 2

Title of the Document	Authors	Year	Source	Times cited
1 Towards mild metal-catalyzed C-H bond activation	Wencel-Delord, J.; Drége, T.; Liu, F.; Glorius, F.	2011	Chemical Society Reviews, 2011, vol. 40, p. 4740-4761 View citing articles Full Text	20
2 Palladium-catalyzed oxidative cross-coupling between pyridine N-oxides and indoles	Gong, X.; Song, G.; Zhang, H.; Li, X.	2011	Organic Letters, 2011, vol. 13, p. 1766-1769 View citing articles Full Text	11
Synthesis of	Duric, S.; Tschucke, C.C.	2011	Organic Letters, 2011, vol. 13, p. 2310-2313 View citing articles Full Text	4

FIG. A.10. Other potentially relevant papers based on an expanded search.

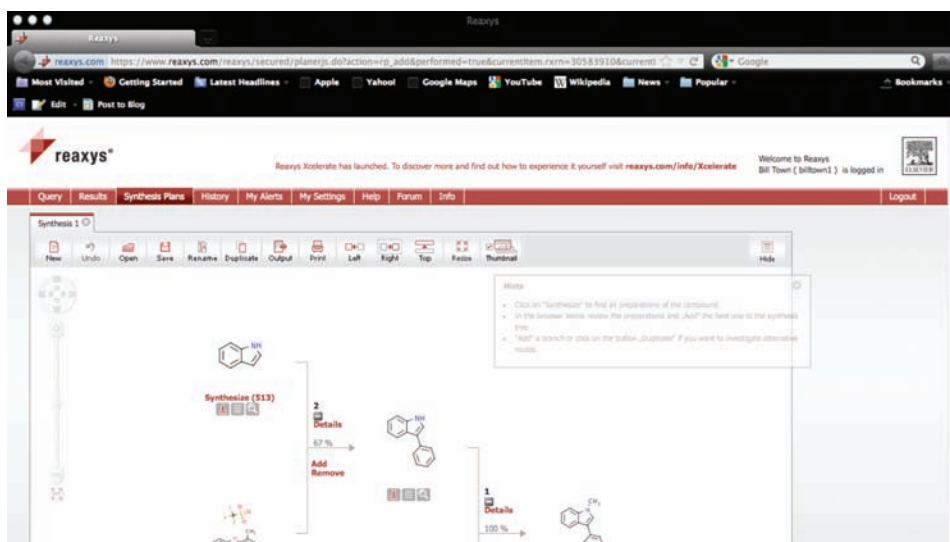


FIG. A.11. Synthesis plan for 3-phenylindole.

search parameters may be constructed. Extensive property data for chemical substances is available at every stage in the process. Reaxys is a valuable addition to the information resources used by synthetic chemists.

Note that Reaxys and the Reaxys[®] trademark are owned by Elsevier Properties SA and used under license. All rights reserved.

Classification of Reactions by Type of Compounds Synthesized

ACETALS

acetals + RM	10-64	carboxylic esters + organometallics	16-82
aldehydes + alcohols	16-05	cleavage of ethers	10-49
by transesterification	10-13	condensation of aldehydes	19-81
from dihalides	10-08	conjugate reduction	15-14
from hydroxy-ethers	14-06	epoxides + organometallics	10-65
ortho esters + RM	10-64	epoxides + silanes	10-55
reductive cleavage of ortho esters	19-56	from alcohols	10-17

ACYLALS (DIESTERS)

aldehydes + anhydrides	16-06	from amines	10-23
		from boranes	10-01
		from boranes	12-27
		from boranes	18-23
		from boronates	18-23
		from epoxides	10-65
		from ethers	10-13
		from silanes	10-16

ACYLOINS: See hydroxy-ketones

ALCOHOLS

addition of other organometallics to carbonyls	16-25	Grignard addition to aldehydes or ketones	16-24
aldehydes + allylic silanes	16-51	hydration of alkenes	15-03
alkenes + alcohols	15-33	hydrolysis of acetals and ketals	10-06
alkenes + aldehydes or ketones	16-54	hydrolysis of alkyl halides	10-01
alkenes-oxymmercuration	15-03	hydrolysis of inorganic esters	10-04
amides + organometallic compounds	16-82	hydrolysis of sulfonate esters	10-04
amines + KOH	10-23	hydrolysis of vinyl ethers	10-06
anhydrides + organometallic compounds	16-82	hydroxylation at aliphatic carbon	19-14
aromatics + carbonyls	11-12	hydroxymethylation of arenes	11-12
arylation of ketones	11-12	organolithium addition to aldehydes or ketones	16-24
boranes + CO; oxidation	18-23	organometallics + oxygen	12-25
boranes + CO; reduction	18-24	oxidation of boranes	12-27
by the Cannizzaro reaction	19-81	oxidation of boranes	15-16
by Wittig rearrangement	18-22	oxidation of boranes	18-23

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Seventh Edition.

Michael B. Smith.

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oxidation of methylene	19-15	from alkyl halides	10-64
oxidation of silanes	10-16	from alkyl halides	10-76
radical addition to carbonyl compounds	16-56	from aryl imines	11-18
rearrangement of ethers	18-22	from dihydrooxazines	10-72
rearrangement of peroxides	18-20	from dithianes	10-71
reduction of acyl halides	19-63	from dithioaldehydes	16-11
reduction of aldehydes or ketones	19-36	from organometallics	12-33
reduction of carbonyls with Grignard reagents	16-24	from oxazines	10-72
reduction of carboxylic acids	19-37	hydration of alkynes	15-04
reduction of carboxylic esters	19-38	hydroformylation	15-37
reduction of carboxylic esters	19-65	hydrolysis of acetals	10-05
reduction of conjugated ketones	15-44	hydrolysis of C=N compounds	16-02
reduction of epoxides	19-35	hydrolysis of <i>gem</i> -dihalides	10-02
reduction peroxides	19-60	hydrolysis of nitro compounds	16-03
ring expansion of amines	18-03	hydrolysis of vinyl ethers	10-06
silanes + aldehydes or ketones	16-26	hydrolysis of vinyl halides	10-04
		Michael addition	15-24
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addition of allylic organometallics to carbonyls	16-25	oxidation of aryl methyl groups	19-18
alkenes + formaldehyde	16-54	oxidation of nitro compounds	19-21
allylic silanes + aldehydes or ketones	16-26	oxidation of primary alkyl halides	19-20
deprotonation of epoxides	17-03	oxidative cleavage of diols	19-07
rearrangement of alkene-sulfoxides	18-35	oxidative cleavage of epoxides	19-07
		ozonolysis of alkenes	19-09
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alkyl halides + organoiron compounds	10-76	reduction of acid anhydrides	19-40
alkylation of aldehydes	10-68	reduction of acyl halides	19-39
alkylation of imines	10-68	reduction of amides	19-41
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and keto-enol tautomerism	12-03	reduction of carboxylic esters	19-40
aromatic compounds:		ALDEHYDES, CONJUGATED	
Friedel-Crafts	11-18	by aldol condensation	16-34
arylation of aldehydes	13-14		
boranes + MeO(ArS)CH ₂ Li	18-24	ALKANES	
by decarboxylation	12-40	alcohols + RM	10-63
by rearrangement of aldehydes	18-04	alkane addition to alkenes	15-18
by the Wacker process	19-25	alkenes + alkyl radicals	15-29
carbonylation of alkenes	15-37	alkenes + diimide	15-12
carbonylation of aromatic compounds	11-18	alkenes + metals	15-12
carbonylation of hydrocarbons	12-33	alkenes + organometallics	15-21
formylation of aromatic compounds	11-18	alkyl halides + metals	10-56
		alkyl halides + metals	10-57
		alkyl halides + organocuprates	10-58
		alkyl halides + RM (Li, Na, K)	10-57
		alkyl halides + RM (other metals)	10-59

alkyl halides + silanes	10-55	reduction of alkyl halides	19-53
Barton–McCombie reaction	19-58	reduction of anhydrides	19-65
by [2 + 2]-cycloaddition	15-63	reduction of carbonyls to	
by [3 + 2]-cycloaddition	15-59	methylene	19-61
by decarboxylation	12-40	reduction of carboxylic esters	19-65
cleavage of alkanes	12-47	reduction of nitriles	19-66
cleavage of ketones	12-46	reduction of nitro compounds	19-67
coupling of boranes	14-26	reduction of silanes	19-52
coupling of carboxylate salts	14-29	reduction of sulfonate esters	19-57
coupling of Grignard reagents	14-24	reduction of sulfur compounds	19-70
coupling of organocuprates	14-25	reduction of thioethers	14-27
coupling of two alkanes	14-15	reduction of thiols	14-27
decarbonylation of aldehydes	14-32	reduction of thiols	19-70
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from alcohols	10-63	reductive cleavage of	
from alcohols	19-58	cyclopropanes	15-15
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from alkanes	12-21	replacement of metals in RM	
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from alkylborates	10-59	sulfonate esters + metals	10-56
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ALKENE-THIOETHERS

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ALKENES

aldehydes or ketones + active

H compounds **16-38**

alkane addition to alkynes **15-18**

alkene addition to alkenes **15-20**

alkene metathesis **18-37**

alkenes + aryl halides **13-10**

alkenes + arylboronic acids **13-10**

alkenes + aryldiazonium

compounds **13-10**

alkenes + carbenes **15-64**

alkenes + carbocations **12-20**

alkynes + alkyl halides + RM

(M = metal) **15-22**

alkynes + metals or metal hydrides **15-12**

allylic esters + RM **10-60**

allylic halides + metals **10-56**

allylic silanes + esters **10-60**

aryldiazonium salts + alkenes **13-26**

base induced elimination of

halosulfones **17-20**

bis(decarboxylation) of

dicarboxylic acids **19-13**

by [2 + 2]-cycloaddition **15-63**

by [3 + 2]-cycloaddition **15-59**

by decarboxylation **12-40**

by McMurry coupling **19-77**

by migration of double bonds **12-02**

by Peterson alkenylation **16-41**

by the Diels–Alder reaction **15-60**

by the ene reaction **15-23**

by the Heck reaction **13-10**

by the heteroatom Diels–Alder

reaction **15-61**

by the Horner–Wadsworth–Emmons

reaction **16-44**

by the Knoevenagel reaction **16-38**

by the Ramberg–Bäcklund reaction **17-20**

by the Sakurai reaction **15-26**

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decarbonylation of acyl halides **17-17**

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hydroxy-carboxylic acids **17-26**

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dehydrogenation **19-02**

deoxygenation of 1,2-diols **17-18**

deprotonation of episulfides

(thiiranes) **17-03**

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(oxiranes) **17-03**

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elimination (1,3-) of diols **17-25**

elimination (1,3-) of haloamines **17-25**

elimination (1,3-) of halohydrins **17-25**

elimination (base) of ammonium

salts **17-07**

elimination (base) of ammonium

salts **17-08**

elimination (base) of halides **17-13**

elimination (base) of sulfonate

esters **17-06**

elimination (base) of sulfonyl

halides **17-14**

elimination (base) of sulfonyl

hydrazones **17-11**

elimination of 1,2-dihalides **17-22**

elimination of boranes **17-15**

elimination of haloethers **17-24**

enamines + boranes **15-16**

esters + organometallics **10-60**

extrusion from oxathiolanes **17-38**

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from alkenes **13-26**

from alkyl halides **10-55**

from allylic esters **10-60**

from bis(xanthates) **17-18**

from boranes **10-59**

from carbenes **12-21**

from dienes **18-37**

from episulfones **16-48**

from epoxides or thiiranes **17-03**

from imines **16-44**

from selenones **10-71**

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hydrogenation of alkynes **15-11**

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ketones or aldehydes + bis(Grignards)	16-24	ALKYNE-ALCOHOLS	
migration of boranes	12-02	addition of alkynes to carbonyls	16-25
migration of double bonds	12-02		
nitrosation of aziridines	17-21	ALKYNES	
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organometallics + tosylhydrazones	16-38	alkyl halides + propargylic RM	10-57
other cycloaddition reactions	15-66	alkynes + arylodonium salts	13-13
oxidative decarboxylation of carboxylic acids	19-12	alkynes + boranes	18-26
Petasis alkenylation	16-45	aryl halides + alkyne-M (M = a metal)	13-13
protonolysis of vinyl boranes	18-25	aryl halides + alkynes	10-74
protonolysis of vinyl boranes	18-26	base-induced isomerization alkynes	12-02
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pyrolysis of ammonium salts (Hofmann)	17-07	elimination of alkenes	17-16
pyrolysis of esters	17-04	elimination of dihalo compounds (by base)	17-16
pyrolysis of hydroxy-alkenes	17-32	elimination of halides (by base) from alkyl halides	17-13
pyrolysis of sulfones	17-12	from alkynes	10-74
pyrolysis of sulfoxides	17-12	hypervalent iodine + alkyne-M (M = a metal)	10-74
pyrolysis of thionocarbonates	17-19	metathesis of alkynes	12-26
pyrolysis of xanthates (Chugaev)	17-05	pyrolysis of bis(ammonium)salts	18-37
pyrolysis of β -lactones	17-26	pyrolysis of thiirene dioxides	17-07
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reduction of thiophene derivatives	19-70		
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reductive coupling of aldehydes or ketones	19-77	by Claisen rearrangement	18-33
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sigmatropic carbon migration	18-30	Cope rearrangement of diynes	18-32
sigmatropic H migration	18-29	elimination of dihalides	17-22
silyl-organometallics + aldehydes or ketones	16-41	propargylic esters + organocuprates	10-60
Tebbe alkenylation	16-45	reduction of alkynes	19-53
vinyl boranes + halogen/base	18-25		
vinyl halides + arylboronic acids	13-10	ALLOPHANATES	
vinyl-cyclopropane rearrangement	18-31	carbamates + isocyanates	16-08
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		aziridines + amides	10-14
		AMIDES	
		acyl halides + ammonia or amines	16-72

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alcohols + cyanogen halides	16-09	N-arylation	10-41
aldehydes + ammonia + oxidant	14-11	nitriles + alcohols	16-91
alkanes + nitriles	14-12	nitriles + amines	16-21
alkenes + amides	15-09	oxidation of methylene in amines	19-17
alkenes + nitriles	16-91	oximes + halogenating or oxidizing agents	18-17
alkyl halides + amides	10-41	pyrolysis of imino esters	18-42
amides + aldehydes	10-41	rearrangement of oximes	18-17
amides + amines	16-76	reduction of imides	19-64
amines + CO + alkenes	15-36	Ritter reaction	16-91
amines + CO	12-53	transamidation	16-70
amines + haloformates	10-53		
amines + organoiron compounds	10-77	AMIDES, CONJUGATED	
amines + vinyl esters	16-75	isocyanates + vinyl-M (metal)	15-22
anhydrides + ammonia or amines	16-73		
aromatic compounds + amides	11-22	AMIDINES	
aromatic compounds + hydroxamic acids	11-06	ketenimines + amines	15-08
aromatic compounds + isocyanates	11-21	nitriles + ammonia or amines	16-21
aryl halides + amides	10-41		
aryl halides + amides	13-05	AMIDO-ALCOHOLS	
aryl halides, DMF and POCl ₃	11-21	alkenes + amides	15-52
by Beckmann rearrangement	18-17		
by Michael addition	15-24	AMINE OXIDES	
by Mitsunobu reaction	10-41	oxidation of amines	19-29
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by the Haller-Bauer reaction	12-46	AMINES	
by the Willgerodt reaction	19-84	addition of organometallics to C=N compounds	16-31
carboxylic acids + amino-boranes	16-74	addition of silanes to C=N	16-31
carboxylic acids and ammonia or amines	16-74	alkenes + amines or ammonia	15-08
carboxylic esters + ammonia or amines	16-75	alkyl halides + amines	10-31
cleavage of ketones	12-46	alkylation of amines	10-31
condensation of methyl ketones	19-84	alkylation of formamides	10-71
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from alcohols	10-41	allylic amination	12-12
from aromatic compounds	11-19	amides + organometallic compounds	16-82
from <i>N</i> -halo amides	11-31	amination of active methylene compounds	12-12
hydrolysis of isonitriles	16-97	amination of alkanes	10-39
hydrolysis of nitriles	16-04	amination of alkanes	12-12
imines + borane + CO	12-33	amination of heterocycles	13-18
insertion of acyl nitrenes	12-13	amination of methylene	19-16
insertion of diazo amides	12-21	amines + aryl halides	13-05
ketenes + amines	15-08	amines + diaryliodonium compounds	11-06
ketones + HN ₃	18-16	amines + diazo compounds	10-34
ketones + ⁻ NH ₂	12-46		

aminomethylation of aromatic compound	11-22	Hofmann–Löffler reaction	18-40
aromatic compounds + amide bases	13-18	hydrolysis of isocyanates	18-13
aromatic compounds + aryl azides	11-06	hydrolysis of isocyanates	18-15
aromatic compounds + haloamines	11-06	hydrolysis of isocyanates	18-16
aromatic compounds + hydrazoic acid	11-06	hydroxylamines + alkyl organometallics	12-32
aryl halides + amines	13-05	imines + allylic silanes	16-51
aryl halides + hydroxylamine- <i>O</i> -sulfonic acid	18-15	insertion of nitrenes	12-13
azides + haloboranes	12-32	Lossen rearrangement	18-15
aziridines + RM	10-66	Michael addition with N nucleophiles	15-31
boranes + ammonia + NaOCl	12-32	phenols + amines or ammonia	13-06
boranes + chloramine	12-32	Pictet–Spengler reaction	10-13
by amidomethylation	11-22	radical addition to C=N compounds	16-56
by reaction with nitrenes	12-13	rearrangement of ammonium salts	13-31
by the Stevens rearrangement	18-21	rearrangement of ammonium salts	18-21
by transamination	10-33	rearrangement of aryl hydroxylamines	13-32
Curtius rearrangement	18-14	reduction nitroso compounds	19-47
cyclization of haloamines	18-40	reduction of amides	19-64
dealkylation of amines	19-73	reduction of amine oxides	19-68
dehydrogenation	19-02	reduction of amines	19-64
displacement of cyano	10-62	reduction of azides	19-50
diynes + amines	15-08	reduction of azo compounds	19-74
enamines + boranes	15-16	reduction of azoxy compounds	19-74
from alcohols	10-31	reduction of C=N compounds	19-42
from alcohols	10-32	reduction of hydrazines	19-74
from alkanes	10-39	reduction of hydroxylamines	19-47
from amides	18-13	reduction of isocyanates	19-51
from amines	10-31	reduction of isothiocyanates	19-51
from amines	10-33	reduction of lactams	19-64
from amines	10-34	reduction of nitriles	19-43
from amines	10-71	reduction of nitro compounds	19-45
from amino-ethers	10-64	reduction of nitrosoamines	19-51
from amino-nitriles	10-62	reduction oximes	19-48
from ammonium salts	11-32	reductive alkylation of aldehydes or ketones	16-17
from boranes	10-31	Schmidt reaction	18-16
from cyanohydrins	10-32	Sommelet–Hauser rearrangement	13-31
from ethers	10-32	Stevens rearrangement	13-31
from haloamines	10-31	transamination	10-33
from hydrazones	10-71		
from hydroxylamines	13-32		
from nitroamines	11-28		
from nitrosamines	11-29		
from organometallics	12-32		
from phenols	11-22		
from phenols	13-06		
Hofmann rearrangement	18-13		
		AMINO ACIDS	
		lactones + ammonia or amines	16-75

AMINO ALCOHOLS

alkenes + amines	15-52
epoxides + amines or ammonia	10-35
from amino epoxides	10-36
from isonitriles	10-40
from nitroalcohols	10-35
oxetanes + amines or ammonia	10-37
rearrangement of haloamines	18-10
reductive coupling of C=N with C=O	19-76

AMINO ALDEHYDES

aldehydes + C=N compounds	16-31
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AMINO ESTERS

diazoesters + amines	15-64
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AMINO ETHERS

aziridines + alcohols	10-14
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AMINO KETONES

base-induced rearrangement of sulfonyl oximes	18-12
ketones + HCHO + amines	16-19
Mannich reaction	16-19

AMINO NITRILES

from amines	12-19
from cyanohydrins	10-32
HCN or cyanide + C=N compounds	16-53

AMINO THIOETHERS

alkenes + sulfonamides	15-55
alkenes + sulfonium salts + amines	15-55

AMINO THIOLS

episulfides + amines or ammonia	10-35
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AMMONIUM SALTS

alkyl halides + amines	10-31
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ANHYDRIDES

acyl halides + carboxylic acids	16-66
aldehydes + acyl peroxides	14-09
carboxylic acids + vinyl esters	16-67
dehydration of carboxylic acids	16-67
dehydration of dicarboxylic acids	16-67

ANHYDRIDES,**ORGANIC-INORGANIC**

anhydrides + mineral acids	16-68
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ARENES

alkyl halides + ArM (Li, Na, K)	10-57
alkyl halides + aryl organometallics	10-57
alkyl halides + arylboronic acids	13-09
alkyl halides + organocuprates	10-58
alkyl halides + organometallics	13-17
aromatic compounds + active H compounds	13-17
aromatic compounds + acylperoxides	14-17
aromatic compounds + alcohols	11-11
aromatic compounds + alkenes	11-11
aromatic compounds + alkyl halides	11-11
aromatic compounds + carboxylic acids	14-19
aromatic compounds + ketones	11-12
aromatic compounds + peroxides	14-17
aryl halides + active methylene compounds	13-14
aryl halides + alkenes	13-10
aryl halides + alkenes	15-21
aryl halides + alkynes	15-21
aryl halides + organocuprates	10-58
aryl halides + RM (other metals)	10-59
aryl halides + trifluoroborates	13-09
aryl halides + vinylboronic acids	13-09
aryldiazonium salts + alkenes	13-26
aryldiazonium salts + alkyl organometallics	13-25
aryldiazonium salts + organometallics	13-25
by decarboxylation	12-40
by radical cyclization	15-30
coupling of aromatic compounds	11-15
cyclodehydration of carbonyl compounds	11-13
Friedel-Crafts alkylation	11-11
from alkylborates	10-59
from boranes	10-59
from ketones	11-13
hydrogen exchange	11-01
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replacement of aryl nitro	13-29	AZIDO AMIDES	
α -halo ketones + organocuprates	10-58	from amides	12-11
AROMATIC COMPOUNDS		AZIDO AMINES	
alkylation of heteroaryls	14-19	from aziridines	10-38
aromatic compounds + carbenes	15-64		
aromatization of six-membered rings	19-01	AZIRIDINES	
cleavage of arenes	11-33	alkenes + alkyl azides	15-54
cleavage of aryl alkyl ethers	11-37	alkenes + halogen + haloamines	15-54
cyclization of ene-dienes	18-27	C=N compounds + sulfur ylids	16-47
cyclotrimerization of alkynes	15-65	extrusion of nitrogen from triazolines	17-34
deamination of aromatic compounds	19-69	form haloamines	10-31
decarbonylation of aryl aldehydes	11-34	from allene amides	15-09
decarboxylation of aryl carboxylic acids	11-35	from azido alcohols	10-43
dehalogenation of aryl halides	11-39	from epoxides	10-36
dehydrogenation of cyclic alkanes	19-01	from halo-azides	15-45
deoxygenation of aryl ethers	11-37	from hydroxy-amines	10-32
desulfonylation of aryl sulfonic acids	11-38	from imines	16-32
from aldehydes	11-34	from triazolines	15-58
from aromatic compounds	11-33	imines + diazo compounds	16-32
from aromatic compounds	18-28		
hydrolysis of aromatic organometallics	11-41	AZIRINES	
protonation of aryl organometallics	11-41	alkynes + amino nitrenes	15-54
pyrolysis of bicyclic dienones	17-28		
reduction aryl diazonium salts	19-69	AZO COMPOUNDS	
reduction of aryl halides	11-39	aryl amines + nitroso compounds	13-24
reduction of phenols	19-55	aryl diazonium salts + aromatic compounds	11-04
reduction of quinones	19-01	from aryldiazonium salts	13-28
		oxidation of hydrazines	19-05
		rearrangement of aryl triazenes	11-30
		rearrangement of azoxy compounds	18-43
		reduction of azoxy compounds	19-68
		reduction of nitro compounds	19-80
		Wallach rearrangement	18-43
AZIDES			
aldehydes + metal azides	16-78	AZOXY COMPOUNDS	
alkenes + hydrazoic acid	15-10	from alkyl halides	10-45
alkenes + metal azides	15-53	nitroso compounds + hydroxylamines	12-51
amides + sulfonyl azides	12-11	reduction of nitro compounds	19-79
from acyl halides	10-43		
from alkyl halides	10-43	BIARYLS	
hydrazines + HONO or nitrosyl compounds	12-49	aromatic compounds + aryl halides (<i>h</i> ν)	14-18
AZIDO ALCOHOLS		aromatic compounds + aryl organometallics	11-16
from epoxides	10-43		

aromatic compounds + aryl organometallics	14-17	BUNTE SALTS from alkyl halides	10-28
aromatic compounds + arylboronates	11-16	CARBAMATES alkyl halides + amines	10-17
aryl halides + alkyl or aryl organometallics	13-09	amines + alkyl halides + CO ₂	12-53
aryl halides + arylboronic acids	13-09	amines + CO ₂	12-53
aryl halides + arylboronic acids	13-12	from aziridines	12-53
aryl halides + metals	13-11	haloformates + amines	16-72
aryl halides + trifluoroborates	13-12	isocyanates + alcohols	16-08
aryldiazonium salts + aromatic compounds	13-27	CARBONATES alcohols + phosphine	16-10
aryldiazonium salts + metal salts	13-28	CARBOXYLIC ACIDS acyl halides + diazo compounds	18-08
arylsulfonic acid + arylboronic acids	13-05	acyl peroxides + alkyl organometallics	12-26
by benzidine rearrangement	18-36	alkylation of carboxylic acids	10-70
coupling 2 aryldiazonium salts	13-28	aromatic compounds + CO ₂	11-20
coupling aryl halides	13-11	aromatic compounds + CO ₂	11-20
coupling of aromatic compounds	11-15	aromatic compounds-carboxylation	11-19
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		insertion of diazo esters	12-21
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		oxidation of aldehydes	19-23
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CONJUGATED			
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acyl halides + ethers	16-61		
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		from active methylene compounds	12-10
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		active methylene compounds +	
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		DIENES	
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		hydrolysis of epoxides	10-07
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ketones + halogenating agents	16-23	pinacol coupling	19-76
		reduction of lactones	19-38
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		aryl halides + sulfides	13-04
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isocyanates + phosphine oxides	16-93	oxidation of thiols	19-34
		reduction of sulfonyl halides	19-71
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acyl halides + active H compounds	16-84	DITHIOACETALS	
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metal carbonyls	15-32	DITHIOKETALS	
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DITHIOLSalkenes + sulfur reagents **15-51****DIYNES**by Cadiot–Chodkiewicz coupling **14-16**by Glaser coupling **14-16**by Sonogashira coupling **14-16**from alkynyl boronates **14-16**metal coupling of alkynes **13-13**metal coupling of alkynes **14-16****ENAMIDES**amines + vinyl halides **12-32****ENAMINES**alkylation of enamines **10-71**alkynes + amines **15-08**from hydroxy-amines **16-13****ENOL ETHERS:** See vinyl ethers**ENOLS**and keto–enol tautomerism **12-03****EPISULFIDES:** See thiiranes**EPOXIDES (Oxiranes)**aldehydes or ketones +
haloorganometallics **16-24**diazonium compounds + aldehydes
or ketones **16-46**epoxidation of alkenes **15-50**from halohydrins **10-09**ketones + alkenes **16-95**sulfur ylids + aldehydes or ketones **16-46****EPOXY ALCOHOLS**allylic alcohols + peroxides **15-50**from epoxy alcohols **10-14****EPOXY AMIDES**epoxidation of conjugated esters **15-50****EPOXY CARBOXYLIC ACIDS**epoxidation of conjugated acids **15-50****EPOXY ESTERS**diazo esters + aldehydes **15-64**epoxidation of conjugated
esters **15-50**halo esters + aldehydes or
ketones **16-40****EPOXY KETONES**epoxidation of conjugated
ketones **15-50****EPOXY NITRILES**epoxidation of conjugated nitriles **15-50****ESTER AMIDES**isonitriles + carboxylic acids +
aldehydes **16-98**isonitriles + carboxylic acids +
ketones **16-98****ESTER SULFIDES**by the Pummerer rearrangement **19-83**rearrangement of sulfoxides **19-83****ESTERS:** See Carboxylic Esters**ESTERS, INORGANIC**from alcohols **10-22**from sulfonyl halides **10-22**phosphites + alkyl halides **16-44****ESTERS, SULFONIC**

(see SULFONATE)

ETHER AMINESrearrangement of halo-amines **18-18****ETHER ESTERS**conjugated esters + alcohols **15-05****ETHER KETONES**acetals + vinyl ethers **10-64**oxidation of methylene **19-15****ETHERS**acyl peroxides + alkyl
organometallics **12-26**alcohols + diazo compounds **10-11**alcohols + ethers **10-13**alcohols + onium salts **10-15**

alcohols + sulfonate esters	10-10	GLYCIDIC ESTERS: See epoxy esters	
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alkenes + alcohols	15-05	HALIDES, ACYL	
alkenes-alkoxymercuration	15-05	acyl halides + HF	16-80
alkylation of ethers	10-71	aldehydes + halogens	14-04
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cleavage of oxonium salts	10-49	carboxyl acids + halogenating agents	16-79
coupling of silanes	14-15	oxidation of primary alcohols	19-22
dehydration of alcohols	10-12		
from alcohols (Williamson ether synthesis)	10-08	HALIDES, ALKYL	
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from alcohols	14-06	alcohols + inorganic acid halides	10-48
from alkyl halides (Williamson ether synthesis)	10-08	aldehydes + halo-boranes	16-23
from alkyl halides	10-10	alkanes + halogenating reagents	14-01
from alkyl sulfates	10-10	alkenes + alkyl halides	15-46
from carboxylic esters	10-10	alkenes + halogenating agents	14-03
from dihalides	10-10	alkenes + HX	15-02
from ethers	10-13	carboxylate salts + halogens	14-30
from haloethers	10-08	cleavage of amides	10-53
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from phenols	13-33	cleavage of oxonium salts	10-49
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		halo-methylation of arenes	11-14
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cleavage of ethers	10-49	alkenes + halogens	14-03
from alcohols and silyl halides	10-08	HALIDES, ARYL	
rearrangement of hydroxy-silanes	18-44	aromatic compounds + halogen	11-10
		aromatic compounds + halo-succinimides	11-10
FORMAMIDES		aryl ammonium salts + halide ion	11-32
amines + trihalides	10-40	aryl halides + halogenating agent	13-07

aryldiazonium salts + metal halides	14-20	HALOAMINES	
aryldiazonium salts + metal iodides	13-22	alkenes + <i>N</i> -haloamines	15-43
by Sandmeyer reaction	14-20	from amines	12-52
from aryl amines	14-20		
from phenols	13-22	HALOAZIDES	
heating aryldiazonium		alkenes + X-N ₃	15-45
tetrafluoroborates	13-23		
phenols + phosphonium halides	13-07	HALOCARBOXYLIC ACIDS	
rearrangement of <i>N</i> -haloamides	11-31	carboxylic acid + halogen	12-05
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halides	11-38	agents	12-05
		from amino acids	10-52
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From silanes	14-02	HALOESTERS	
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HALIDES, SULFONYL			
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aromatic compounds + sulfonyl		from alkene-alcohols	15-51
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		from enol borinates	12-04
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		ketone + halogenating agents	12-04
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elimination of halides (by base)	17-13	halolactamization	15-41
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from alkenes	15-40	HALONITROSO COMPOUNDS	
		alkenes + NOX	15-44
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aldehydes + halogenating agent	12-04	from silanes	10-16
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		sulfones + halogenation agents	12-06
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