COMPREHENSIVE ORGANIC FUNCTIONAL GROUP TRANSFORMATIONS II

Editors-in-Chief
Alan R. Katritzky, Richard J.K. Taylor

Volume 3

Carbon with One Heteroatom Attached by a Multiple Bond

Volume Editor
Keith Jones

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Editors-in-Chief:
A.R. Katritzky, University of Florida, Gainesville, USA
R.J.K. Taylor, Department of Chemistry, University of York, UK

Volumes 1-7 - 7-Volume Set
Hardbound, ISBN: 0-08-044256-0, 6788 pages,
publication date: 2004
Imprint: ELSEVIER

Description

Comprehensive Organic Functional Group Transformations II (COFGT-II) will provide the first point of entry to the literature for all scientists interested in chemical transformations. Presenting the vast subject of organic synthesis in terms of the introduction and interconversion of all known functional groups, COFGT-II will provide a unique information source documenting all methods of efficiently performing a particular transformation. Organised by the functional group formed, COFGT-II will consist of 144 specialist reviews, written by leading scientists who will evaluate and summarise the methods available for each functional group transformation.

Volumes

Volume 1: **Carbon with No Attached Heteroatoms**

Volume 2: **Carbon with One Heteroatom Attached by a Single Bond**

Volume 3: **Carbon with One Heteroatom Attached by a Multiple Bond**

Volume 4: **Carbon with Two Heteroatoms, Each Attached by a Single Bond**

Volume 5: **Carbon with Two Attached Heteroatoms with at Least One Carbon-to-Heteroatom Multiple Link**

Volume 6: **Carbon with Three or Four Attached Heteroatoms**

Volume 7: **Author Index and Cumulative Subject Index**

Editors-in-Chief

Alan Katritzky, educated at Oxford, held faculty positions at Cambridge and East Anglia before migrating in 1980 to the University of Florida, where he is Kenan Professor and Director of the Center for Heterocyclic Compounds. He has trained some 800 graduate students and postdocs, and lectured and consulted worldwide. He led the team which produced *Comprehensive Heterocyclic Chemistry* and its sequel *CHECII*, has edited *Advances in Heterocyclic Chemistry*, Vols. 1 through 86 and conceived the plan for *Comprehensive Organic Functional Group Transformations*. He founded Arkat-USA, a nonprofit organization which publishes *Archive for Organic Chemistry* (ARKIVOC) electronic journal completely free to authors and readers at (www.arkat-usa.org). Honors include 11 honorary doctorates from eight countries and membership or foreign membership of the National Academies of Britain, Catalonia, India, Poland, Russia, and Slovenia.

Richard Taylor is currently Professor of Organic Chemistry at the University of York, where his research focuses on the development of novel synthetic methodology and the synthesis of natural products and related compounds of biological/medicinal interest. The methodology is concentrated primarily on organometallic, organosulfur, and oxidation processes, and the targets include amino acids, carbohydrates, prostaglandins, and polyene and polyoxygenated natural products, particularly with activity as antibiotics and anti-cancer agents.

Richard Taylor is a graduate and postgraduate of the University of Sheffield. After his studies at Sheffield, he carried out postdoctoral research at Syntex, California (Dr. I. T. Harrison) and University College London (Professor F. Sondheimer). His first academic appointment was at the Open University in Milton Keynes. This post gave Professor Taylor the opportunity to contribute to Open University textbooks, radio programs and television productions on various aspects of organic chemistry. Professor Taylor then moved to UEA, Norwich, where he established his independent research program, before taking up his present position in York in 1993.

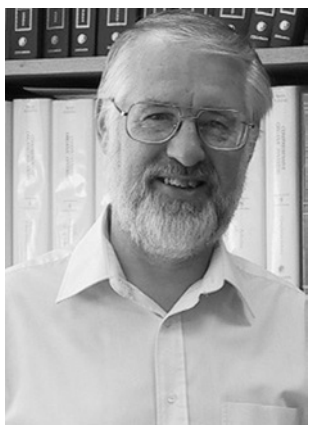
Richard Taylor has just finished his term as President of the Organic Division of the Royal Society of Chemistry and was awarded the 1999 RSC Tilden Lectureship and the 1999 RSC Heterocyclic Prize. He is currently the UK Regional Editor of the international journal *Tetrahedron*.

Volume Editors

EDITOR OF VOLUME 1

Janine Cossy did her undergraduate and graduate studies at the University of Reims. After a postdoctoral stay with Barry Trost, for two years (1980–1982) at the University of Wisconsin, she returned to Reims, where she became a Director of Research of the CNRS in 1990. In the same year she moved to Paris to become Professor of Organic Chemistry at the ESPCI (Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris). She is interested in synthetic methodologies (radicals, organometallics, photochemistry, thermal reactions, ring expansions, enantioselectivity, synthesis of heterocycles, synthesis of solid support) and in their applications to the synthesis of natural products and biologically active molecules.

EDITOR OF VOLUME 2



Chris Ramsden was born in Manchester, UK in 1946. He is a graduate of Sheffield University and received his Ph.D. (W. D. Ollis) in 1970 and D.Sc. in 1990. After postdoctoral work at the University of Texas (M. J. S. Dewar)(1971–1973) and University of East Anglia (A. R. Katritzky)(1973–1976), he worked in the pharmaceutical industry. He moved to Keele University as Professor of Organic Chemistry in 1992. His research interests are heterocycles and three-center bonds and applications of their chemistry to biological problems.

EDITOR OF VOLUME 3

Keith Jones was born in Manchester. He studied at Cambridge University for his B.A. in Natural Sciences (1976) and stayed to carry out research with Professor Sir Alan Battersby obtaining his Ph.D. in 1979. In 1979, he moved to a lectureship at King's College London. In 1984, he caught up with his postdoctoral research by spending a year working with Professor Gilbert Stork at Columbia University, New York. After returning to King's College, he became a reader in 1995. In 1998, he moved to a chair in organic and medicinal chemistry at Kingston University. His research interests cover natural product synthesis, heterocyclic chemistry and the use of radicals in synthesis. He has been a visiting professor at Neuchatel and Barcelona Universities as well as the Australian National University.

EDITOR OF VOLUME 4

Professor Gary Molander was born in Cedar Rapids, Iowa. He received his B.S. degree at Iowa State University and subsequently entered the graduate chemistry program at Purdue University in 1975, obtaining his Ph.D. degree in 1979 under the direction of Professor Herbert C. Brown. He joined Professor Barry Trost's group at the University of Wisconsin, Madison 1980 as a postdoctoral research associate, and in 1981 he accepted an appointment at the University of Colorado, Boulder, as an Assistant Professor of chemistry, where he rose through the academic ranks. In 1999 he joined the faculty at the University of Pennsylvania, and in 2001 was appointed Allan Day Professor of Chemistry. Professor Molander's research interests focus on the development of new synthetic methods for organic synthesis and natural product synthesis. A major focus of his research has been the application of organolanthanide reagents and catalysts to selective organic synthesis.

EDITOR OF VOLUME 5

Ray Jones started his chemistry career as an undergraduate and then completing a Ph.D. at Cambridge University under the supervision of Professor Sir Alan Battersby, in the area of alkaloid biosynthesis. After a year as an ICI Postdoctoral Fellow in the laboratories of Professor Albert Eschenmoser at the ETH Zurich, he was appointed as Lecturer in Organic Chemistry at University of Nottingham in 1974. He progressed to Senior Lecturer at Nottingham and then took up the Chair of Organic Chemistry at the Open University in 1995, before moving to the Chair of Organic and Biological Chemistry at Loughborough University in 2000.

His research interests span heterocyclic and natural product chemistry, with over 100 publications. Example topics include the acyltetramic acids and pyridones, Mammea coumarins, spermine and spermidine alkaloids, imidazolines as templates for (asymmetric) synthesis, dipolar cycloadditions, and unusual amino acids and peptide mimetics.

EDITOR OF VOLUME 6

Eric F. V. Scriven is a native of Wales, UK. After working at BISRA and ESSO Ltd, he attended the University of Salford and graduated in 1965. He obtained his M.Sc. from the University of Guelph, and his Ph.D. from the University of East Anglia (with Professor A. R. Katritzky) in 1969. After postdoctoral years at the University of Alabama and University College London, he was appointed Lecturer in organic chemistry at the University of Salford. There, his research interests centered on the reactivity of azides and nitrenes. While at Salford, he spent two semesters on secondment at the University of Benin in Nigeria. He joined Reilly Industries Inc. in 1979 and was director of Research from 1991 to 2003. He is currently at the University of Florida. He edited *Azides & Nitrenes* (1984), and he and Professor H. Suschitzky were founding editors of *Progress in Heterocyclic Chemistry*, which has been published annually since 1989 by the International Society of Heterocyclic Chemistry. He also collaborated with Professors A. R. Katritzky and C. W. Rees as Editors-in-Chief of *Comprehensive Heterocyclic Chemistry II* (1997). His current research interests are in novel nitration reactions, ionic liquids, and applications of polymers in organic synthesis.

Preface

Comprehensive Organic Functional Group Transformations (COFGT 1995) presented the vast subject of organic synthesis in terms of the introduction and interconversion of functional groups, according to a rigorous system, designed to cover all known and as yet unknown functional groups.

Comprehensive Organic Functional Group Transformations II (COFGT-II), designed for specialist and nonspecialist chemists, active in academic, industrial, and government laboratories, now updates the developments of functional group transformations since the publication of the COFGT 1995. COFGT-II is structured in precisely the same manner as the original COFGT work, allowing truly comprehensive coverage of all organic functional group transformations.

COFGT-II, in combination with COFGT 1995, provides an essential reference source for the all-important topic of methodologies for the interconversion of functional groups in organic compounds, and provides an efficient first point of entry into the key literature and background material for those planning any research involving the synthesis of new organic compounds. With the increase in our understanding of the way in which the chemical structure of compounds determines all physical, chemical, biological, and technological properties, targeted synthesis becomes ever more important. The making of compounds is germane not only to organic chemistry but also to future developments in all biological, medical, and materials sciences.

The availability of the work in electronic format through ScienceDirect will greatly enhance its utility.

The Editors-in-Chief would like to extend their warm thanks to the Volume Editors, the chapter authors, and the Elsevier staff for operating in such an efficient and professional manner.

A. R. Katritzky
R. J. K. Taylor

Introduction to Volume 3

Since the publication of *Comprehensive Organic Functional Group Transformations* (COFGT) in 1995, there has been an increased effort on the part of synthetic chemists to develop new methods for the synthesis of organic molecules. More sophisticated methods operating under milder conditions and with better control of stereochemistry are emerging all the time. Volume 3 contains an update on the synthesis of functional groups carrying one heteroatom attached to carbon via a multiple bond. This includes much of the chemistry of what is perhaps the most important of all organic functional groups, the carbonyl group. Ketones and aldehydes in their variously substituted forms represent some 30% of this volume and constitute the first seven chapters. New oxidants feature strongly in their preparation along with routes utilizing new organometallic chemistry. Chapters 3.8 and 3.9 cover the sulfur and selenium versions of aldehydes and ketones. Chapters 3.10–3.12 provide comprehensive coverage of functional groups with nitrogen doubly bonded to carbon. Particularly evident in these chapters are advances in asymmetric synthesis using the extra valency of nitrogen as a way of carrying a chiral auxiliary. Chapters 3.13–3.15 cover the group V ylides and doubly bonded metalloid and metal functional groups. Advances in the use of metals in organic synthesis are apparent in Chapter 3.15, where metathesis reactions have led to an explosion of interest in such metallocarbenes. Chapters 3.16 and 3.17 cover the functional groups in which a carbon is doubly bonded to a heteroatom and to another carbon. Ketenes, ketenimines, and their various analogs are somewhat off the beaten track nowadays but provide useful intermediates. Finally Chapters 3.18–3.21 cover the chemistry of nitriles and isonitriles. In Chapter 3.18, the advances in the asymmetric synthesis of cyanohydrins feature strongly whilst interest in isonitriles as partners in multicomponent coupling reactions generates new chemistry (Chapter 3.21). In addition to the advances noted above, examples of the use of solid-phase chemistry, ultrasound, and microwaves can be seen in nearly every chapter.

Keith Jones
Kingston-upon-Thames, UK
July 2004

Explanation of the reference system

Throughout this work, references are designated by a number-lettering coding of which the first four numbers denote the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted. This system has been used successfully in previous publications and enables the reader to go directly to the literature reference cited, without first having to consult the bibliography at the end of each chapter.

The following additional notes apply:

1. A list of journal codes in alphabetical order, together with the journals to which they refer is given immediately following these notes. Journal names are abbreviated throughout using the CASSI "Chemical Abstracts Service Source Index" system.
2. The references cited in each chapter are given at the end of the individual chapters.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, and (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, etc.
5. For non-twentieth-century references, the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are not included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three-letter codes.
9. Frequently cited books are assigned codes.
10. Less common journals and books are given the code "MI" for miscellaneous with the whole code for books prefixed by the letter "B-".
11. Where journals have changed names, the same code is used throughout, e.g., CB refers to both *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

JOURNAL ABBREVIATIONS

AAC	*Antimicrob. Agents Chemother.*
ABC	*Agric. Biol. Chem.*
AC	*Appl. Catal.*
ACA	*Aldrichim. Acta*
AC(P)	*Ann. Chim. (Paris)*
AC(R)	*Ann. Chim. (Rome)*
ACH	*Acta Chim. Acad. Sci. Hung.*
ACR	*Acc. Chem. Res.*
ACS	*Acta Chem. Scand.*
ACS(A)	*Acta Chem. Scand., Ser. A*
ACS(B)	*Acta Chem. Scand., Ser. B*
AF	*Arzneim.-Forsch.*
AFC	*Adv. Fluorine Chem.*
AG	*Angew. Chem.*
AG(E)	*Angew. Chem., Int. Ed. Engl.*
AHC	*Adv. Heterocycl. Chem.*
AHCS	*Adv. Heterocycl. Chem. Supplement*
AI	*Anal. Instrum.*
AJC	*Aust. J. Chem.*
AK	*Ark. Kemi*
AKZ	*Arm. Khim. Zh.*
AM	*Adv. Mater. (Weinheim, Ger.)*
AMLS	*Adv. Mol. Spectrosc.*
AMS	*Adv. Mass Spectrom.*
ANC	*Anal. Chem.*
ANL	*Acad. Naz. Lincei*
ANY	*Ann. N. Y. Acad. Sci.*
AOC	*Adv. Organomet. Chem.*
AP	*Arch. Pharm. (Weinheim, Ger.)*
APO	*Adv. Phys. Org. Chem.*
APOC	*Appl. Organomet. Chem.*
APS	*Adv. Polym. Sci.*
AQ	*An. Quim.*
AR	*Annu. Rep. Prog. Chem.*
AR(A)	*Annu. Rep. Prog. Chem., Sect. A*
AR(B)	*Annu. Rep. Prog. Chem., Sect. B*
ARP	*Annu. Rev. Phys. Chem.*
ASI	*Acta Chim. Sin. Engl. Ed.*
ASIN	*Acta Chim. Sin.*
AX	*Acta Crystallogr.*
AX(A)	*Acta Crystallogr., Part A*
AX(B)	*Acta Crystallogr., Part B*
B	*Biochemistry*
BAP	*Bull. Acad. Pol. Sci., Ser. Sci. Chim.*
BAU	*Bull. Acad. Sci. USSR, Div. Chem. Sci.*
BBA	*Biochim. Biophys. Acta*
BBR	*Biochem. Biophys. Res. Commun.*
BCJ	*Bull. Chem. Soc. Jpn.*
BEP	*Belg. Pat.*
BJ	*Biochem. J.*
BJP	*Br. J. Pharmacol.*
BMC	*Biorg. Med. Chem.*
BMCL	*Biorg. Med. Chem. Lett.*
BOC	*Bioorg. Chem.*
BP	*Biochem. Biopharmacol.*
BPJ	*Br. Polym. J.*
BRP	*Br. Pat.*
BSB	*Bull. Soc. Chim. Belg.*
BSF	*Bull. Soc. Chim. Fr.*
BSF(2)	*Bull. Soc. Chim. Fr., Part 2*
BSM	*Best Synthetic Methods*
C	*Chimia*
CA	*Chem. Abstr.*
CAN	*Cancer*
CAR	*Carbohydr. Res.*
CAT	*Chim. Acta Turc.*
CB	*Chem. Ber.*
CBR	*Chem. Br.*
CC	*J. Chem. Soc., Chem. Commun.*
CCA	*Croat. Chem. Acta*
CCC	*Collect. Czech. Chem. Commun.*
CCHT	*Comb. Chem. High T. Scr.*
CCR	*Coord. Chem. Rev.*
CE	*Chem. Express*
CEJ	*Chem. -Eur. J.*
CEN	*Chem. Eng. News*
CHE	*Chem. Heterocycl. Compd. (Engl. Transl.)*
CHECI	*Comp. Heterocycl. Chem., 1st edn.*
CHECII	*Comp. Heterocycl. Chem., 2nd edn.*
CHIR	*Chirality*
CI(L)	*Chem. Ind. (London)*
CI(M)	*Chem. Ind. (Milan)*
CJC	*Can. J. Chem.*
CJS	*Canadian J. Spectrosc.*
CL	*Chem. Lett.*
CLY	*Chem. Listy*
CM	*Chem. Mater.*
CMC	*Comp. Med. Chem.*
COC	*Comp. Org. Chem.*
COFGT	*Comp. Org. Func. Group Transformations*
COMCI	*Comp. Organomet. Chem., 1st edn.*
CONAP	*Comp. Natural Products Chem.*
COS	*Comp. Org. Synth.*
CP	*Can. Pat.*
CPB	*Chem. Pharm. Bull.*
CPH	*Chem. Phys.*
CPL	*Chem. Phys. Lett.*
CR	*C.R. Hebd. Seances Acad. Sci.*
CR(A)	*C.R. Hebd. Seances Acad. Sci., Ser. A*
CR(B)	*C.R. Hebd. Seances Acad. Sci., Ser. B*
CR(C)	*C.R. Hebd. Seances Acad. Sci., Ser. C.*
CRAC	*Crit. Rev. Anal. Chem.*
CRV	*Chem. Rev.*
CS	*Chem. Scr.*
CSC	*Cryst. Struct. Commun.*
CSR	*Chem. Soc. Rev.*
CT	*Chem. Tech.*
CUOC	*Curr. Org. Chem.*
CZ	*Chem.-Ztg.*
CZP	*Czech. Pat.*
DIS	*Diss. Abstr.*
DIS(B)	*Diss. Abstr. Int. B*
DOK	*Dokl. Akad. Nauk SSSR*
DOKC	*Dokl. Chem. (Engl. Transl.)*
DP	*Dyes Pigm.*
E	*Experientia*
EC	*Educ. Chem.*
EF	*Energy Fuels*
EGP	*Ger. (East) Pat.*
EJI	*Eur. J. Inorg. Chem.*
EJM	*Eur. J. Med. Chem.*
EJO	*Eur. J. Org. Chem.*
EUP	*Eur. Pat.*
FCF	*Fortschr. Chem. Forsch.*
FCR	*Fluorine Chem. Rev.*
FES	*Farmaco Ed. Sci.*
FOR	*Fortschr. Chem. Org. Naturst.*
FRP	*Fr. Pat.*
G	*Gazz. Chim. Ital.*
GAK	*Gummi Asbest Kunstst.*
GC	*Green Chem.*
GEP	*Ger. Pat.*
GSM	*Gen. Synth. Methods*
H	*Heterocycles*
HAC	*Heteroatom Chem.*
HC	*Chem. Heterocycl. Compd. [Weissberger-Taylor series]*
HCA	*Helv. Chim. Acta*
HCO	*Heterocycl. Commun.*
HOU	*Methoden Org. Chem. (Houben-Weyl)*
HP	*Hydrocarbon Process*
IC	*Inorg. Chem.*
ICA	*Inorg. Chim. Acta*
IEC	*Ind. Eng. Chem. Res.*
IJ	*Isr. J. Chem.*
IJC	*Indian J. Chem.*
IJC(A)	*Indian J. Chem., Sect. A*
IJC(B)	*Indian J. Chem., Sect. B*
IJM	*Int. J. Mass Spectrom. Ion Phys.*
IJQ	*Int. J. Quantum Chem.*
IJS	*Int. J. Sulfur Chem.*
IJS(A)	*Int. J. Sulfur Chem., Part A*
IJS(B)	*Int. J. Sulfur Chem., Part B*
IS	*Inorg. Synth.*
IZV	*Izv. Akad. Nauk SSSR, Ser. Khim.*
JA	*J. Am. Chem. Soc.*
JAN	*J. Antibiot.*
JAP	*Jpn. Pat.*
JAP(K)	*Jpn. Kokai*
JBC	*J. Biol. Chem.*
JC	*J. Chromatogr.*
JCA	*J. Catal.*
JCC	*J. Coord. Chem.*
JCO	*J. Comb. Chem.*
JCE	*J. Chem. Ed.*
JCED	*J. Chem. Eng. Data*
JCI	*J. Chem. Inf. Comput. Sci.*
JCP	*J. Chem. Phys.*
JCPB	*J. Chim. Phys. Physico-Chim. Biol.*
JCR(M)	*J. Chem. Res. (M)*
JCR(S)	*J. Chem. Res. (S)*

JCS	*J. Chem. Soc.*
JCS(A)	*J. Chem. Soc. (A)*
JCS(B)	*J. Chem. Soc. (B)*
JCS(C)	*J. Chem. Soc. (C)*
JCS(D)	*J. Chem. Soc., Dalton Trans.*
JCS(F1)	*J. Chem. Soc., Faraday Trans. 1*
JCS(F2)	*J. Chem. Soc., Faraday Trans. 2*
JCS(P1)	*J. Chem. Soc., Perkin Trans. 1*
JCS(P2)	*J. Chem. Soc., Perkin Trans. 2*
JCS(S2)	*J. Chem. Soc., (Suppl. 2)*
JEC	*J. Electroanal. Chem. Interfacial Electrochem.*
JEM	*J. Energ. Mater.*
JES	*J. Electron Spectrosc.*
JFA	*J. Sci. Food Agri.*
JFC	*J. Fluorine Chem.*
JGU	*J. Gen. Chem. USSR (Engl. Transl.)*
JHC	*J. Heterocycl. Chem.*
JIC	*J. Indian Chem. Soc.*
JINC	*J. Inorg. Nucl. Chem.*
JLC	*J. Liq. Chromatogr.*
JMAC	*J. Mater. Chem.*
JMAS	*J. Mater. Sci.*
JMC	*J. Med. Chem.*
JMOC	*J. Mol. Catal.*
JMR	*J. Magn. Reson.*
JMS	*J. Mol. Sci.*
JNP	*J. Nat. Prod.*
JOC	*J. Org. Chem.*
JOM	*J. Organomet. Chem.*
JOU	*J. Org. Chem. USSR (Engl. Transl.)*
JPC	*J. Phys. Chem.*
JPJ	*J. Pharm. Soc. Jpn.*
JPO	*J. Phys. Org. Chem.*
JPP	*J. Pharm. Pharmacol.*
JPR	*J. Prakt. Chem.*
JPS	*J. Pharm. Sci.*
JPS(A)	*J. Polym. Sci., Polym. Chem., Part A*
JPU	*J. Phys. Chem. USSR (Engl. Transl.)*
JSC	*J. Serbochem. Soc.*
JSP	*J. Mol. Spectrosc.*
JST	*J. Mol. Struct.*
K	*Kristallografiya*
KFZ	*Khim. Farm. Zh.*
KGS	*Khim. Geterotsikl. Soedin.*
KO	*Kirk-Othmer Encyc.*
KPS	*Khim. Prir. Soedin.*
L	*Langmuir*
LA	*Liebigs Ann. Chem.*
LC	*Liq. Cryst.*
LS	*Life. Sci.*
M	*Monatsh. Chem.*
MC	*Mendeleev Communications*
MCLC	*Mol. Cryst. Liq. Cryst.*
MI	*Miscellaneous [journal or B-yyyyMI for book]*
MIP	*Miscellaneous Pat.*
MM	*Macromolecules*
MP	*Mol. Phys.*
MRC	*Magn. Reson. Chem.*
MS	*Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds', Wiley, New York, 1971*
N	*Naturwissenschaften*
NAT	*Nature*
NEP	*Neth. Pat.*
NJC	*Nouv. J. Chim.*
NJC	*New J. Chem.*
NKK	*Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)*
NKZ	*Nippon Kagaku Zasshi*
NMR	*T. J. Batterham, 'NMR Spectra of Simple Heterocycles', Wiley, New York, 1973*
NN	*Nucleosides & Nucleotides*
NZJ	*N. Z. J. Sci. Technol.*
OBC	*Organic and Biomolecular Chemistry*
OCS	*Organomet. Synth.*
OL	*Org. Lett.*
OM	*Organometallics*
OMR	*Org. Magn. Reson.*
OMS	*Org. Mass Spectrom.*
OPP	*Org. Prep. Proced. Int.*
OPRD	*Org. Process Res. Dev.*
OR	*Org. React.*
OS	*Org. Synth.*
OSC	*Org. Synth., Coll. Vol.*
P	*Phytochemistry*
PA	*Polym. Age*
PAC	*Pure Appl. Chem.*
PAS	*Pol. Acad. Sci.*
PB	*Polym. Bull.*
PC	*Personal Communication*
PCS	*Proc. Chem. Soc.*
PH	*'Photochemistry of Heterocyclic Compounds', O. Buchardt, Ed.; Wiley, New York, 1976*
PHA	*Pharmazi*
PHC	*Prog. Heterocycl. Chem.*
PIA	*Proc. Indian Acad. Sci.*
PIA(A)	*Proc. Indian Acad. Sci., Sect. A*
PJC	*Pol. J. Chem.*
PJS	*Pak. J. Sci. Ind. Res.*
PMH	*Phys. Methods Heterocycl. Chem.*
PNA	*Proc. Natl. Acad. Sci. USA*
POL	*Polyhedron*
PP	*Polym. Prepr.*
PRS	*Proceed. Roy. Soc.*
PS	*Phosphorus Sulfur (formerly); Phosphorus Sulfur Silicon (currently)*
QR	*Q. Rev., Chem. Soc.*
QRS	*Quart. Rep. Sulfur Chem.*
QSAR	*Quant. Struct. Act. Relat.*
RC	*Rubber Chem. Technol.*
RCB	*Russian Chemical Bull.*
RCC	*Rodd's Chemistry of Carbon Compounds*
RCM	*Rapid Commun. Mass Spectrom.*
RCP	*Rec. Chem. Prog.*
RCR	*Russ. Chem. Rev. (Engl. Transl.)*
RHA	*Rev. Heteroatom. Chem.*
RJ	*Rubber J.*
RJGC	*Russ. J. Gen. Chem. (Engl. Transl.)*
RJOC	*Russ. J. Org. Chem. (Engl. Transl.)*
RP	*Rev. Polarogr.*
RRC	*Rev. Roum. Chim.*
RS	*Ric. Sci.*
RTC	*Recl. Trav. Chim. Pays-Bas*
RZC	*Rocz. Chem.*
S	*Synthesis*
SA	*Spectrochim. Acta*
SA(A)	*Spectrochim. Acta, Part A*
SAP	*S. Afr. Pat.*
SC	*Synth. Commun.*
SCI	*Science*
SH	*W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds', Wiley, New York, 1977, parts 1 and 2.*
SL	*Synlett*
SM	*Synth. Met.*
SR	*Sulfur Reports*
SRC	*Supplements to Rodd's Chemistry of Carbon Compounds*
SRI	*Synth. React. Inorg. Metal-Org. Chem.*
SS	*Sch. Sci. Rev.*
SSR	*Second Supplements to Rodd's Chemistry of Carbon Compounds*
SST	*Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]*
SUL	*Sulfur Letters*
SZP	*Swiss Pat.*
T	*Tetrahedron*
T(S)	*Tetrahedron, Suppl.*
TA	*Tetrahedron Asymmetry*
TAL	*Talanta*
TCA	*Theor. Chim. Acta*
TCC	*Top. Curr. Chem.*
TCM	*Tetrahedron, Comp. Method*
TFS	*Trans. Faraday Soc.*
TH	*Thesis*
TL	*Tetrahedron Lett.*
TS	*Top. Stereochem.*
UK	*Usp. Khim.*
UKZ	*Ukr. Khim. Zh. (Russ. Ed.)*
UP	*Unpublished Results*
URP	*USSR Pat.*
USP	*U.S. Pat.*
WOP	*PCT Int. Appl. WO* (World Intellectual Property Organization Pat. Appl.)
YGK	*Yuki Gosei Kagaku Kyokaishi*
YZ	*Yakugaku Zasshi*
ZAAC	*Z. Anorg. Allg. Chem.*
ZAK	*Zh. Anal. Khim.*
ZC	*Z. Chem.*
ZN	*Z. Naturforsch.*
ZN(A)	*Z. Naturforsch., Teil A*
ZN(B)	*Z. Naturforsch., Teil B*
ZOB	*Zh. Obshch. Khim.*
ZOR	*Zh. Org. Khim.*
ZPC	*Hoppe-Seyler's Z. Physiol. Chem.*
ZPK	*Zh. Prikl. Khim.*

List of Abbreviations

TECHNIQUES/CONDITIONS

18-C-6	18-crown-6
)))))	ultrasonic (sonochemistry)
Δ	heat, reflux
AAS	atomic absorption spectroscopy
AES	atomic emission spectroscopy
AFM	atomic force microscopy
approx.	approximately
aq.	aqueous
b.p.	boiling point
CD	circular dichroism
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
conc.	concentrated
CT	charge transfer
ee	enantiomeric excess
equiv.	equivalent(s)
ESR	electron spin resonance
EXAFS	extended X-ray absorption fine structure
FVP	flash vacuum pyrolysis
g	gaseous
GC	gas chromatography
GLC	gas–liquid chromatography
h	Planck's constant
h	hour
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
$h\nu$	light (photochemistry)
ICR	ion cyclotron resonance
INDO	incomplete neglect of differential overlap
IR	infrared
l	liquid
LCAO	linear combination of atomic orbitals
LUMO	lowest unoccupied molecular orbital
MCD	magnetic circular dichroism
MD	molecular dynamics
min	minute(s)
MM	molecular mechanics
MO	molecular orbital
MOCVD	metal organic chemical vapor deposition
m.p.	melting point
MS	mass spectrometry

MW	molecular weight
NMR	nuclear magnetic resonance
NQR	nuclear quadrupole resonance
ORD	optical rotatory dispersion
PE	photoelectron
ppm	parts per million
rt	room temperature
s	solid
SCF	self-consistent field
SET	single electron transfer
S_N1	first-order nucleophilic substitution
S_N2	second-order nucleophilic substitution
S_Ni	internal nucleophilic substitution
STM	scanning tunneling microscopy
TLC	thin-layer chromatography
UV	ultraviolet
vol.	volume
wt.	weight

REAGENTS, SOLVENTS, ETC.

Ac	acetyl CH_3CO-
acac	acetylacetonato
acam	acetamide
AcO	acetate
AcOH	acetic acid
AIBN	2,2′-azobisisobutyronitrile
Ans	ansyl
Ar	aryl
ATP	adenosine 5′-triphosphate
9-BBN	9-borabicyclo[3.3.1]nonyl
9-BBN-H	9-borabicyclo[3.3.1]nonane
BEHP	bis (2-ethylhexyl) phthalate
BHT	2,6-di-*t*-butyl-4-methylphenol (butyrated hydroxytoluene)
binap	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
bipy	2,2′-bipyridyl
Bn	benzyl $C_6H_5CH_2$- (NB avoid confusion with Bz)
t-BOC	*t*-butoxycarbonyl
bpy	2,2′-bipyridyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
BSTFA	*N*,*O*-bis(trimethylsilyl)trifluoroacetamide
Bt	benzotriazole
BTAF	benzyltrimethylammonium fluoride
Bz	benzoyl C_6H_5CO- (NB avoid confusion with Bn)
Bzac	benzoylacetone
CAN	ceric ammonium nitrate
Cbz	carbobenzoxy
chalcogens	oxygen, sulfur, selenium, tellurium
CH_2Cl_2	dichloromethane
COD	1,5-cyclooctadiene
COT	cyclooctatetraene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
CTAB	cetyl trimethyl ammonium bromide
DABCO	1,4-diazabicyclo[2.2.2]octane

DBA	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAC	diethylaluminum chloride
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate (+ or −)
DHP	dihydropyran
DIBAL-H	diisobutylaluminum hydride
diglyme	diethylene glycol dimethyl ether
dimsyl Na	sodium methylsulfinylmethide
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPT	diisopropyl tartrate (+ or −)
DMA	dimethylacetamide
DMAC	dimethylaluminium chloride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMI	*N*,*N*′-dimethylimidazolidinone
DMN	diaminomaleonitrile
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio)sulfonium fluoroborate
DPPB	1,2-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1′-bis(diphenylphosphino)ferrocene
DPPP	1,2-bis(diphenylphosphino)propane
E^+	electrophile
EADC	ethylaluminium dichloride
EDG	electron-donating group
EDTA	ethylenediaminetetraacetate
EEDQ	*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
EWG	electron-withdrawing group
HMPA	hexamethyl phosphoramide
HMPT	hexamethylphosphoric triamide
$IpcBH_2$	isopinocampheylborane
Ipc_2BH	diisopinocampheylborane
KAPA	potassium 3-aminopropylamide
K-selectride	potassium tri-*s*-butylborohydride
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LICA	lithium isopropyl cyclohexylamide
LITMP	lithium tetramethyl piperidide
L-selectride	lithium tri-*s*-butyl borohydride
LTA	lead tetraacetate
MAO	monoamine oxidase
MCPBA	3-chloroperoxybenzoic acid
MCT	mercury cadmium telluride
Me	methyl
MEM	methoxyethoxymethyl
MEM-Cl	methoxyethoxymethyl chloride
MeOH	methanol
MMA	methyl methacrylate
MMC	methylmagnesium carbonate
MOM	methoxymethyl

Ms	methanesulfonyl (mesylate)
MSA	methanesulfonic acid
MsCl	methanesulfonyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
Nu^-	nucleophile
PPA	polyphosphoric acid
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
phen	1,10-phenanthroline
Phth	phthaloyl
PPE	polyphosphate ester
PPO	2,5-diphenyloxazole
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Pyr	pyridine
Red-Al	sodium bis(methoxyethoxy)aluminum dihydride
SDS	sodium dodecyl sulfate
SEM	trimethylsilylethoxymethyl
Sia_2BH	disiamylborane
SM	starting material
TAS	tris(diethylamino)sulfonium
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDMS-Cl	*t*-butyldimethylsilyl chloride
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TCE	2,2,2-trichloroethanol
TCNE	tetracyanoethylene
TEA	tetraethylammonium
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPBSCl	2,4,6-triisopropylbenzenesulfonyl chloride
TIPSCl	triisopropylsilyl chloride
TMEDA	tetramethylethylenediamine [1,2-bis(dimethylamino)ethane]
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
Tol	tolyl $C_6H_4(CH_3)$–
TosMIC	tosylmethyl isocyanide
TPP	meso-tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Tris	tris(hydroxymethyl)aminomethane
Ts	4-toluenesulfonyl (tosyl)
TTFA	thallium trifluroacetate
TTMSS	tris(trimethylsilyl)silane
TTN	thallium(III) nitrate
X	halogen or leaving group

Volume 3 - Synthesis: Carbon With One Heteroatom Attached by a Multiple Bond

Part I: Tricoordinated Carbon Functions, R_2C Y

3.01
Aldehydes: Alkyl Aldehydes

S. HANDA
University of Leicester, Leicester, UK

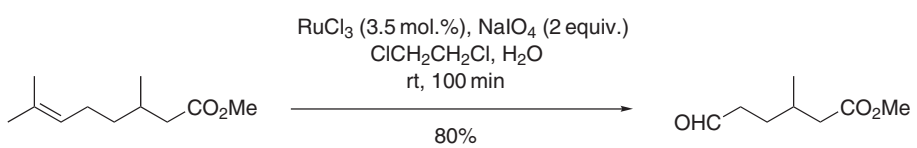
3.01.1 SATURATED UNSUBSTITUTED ALDEHYDES

3.01.1.1 From Alkanes

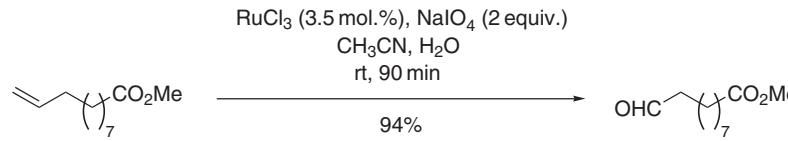
The direct oxidation of terminal methyl groups of alkanes to the corresponding aldehydes remains a difficult challenge and there are still no generally employed and synthetically useful methods for this conversion. Although the transformation can be achieved without over-oxidation to the carboxylic acid using osmium trichloride in acetonitrile, low regioselectivity and hence competitive formation of ketones, limits the usefulness of this reaction <2002MI233>. Despite these difficulties, there is considerable interest in the direct metal-catalyzed oxidation of hydrocarbons and this area has recently been reviewed <2003CR163>. An alternative approach to simple alkyl aldehydes involves the photochemical carbonylation of alkanes in the presence of a rhodium catalyst ($Rh(PMe_3)_2(CO)Cl$) <1995JOM(504)115>. However, careful control of reaction conditions is required to ensure the necessary regioselectivity for linear aldehydes. Ethane has also been converted into propionaldehyde using this method under supercritical conditions <2001AG(E)2692>.

3.01.1.2 From Alkenes

Chapter 3.01.1.2 of <1995COFGT(3)1> described the use of ozone and hydroformylation for the conversion of alkenes into aldehydes (via cleavage and homologation respectively) and these are still the most widely used methods. The use of ozone for the cleavage of alkenes has been made more straightforward with the development of novel polymer-supported phosphines <1999JOC5188> and tertiary amines <2003T493> that significantly simplify the reductive work-up of these reactions. A ruthenium trichloride (catalytic)–sodium periodate system has also been used to cleave alkenes to aldehydes <2001JOC4814>. The reaction conditions employed are crucial to the efficiency of this transformation; thus di- and trisubstituted alkenes are cleaved in good yields using a biphasic 1,2-dichloroethane–water solvent system (Equation (1)), whereas monosubstituted aliphatic alkenes require homogeneous conditions of acetonitrile–water system (Equation (2)).



(1)



(2)

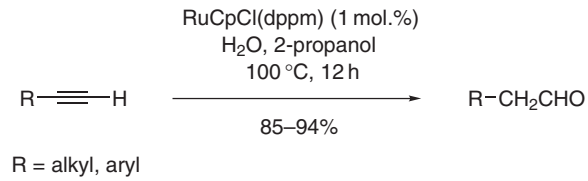
The oxidation of alkylboranes (formed by the hydroboration of alkenes) to aldehydes using tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) also provides a direct one-pot conversion of alkenes into aldehydes <1997TL2813>.

The hydroformylation of alkenes is still an extremely important method for the industrial formation of aliphatic aldehydes. A great many advances have been made in this area and its current status and importance has been reviewed <B-2002MI001>. In contrast to its industrial importance, alkene hydroformylation remains relatively under-utilized in synthesis and this is most probably due to the difficulties in controlling the selectivity of the reaction. A large number of studies have sought to address this problem and the reader in encouraged to examine two recent reviews in this area <2001S1, 2003ACR264>.

3.01.1.3 From Alkynes

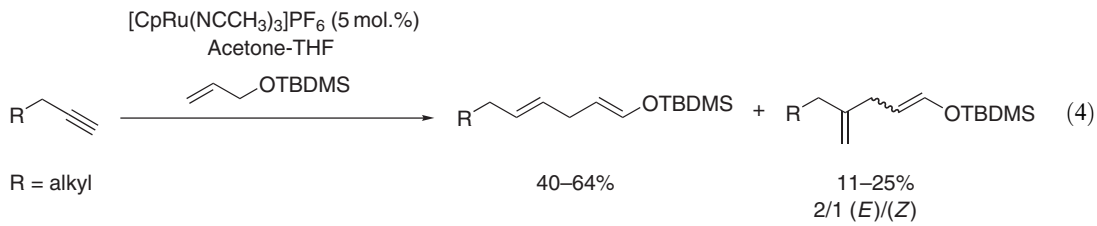
The conversion of alkynes into aldehydes by hydroboration and oxidation of the resulting vinylboranes was discussed in chapter 3.01.1.3 of <1995COFGT(3)1>. The greatest challenge in this conversion is controlling the regioselectivity of the hydroboration step. This methodology can be significantly improved by the use of isopinocampheyliodoborane-dimethyl sulfide <1994MI687>, which carries out the transformation with increased regioselectivity compared to the previously employed thexyl- and dimesitylboranes. The selective hydroboration of terminal alkynes in the presence of carbonyl groups has also been achieved using dicyclohexylborane to generate, after oxidation, dicarbonyl compounds <1997TL7681>.

The ruthenium-catalyzed *anti*-Markovnikov hydration of terminal alkynes has recently emerged as a significant development in the synthesis of aldehydes. Thus, either $RuCl_2$-(C_6H_6)($C_6F_5PPh_2$) (10 mol.%) in the presence of $C_6F_5PPh_2$ (30 mol.%) <1998AG(E)2867>, Ru(η^5-C_9H_7)Cl(PPh_3)$_2$ (5 mol.%) <2001TL8467>, or RuCpCl(dppm) (1 mol.%) <2001OL735> catalyze this hydration to generate aldehydes in excellent yield (Equation (3)). These reactions are thought to involve protonation of a η^2-alkyne complex <2001JA11917>. Notably, a ruthenium catalyst that operates at near-neutral conditions and is therefore compatible with silicon-based and acetal-based alcohol protecting groups has also been reported <2001AG(E)3884>.



(3)

Synthetic methodology for the ruthenium-catalyzed formation of enol silanes from alkynes has been introduced by Trost and co-workers (Equation (4)) <2001JA2897>. Since hydrolysis of the linear enol silane products delivers the corresponding aldehydes, thus this methodology enables the formal three-carbon chain extension of alkynes to aldehydes.

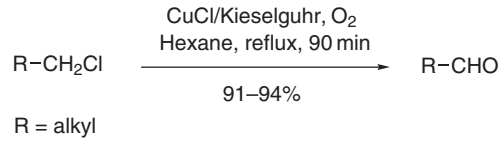


(4)

3.01.1.4 From Halides

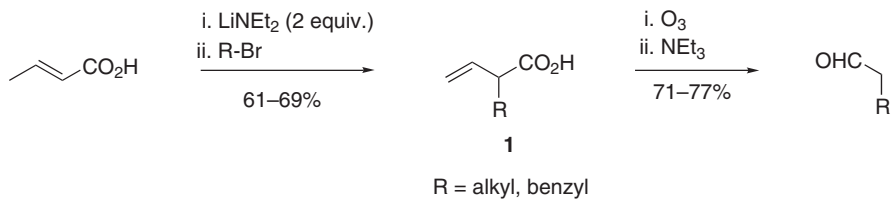
The oxidation of primary alkyl halides to aldehydes by treatment with a variety of reagents (including *N*-oxides and sulfoxides) was described in chapter 3.01.1.4 of <1995COFGT(3)1>. The difficulty with this approach is the harsh conditions (high temperatures and/or long reaction times) that are often required. However, this conversion can now be carried out under milder conditions (150 °C/40–60 min) using $NaIO_4$ (1 equiv.) in dimethylformamide (DMF) <2003TL1375>. More significant is the report that treatment of primary alkyl halides with

copper(I) chloride adsorbed on Kieselguhr in refluxing hexane and in the presence of oxygen furnishes the corresponding aldehydes in excellent yields <1999JCR(S)434>. Particularly noteworthy is the successful reaction of unactivated alkyl chlorides (Equation (5)) and the fact that the catalyst can be recovered from the reaction by simple filtration and can be reused with no notable drop in chemical yield.

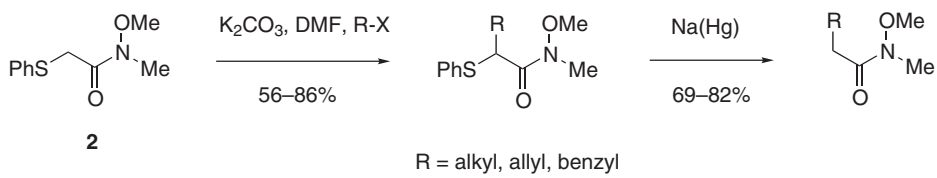


(5)

In addition to the above methods, a solid-phase synthesis of aldehydes from the corresponding halides has also been reported <2002JOC2677>. The oxidative conversion of alkyl halides into *N*,*N*-dimethylhydrazones <2000SL1673> also provides access to aldehydes via hydrolysis of these products. The reduction of alkyl halides by electrogenerated nickel(I) salen in DMF in the presence of water, oxygen, and light also produces aldehydes, presumably via the corresponding alkyl radical <2003TL3245>. Finally, two convenient procedures for the two-carbon homologation of alkyl halides to aldehydes have been reported. The first involves α-alkylation of dienediolates prepared from α,β-unsaturated carboxylic acids, followed by ozonolysis of the resulting β,γ-unsaturated carboxylic acids **1** and subsequent *in situ* decarboxylation (Scheme 1) <1997T10883>. Alternatively, reaction of alkyl halides with the sulfonyl-acetamide **2** leads to chain-elongated products that can be subsequently desulfonated to produce the corresponding Weinreb amides which are precursors to aldehydes (Scheme 2) <2000S375>.



Scheme 1



Scheme 2

3.01.1.5 From Alcohols and Their Derivatives

3.01.1.5.1 By oxidation of primary alcohols

The search for mild, selective, clean (e.g., efficient and readily worked-up), and environmentally friendly methods for the oxidation of primary alcohols to the corresponding aldehydes remains an extremely important area in organic synthesis. Numerous reports have been published since the 1990s but the majority of those most synthetically useful fall into the same six categories that were used in chapter 3.01.1.5.1 of <1995COFGT(3)1>, namely: (i) metal reagents, (ii) activated DMSO reagents, (iii) halogen-based oxidants, (iv) Oppenauer-type oxidations, (v) electrochemical and photochemical oxidations, and (vi) miscellaneous methods. Recent advances will be discussed in these areas with the emphasis on methods which hold advantages over those that were described previously.

(i) Using metal ion-based oxidants

(a) Chromium reagents. The oxidation of alcohols to aliphatic aldehydes using chromium-based reagents such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), and numerous derivatives thereof was described in detail in chapter 3.01.1.5.1 of <1995COFGT(3)1>. A wide variety of such derivatives exist allowing for control and selectivity of the oxidation step. Whilst a number of new systems have been reported since the earlier discussion, the majority of these complement "older" reagents and do not necessarily offer major advantages. However, some notable advances have been made, and these include the use of microwaves to increase the efficiency of PCC reactions <1999JCR(S)118> and the development of tetramethylammonium fluorochromate, which has been shown to require shorter reaction times and give higher yields than similar reagents <2003TL4555>. Additionally, ammonium dichromate either adsorbed on alumina <1997SC953> or in the presence of silica chloride/wet silica (resulting in the *in situ* generation of low levels of chromic acid) <2003MI1021> can also be used for the controlled oxidation of alcohols to aldehydes.

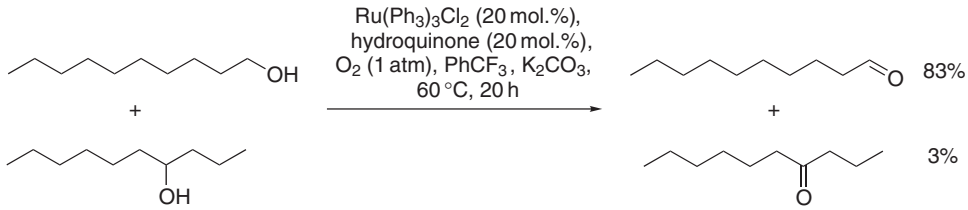
The use of chromium trioxide for the preparation of aldehydes has been reinvestigated and a number of simple procedures are now available for this transformation. Thus, solvent-free conditions offer a new and efficient method for this oxidation <2002TL6095> and the use of CrO_3 and zeolite H-ZSM 5 (in place of the sulfuric acid commonly employed in the Jones oxidation) gives conditions that are compatible with acid-sensitive groups such as acetals <1997JCR(S)462>. Alternatively, a silica gel-supported version of the Jones reagent can also be used <2001SC3383>. Chromium trioxide, either supported or entrapped on silica and zirconia, can also be employed <2003T4997>. This gives a reagent that can be easily removed (by filtration) from the reaction (without leaching of chromium into the solution) and that can be repeatedly recycled without significant loss in activity. Chromium dioxide (Magtrieve^{TM}) is a magnetic solid that can be used as a mild oxidant for primary alcohols <1997TL3857>. It offers the considerable advantage that it can be readily removed from the reaction (by virtue of its magnetism), regenerated, and reused. The use of microwave conditions in this process has been shown to be beneficial <2003T649>.

The oxidation of unactivated primary alcohols to aldehydes with systems that are catalytic in chromium is relatively rare. One notable example is the use of chromium(III) acetylacetonate (10 mol.%)–periodic acid (1.5 equiv.) <2003TL2553>.

(b) Manganese reagents. Whilst simple Mn(VI) or Mn(VII) salts are generally too powerful to be useful for the conversion of primary alcohols into saturated aldehydes, a number of modified reagents are available for this transformation. Thus, under hetereogeneous conditions the reactivity of potassium permanganate is sufficiently lowered to prevent over-oxidation of the product aldehyde, and the reaction has been successfully carried out using alumina under solvent-free conditions <2001TL5833> and using silica–sulfuric acid (formed from silica gel and chlorosulfonic acid) plus wet silica <2003MI400>. An alternative approach involves the use of Mn(III) species together with a co-oxidant such as hydrogen peroxide <2002ICA(337)75> or Oxone® <2003TL8943>. Finally, whilst manganese dioxide is generally used only for the oxidation of activated (e.g., allylic and benzylic) alcohols, it can somewhat surprisingly carry out the analogous oxidation of unactivated primary alcohols under *in situ* oxidation-Wittig conditions <1999CC1337>. Aldehydes are not isolated from the reaction as they undergo immediate Wittig homologation, and therefore this procedure is particularly useful for cases where aldehyde instability would make isolation difficult.

(c) Ruthenium reagents. The use of bis(triphenylphosphine)ruthenium(II) chloride ($RuCl_2(PPh_3)_2$) as a homogeneous catalyst for the oxidation of alcohols to aldehydes in the presence of a suitable primary oxidant was described in chapter 3.01.1.5.1 of <1995COFGT(3)1>. Oxygen can also be employed as a clean and inexpensive oxidant for this reaction in the presence of $RuCl_2(PPh_3)_2$ (1.5 mol.%) and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (4.5 mol.%), albeit at relatively high temperatures and pressures <1999CC1591>. The same ruthenium catalyst also oxidizes primary alcohols via hydrogen transfer from methyl vinyl ketone under microwave irradiation <2003TL9201>. In an effort to aid catalyst recovery and separation, a number of heterogeneous Ru-based oxidizing systems have also been developed. Thus, ruthenium supported on aluminia <2002AG(E)4538>, on poly(4-vinylpyridine) <2000TL3971>, and in the form of a multimetal cluster <2003MI615> have all been shown to produce saturated aldehydes from the corresponding alcohols. The addition of a small amount of hydroquinone to these systems can often prevent any over-oxidation to the corresponding

carboxylic acid. An interesting feature of some catalytic ruthenium systems is their ability to selectively oxidize primary alcohols in the presence of secondary ones (Equation (6)) <1998TL5557>. This selectivity is such that primary saturated alcohols can even be selectively oxidized in the presence of secondary benzylic ones under photochemical conditions and using a ruthenium–salen complex in the presence of air <2001TL7067>.



(6)

TPAP is perhaps one of the most important oxidizing reagents for the formation of aldehydes from saturated alcohols, and advances continue to be made in the application of this reagent. Most significantly, molecular oxygen can now be used as the co-oxidant (in place of the *N*-methylmorpholine *N*-oxide (NMO) usually employed) thus greatly simplifying both the reaction and the purification procedure <1997JCS(P1)3291, 1997JA12661, 2002JMOC(180)77>. Interestingly, the reaction of primary aliphatic alcohols is found to be more efficient in the absence of the 4 Å molecular sieves normally employed in the reaction, although the specific reasons for this remain unclear <1997JA12661>. The TPAP reagent has also been immobilized on such supports as Amberlyst anion exchange resin <1997JCS(P1)1907> and Sol–gel silica <2001TL4511>, both of which aid catalyst separation and recycling. Similarly, polymer-supported NMO can also be used as a recyclable co-oxidant <2001SL1257>.

(d) Miscellaneous metal oxidants. The palladium-catalyzed oxidation of primary alcohols, especially using oxygen as a co-oxidant, has recently undergone extensive investigation. This reaction offers a potentially very mild method for the formation of saturated aldehydes and many of the most recent developments in this area can be found in an extensive review by Muzart <2003T5789>. The reaction has also been carried out using a fluorous biphase system together with a novel perfluoroalkylated-pyridine ligand and, although yields of saturated aldehydes are modest, the active palladium species may be easily separated and can be reused several times without significant loss in activity <2000JCS(P1)4301>. Copper-catalyzed oxidations can also be employed for the production of saturated aldehydes. Thus, Markó and co-workers have reported a novel catalytic protocol employing 5 mol.% of a simple copper complex CuCl·Phen (Phen = 1,10-phenanthroline) and 5 mol.% of di-*t*-butyl azodicarboxylate together with oxygen as the stoichiometric oxidant <1999JOC2433>. The reaction can also be run under anaerobic conditions if greater than 1 equiv. of the azodicarboxylate is used <1997AG(E)2208>. Copper(I) bromide-mediated oxidations can also be performed successfully under fluorous biphasic conditions allowing for catalyst recovery and recycling <2000TL4343>.

Other metal-based oxidants include: polymer-supported anionic peroxomolybdenum complexes <1999MI1445>, osmium tetroxide in association with sulfoxides or NMO <2000CR(C)765>, and cobalt nitrate supported on silica gel <2003SC601>. In the last of these cases, the use of microwaves can lead to dramatic enhancements in both the rate and yield of the reaction. A zirconium-based procedure can also be used although care must be taken to avoid over-oxidation to the carboxylic acid <1996JOC1467>.

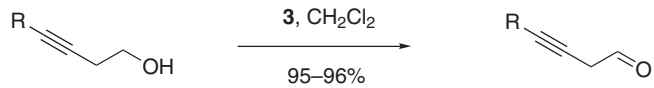
(ii) Using DMSO reagents

Procedures for the oxidation of primary alcohols to saturated aldehydes based upon activated DMSO (e.g., the Swern oxidation) are amongst the most commonly used reactions for this transformation due in part to the mild conditions involved and the resulting functional group compatibility. However, there are two potential drawbacks to these procedures, namely, the production of the unpleasant smelling volatile by-product dimethyl sulfide and the use of activating agents, such as oxalyl chloride, that are moisture-sensitive and toxic and which react violently with DMSO, thus potentially limiting the use of this reaction in large-scale work. The first issue has been addressed by using soluble polymer-bound sulfoxides attached to polystyrene <2003T7171> or poly(ethylene glycol) <1998JOC2407>, both of which can be recycled as necessary. Alternatively, a fluorous sulfoxide has been reported and this reagent can be efficiently

recovered for reuse by a simple continuous fluorous-extraction of the reaction mixture <2002T3865>. Perhaps more straightforward, and certainly cheaper, is the use dodecyl methyl sulfoxide in place of DMSO, and although slightly longer reaction times are required (compared to the traditional Swern procedure) the whole process is odor free <2002TL5177>. In a similar manner, replacement of oxalyl chloride by either cyanuric chloride <2001JOC7907> or triphenylphosphine dibromide ($Ph_3P{\cdot}Br_2$) <2002TL8355> is especially useful for large-scale preparations.

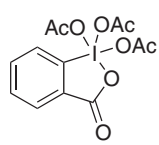
(iii) Using halogen-based reagents

The hypervalent iodine reagent Dess–Martin periodinane **3** (DMP) was discussed in chapter 3.01.1.5.1 of <1995COFGT(3)1>. In recent years this oxidant has become one of the reagents of choice for the oxidation of primary alcohols to saturated aldehydes. The mild reaction conditions, ease of use and excellent chemoselectivity associated with **3** have made it successful in many cases where more traditional approaches have failed due to the sensitivity of the starting material or product. For numerous examples of such situations the reader is directed to the relevant section in a recent review of polyvalent iodine compounds <2002CRV2523>. The use of **3** has been further enhanced by the discovery that water can accelerate DMP-mediated oxidations <1994JOC7549> and by the use of a modified anhydrous work-up procedure that is particularly suitable for very sensitive homoallylic and homopropagylic aldehydes (Equation (7)) <2002S326>.



R = alkyl (7)

The synthetic precursor to DMP is 2-iodoxybenzoic acid **4** (IBX, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) and this reagent had previously only seen limited use in organic synthesis mainly due to its insolubility in all common organic solvents except DMSO. However, the easy preparation, cheaper cost, and moisture insensitivity of IBX when compared to DMP has led to a series of investigations into its use as an oxidizing reagent. Thus, solutions of IBX in DMSO have been shown to act as a mild and efficient oxidizing agent for the synthesis of saturated aldehydes <1995JOC7272>. Additionally, the same reaction can be carried out in a water–acetone mixture employing β-cyclodextrin (10 mol.%) as a supramolecular catalyst <2003JOC2058>. The range of solvents that can be used for this reaction has been expanded by employing polymer-bound reagents on either silica <2001AG(E)4393> or polystyrene <2003TL1635> supports. The synthetic routes to these supported reagents are relatively lengthy and therefore a novel two-step procedure to a highly active polystyrene-supported IBX amide has been developed <2003TL9251>. Alternatively, IBX is soluble in imidazolium-based ionic liquids allowing the reactions to be carried out under homogeneous conditions <2003OL3321, 2003SL2249>. However, the use of all these protocols may be negated somewhat by the fact that suspensions of IBX in refluxing ethyl acetate will smoothly oxidize alcohols to aldehydes <2002OL3001>. The procedure is broadly applicable (although the number of saturated alkyl aldehydes that have been produced to date is limited), insensitive to both air and moisture, and allows the IBX to be recycled by simple filtration of the by-products which can then be readily re-oxidized to IBX. Finally, it should be noted that large-scale and industrial applications of IBX (and DMP) have tended to be limited by safety concerns relating to its preparation and potential violent decomposition when heated or under impact. These issues have been addressed by a more convenient preparation <1999JOC4537> and the development of nonexplosive formulations of the reagent <2003OL2903>.



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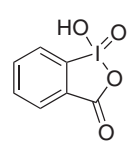


4

(iv) Oppenauer and related oxidations

Traditional Oppenauer oxidations involve the aluminum alkoxide-catalyzed hydrogen transfer from alcohols to an excess of an acceptor ketone or aldehyde (see chapter 3.01.1.5.1) of <1995COFGT(3)1> and <1994S1007> for a review. The oxidation of primary alcohols, however, is often problematic due to competing side-reactions of the product aldehyde, including aldol condensation with the acceptor ketone and Tishchenko reactions leading to esters. These potential problems have meant that only a limited number of metal-catalyst–hydrogen-acceptor systems have been employed successfully and these include $Zr(OBu^t)_4$—CCl_3CHO <1996S1341>. Two iridium catalysts have also been reported, and both these systems have the advantage that inexpensive acetone or 2-butanone can be used as the hydrogen-acceptor, although the yields of saturated aliphatic aldehydes are often moderate <2003JOC1601, 2002JOM(649)289>. A homogeneous $Ru_3(CO)_{12}$—PPh_3-based system can also be successfully employed <2004T1065>.

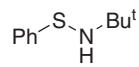
(v) Electrochemical and photochemical oxidations

Whilst the electrochemical and photochemical oxidation of primary alcohols has the potential to be a mild and selective method for this transformation, there have been very few advances made in this area since it was last described in chapter 3.01.1.5.1 of <1995COFGT(3)1>. One significant report is the electrocatalytic oxidation of primary alcohols mediated by decahydroquinolinyl-*N*-oxyl radicals <1999H1945>.

(vi) Miscellaneous oxidations

The use of stable organic nitroxyl radicals for the oxidation of alcohols plays an increasingly important role in organic synthesis. This is due to the mild reaction conditions involved, together with the excellent chemoselectivity for the oxidation of primary hydroxyl groups in the presence of secondary alcohols that is often observed. An extensive review of the area up to 1996 and including tabulated examples has been published <1996S1153>. The most frequently used radical in this class is TEMPO and, although this reagent was originally used in stoichiometric amounts, it is now most commonly employed as a catalyst together with a suitable co-oxidant. Since 1996 a number of different co-oxidants that can be successfully used to furnish saturated aldehydes have been reported, including [bis(acetoxy)iodo]benzene ($PhI(OAc)_2$) <1997JOC6974>, *N*-chlorosuccinimide <1996JOC7452>, trichloroisocyanuric acid <2001OL3041>, and Oxone® <2000OL1173>. Molecular oxygen can also be used, although this normally requires the additional presence of transition metal catalysts such as ruthenium ($RuCl_2(PPh_3)_3$) <2001JA6826> and Mn(II)–Co(II) or Mn(II)–Cu(II) nitrate <2001TL6651>. The drive to meet the demands for simplified work-up procedures and reagent recycling has also led to the development of both polymer-supported <2003TL1639, 2000CC271> and silica-supported <2001JOC8154> TEMPO catalysts. Alternatively, polymer-attached co-oxidants based on 4-(diacetoxyiodo)styrene <2003S21> and bromite(I) <2000OL3781> can be used, although the latter system is incompatible with alkene functionality. The transformation can also be carried out in an ionic liquid although the yields obtained with saturated primary aliphatic alcohols are moderate <2002OL1507>. Finally, whilst the majority of TEMPO-mediated reactions will preferentially oxidize primary alcohols over secondary ones, this selectivity can be completely reversed by using a TEMPO–periodic-acid system <2002SL616>.

A number of other oxidation procedures should be noted. Thus, sodium hypochlorite will cleanly convert saturated primary alcohols into the corresponding aldehydes under phase-transfer conditions <1998TL7263>. The same transformation can also be achieved with catalytic *N*-*t*-butylbenzenesulfenamide **5** in the presence of *N*-chlorosuccinimide <2003T6739>. The reaction is thought to proceed via the corresponding sulfinimidoyl chloride **6**, and this reagent has also been successfully attached to polystyrene to give a polymer-supported reagent for this reaction which may be efficiently recycled <2003BCJ1433>.



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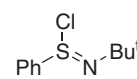
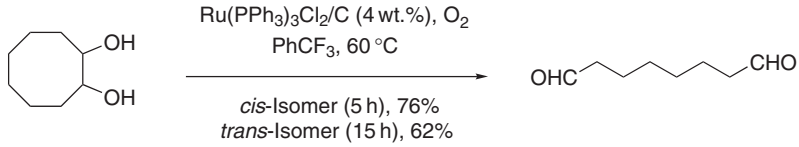


6

3.01.1.5.2 From diols

The formation of aldehydes by the oxidative cleavage of 1,2-diols was discussed in chapter 3.01.1.5.2 of <1995COFGT(3)1>, and there have been relatively few advances on the reagents mentioned previously (e.g., periodate and lead(IV) acetate). Taylor and co-workers have described a procedure for 1,2-diol cleavage with *in situ* trapping of the resultant aldehyde with a stabilized phosphorane <2002TL6185>. Additionally, the use of catalytic $Ru(PPh_3)_3Cl_2$ on active carbon has also been shown to cleave 1,2-diols by reaction with oxygen generating aldehydes in fair-to-good yields although over-oxidation to the corresponding carboxylic acids can be a problem <1999OL713>. This system reacts with both *cis*- and *trans*-1,2-cyclooctanediol although the latter isomer is somewhat slower to react (Equation (8)). In a related reaction, 1,2-amino alcohols and diamines have been oxidatively cleaved to give the corresponding aldehydes and imines in high yields by treatment with $BF_3{\cdot}OEt_2$ under an atmosphere of oxygen <2001TL8865>.

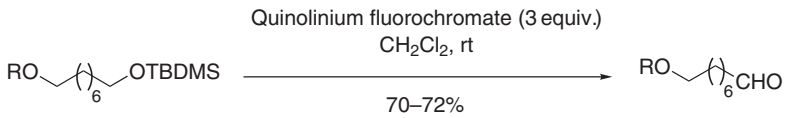


(8)

3.01.1.5.3 Oxidation of alcohol derivatives

(i) Ethers

Chapter 3.01.1.5.3 of <1995COFGT(3)1> described the oxidative conversion of alkyl and silyl ethers of primary alcohols to give aldehydes via reaction with hydride-abstracting reagents (e.g., trityl tetrafluoroborate) or with traditional alcohol oxidizing reagents (e.g., DMSO/oxalyl chloride). Synthetically, most interest has been focused on the direct oxidation of *O*-silyl and *O*-tetrahydropyranyl-protected alcohols and toward the development of reagents that function under mild conditions and with increased selectivity. For example, freshly prepared quinolinium fluorochromate has been shown to carry out the selective oxidation of primary *t*-butyldimethylsilyl ethers to aldehydes in the presence of secondary silyl ethers and under conditions compatible with other acid-sensitive protective groups such as tetrahydropyranyl and methoxymethyl ethers <1997JOC2628> (Equation (9)). Other reagents that have been reported to selectively oxidize protected primary alcohols include: 3-carboxypyridinium chlorochromate (trimethylsilyl ethers in the presence of tetrahydropyranyl ethers) <1997S756>, 2-iodoxybenzoic acid (triethylsilyl ethers in the presence of ketals and dithianes) <2002OL2141>, and *n*-butyltriphenylphosphonium peroxodisulfate (trimethylsilyl and tetrahydropyranyl ethers in the presence of ethylene acetals and ketals) <2002SC1311>. Many other reagents have also been reported for this conversion, although with no indication as to their potential selectivity. These include, 4-(dimethylamino)pyridinium and 2,2′-bipyridinium chlorochromates (tetrahydropyranyl ethers) <1998JCR(S)146>, montmorillonite-supported bis(trimethylsilyl)chromate (trimethylsilyl ethers) <1998JCR(S)620>, tetramethylammonium chlorochromate-aluminum trichloride <2003SC871> and zeolite-supported iron(III) nitrate (zeofen) <2001SC2097> (both of which oxidize trimethylsilyl and tetrahydropyranyl ethers).

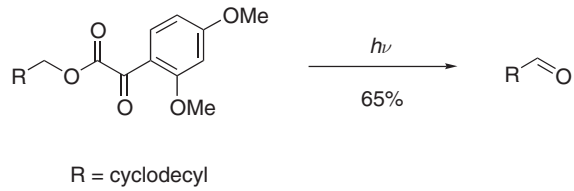


(9)

R = THP, MOM

(ii) Esters

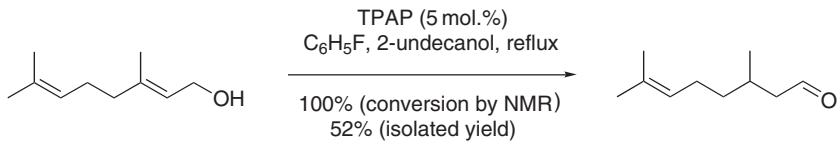
Very few advances have occurred in this area since the publication of chapter 3.01.1.5.3 in <1995COFGT(3)1>, although the photochemical oxidation of substituted benzoylformate esters of primary alcohols via hydrogen atom transfer is one exception (Equation (10)) <1995JOC2461>. Additionally, primary toluenesulfonate esters can be converted into the corresponding aldehydes using the copper(I) chloride–Kieselguhr–O_2 system described for halides in Section 3.01.1.4 <1999JCR(S)434>.



(10)

3.01.1.5.4 Rearrangement of allylic alcohols

Allylic alcohols can be isomerized to aldehydes by transposition of the double bond to give, in the first instance, the corresponding enol. As described in chapter 3.01.1.5.4 of <1995COFGT(3)1>, this transformation is usually achieved by treatment of allylic alcohols with *N*-lithiodiamines or via ruthenium(II)-catalyzed rearrangements. A number of transition metal complexes have now been reported to carry out this synthetically useful conversion. Thus, TPAP can catalyze the isomerization of geraniol (amongst other allylic alcohols) to citronellal in the presence of a sacrificial alcohol additive to suppress direct oxidation of the starting material (Equation (11)) <1999AG(E)1960>. Other transition metal complexes that have been used include: $Fe(CO)_5$ <2001TL2379> and water-soluble rhodium catalysts <2001NJC11>; the latter are employed under biphasic conditions, thus significantly facilitating catalyst separation, recovery, and reuse. This area has been the subject of two extensive recent reviews to which the reader is directed <2002JOM(650)1, 2003CRV27>. The use of chiral transition metal complexes to catalyze the asymmetric isomerization of allylic alcohols has met with limited success. However, a recent report has shown the efficiency of a new rhodium complex based on the phosphaferrocene ligand **7** to carry out this reaction with improved yield, scope, and enantioselectivity over existing methods <2001JOC8177> (Equation (12)). Conveniently, the ligand **7** is air-stable and can be readily recovered and reused at the end of the reaction.



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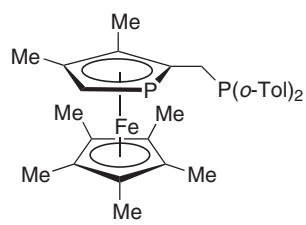

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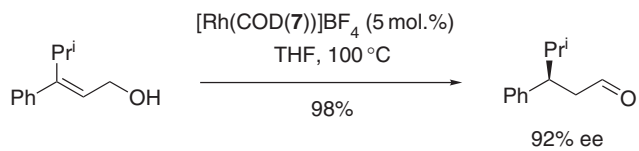
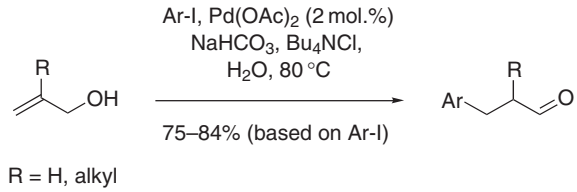
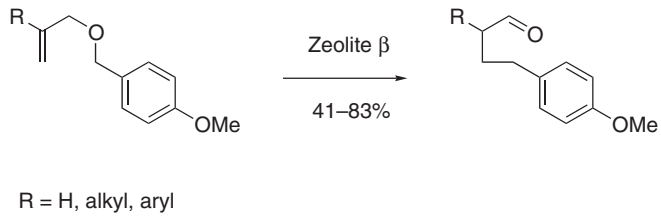


(12)

Allylic alcohols can be converted into β-aryl aldehydes by a palladium-catalyzed Heck reaction (Equation (13)) <2001SC3665>. The reaction can be carried out in water and is highly regioselective with respect to addition of the aromatic group. Finally, a novel, Lewis acid-catalyzed, 1,4-rearrangement of *p*-methoxybenzyl-protected allylic alcohols to aldehydes has been reported (Equation (14)) <1998JOC3595>. Whilst the reaction is conceptually similar to a base-induced 1,4-Wittig rearrangement, it gives higher yields in comparison. However, a rather limited combination of electron-rich benzyl ethers and either $BF_3{\cdot}OEt_2$ or zeolite β are required for a successful reaction.



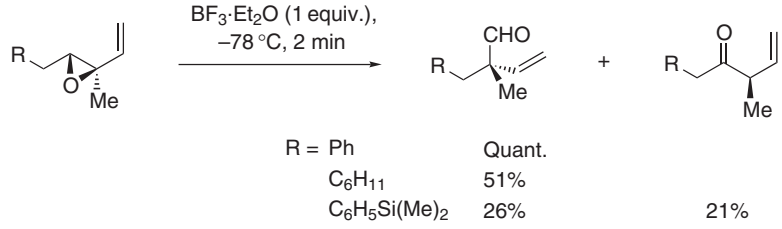
(13)



(14)

3.01.1.6 From Epoxides

The Lewis acid-mediated ring-opening of epoxides to generate aldehydes was discussed in chapter 3.01.1.6 of <1995COFGT(3)1> and has recently been employed for the synthesis of optically active quaternary aldehydes as shown (Scheme 3) <1995JA7379>. However, as evident from this example, this transformation has generally been limited by incomplete regioselectivity (leading to mixtures of aldehydes and ketones) and the requirement for stoichiometric amounts of Lewis acid. Advances in this area have sought to tackle both these problems. Thus, significant progress has been made in the development of reactions that are catalytic in Lewis acid. Some of the most efficient systems are: $BiOClO_4{\cdot}xH_2O$ (10–50 mol.%) <2000TL1527>, $InCl_3$ (50 mol.%) <1998JOC8212>, $Bi(OTf)_3{\cdot}xH_2O$ (0.01–0.1 mol.%) <2001TL8129>, $IrCl_3{\cdot}H_2O$ (1 mol.%) <2003TL7687>, Fe-based Lewis acid (10 mol.%) <1998TL2681> and metalloporphyrin (2 mol.%) <1999TL7243>, and $Pd(OAc)_2$-PR_3 (R = Bu, Ph) (5 mol.%) <1997JOC6547>. The functional group compatibility of this final Pd-mediated method is particularly noteworthy as alcohols, esters, and nitriles are all unaffected by the reaction. However, the issue of regioselectivity of epoxide-opening can be a problem with all these methods and is highly dependant on both the substrate and Lewis acid employed. Thus, monosubstituted epoxides can be regioselectively isomerized to aldehydes using 0.5 equiv. of $VO(OEt)Cl_2$ <2000JCS(P1)1749>, whereas trisubstituted epoxides give aldehydes on treatment with 1.1 equiv. of an aluminum-based Lewis acid <1994T3663>.



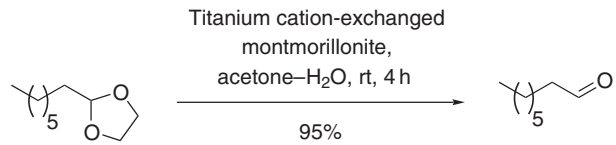
Scheme 3

3.01.1.7 From Acetals, Enol Ethers, and Enol Esters

Acetals continue to be an important class of protecting groups for carbonyl compounds and as such play a vital role in modern organic synthesis. An up-to-date discussion of their use in this arena can be found in the latest edition's of Greene and Wuts and Kocienski's authoritative works on protecting groups <B-1999MI001, B-2003MI002>. One of the reasons for the utility of acetals as protecting groups lies with the wide variety of conditions that can be employed for the regeneration of the aldehyde. The most important advances since the discussion in chapter 3.01.1.7 of

<1995COFGT(3)1> are the continued development of transformations that are both mild and chemoselective and thus compatible with other protecting and functional groups. Simple aliphatic saturated acteals are less reactive than their α,β-unsaturated counterparts and consequently many of the reported conversions cannot be applied to these systems. Thus, the discussion below will be restricted to those reactions that have been shown to work with saturated aldehydes. In general, the reactivity of aldehyde acetals is in the order: dialkyl acetals > 1,3-dioxanes > 1,3-dioxolanes.

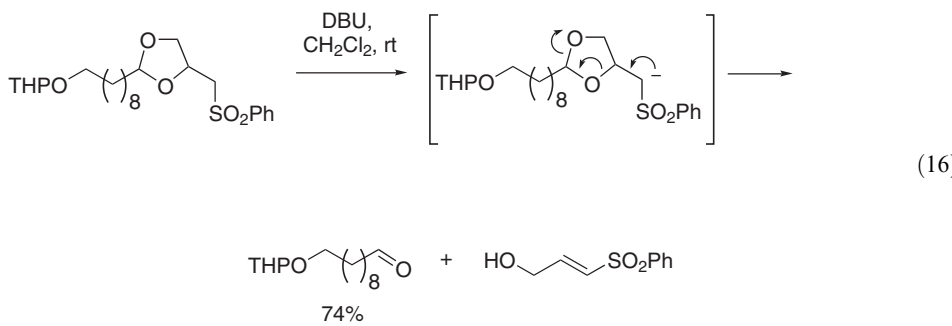
Iron(III) chloride hexahydrate (3.5 equiv.) in dichloromethane will readily deprotect dimethyl acetals and dioxolanes to give the corresponding saturated aldehyde <1997JOC6684>. The yields for difficult transformations can be increased by simply heating or adding acetone (to participate in transacetalization). Perhaps more convenient is the use of catalytic procedures involving metal salts. Thus, cerium(III) trifluoromethanesulfonate hydrate (5–30 mol.%) will cleave alkyl and cyclic acetals at room temperature in wet nitromethane whilst leaving tetrahydropyranyl and silyl ethers unaffected <2002JOC9093>. Similarly, cerium(IV) ammonium nitrate (CAN) can be used to deprotect acetals in both stoichiometric (2.5 equiv. in CH_3CN–H_2O) <1999TL1799> and catalytic (3 mol.% in CH_3CN-pH 8 aqueous buffer) amounts <1999AG(E)3207>. A variety of functional and protecting groups (including triisopropylsilyl and trityl ethers) are left unaffected and acid-mediated epimerizations are suppressed under the catalytic conditions. Studies have suggested that the stoichiometric reaction involves single electron-transfer, whilst the catalytic protocol appears to involve Lewis acidic Ce(IV) salts <2003T8989>. Bismuth salts can also be used to cleave acetals including $BiCl_3$ (50 mol.% in methanol) <2000CL1074>, which can be used in the presence of silyl, benzyl, and tetrahydropyranyl ethers, and $Bi(OTf)_3$ (0.1–1 mol.% in THF–H_2O) <2002JOC1027>, which can be used without affecting *t*-butyldimethylsilyl ethers. Dimethyl acetals of some simple aliphatic aldehydes can be resistant to hydrolysis with this latter reagent. Molybdenum(VI) acetylacetonate (10 mol.% in acetonitrile) can also be used <1995SC2529>. A number of heterogeneous catalysts also successfully carry out this transformation and these systems can often allow for easier product isolation and the potential for catalyst recycling. Examples of such systems include, polymer-supported π-acids <2001SL1311>, mesoporous molecular sieves <2000MI951>, peroxymonosulfate on alumina <2000S67>, and silica-supported guanidinium chloride in the presence of acetyl chloride <1995JCR(S)196>. Particularly noteworthy is the use of titanium cation-exchanged montmorillonite as a recyclable catalyst with sufficient activity to convert unreactive dioxolanes into the corresponding aldehydes (Equation (15)) <2003CL648>.



(15)

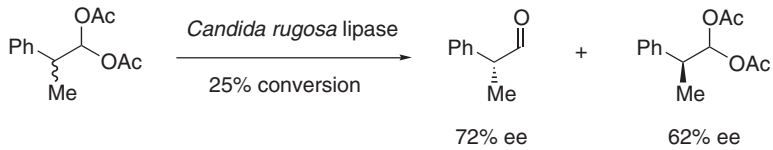
Acetal cleavage can also be achieved in an anhydrous solvent without the addition of water or an alcohol. Thus, tungsten hexachloride (15–20 mol.% in dry dichloromethane) is a mild and efficient reagent for the deprotection of 1,3-dioxolanes of aldehydes <1998JCR(S)664>. Similarly, both (trimethylsilyl)bis(fluorosulfuryl)imide (5 mol.% in dichloromethane) <1998JOC2365> and pyridinium poly(hydrogen fluoride) (excess in acetonitrile) <2001TL4641> cleave dialkyl acetals under anhydrous conditions. In the second case, the reaction is reversible and addition of chloral or chloral hydrate is required to shift the equilibrium of the reaction in the required direction.

Finally, a new class of acetal protecting group that can be cleaved under basic conditions has been developed <1998TL2401>. The mechanism of cleavage is thought to involve a β-elimination as shown and conveniently produces a water-soluble by-product (Equation (16)).



(16)

Acylals are acetals with acyloxy-substituted alcohol moieties that can also be used as protecting groups for carbonyls. Lipase-catalyzed hydrolysis of an enantiotopic ester group of racemic acylals leads to a "hemiacylal," which readily loses the remaining carboxylate to liberate the corresponding aldehyde. Overall, this approach can be used to prepare chiral aldehydes (Equation (17)) <1997TL8109>. No significant advances have occurred in the hydrolysis of enol ethers and esters since the publication of chapter 3.01.1.7 in <1995COFGT(3)1>.



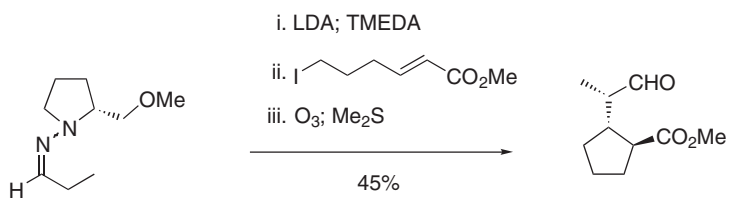
(17)

3.01.1.8 From Aldehydes or Ketones

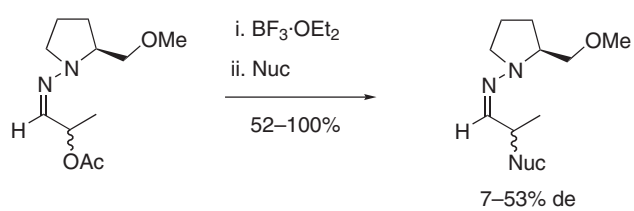
3.01.1.8.1 From saturated aldehydes or ketones

(i) Alkylation

As discussed in chapter 3.01.1.8.1 of <1995COFGT(3)1>, the α-alkylation of simple aldehydes via their metal enolates suffers from a number of associated problems (e.g., *O*- versus *C*-alkylation and competing polyalkylations and aldol reactions). Consequently, this conversion is best carried out using hydrazone derivatives. Of particular importance is the methodology developed by Enders employing (*S*)- or (*R*)-1-amino-2-methoxymethylpyrrolidine-derived hydrazones (commonly abbreviated as SAMP and RAMP, respectively) which allows for asymmetric α-alkylation with excellent enantioselectivity and is therefore applicable to the synthesis of aldehydes having an α-chiral centre. The enolates generated from aldehyde-derived SAMP- and RAMP-hydrazones also undergo stereoselective Michael reactions and, when combined with intramolecular trapping of the resulting enolate, this gives an elegant approach to homochiral carbocyclic aldehydes (Scheme 4) <1999TL3583>. The numerous and varied uses of SAMP- and RAMP-hydrazone methodology for the synthesis of aldehydes in particular, and for asymmetric synthesis in general, are beyond the scope of this discussion, and the reader is encouraged to examine the comprehensive and excellent review recently published by Enders and co-workers <2002T2253>. The utility of these systems has also been expanded by the fact that asymmetric nulceophilic displacements of an acetate leaving group can also be carried out by a variety of carbon, sulfur, and oxygen-nucleophiles in the presence of Lewis acids as shown (Scheme 5) <1998TA2155>. Although the yields for these reactions are good-to-excellent, they show only low-to-moderate diastereoselectivity.



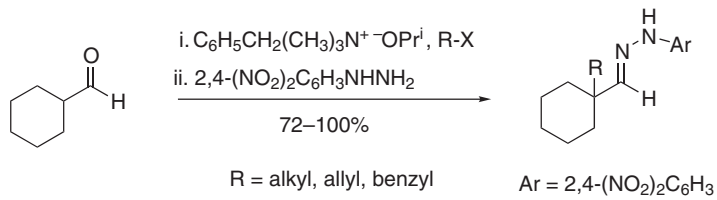
Scheme 4



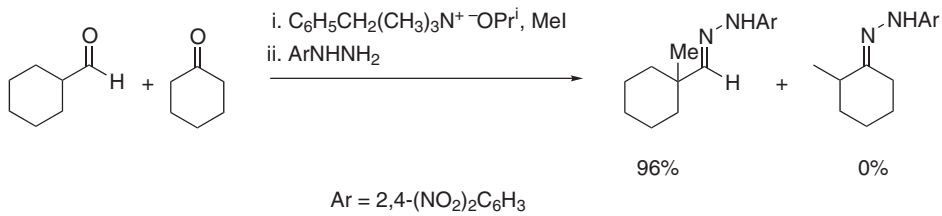
Nuc = silylketene acetal, RS^-, RO^-, C^-

Scheme 5

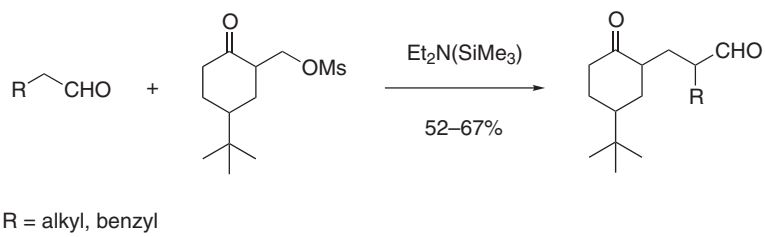
The use of nonmetallic cations can suppress the unwanted side-reactions that are often seen in the attempted alkylation of metal enolates. Thus, α-substituted aldehydes can be directly alkylated using benzyltrimethylammonium 2-propoxide as base to form the corresponding ammonium enolate and the products are isolated as their 2,4-dinitrophenylhydrazones (Scheme 6) <1996JOC9076>. Activated allylic and benzylic halides give almost quantative yields of *C*-alkylated products and, although primary iodides do give some *O*-alkylation, this method gives an unprecedented yield of *C*-alkylated product with the relatively unreactive *n*-butyl iodide; secondary iodides can also be employed. Perhaps the most significant result with this system is the chemoselective alkylation of aldehydes in the presence of ketones, suggesting that this base is of just the right strength to differentiate between the two acidic protons (Scheme 7). Finally, aldehydes undergo a diethylamino(trimethyl)silane-mediated direct 1,4-conjugate addition to electron-deficient alkenes giving α-substituted products <2001JCS(P1)316>. The reaction is thought to proceed via the aldehyde-derived enamine and the alkenes can be used directly or can be generated *in situ* from the corresponding methylsulfonyl esters (Equation (18)).



Scheme 6



Scheme 7

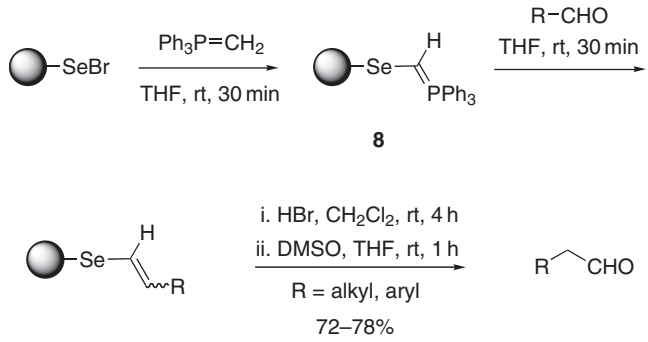


(18)

(ii) Homologation

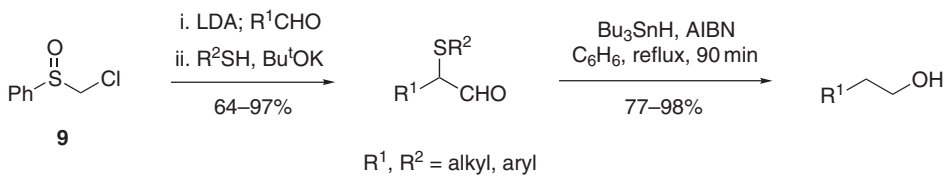
The conversion of aldehydes into the corresponding one-carbon homologated analog without any other increase in functional group complexity was discussed in chapter 3.01.1.8.1 of <1995COFGT(3)1>, and this transformation is still most conveniently carried out via the two-step sequence described previously. This involves an initial conversion of the aldehyde to a functionalized alkene (usually an enol ether derivative) using either Wittig and related phosphorus chemistry or the Peterson reaction. This is then followed by a hydrolysis step, often requiring acidic conditions, to give the homologated aldehyde. Many of the reagents that were discussed previously are still the best methods to achieve this conversion, although a few additional modifications have been reported. Thus, the alkenation step can also be carried out by reaction of aromatic aldehydes with trimethylsilyldiazomethane under rhodium(I) catalysis <2001JA2442>, and acidic conditions can be avoided by using tris(ethylenedioxyboryl)methane to form a vinyl boronate that can be hydrolyzed using aqueous sodium perborate

<1995T11219>. Additionally, homologation can also be carried out using a polymer-supported selenoalkylidenetriphenylphosphorane **8** to give a vinylic selenide resin which can be cleaved to the homologated aldehyde by reaction with hydrogen bromide followed by solvolysis in anhydrous DMSO (Scheme 8) <2001TL9035>.



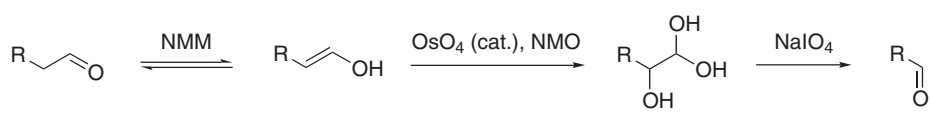
Scheme 8

In addition to the alkenation–hydrolysis approach, a number of other methods for one-carbon homologation can be applied. One such approach involves conversion of aldehydes into chain-extended nitriles followed by reduction of the cyano group, using standard methods, to give the homologated aldehyde. This aldehyde-to-nitrile conversion can be achieved for sterically hindered aldehydes via the corresponding cyanohydrin even in the presence of acid- and base-labile functionalities <2000OL1895>. Alternatively, the addition of metal cyanides to aldehyde-derived tosylhydrazones also provides a route to the homologated nitriles <2003S1049>. Another approach to homologation involves chloromethyl phenyl sulfoxide **9**, which reacts with aldehydes in a two-step process to give the corresponding α-thio aldehydes (Scheme 9) <2000TL2121>. Direct desulfurization of these products is difficult, although they can be converted into the homologated alcohols in excellent yield using tributyltin hydride and AIBN. Finally, methods for the two-carbon chain homologation of aldehydes are also available <1999AG(E)2447>.

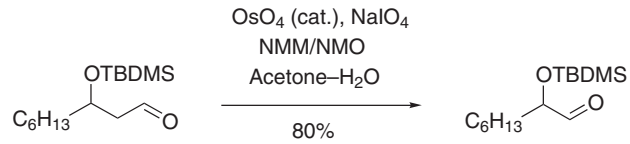


Scheme 9

In addition to chain extension, the chain reduction of aldehydes is also possible. This can be achieved directly using a catalytic amount of osmium tetroxide together with sodium periodate and a mixture of *N*-methylmorpholine (NMM) and NMO (Scheme 10) <2003TL3613>. The reaction presumably involves dihydroxylation of the corresponding enol followed by periodate-mediated cleavage of the resulting diol and is therefore most suitable to the formation of aldehydes having a quaternary α-carbon, although the presence of a protected hydroxy group also seems to prevent further enolization and degradation (Equation (19)). Aldehyde-derived silyl enol ethers can also be cleaved using aqueous hydrogen peroxide in the presence of catalytic peroxotungstophophate, again resulting in a one-carbon dehomologation <1999JOC5954>.

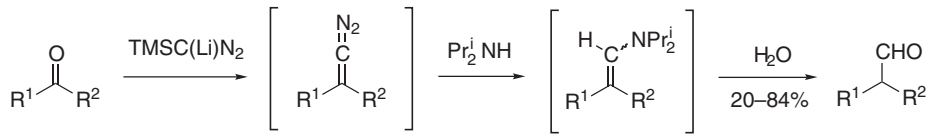


Scheme 10



(19)

The reaction of ketones with lithium trimethylsilyldiazomethane in the presence of excess diisopropylamine generates enamines, which may be readily hydrolyzed to the corresponding homologated aldehydes in good yield (Scheme 11) <1994SL109>.

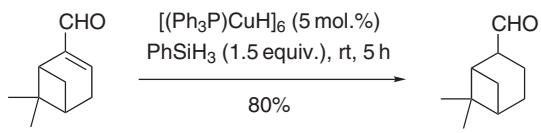


Scheme 11

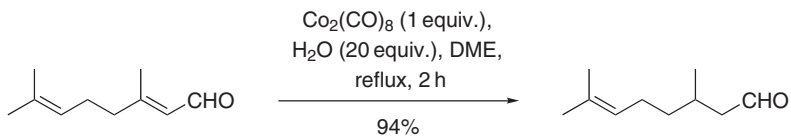
3.01.1.8.2 From unsaturated aldehydes

(i) Conjugate reduction

Chapter 3.01.1.8.2 of <1995COFGT(3)1> discussed the 1,4-reduction of α,β-unsaturated aldehydes to give the corresponding saturated analogs. Only a limited number of reagents were described due to the difficulties in achieving 1,4- versus 1,2-reduction of the enal. Perhaps the most widely used of these is Stryker's reagent $[(Ph_3P)CuH]_6$, and Lipshutz and co-workers have recently shown that this copper hydride cluster can be used in catalytic quantities ($\leq$5 mol.%) together with stoichiometric amounts of phenylsilyl hydride ($PhSiH_3$) as a co-reductant (Equation (20)) <1998TL4627>. A new and efficient preparation of Stryker's reagent has also been reported <2003TL455>. Other metal hydrides can also be employed for this transformation. Thus, selective 1,4-reduction occurs with DIBAL-H—*t*-butyllithium in the presence of a bulky Lewis acid that effectively blocks the 1,2-reaction <1996JOC2928>. A $Co_2(CO)_8$—H_2O system has also been employed and presumably reacts by the formation of $CoH(CO)_4$ *in situ* <2003TL2775>. Significantly, this reagent will even reduce β,β-disubstituted enals (Equation (21)), although cyclic unsaturated aldehydes are not reactive under these conditions. A novel tin hydride complex can also be used <1999OM3965>, and tributyltin hydride in the presence of tetrakis(triphenylphosphine)palladium as a catalyst together with a proton donor such as acetic acid is also effective <1998JMC540>. α,β-Enals can also be converted into the saturated analogs by hydrogenation using Lindlar catalysis <1996SC1321, 2002JOC1314>. Raney-nickel is particularly useful for this reaction as other isolated alkenes are not reduced under the reaction conditions <1999SL1663>. Finally, sodium dithionite in water–dioxane is a useful alternative to the metal hydride-based approaches discussed above and again nonconjugated alkenes are not affected by this reagent <1995TL1107>.



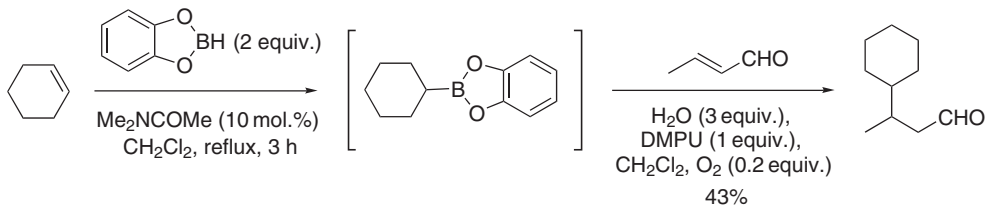
(20)



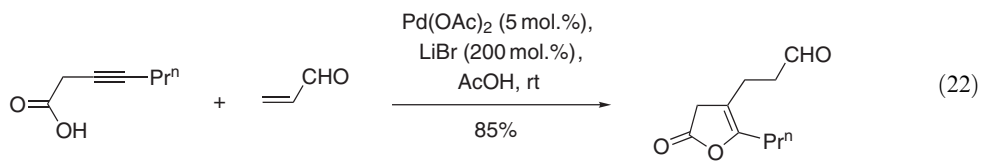
(21)

(ii) Conjugate additions of carbon nucleophiles

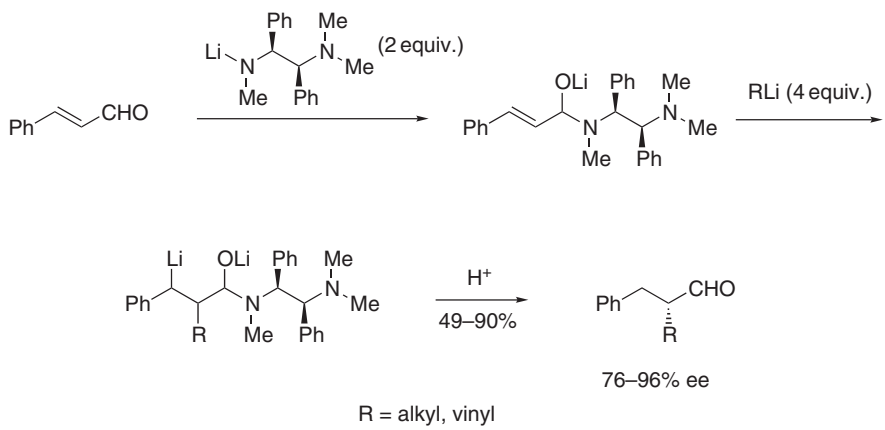
The addition of carbon nucleophiles to α,β-unsaturated aldehydes can take place in a 1,2- or 1,4-manner. Selective conjugate 1,4-additions are normally carried out using organocuperates and this transformation was discussed in chapter 3.01.1.8.2 of <1995COFGT(3)1>. In addition to the examples discussed previously, copper-catalyzed conjugate additions to α,β-enals have been reported for trialkylaluminum <1995T743> and organomanganese reagents <1999TL6407>. Importantly, asymmetric copper-catalyzed conjugate additions can be carried out using chiral ligands to generate homochiral aldehydes and a review of this expanding area has recently appeared <2002EJO3221>. Other organometallic reagents show little or no selectivity, although bulky Lewis acids can be used to block the competing 1,2-addition using either alkyllithiums <1998CL403>, perfluoroalkyllithiums <1994SL847>, or allylcerium reagents <1997TL3947>. Alkyl radicals also reactive selectively in a 1,4-manner to give β-functionalized saturated aldehydes <2003T947> and this can be used in a one-pot approach for the addition of alkenes to unsaturated aldehydes via the corresponding alkylborane (Scheme 12) <1999MI1468>. Palladium has also been employed to catalyze conjugate additions of organosiloxanes <2003JOC6997> and tetraphenylborates or arylboronic acids <1995JOC883> to α,β-unsaturated aldehydes. In an analogous manner, rhodium can be used to catalyze the conjugate addition of aryl- and alkenyl-stannanes <2002T91>. A tandem nucleopalladation conjugate addition approach has also been employed to access γ,δ-unsaturated carbonyls (Equation (22)) <1996JOC2254>. Finally, although not strictly a conjugate addition, a convenient one-pot, two-step procedure allows the conversion of α,β-enals to enantio-enriched α,β-disubstituted aldehydes (Scheme 13) <2001TL1883>.



Scheme 12



(22)



Scheme 13

3.01.1.8.3 From α-functionalized aldehydes

As discussed in chapter 3.01.1.8.3 of <1995COFGT(3)1>, the selective reduction of α-functionalities without affecting the carbonyl moiety is rather difficult. The transformation can be achieved, however, in the mild hydro-debromination of α-bromo imines derived from aldehydes using tin(II) chloride in methanol <2000SL1283>.

3.01.1.9 From Carboxylic Acids and Their Derivatives

3.01.1.9.1 Reaction of nucleophiles with acids and their derivatives

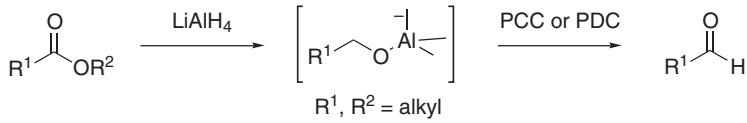
The reduction of carboxylic acids and their derivatives to generate aldehydes was discussed in chapter 3.01.1.9.1 of <1995COFGT(3)1>. This transformation requires the use of reagents and conditions that will selectively reduce the acid, or acid derivative, whilst without further reducing the aldehyde to an alcohol. A significant number of novel protocols for this transformation have been reported since the original discussion and these will be considered for each acid derivative in turn.

New methods have been developed for the reduction of acid chlorides to aldehydes (Table 1). These reactions complement the methods described previously (e.g., Rosenmund reduction or the use of borohydride-derived reagents) and can offer advantages of milder reaction conditions, ease of work-up, and enhanced functional group compatibility. Thus, these methods can be employed in the presence of alkene (entries 1–4), alkyne (entry 1), and ester (entry 2) functional groups and are also particularly useful for reducing hindered tertiary acid chlorides (entries 1 and 2). Over-reduction to the primary alcohol is not an issue with any of these methods. In addition to these direct reductions, acid chlorides can also be converted into aldehydes via DIBAL-H reduction of 1-(acylmethylamino)-3methylimidazolium salts <1995TL455>.

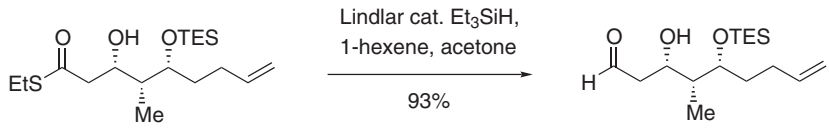
Table 1 Preparation of aldehydes by the reduction of acid chlorides

Entry	*Conditions*	*References*
1	HCO_2H, NH_4OH, rt, 15–40 min	<1998TL8153>
2	(i) PBu_3; (ii) Zn–Cu, CH_3SO_3H, 0 °C, 1 h	<1995TL2247>
3	Bu_3SnH, Ni(dppe)Cl_2 (cat.), 25 °C, 15 min	<1997TL8093>
4	Bu_3SnH, $InCl_3$ (cat.), PPh_3 (cat.), −30 °C, 2 h	<2000TL113>

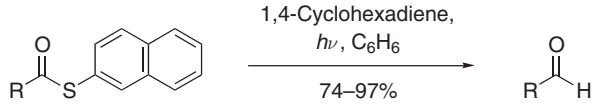
The reduction of esters to the corresponding aldehydes is still most commonly and conveniently carried out using DIBAL-H at low temperatures. Two alternative procedures that can be carried out nearer to room temperature employ sodium gallium hydride <1995MI474> and pyrrolidine-modified aluminum reagents in the presence of potassium *t*-butoxide <2001T2701>. Alternatively, the direct treatment of alkoxyaluminum intermediates (formed by lithium aluminum hydride reduction of esters) with pyridinium chlorochromate or pyridinium dichromate gives aldehydes from esters in a one-pot "reductive oxidation" process (Scheme 14) <1999MI1373>. The reduction of thiol esters to aldehydes with triethyl silane in the presence of palladium on carbon was discussed in chapter 3.01.1.9.1 of <1995COFGT(3)1>. Two modifications to this procedure have been introduced to overcome the possible problem of concomitant undesirable alkene reduction. Thus, the use of homogeneous catalysis ($Pd(OAc)_2$) allows the reaction to be monitored visually and stopped at the end point (as indicated by precipitation of Pd(0)) before over-reduction occurs <1994JOC7249>. Alternatively, the use of Lindlar catalysts together with a sacrificial monosubstituted terminal alkene (e.g., 1-decene) can also be used (Equation (23)) <1999T8671>. Finally, irradiation of *S*-2-naphthyl thioesters generates acyl radicals which can be reduced by a suitable hydrogen source (e.g., 1,4-cyclohexadiene) to give the corresponding aldehydes (Equation (24)) <1994JOC2608>.



Scheme 14



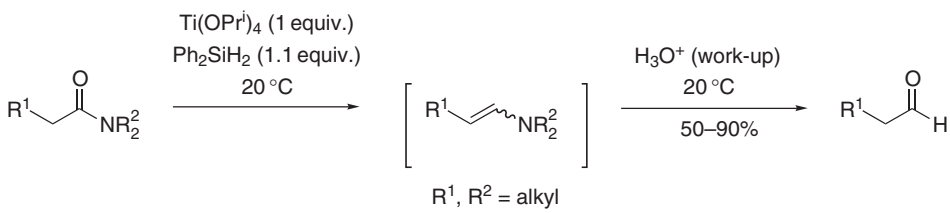
(23)



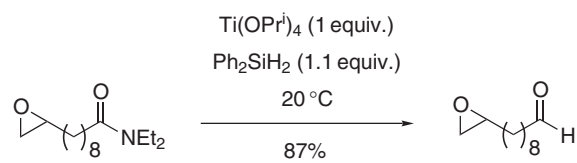
(24)

R = alkyl, aryl

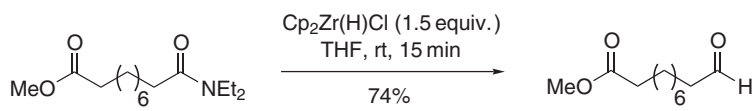
Previously reported methods for the reduction of simple amides to aldehydes normally involve the use of aluminum hydride or borohydride reagents and often require high temperatures. However, several milder methods that do not use these harsh reducing conditions are now available and, as a consequence, it is often possible to selectively reduce amides in the presence of other carboxylic acid-derived functionalities. Thus, treatment of tertiary amides, in the absence of any solvent, with stoichiometric titanium(IV) isopropoxide and diphenyl disilane at room temperature efficiently produces aldehydes in a one-pot procedure via the corresponding enamines <1996AG(E)1515> (Scheme 15). This remarkably mild procedure is compatible with alkenes, alkynes, nitriles, silyloxyethers, and epoxides (Equation (25)). An alternative approach involves reaction of tertiary amides and *N*-acyl oxazolidinones with 1.5–2 equiv. of the Schwartz reagent ($Cp_2Zr(H)Cl$) <2000JA11995>. Again, this method shows excellent chemoselectivity (Equation (26)) and provides aldehydes in excellent yield and in short reaction times (~15–30 min). Finally, tertiary amides can be converted into aldehydes by reduction using sterically hindered dialkylboranes, amines are produced otherwise <1997TL1717> (Scheme 16).



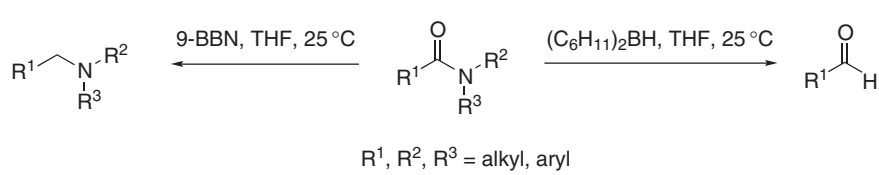
Scheme 15



(25)

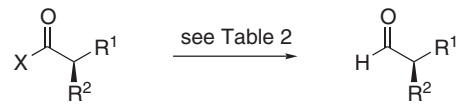


(26)



Scheme 16

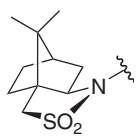
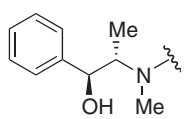
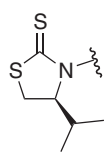
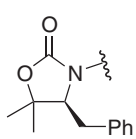
N-Acyl chiral auxiliaries are commonplace in asymmetric synthesis and the use of these systems has been enhanced by methods for their direct conversion into chiral aldehydes without racemization (Scheme 17 and Table 2).



R^1, R^2 = alkyl, aryl
X = chiral auxiliary (see Table 2)

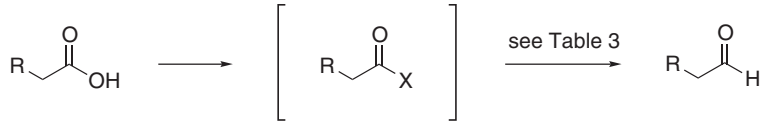
Scheme 17

Table 2 Preparation of aldehydes by the reduction of *N*-acyl chiral auxiliaries

X	*Conditions*	*References*
	DIBAL-H, CH_2Cl_2, −78 °C	<1997HCA1319>
	$LiAlH(OEt)_3$, hexanes-THF, 0 °C	<1997JA6496>
	DIBAL-H, THF	<1995TL2097>
	DIBAL-H, CH_2Cl_2, −78 °C	<2003OBC2886>

The convenient reduction of Weinreb amides to aldehydes was discussed in chapter 3.01.1.9.1 of <1995COFGT(3)1> and the synthetic utility of this class of compound has been recently reviewed <2000JPR340>. In addition, this readily achieved transformation has been utilized in the solid-phase synthesis of aldehydes <1996TL1161, 1999JOC1823>.

The direct reduction of carboxylic acids to aldehydes has been achieved with various metal hydrides, including lithium gallium hydride <1995MI469> and cyclic dialkyldiaminoaluminum hydrides <2002MI1340>. However, this conversion is more commonly achieved via transformation of the acid to an activated intermediate which is subsequently reduced either in the same pot or in a multistep process (Scheme 18 and Table 3). Esters, nitriles, and alkenes are compatible to some, if not all, of these conditions. Particularly noteworthy, amongst these entries, is the reduction of carboxylic acids with sodium hypophosphite in the presence of pivalic anhydride (which generates the mixed anhydride *in situ*) as it can be carried out without the need for dry conditions or high pressures <2002CC836>. An analogous approach is via the corresponding 2-imidazolines, which can be reduced with sodium <1997CS2701>. Alternatively, carboxylic acid salts can be readily converted into aldehydes in a single pot by a stepwise reduction with lithium aluminum hydride <1999MI400> or borane <2001MI1089> followed by oxidation with pyridinium chlorochromate.



R = alkyl, aryl
X = see Table 3

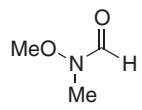
Scheme 18

Table 3 Preparation of aldehydes by the two-step reduction of carboxylic acids

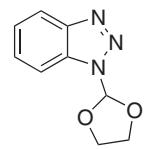
X	*Conditions for reduction step*	*References*
$OSiMe_3$	DIBAL-H, −78 °C	<1998TL909>
$OS(O)OCH{=}NMe_2{\cdot}Cl$	$LiBEt_3H$, LiI (cat.), −78 °C	<1998JCR(S)402>
$O(C_3N_3)(OMe_2)$	H_2 Pd/C	<1999JOC8962>
$OCOBu^t$	H_2 (3.0 MPa), $Pd(PPh_3)_4$, 80 °C	<2001BCJ1803>
$OCOBu^t$	NaH_2PO_2, K_3PO_4, $Pd(OAc)_2$, $P(Cy)_3$, 60 °C	<2002CC836>

3.01.1.9.2 Formylation reactions

The formylation of Grignard reagents using tertiary amides to produce aldehydes was described in chapter 3.01.1.9.2 of <1995COFGT(3)1>. Whilst DMF is by far the most commonly employed formylating reagent due to its low cost and ready availability, these transformations have to be carefully controlled to avoid further competing secondary reactions. These competing reactions can be avoided by using the readily prepared "Weinreb" formamide **10** which will react with organolithiums, Grignard reagents, and enolates to give formylated products in good yields. <1999TL7889>. Alternatively, the benzotriazole reagent **11** can also be used to introduce a masked formyl group in the form of the corresponding acetal <2000JOC1886>. This reagent has the added advantage that it will also react with organozinc species under mild conditions (THF, room temperature).

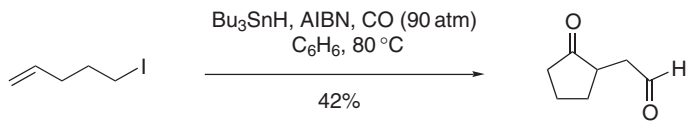


10



11

The introduction of a formyl group using carbon monoxide is usually effected under free-radical conditions and the use of this reaction for the synthesis of aldehydes has been reviewed <1996AG(E)1050>. Double carbonylations leading to keto-aldehydes are also possible (Equation (27)) <1996JA10670>. Transition metal-catalyzed carbonylations can also be carried out using palladium <2002MI1097> and rhodium <2000OL3205> catalysts.



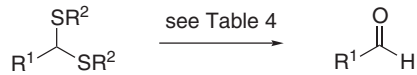
(27)

3.01.1.9.3 Other preparations from acids and acid derivatives

No significant advances have occurred in this area since the publication of chapter 3.01.1.9.3 in <1995COFGT(3)1>.

3.01.1.10 From Sulfur-containing or Other Lower-chalcogen-containing Precursors

Thioacetals are often employed as protecting groups for carbonyl compounds and an up-to-date discussion of their use in this area can be found in Greene and Wuts and Kocienski's latest works on protecting groups <B-1999MI001, B-2003MI002>. Similarly, the role of 1,3-dithianes in natural product synthesis has also been recently reviewed <2003T6147>. Thioacetals have been traditionally converted into carbonyls by hydrolysis with heavy-metal reagents such as mercury(II) salts, or by oxidation, and these approaches were discussed in chapter 3.01.1.10 of <1995COFGT(3)1>. However, new methods to carry out this transformation continue to be of considerable interest, especially those that employ reagents less toxic, can be used catalytically and show increased selectivity and functional group tolerance. A selection of such reagents are given in Scheme 19 and Table 4. An extensive review of this area has also appeared recently <2003OPP527>.



R^1 = alkyl
R^2 = see Table 4

Scheme 19

Table 4 Preparation of aldehydes from thioacetals

R^2	*Conditions*	*References*
$(CH_2)_3$	$Bi(NO_3)_3 \cdot 5H_2O$ (20 mol.%) + O_2	<2001MI473>
	Dess–Martin Periodinane **3**	<2003OL575>
	2,4,6-trichloro-1,3,5-triazine + DMSO	<2003S2547>
	Selectfluor™ (2.5 equiv.)	<2002TL4037>
$(CH_2)_2$	$CeCl_3 \cdot 7H_2O$–NaI	<2002TL4679>
Et	$Bi(OTf)_3 \cdot xH_2O$ (0.1 mol.%)	<2003TL2857>
	$FeCl_3 \cdot 6H_20$ (3 equiv.)	<2000SL1476>
	1-Benzenesulfinyl piperidine, triflic anhydride	<2003SL1257>

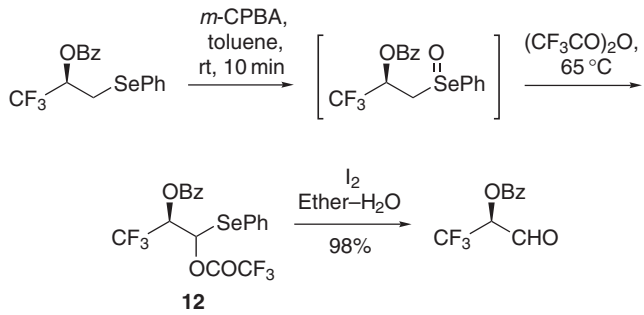
In addition to the methods listed above, thioacetals can also be cleaved to aldehydes by: electro-oxidation <1997MI497>, clay-supported ammonium nitrate <1997TL8891>, natural kaolinitic clay under microwave irradiation <2000GC154>, "nitrogen oxides" <1996TL1897>, and periodic acid under nonaqueous conditions <1996TL4331>. As well as thioacetals, *O*,*S*-acetals (e.g., 1,3-oxathiolanes) are also useful protecting groups in organic synthesis. These functional groups can be converted into the corresponding aldehydes using a variety of methods, including the use of amberlyst-15 and excess glyoxylic acid <2001SL1251> and catalytic *n*-tetrabutylammonium tribromide <2002TL2843>.

The Pummerer reaction was discussed in chapter 3.01.1.10 of <1995COFGT(3)1> as an important route to aldehydes from sulfoxides. By using *o*-hydroxymethyl aryl sulfoxides this reaction can be carried out in a single step via neighboring group participation of the hydroxyl group, although this system has yet to be applied to saturated aldehydes <1997H177>. Pummerer rearrangements of selenoxides have been shown to offer some advantages over the complementary sulfoxide-based methods due to less over-oxidation of the chalcogen and more efficient hydrolysis of the α-functionalized selenide intermediate **12** (Scheme 20) <1999T9163>. Aldehydes can be regenerated from their bisulfite adducts by reaction with chlorotrimethylsilane under nonaqueous conditions <1999JOC5722>.

3.01.1.11 From Nitrogen-containing Precursors

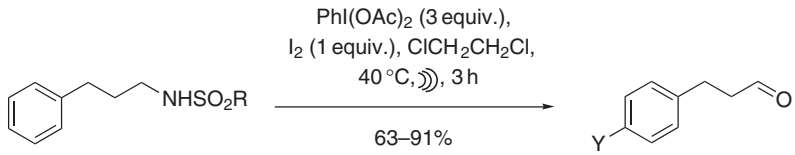
3.01.1.11.1 From amines

The conversion of amines and their derivatives into aldehydes can be achieved by either direct oxidation or by conversion to another functional group that can act as a precursor to the



Scheme 20

carbonyl moiety. Thus, direct oxidation of primary amines can be carried out with sodium hypochlorite adsorbed on montmorilllonite K10 <2000JCR(S)224> in a procedure that offers mild reaction conditions, ease of work-up, and the potential for reagent recycling. Other methods for this transformation include the use of solid-supported iron-permanaganate <2002SC3407> and electrochemically in a reaction mediated by nitroxyl radicals <2000H1583>. In addition to free amines, *N*-alkylsulfonyl-protected phenylalkylamines can be oxidatively cleaved to the corresponding aldehydes (together with free sulfonamides) by reaction with (diacetoxyiodo)benzene and iodine under ultrasonic irradiation. However, considerable iodination of the aromatic ring occurs under the reaction conditions (Equation (28)) <2001T7481>.

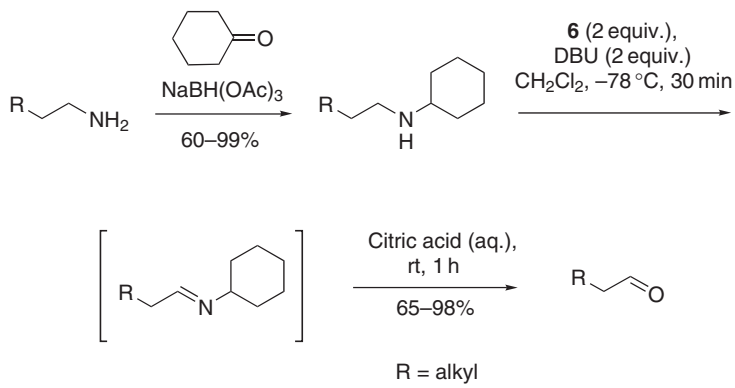


(28)

R = alkyl, aryl

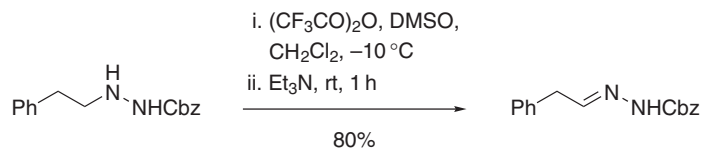
Y = H:I (ratio 5:1–1:1.6)

Amines can also be transformed to aldehydes indirectly by conversion into functional groups which can be subsequently converted into the carbonyl. Thus, in a manner similar to the one applied to their oxygen counterparts, allylamines can be isomerized to enamines and thence aldehydes under rhodium(I) catalysis, and this can be achieved in an asymmetric fashion <2001HCA230>. Linear primary amines can be oxidatively deaminated by reaction of their *N*-cyclohexylated derivatives with *N*-*t*-butylphenylsulfiniumidoyl chloride **6** in a reaction that proceeds via the corresponding imine and displays excellent functional group tolerance (Scheme 21) <2001CL712>. With other secondary amines, regioselectivity issues can become a problem under these conditions <2001CL390>, although this can be solved to some extent by using a different procedure based upon iridium-catalyzed transfer dehydrogenation <2002JMOC(189)119>. Conversion of carbamate-*N*-protected alkylhydrazines into the



Scheme 21

corresponding hydrazones can be achieved under Swern conditions permitting access to the aldehyde (Equation (29)) <2001TL1453>. Finally, primary amines can be oxidized to nitriles with trichloroisocyanuric acid <2003S2629>.



(29)

3.01.1.11.2 *From oximes, hydrazones, and their derivatives*

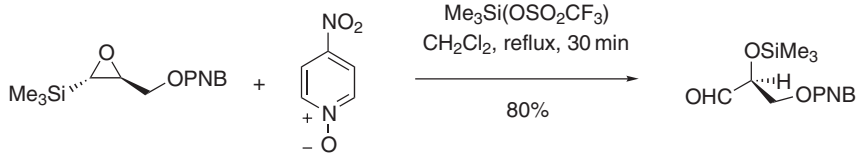
As discussed in chapter 3.01.1.11.2 of <1995COFGT(3)1>, the conversion of oximes, hydrazones, and related derivatives into the corresponding saturated aldehydes can be performed under oxidative, hydrolytic and, to a lesser extent, reductive conditions. The importance of this transformation lies in the fact that these derivatives are often employed as stable precursors of aldehydes. Since this original discussion there have been continued developments to discover methods for this transformation that are both mild and selective and the reader is directed to several detailed reviews of this area <2003OPP527, 2001S1903> (oximes), and <2000ACR157> (*N*,*N*-diakylhydrazones). Of the new methods that have been introduced, particular attention has been focused on those that are catalytic in nature. Thus, transition metal complexes <2000SL1482>, the multimetal complex $K_5CoW_{12}O_{40}{\cdot}3H_2O$ <2003S1883>, antimony pentachloride <2003S1881>, and palladium(II) acetate–tin(II) chloride <1999S2024> (and microwave-assisted <2002M1413>) can all be used catalytically to access aldehydes from oximes and/or hydrazones. Similarly, a number of heterogeneous methods have been developed to aid reaction work-up and reagent recovery. These include, silica-supported CAN <2002JCR(S)556>, potassium permananganate <2003JOC4553>, copper(II) nitrate <2000SC3865> and peroxymonosulfate <2000SC3121> (this last methods can be employed under solvent-free conditions), poly[4-vinyl-*N*,*N*-dichlorobenzenesulfonamide] <2002TL3073> and zeolites under microwave irradiation <2002SC2195>.

3.01.1.11.3 *From nitroalkanes*

The Nef reaction remains the most common approach for the conversion of nitroalkanes into saturated aldehydes. A number of modifications of this method have been reported and the area has been extensively covered in a recent review article <2004T1017>.

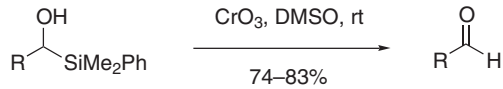
3.01.1.12 From Organosilanes

The formation of aldehydes from vinyl silanes via epoxidation and subsequent rearrangement was discussed previously in chapter 3.01.1.12 of <1995COFGT(3)1>. These epoxysilanes can also undergo oxidation with pyridine *N*-oxides in the presence of silylating agents to generate glyceraldehyde derivatives (Equation (30)) <1994TL3387>. The oxidation of α-hydroxy silanes with chromium trioxide gives aldehydes rather than the corresponding acyl silanes (Equation (31)) <1994JCS(P1)257>. Additionally, vinyl silanes of the form **13** (generated from the silylformylation of terminal alkynes) have been shown to undergo a 1,2-anionotropic rearrangement upon treatment with fluoride to give 2-(arylmethyl)aldehydes as shown (Equation (32)) <2003JOC9292>. Finally, the aza-Brook rearrangement of (α-silyl)allylamines can be used to access functionalized aldehydes (Scheme 22) <1996JOC1196> and, in an analogous manner, photolysis of (α-silyl)nitrites generates aldehydes via a radical-Brook rearrangement <2000JOC2292>.



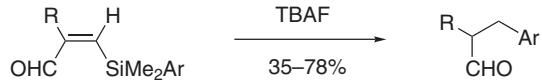
PNB = *p*-nitrobenzoyl

(30)



(31)

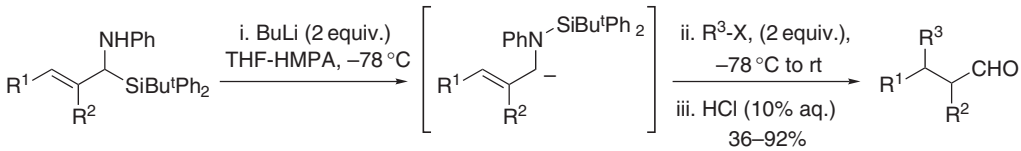
R = alkyl



(32)

13

R = alkyl



R^1, R^2, R^3 = alkyl

Scheme 22

3.01.1.13 From Organoboranes

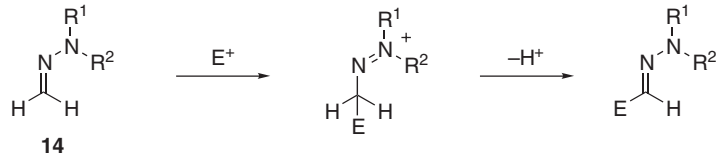
Very few advances have occurred in this area since the publication of chapter 3.01.1.13 in <1995COFGT(3)1>. The direct oxidation of alkylboranes to aldehydes using TPAP and NMO <1997TL2813> was mentioned in Section 3.01.1.2.

3.01.1.14 Methods Involving Umpolung

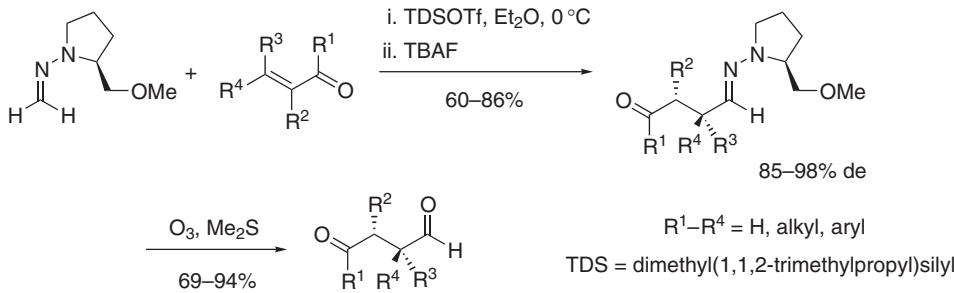
The use of reagents involving polarity reversal has significantly added to the progress of organic synthesis. As previously discussed in chapter 3.01.1.14 of <1995COFGT(3)1>, the umpolung synthons that have been developed for the preparation of aldehydes are best considered under two classes; the d^1 (formyl anion) reagents and the d^3 (homoenolate) equivalents.

3.01.1.14.1 Formyl anion equivalents

The use of d^1 synthons for the preparation of aldehydes was discussed in depth in chapter 3.01.1.14.1 of <1995COFGT(3)1> and the subject has been recently reviewed <2001AHC89>. These reagents have traditionally employed sulfur-based acetals (e.g., 1,3-dithianes, for a recent review see <2003T6147>) or metal carbonyl derivatives (for a recent example involving electroreductively generated iron-carbonyl anion see <1996JCS(P1)1873>) to provide the C-1-building block. In addition to these approaches, formaldehyde *N*,*N*-dialkylhydrazones **14** have been introduced as neutral reagents equivalent to a d^1 synthon <1996T9143> whereby the aza-enamine character of **14** allows reaction with a variety of electrophiles (Scheme 23). These reagents are especially useful for accomplishing conjugate additions and the use of proline-derived hydrazones means that these systems can be employed as chiral formyl anion equivalents (Scheme 24) <1997JOC5144>. A review of this area has recently been published <2000SL1228>. A number of chiral formyl anion equivalents, mainly based on chiral auxiliaries, have now been developed and for a summary of these the reader is directed to an article by Seebach and co-workers <2001JOC3059>. Many of these chiral d^1 synthons will react with ketones and aldehydes generating, after cleavage of the auxiliary, α-hydroxy aldehydes, and will therefore be considered in greater detail in Section 3.01.4.1.



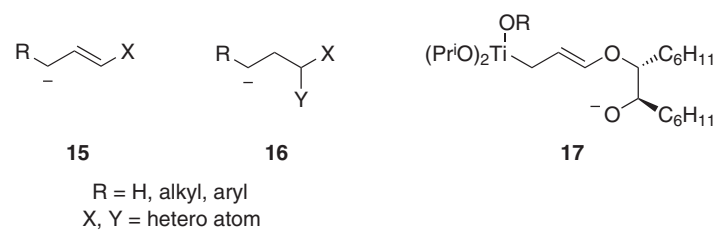
Scheme 23

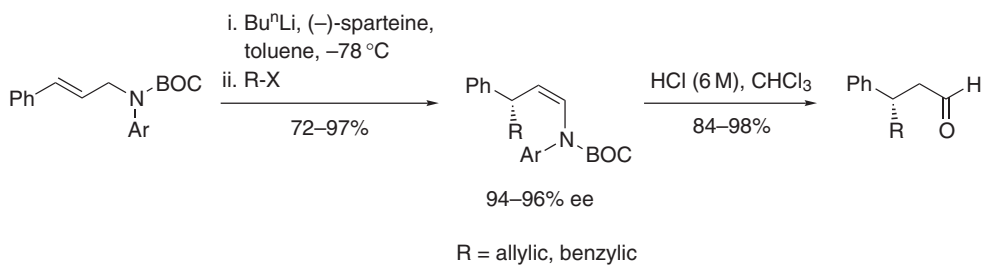


Scheme 24

3.01.1.14.2 Other anion equivalents

The use of homoenolate equivalents as d^3 synthons allows substitution β to a carbonyl group and these reagents are consequently valuable synthetic tools in organic chemistry. As discussed in chapter 3.01.1.14.2 of <1995COFGT(3)1> the majority of these synthons are based on heteroallyl anions such as **15** although acetal-protected carbanions of the type **16** can also be employed. Chiral auxiliaries can be introduced in both these approaches, thus allowing for asymmetric alkylation and hydroxyalkylation of the homoenolate equivalent and this area has been comprehensively reviewed <1999S365>. Particular examples reported since this review include a chiral propionaldehyde homoenolate equivalent **17** <2001JA3462> and auxiliaries based on oxazolidin-2-ones <2002HCA963>. In a complementary manner, lithiation of achiral *N*-protected allylamines in the presence of (−)-sparteine generates chiral homoenolates which can be employed to access chiral β-substituted aldehydes (Scheme 25) <2003JOC1207>. A similar approach is possible using (cycloalkyl-1-enyl)methyl carbamates <2002EJO414>.





Scheme 25

3.01.2 β- AND MORE REMOTELY UNSATURATED ALDEHYDES

Many of the methods described in Section 3.01.1 can, in principle, be applied to the synthesis of remotely unsaturated aldehydes. The major restriction is the formation of β,γ-unsaturated aldehydes where the potential for alkene migration to give the corresponding conjugated aldehyde can severely limit the reagents and conditions that may be employed. Therefore, these sensitive products have to be produced using modified variants of the procedures already discussed. Typical examples include DMP oxidation of homoallylic alcohols employing a modified work-up <2002S326> (see Equation (7), Section 3.01.1.5.1), careful hydrolysis of β,γ-unsaturated dimethylhydrazones using copper dichloride <1997JOC734> and careful cleavage of 1,2-diols using lead(IV) acetate <1999TL7179>. This section will discuss methods where the unsaturation is an integral part of the reaction.

3.01.2.1 Alkyl Aldehydes with One Double Bond

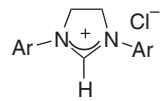
3.01.2.1.1 From aldehydes

No significant advances have occurred in this area since the publication of chapter 3.01.2.1.1 in <1995COFGT(3)1>.

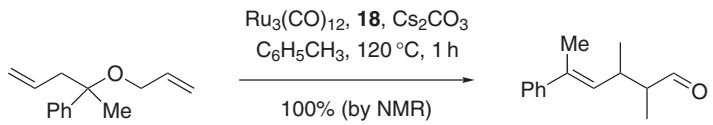
3.01.2.1.2 Preparations involving rearrangements

(i) Claisen rearrangements

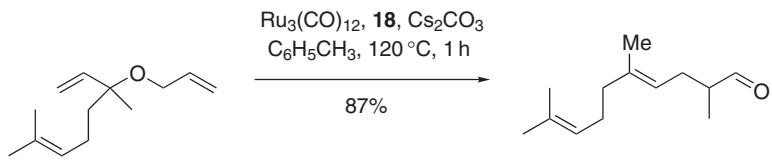
The Claisen rearrangement of allyl vinyl ethers remains an excellent method for producing γ,δ-unsaturated aldehydes. Recent progress has focused on the development of asymmetric variants of this [3,3]-sigmatropic rearrangement and these have been reviewed <1999CSR43, 2003S961>. Particular success has been achieved using chiral Lewis acid catalysis to generate β-substituted γ,δ-unsaturated aldehydes in high enantioselectivity (61–95% = ee) <1995JA1165>. A three-component catalyst based on $Ru_3(CO)_{12}$/1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride **18**/Cs_2CO_3 (molar ratio 1:3:6) has been shown to promote both allyl to vinyl isomerization and Claisen rearrangement <2002CC1772>. The significance of this finding is that it allows readily prepared allyl homoallyl, and diallyl ethers to be converted directly into γ,δ-unsaturated aldehydes (Equations (33) and (34)).



18 Ar = 2,6-diisopropylphenyl



(33)

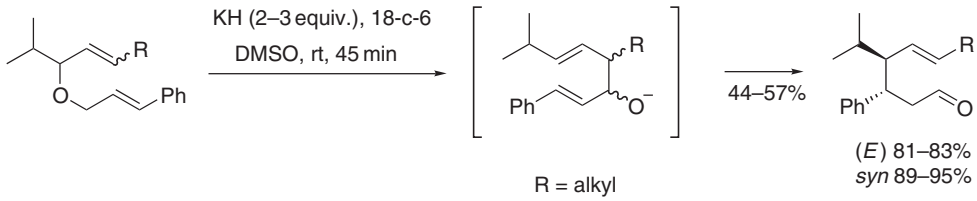


(34)

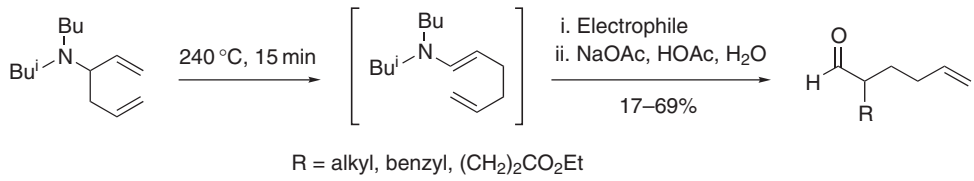
(ii) Oxy-Cope and related rearrangements

The oxy-Cope and anionic oxy-Cope rearrangements remain a good general method for the formation of δ,ε-unsaturated aldehydes. In particular, the tandem [2,3]-Wittig-anionic-oxy-Cope rearrangement has been used to generate products having an (*E*)-*syn* stereochemistry regardless of

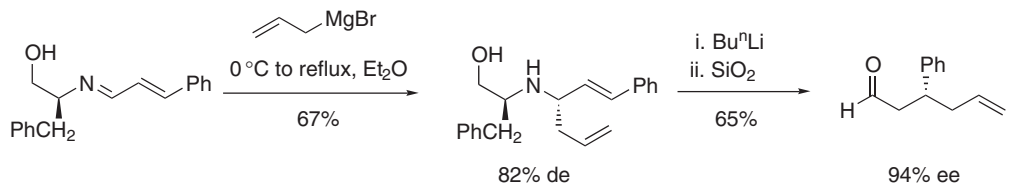
the substrate geometry (Scheme 26) <1994TL7077>. The nitrogen analog of the oxy-Cope reaction is also known. Such amino-Cope rearrangements generate enamine intermediates that can be subsequently alkylated to produce α-alkyl δ,ε-unsaturated aldehydes (Scheme 27) <1997SL725>. In addition, the stereoselective formation of 3-amino-1,5-dienes and their subsequent asymmetric anionic amino-Cope rearrangement leads to enantioenriched β-aryl δ,ε-unsaturated aldehydes as shown (Scheme 28) <1998SL1117>.



Scheme 26



Scheme 27

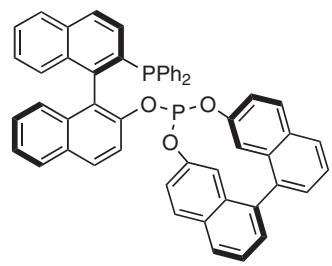


Scheme 28

3.01.2.1.3 Other preparations

(i) Formylation reactions

The hydroformylation of 1,3-dienes can be used to generate γ,δ-unsaturated aldehydes although the regioselectivity of the reaction needs to be carefully controlled to avoid generating mixtures of products <2003NJC533>. Asymmetric hydroformylation can also be carried out using the chiral phosphine–phosphite ligand **19**–Rh(I) complex as a catalyst and the reaction occurs with excellent enantioselectivity and with good regioselectivity for the branched product (Equation (35)) <1997T7795>. Cyclic alkenes (R^2, $R^3 = (CH_2)_4$) give the highest enantioselectivity in this reaction.



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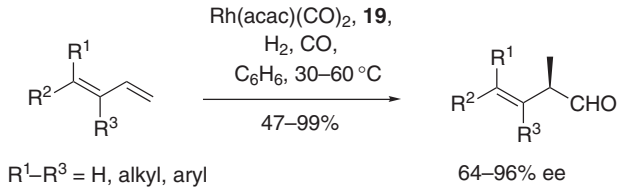
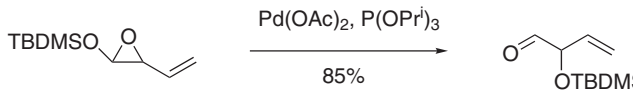


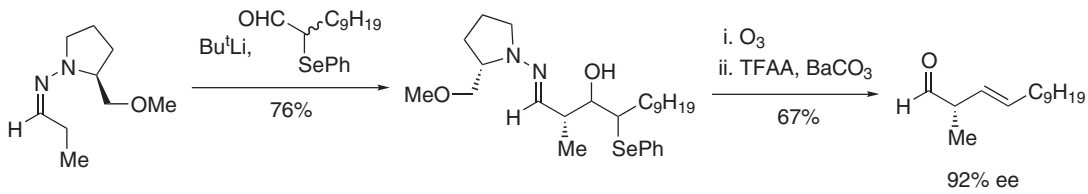
(35)

(ii) Miscellaneous preparations

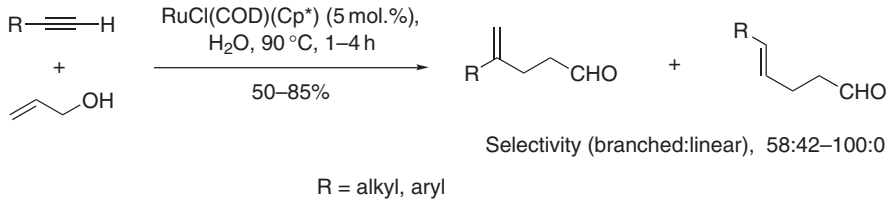
Vinyloxiranes have proved to be valuable intermediates in the synthesis and reactions of β,γ-unsaturated aldehydes. Thus, the palladium(0)-catalyzed ring-opening of silicon-substituted epoxides provides a method for the stereocontrolled synthesis of α-trialkylsilyloxy, β,γ-unsaturated aldehydes (Equation (36)) <1996T7487>. In addition, the Lewis acid-mediated ring-opening of vinyloxiranes has been coupled with *in situ* nucleophilic addition reactions, thus avoiding some of the problems associated with the purification and handling of the sensitive β,γ-unsaturated aldehyde intermediates <2000AG(E)4079>. The enantioselective synthesis of α-substituted β,γ-unsaturated aldehydes can be achieved using Enders' SAMP hydrazone methodology <1996S621>. The process involves a sequential aldol reaction–elimination approach that is equivalent to an overall α-alkenylation (Scheme 29). Finally, γ,δ-unsaturated aldehydes and acetals can be obtained by the ruthenium-catalyzed coupling of allyl alcohol with alkynes <1996T5511>. The reaction proceeds in excellent yield and with good regioselectivity for the branched isomer (Scheme 30) and can be carried out under solvent-free conditions.



(36)



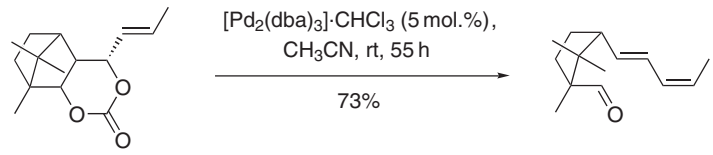
Scheme 29



Scheme 30

3.01.2.2 Alkyl Aldehydes with More Than One Double Bond

In general aldehydes containing more than one alkene can be prepared by the methods described in Sections 3.01.1 and 3.01.2.1. One specific method for the formation of this class of molecule is the β-decarbopalladation of bi- and tricyclic carbonates in the presence of catalytic palladium(0) species (Equation (37)) <1997AG(E)2352>.



(37)

3.01.2.3 Alkyl Aldehydes with Aryl or Hetaryl Substitutents

The palladium(0)-catalyzed cross-coupling of aryl halides with α,β-unsaturated carbonyl derivatives followed by conversion of the carbonyl moiety into the corresponding aldehyde was discussed in chapter 3.01.2.3 of <1995COFGT(3)1> and this remains the most efficient method for the synthesis of aryl-substituted aldehydes. Other methods have been mentioned elsewhere in this chapter and include the Lewis acid-catalyzed 1,4-rearrangement of *p*-methoxybenzyl-protected allylic alcohols to aldehydes (Equation (14); Section 3.01.1.5.4) <1998JOC3595>.

3.01.2.4 Alkynyl-substituted Alkyl Aldehydes

No significant advances have occurred in this area since the publication of chapter 3.01.2.4 in <1995COFGT(3)1>.

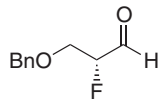
3.01.3 HALOALKYL ALDEHYDES (α, β- AND MORE REMOTE HALOGEN)

3.01.3.1 Introduction

A variety of methods for the preparation of haloalkyl aldehydes were described in detail in chapter 3.01.3 of <1995COFGT(3)1>. This discussion will review the significant advances made since that time and will concentrate mainly on the preparation of α-haloaldehydes by methods involving introduction of the halogen atom. In comparison, β- and more remotely functionalized haloaldehydes are generally prepared from halogenated starting materials by the methods described in Section 3.01.1 and these syntheses will therefore not be described here.

3.01.3.2 α-Fluoro Aldehydes

Compounds containing an α-fluoro carbonyl functionality often exhibit significant biological activities and thus there is great interest in their synthesis and the subject has recently been reviewed <1999OPP125>. However, although α-fluoro ketones are relatively well described, there are very few reports of the synthesis of α-fluoro aldehydes. This is presumably due to the inherent instability of these compounds due to carbonyl activation by the strongly electron-withdrawing fluorine atom and this often results in the isolation of these aldehydes as the corresponding hydrates. Thus, preparations involving the formylation of α-fluoro anions with *N*,*N*-dimethylamides <1997T10623, 1995JFC103, 1997JFC33> and Swern oxidation of α,α-difluoroalcohols <2003BMC1047> all generate α-fluoro aldehydes, although isolation of these compounds in the nonhydrated form is a nontrivial task. Alternatively, the recent advances in electrophilic fluorination have considerably increased the number of synthetic approaches to α-fluoro carbonyl compounds in both racemic and homochiral form, and this methodology has been comprehensively reviewed <1999T12431>. However, the application of these methods for the synthesis of aldehydes remains limited to-date with only a single report of the preparation of chiral nonracemic α-fluoro aldehydes such as **20** <1997JOC7546>. Molecular fluorine can also be used for α-fluorination of activated α-hydroxymethylene carbonyls leading to compounds of general structure **21**, and these intermediates are readily deformylated on treatment with weak bases giving an overall method for selective monofluorination <1997TL587>. Finally, α-fluoro α,β-unsaturated aldehydes have been produced by employing an anodic fluorination step <1997T647>.



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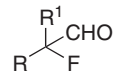
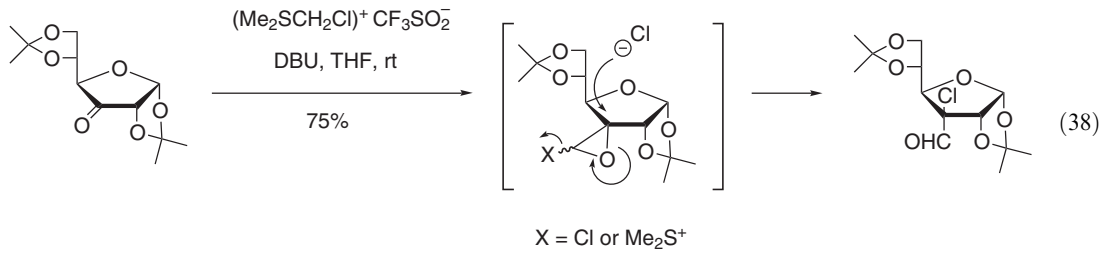


R, R^1 = CO_2Et, CN, Ph

21

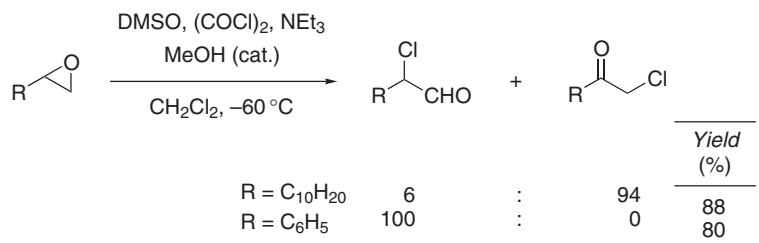
3.01.3.3 α-Chloro Aldehydes

Aliphatic α,α-dichloro aldehydes can be readily produced from the corresponding saturated aldehydes using chlorine in the presence of hydrochloride salts of pyridines, such as 2-picoline <2000SL146> and 2,6-lutidine <2000T7507>. The latter system is particularly suitable for scale-up due to its efficiency and environmentally benign nature. In an analogous reaction, tetraethylammonium trichloride (prepared by bubbling chlorine through a solution of tetraethylammonium chloride) also carries out this conversion <1997AG(E)2342> and a variety of other quaternary ammonium chloride salts can also be employed <2003S2173>. These latter systems can also produce α,α-dichloro aldehydes directly from the corresponding alcohols by an oxidation–chlorination pathway. Ketones are converted into α-chloro aldehydes by reaction with chloromethylsulfonium salts by way of an intermediate epoxide as shown (Equation (38)) <2001TL3625>. Epoxides in general can be converted into α-chlorocarbonyl compounds under Swern oxidation condition in the presence of catalytic methanol <1995T2467>. The reaction involves epoxide-opening to give an alkoxysulfonium salt which generates a carbonyl group on reaction with base by the usual Swern mechanism. Opening of the epoxide occurs preferentially at the least hindered carbon atom, thus generating ketones as the major products, although phenyl-substituted epoxides give good yields of chloroaldehydes (Scheme 31). The reduction of dichlorobutanones by sodium borohydride results in an *in situ* semibenzilic Favorskii rearrangement generating *cis*-2-aryl- and 2-alkyl-1-chlorocyclopropanecarboxaldehydes as shown (Scheme 32) <2002TL599>. A novel method for the synthesis of α-chloro aldehydes based on sulfoxide starting materials has also been reported <1994T4957>.



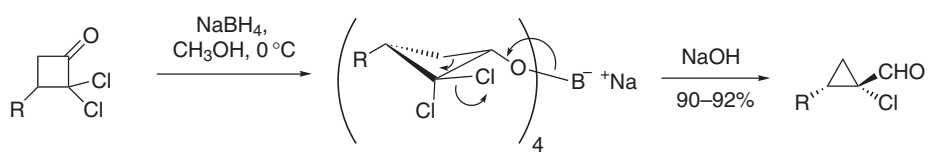
(38)

X = Cl or Me_2S^+



				Yield (%)
R = $C_{10}H_{20}$	6	:	94	88
R = C_6H_5	100	:	0	80

Scheme 31

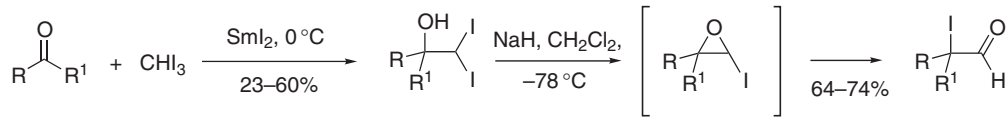


R = alkyl or aryl

Scheme 32

3.01.3.4 α-Bromo and α-Iodo Aldehydes

There have been few advances in the preparation of α-bromo and α-iodo aldehydes. Those that have been reported include the use of polymer-supported 4-(phenylseleno)morpholine for the solid-phase synthesis of bromo aldehydes <2003OPP383>, the photochemical addition of bromo- and iodo-heterocycles across enals <2000EJO1653> and the formation of α-iodo aldehydes by iodination of silyl enolates <1998JOC4558>. A novel transformation is the two-step conversion of ketones into α-iodo aldehydes by way of diiodo alcohols as shown (Scheme 33) <1998TL1409>. The reaction mechanism is thought to involve an iodoepoxide intermediate which rearranges to give the iodo aldehyde in good yield, although purification of the final products is hampered by their instability.



R, R^1 = aryl, alkyl, cycloalkyl

Scheme 33

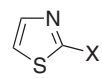
3.01.4 ALDEHYDES BEARING AN OXYGEN FUNCTION

The preparation of oxygen functionalized aldehydes was described in detail in chapter 3.01.4 of <1995COFGT(3)1>. This discussion will concentrate on the advances made since then.

3.01.4.1 α-OH- and OR-Functionalized Aldehydes

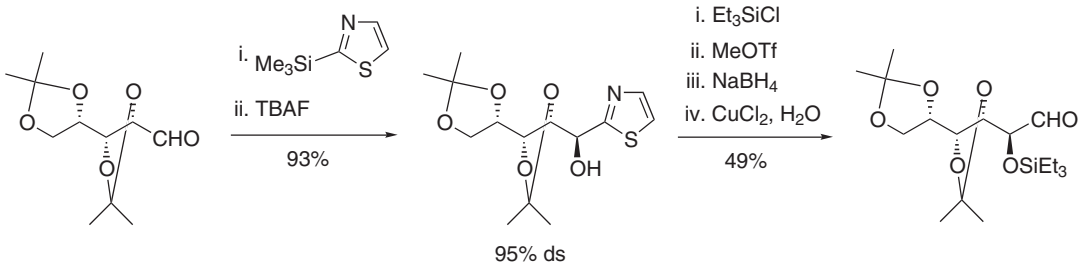
Conceptually, the simplest preparation of α-hydroxylated aldehydes is by selective oxidation of the primary alcohol of the corresponding 1,2-diol. However, whilst this is relatively straightforward in cases where the secondary diol is protected, there are very few examples of the selective oxidation occurring with unprotected diols, presumably due to the instability of the product hydroxy aldehydes. Those examples that have been reported (<1999JOC6147, 1996JOC6856>) usually employ oxidation systems based on TEMPO catalysis that are capable of selectively oxidizing primary alcohols in the presence of secondary ones (see Section 3.01.1.5.1).

As discussed previously in chapter 3.01.4.1.1 of <1995COFGT(3)1>, the preparation of aldehydes containing an α-hydroxyl functional group is most commonly achieved by the addition of a formyl anion equivalent to an aldehyde or ketone. One of the most successful approaches is based on the thiazole aldehyde synthesis as developed by Dondoni and co-workers. A variety of 2-substituted thiazole intermediates **22** are readily available and it is the reaction of the metallated (X = Li, $SiMe_3$, $SnMe_3$) derivatives with aldehydes and ketones that is most commonly used to access α-hydroxylated aldehydes after thiazole-to-formyl unmasking. This approach has been particularly successful for the homologation of carbohydrates as shown (Scheme 34) <1997JOC6261>. The reader is directed to an extensive review for a great many examples of the preparation of α-hydroxylated aldehydes using this approach <1998S1681>. The use of *N*,*N*-dialkylhydrazones as formyl anion equivalents was mentioned in Section 3.01.1.14.1. These compounds react with aldehydes and ketones to generate α-hydroxyhydrazones that can be converted into the corresponding aldehydes by treatment with ozone, usually after protection of the OH group (Scheme 35) <2001JOC5201>. Activated carbohydrate-derived α-alkoxyaldehydes and trifluoromethyl ketones <1999JOC8846> react directly with these reagents whereas "simpler" aldehydes require the presence of $ZnCl_2$ or Et_2AlCl (Scheme 36) <2001SL1158>.

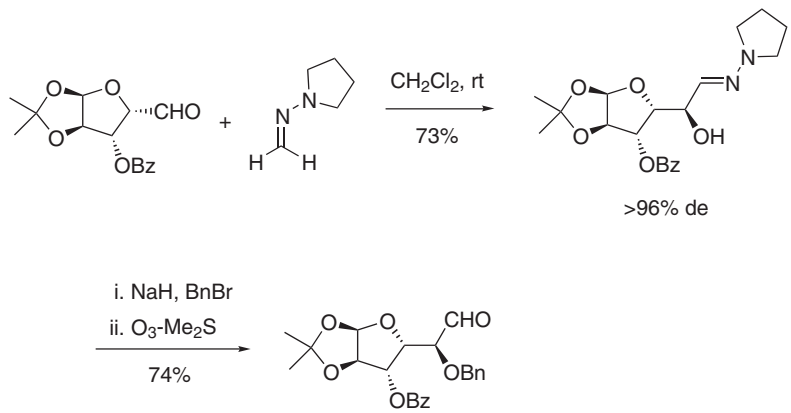


X = metal, CHO, $COCH_3$
$COCHPPh_3$, CNO

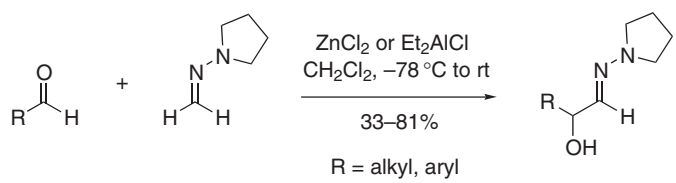
22



Scheme 34

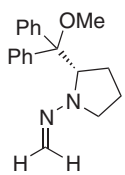


Scheme 35



Scheme 36

The synthesis of homochiral α-hydroxylated aldehydes is of considerable interest due to their synthetic use as chiral building blocks. In this regard, significant progress has been made in the asymmetric addition of chiral formyl anion equivalents to achiral aldehydes. A number of systems have been reported including those based on: chiral *N*,*N*-dialkylhydrazones **23** <2001SL1158>, oxazolidines **24** in the presence of sparteine <1998TA3125>, camphor-derived oxazolidinones **25** <2002TA29>, dithioacetals in combination with bis(oxazolines) **26** <2004JOC1581>, thiazolidines **27** <2000TA2093>, and (methylthiomethyl) oxazolidinones **28** <2001JOC3059>.



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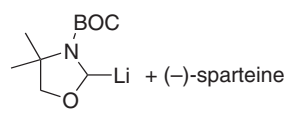

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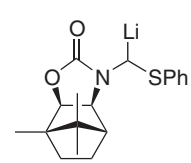

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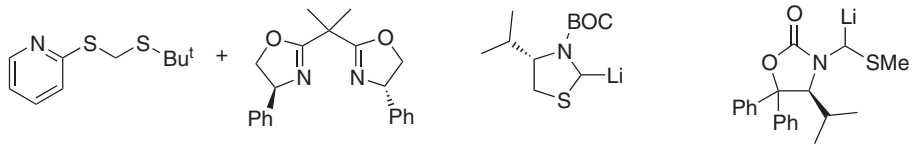
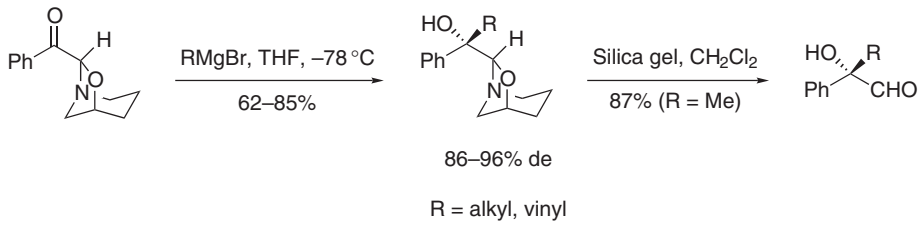
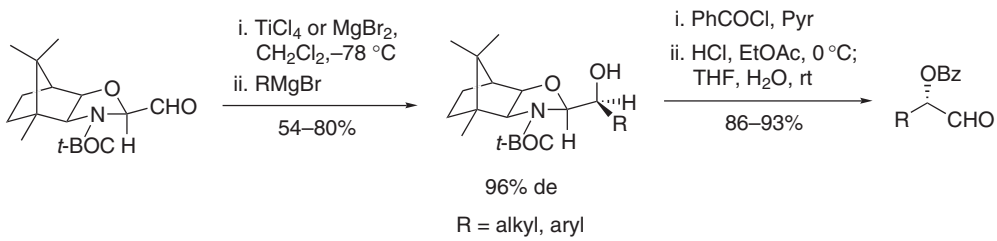


26 **27** **28**

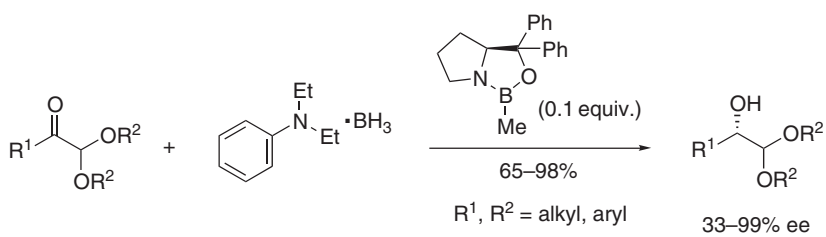
A complementary approach to homochiral α-hydroxylated aldehydes comes from the nucleophilic addition to a keto group in the presence of a masked formyl moiety that also acts as a chiral auxiliary. The reaction has been successfully carried out using SAMP-hydrazones, albeit with moderate stereoselectivity <1999T1087>, as well as with cyclic aminals (Scheme 37) <2001JOC2484> and (Scheme 38) <1999TL1977>. Alternatively, the reaction can involve diastereoselective attack on chiral substrates <1995JOC7927> or may employ chiral reducing reagents (Scheme 39) <1999JCS(P1)2095>.



Scheme 37



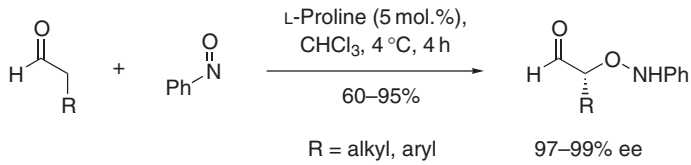
Scheme 38



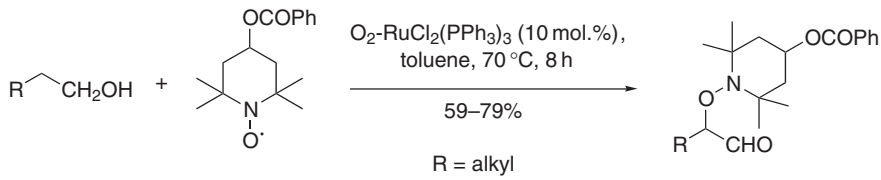
Scheme 39

A significant advance in the preparation of α-hydroxylated aldehydes is the direct and enantioselective α-oxidation of aldehydes catalyzed by proline. Two simultaneous reports of this reaction have appeared <2003TL8293, 2003JA10808> and indicate that nitrosobenzene will amino-oxylate a wide variety of aliphatic aldehydes in good yield and with excellent enantioselectivity in the presence of 5 mol.% proline as catalyst (Scheme 40). The reaction can be employed in a novel one-pot procedure, involving amino-oxylation followed by borohydride reduction, for the synthesis of enantiopure 1,2-diols from aldehydes <2003AG(E)4247>. A similar reaction is the one-pot conversion of primary alcohols into α-oxygenated aldehydes upon treatment with a benzoloxy TEMPO derivative in combination with a ruthenium complex and oxygen (Scheme 41) <1995TL3223>. The

reaction proceeds via the corresponding aldehyde, and aldehydes can also be converted into α-oxygenated products under these reaction conditions.

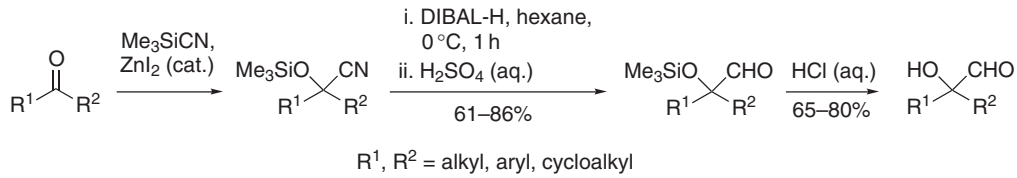


Scheme 40

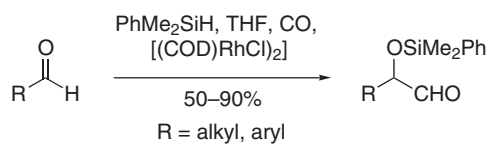


Scheme 41

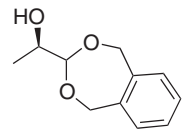
A number of miscellaneous methods for the synthesis of α-hydroxylated aldehydes have been reported. Thus, improved conditions for the Killani–Fischer synthesis (aldehyde $\rightarrow$ cyanohydrin $\rightarrow$ hydroxyaldehyde) have been reported <1996TL5893> and the use of nitrilase enzymes to prepare chiral cyanohydrins allows, after protection and DIBAL-H reduction, access to relatively unstable homochiral *O*-protected α-hydroxy aldehydes <2000T2491>. Ketones have also been used as substrates for the synthesis of α-trialkylsilyloxy aldehydes via reduction of the corresponding *O*-silyl cyanohydrins (Scheme 42) <1994T2821>. The rhodium(I)-catalyzed silylformylation of aldehydes also produces α-silyloxy carbonyls (Scheme 43) <1996OM317>. An efficient procedure to α-hydroxyacetals has been reported <1994TL7897>. Lipase enzymes can be used to resolve α-hydroxyacetals **29** <1996BMCL71> and 2-(1-hydroxyalkyl)thiazoles **30** <1996JOC4144> into single enantiomers and more significantly the introduction of a ruthenium catalyst allows the first process to become a lipase-catalyzed dynamic kinetic resolution <2001JOC4736>. The direct oxidation of silyl enol ethers remains an important approach to α-hydroxy aldehydes and use of the Sharpless asymmetric dihydroxylation allows preparation of homochiral products in excellent enantioselectivity (Scheme 44) <1994TL7813>. Enantiopure products can also be obtained by alkylation of SAMP-hydrazones derived from α-hydroxy acetaldehyde <1996LA11>. Finally, the vinyl moiety can often be used as a masked formyl group in the preparation of homochiral α-hydroxy aldehydes (Scheme 45) <1996TL1421, 1997TA779>.



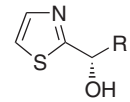
Scheme 42



Scheme 43

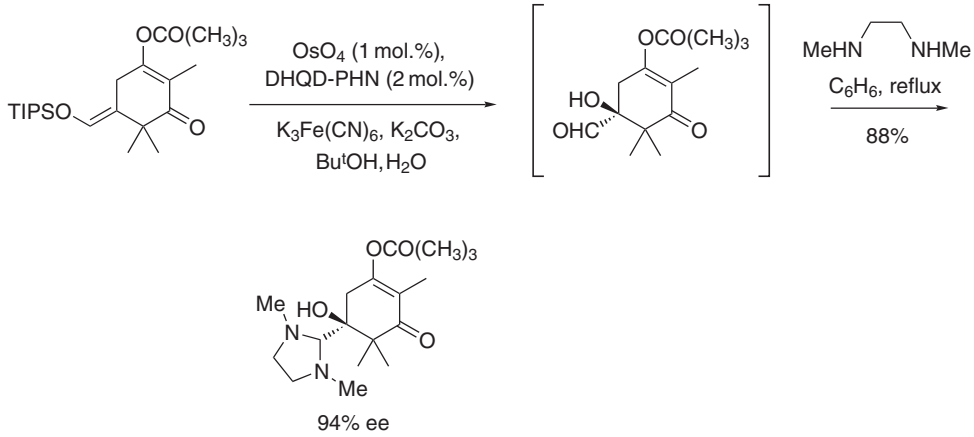


29

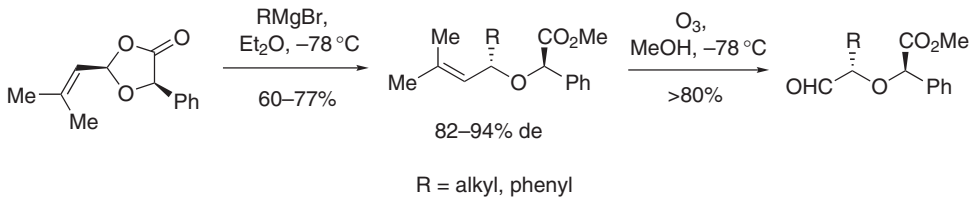


30

R = alkyl



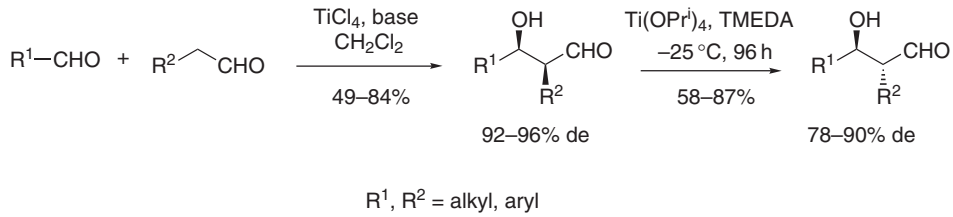
Scheme 44



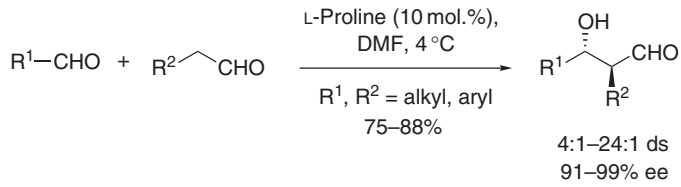
Scheme 45

3.01.4.2 β- and More Remotely OH- and OR-Functionalized Aldehydes

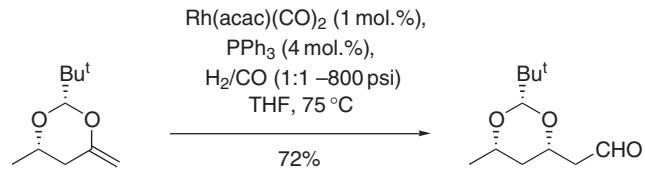
β-Hydroxyaldehydes can be generated by the selective oxidation of 1,3-diols and although there are relatively few reported examples success has been achieved using oxidations catalytic in TEMPO <2002TL6005>. However, the β-hydroxycarbonyl moiety is most conveniently generated by an aldol addition reaction. Indeed, there are countless examples of diastereo- and enantioselective aldol reactions that employ carboxylic acid-derived enolates or their equivalents. Many of the resulting aldol products can be converted into β-hydroxyaldehydes by reduction of the carboxylic acid-derived functional group using the standard methods discussed in Section 3.01.1.9. Indeed application of this approach on solid-phase can be used to generate β-hydroxyaldehyde libraries <1996TL5569>. The direct diastereoselective aldol addition of aldehydes however has only recently been reported. Thus, *syn*-β-hydroxyaldehydes can be produced in good yields and with excellent stereoselctivity by aldol reaction in the presence of titanium(IV) chloride (Scheme 46) <1998S262>. Conveniently, equilibration of the products with catalytic amounts of titanium(IV) isopropoxide results in the formation of the thermodynamically more stable *anti*-isomers. The first direct enantioselective crossed-aldol reaction of aldehydes has also been reported. This proline-catalyzed reaction generates *anti*-β-hydroxyaldehydes in excellent yields and with remarkable enantioselectivity using relatively low catalyst loadings (Scheme 47) <2002JA6798>. Crossed-aldol reactions can be achieved by carefully controlled slow addition of the aldehyde donor to the acceptor in the presence of the catalyst as homodimerization is suppressed under these conditions. Finally, diastereoselective rhodium-catalyzed hydroformylation of enol ethers can be used to generate protected 3,5-dihydroxyaldehydes as shown (Equation (39)) <1997JA11118>.



Scheme 46



Scheme 47

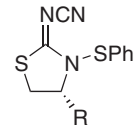


(39)

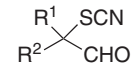
3.01.5 ALDEHYDES BEARING A SULFUR FUNCTION

3.01.5.1 SH-, SR-, and Higher-coordinated Sulfur-functionalized Aldehydes

There have been no advances in the synthesis of α-thiol aldehydes and so this discussion will restrict itself to the preparation of α- and more remotely functionalized sulfenyl and sulfonyl aldehydes. As discussed in chapter 3.01.5.1 of <1995COFGT(3)1>, α-sulfenyl aldehydes are most readily prepared by the direct sulfenylation of aldehydes or their derivatives (e.g., silyl enol ethers), employing electrophilic sources of sulfur such as sulfenyl chlorides. In a continuation of this approach, it has been shown that aldehydes will react with *N*-(phenylthio)-succinimide under acidic conditions to give the corresponding α-sulfenyl aldehydes, although reasonable yields are only achieved with α-substituted starting materials <2000TL3911>. A new type of sulfenylating reagent in both achiral **31** and chiral form **32** has been shown to α-sulfenylate ketone-derived enamines and silyl enol ethers <2000SL32>. The yields are good and enantioselectivities, with **32**, are moderate, but it remains to be seen if this methodology can be applied to aldehyde-derived substrates. The synthesis of optically active α-sulfenylated aldehydes can be problematic due to the fact that these compounds are easily racemized by enolization. Nevertheless, this class of compounds can be produced by employing Evans' oxazolidinone methodology (Scheme 48) <1994TL3991>, although the correct choice of oxidant for the final step is crucial (Swern oxidation gave racemization and/or poor yields). In a complementary manner, α-sulfenylation of SAMP/RAMP hydrazones can also be employed (Scheme 49) to give the relatively unstable chiral aldehydes is good yield and excellent ee, although racemization is observed in the benzyl-substituted case <1998T10239>. The thiocyanato group can also be introduced into the α-position of aldehydes, either directly or via the corresponding silyl enol ethers, using thiocyanatotrimethylsilane (TMSNCS) and sulfuryl chloride <1994CL2275>. This is the only general method for preparing relatively unstable α-thiocyanato aldehydes **33**.

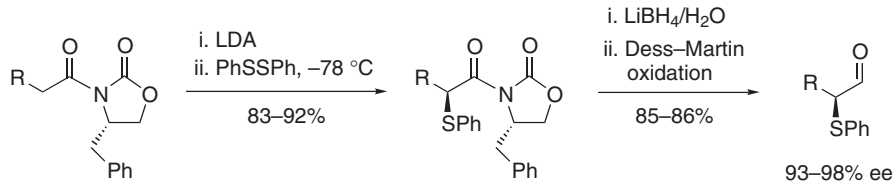


31 R = H
32 R = CH_2Ph



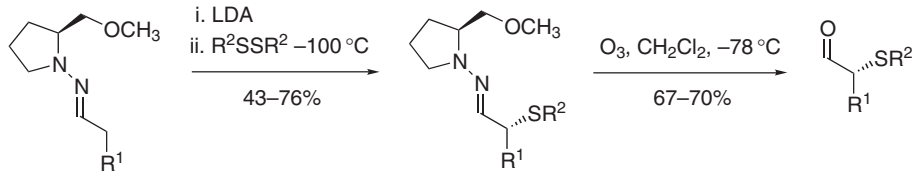
R^1 = alkyl, R^2 = H, alkyl

33



R = alkyl

Scheme 48

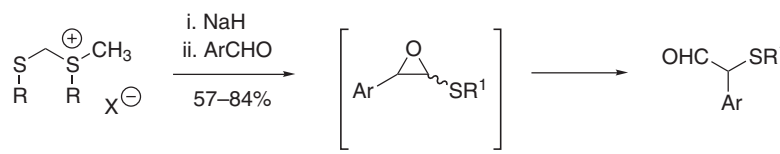


70–93% de 45–93% ee

R^1= alkyl, benzyl; R^2 = alkyl

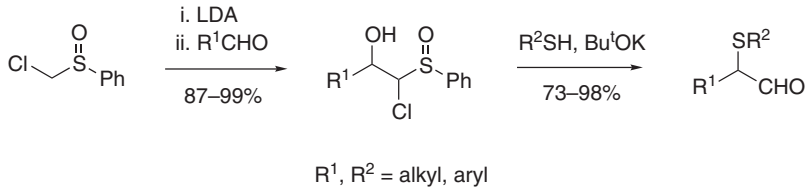
Scheme 49

A number of miscellaneous methods for the synthesis of α-sulfenyl aldehydes have been reported. Thus, the reaction of sulfonium salts of formaldehyde dithioacetals with aromatic aldehydes generates 2-thioalkyl-3-arylepoxides which can undergo spontaneous rearrangement (depending on the substituents on the aryl ring) generating α-sulfenyl aldehydes as shown (Scheme 50) <1995T10593>. A two-step procedure for the formation of α-sulfenyl aldehydes from aldehydes with a one-carbon elongation is also possible using chloromethyl phenyl sulfoxide (Scheme 51) <2000TL2121>. A variety of thiols can be employed to open the sulfinylepoxide intermediate in the second step, although the best yields are obtained with benzyl mercaptan. Additionally, repetition of the procedure on the product aldehyde generates α,β-disulfenyl aldehydes. The asymmetric hydroformylation of vinyl sulfides, allyl sulfides, and allyl sulfones also produces chiral sulfur-functionalized aldehydes <1995TA2583>. Vinylsulfides give regioselective reactions generating α-sulfenyl aldehydes in good yield and with moderate enantioselectivity (Scheme 52). The reactions with allyl species, however, are less selective and mixtures of branched and linear aldehydes are produced. Finally, a number of preparations of α-sulfenyl α,β-unsaturated aldehydes have been reported <1999T7421, 1998JOC4475>.

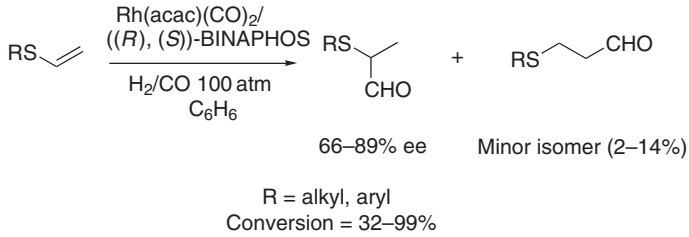


R = CH_3 or $-(CH_2)_3-$
R^1 = CH_3 or $(CH_2)_3SCH_3$

Scheme 50

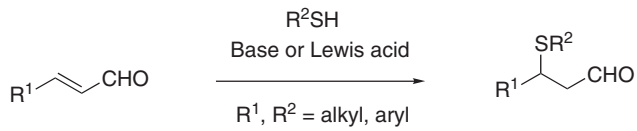


Scheme 51

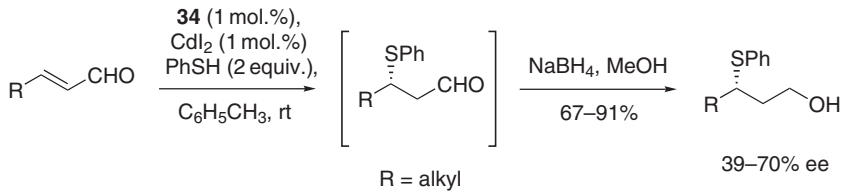


Scheme 52

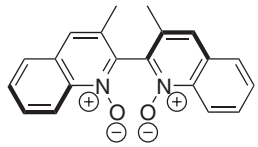
The synthesis of β-sulfenyl aldehydes can be achieved by the 1,4-addition of thiols to enals. These reactions usually require either activation of the thiol by a base or of the α,β-unsaturated aldehyde by a Lewis acid (Scheme 53). A number of novel catalysts can be used in this reaction including, tetrabutylammonium bromide ionic liquid <2003T2417>, H-Rho-zeolite <1999SL1921>, NaY-zeolite <1997TL6557> and heterobimetallic species <2003TA113, 1999T2721>. However, perhaps the most significant advance in this area is the first ever report of the enantioselective conjugate addition of thiols to enals catalyzed by a chiral *N*,*N*′-dioxide **34**–cadmium iodide complex (Scheme 54) <2000T9589>. Using only 1 mol.% of the catalyst system, the reaction proceeds in high yields, with moderate-to-good enantioselectivity and is tolerant to a range of alkyl thiols. Interestingly, the alkene geometry of the starting α,β-unsaturated aldehyde has no affect on the enantioselectivity of the reaction. Aldehyde-derived enamines can be functionalized to give β-sulfenyl aldehydes by reaction with sulfoxides bearing α-hydrogens in the presence of a magnesium amide <1998T2691>. The reaction is thought to involve the electrophilic sulfenating agent **35**, which is generated *in situ* from the corresponding sulfoxide. Finally, γ-sulfonated aldehydes **36** can be generated from the conjugate addition of aldehyde enamines (produced *in situ* directly from the aldehyde) to α,β-unsaturated sulfones <2001JCS(P1)316>.



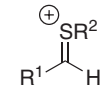
Scheme 53



Scheme 54

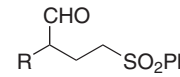


34



R^1 = H, alkyl, aryl
R^2 = alkyl, aryl

35



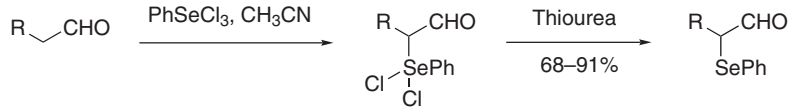
R = alkyl

36

3.01.6 ALDEHYDES BEARING A SELENIUM OR TELLURIUM FUNCTION

3.01.6.1 Se-, Te-, SeR-, or TeR-Functionalized Aldehydes

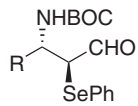
The preparation of α-alkylselenyl- and α-arylselenyl aldehydes is of primary importance for their subsequent conversion into α,β-unsaturated carbonyls by oxidation to the selenoxide, followed by elimination of a selenic acid. Indeed, this methodology has now been adapted to allow for the synthesis of α,β-unsaturated aldehydes using polymer-supported α-selenoaldehydes <2003JCR(S)258>. As discussed in chapter 3.01.6 of <1995COFGT(3)1>, α-selenyl aldehydes are most readily prepared by the reaction of an aldehyde-derived d^2-synthon with a selenium(II) regent such as phenylselenyl chloride. Relatively few advances have been made to this methodology, although phenylselenium trichloride has been shown to act as an efficient phenylselenylating agent for linear aliphatic aldehydes in acetonitrile without the requirement of added acid <1997S101>. The reaction can be conveniently carried out on large scale and proceeds via the dichloro adduct **37**, which is directly reduced by addition of thiourea to the reaction mixture (Scheme 55). The only limitation is that α-branched aldehydes give α-chlorinated products under the reaction conditions. The reaction of phenylselenyl chloride with amino acid-derived enol ethers can be made stereoselective by employing titanium *iso*-propoxide, thus generating homochiral α-phenylselenyl aldehydes such as **38** <1999TL4417>. In an analogous reaction to the α-selenylation of d^2 synthons, enolates derived from β-phenylselenyl silyl enol ethers **39** undergo allylation and benzylation to give γ-unsaturated α-selenyl aldehydes, although the degree of *O*-alkylation in this reaction can become problematical as the size of R increases <1997T6365>. The use of $ZnCl_2$ has been shown to greatly promote the regioselective addition of phenylselenyl chloride across electron-deficient alkenes including α,β-enals, thus giving β-chloro-α-selenyl aldehydes <2000TL3701>. Finally, an unusual side-reaction producing an α-phenylselenyl aldehyde has been reported <1995TL8097>.



37

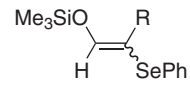
R = H, alkyl, aryl

Scheme 55



R = alkyl

38

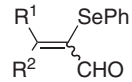


R = alkyl, aryl

39

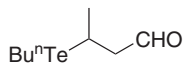
There have been few advances in the preparation of selenyl aldehydes using nucleophilic sources to introduce the selenium since the topic was discussed in chapter 3.01.6 of <1995COFGT(3)1>. α-Bromo acetals can be readily converted into the α-phenylselenyl analogs by nucleophilic displacement by potassium benzene-selenoate prepared by the hydrazine reduction of diphenyl diselenide in the

presence of potassium carbonate <2000JOC2151>. Interestingly, the sodium anion, generated by sodium borohydride reduction of diphenyl diselenide, left the bromides untouched. α,β-Unsaturated selenyl aldehydes **40** can be produced by a formyl-olefination reaction <1998JOC4475>. β-Seleno and telluroaldehydes **41** can be formed by the 1,4-addition of the corresponding alkylselenols and tellurols with α,β-enals, although the reaction is unsuccessful for β,β-disubstituted substrates <2002TL1625>. A similar reaction of enals with a selenium-stabilized copper reagent **42** leads to γ-selenoaldehydes <1999JCR(S)26>.

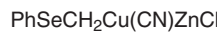


R^1 = alkyl, vinyl, aryl
R^2 = H, Me

40



41



42

3.01.7 ALDEHYDES BEARING A NITROGEN FUNCTION

3.01.7.1 NH_2-, NHR-, and NR_2-Functionalized Aldehydes

A great deal of progress has been made in the synthesis of amino-functionalized aldehydes since it was discussed in chapter 3.01.7.1 of <1995COFGT(3)1>. This section will deal with only the most significant advances in this area and, where relevant, the reader will be directed to suitable reviews that cover the subject in greater depth than is possible here.

3.01.7.1.1 α-NH_2-, NHR-, and NR_2-Functionalized aldehydes

The synthesis of α-amino-substituted aldehydes continues to be an extremely active area due, in the main, to their importance as synthetic building blocks. The aldehydes are often produced with either the formyl or amino group suitably protected and they are usually available in either enantiomeric form, although often special precautions are needed to prevent epimerization at the α-position. The stability of free α-amino aldehydes has been investigated and they have been shown to form stable solvent adducts in mildly acidic polar media (H_2O or MeOH) which can be stored indefinitely without racemization <2000JA3236>. In accordance to their importance, a number of detailed reviews of the synthesis and reactions of these compounds have recently appeared <2003CHIR514> (*N*-protected-α-amino aldehydes), <1999CRV1121> (*N*,*N*-dibenzylamino aldehydes), and <2001JCS(P1)2136> ((*S*)-1,1-dimethyl-4-formyl-2,2-dimethyloxazolidsine-3-carboxylate—Garner's aldehyde). The reader is directed to these for an in-depth discussion of the subject.

One of the most widely applicable methods for the synthesis of homochiral α-amino aldehydes is from the reduction of the corresponding *N*-protected α-amino acid derivatives. The major issues with this transformation are over-reduction to the corresponding amino alcohol and, perhaps more significantly, racemization of the chiral center during either the reaction or the work-up and purification procedures. Many methods have been reported that seek to avoid these issues and a comprehensive tabulated list of available approaches can be found in one of the reviews in this area <2003CHIR514>. The majority of these procedures have already been discussed in Section 3.01.1.9.1 and they include reduction of morpholine amides with lithium aluminum hydride <2000TL37>, of ethanethiol esters with triethyl silane-Pd(C) <2002S1121>, of acid halides with lithium tris-(*t*-butoxy)-aluminum hydride <1995TL7281>, of Weinreb amides with lithium aluminum hydride <1998TA1855> and of amino acid-derived *N*-carboxyanhydrides **43** with lithium tris-(*t*-butoxy)-aluminum hydride <1994TL9031>. In general, these procedures can be carried out with any of the three most commonly used *N*-protecting groups, namely, carbobenzoxy (Cbz), *t*-butoxycarbonyl (*t*-BOC) and 9-(9-phenylfluorenyl) (Fmoc), without any significant loss in optical purity.

In cases where the corresponding α-amino alcohol is more readily available (or is formed in significant amounts by over-reduction of the carboxylic acid derivative) the corresponding aldehyde is accessed by oxidation procedures. The methods used are those generally employed for the corresponding reactions of nonfunctionalized aliphatic alcohols but with the added caveat that problems of racemization often need to be addressed. Again, this general approach (with particular emphasis on the

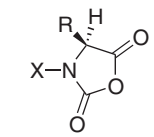
problems of racemization) has been reviewed in detail elsewhere <2003CHIR514>. Of the numerous methods that are available, the two mildest are the TEMPO-mediated oxidation <1998T6051> (especially employing trichloroisocyanuric acid as co-oxidant <2001OL3041>) and the use of DMP **3**, which has been found to be particularly suited for the oxidation of highly epimerizable Fmoc and trifluoroacetyl *N*-protected α-amino aldehydes such as **44** (Scheme 56) <2000TL1359>. However, it should be noted that the use of this later procedure with *N*-*t*-BOC-protected analogs is less straightforward and the optical purity of the product can be variable <1995CCC693>.

44

Oxidation method	*Yield* (%)	*ee* (%)
Swern (Pr^i_2NEt)	37	50
TEMPO	87	95
Dess–Martin	>95	99

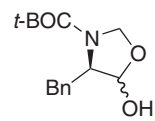
Scheme 56

Despite the methods outlined above, homochiral α-amino aldehydes are still generally used immediately after isolation due to problems of racemization and chemical stability on long-term storage. A novel solution to these problems has recently been introduced and involves use of a *N*-hydroxymethyl group to generate cyclic hemiacetals such as **45** that are configurationally and chemically stable precursors to the corresponding *N*-*t*-BOC-protected α-amino aldehydes <1998TL4299>. However, with some systems, chemical stability and racemization may be such a problem that it is more convenient to use stereochemically stable synthetic equivalents in place of the aldehyde including *N*,*S*-ketals **46** <1998JOC7236> and acyl silanes (Scheme 57) <1999EJO437>.

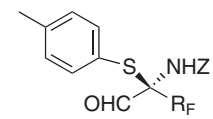


X = *t*-BOC, Fmoc, Z

43

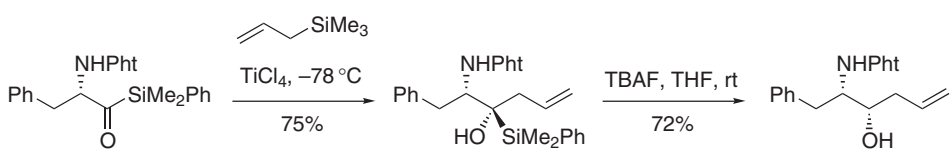


45



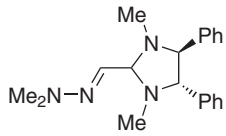
$R_F = CF_3, CHF_2$

46

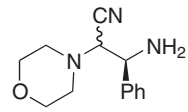


Scheme 57

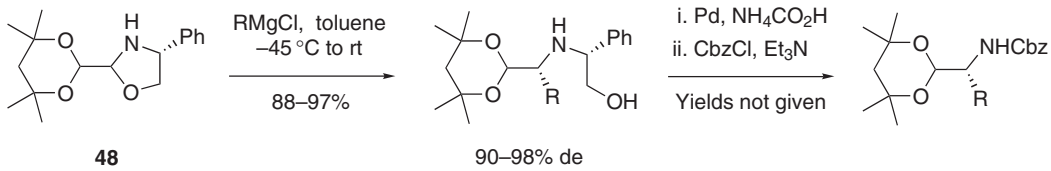
Homochiral α-amino aldehyde derivatives can also be produced from non-amino acid starting materials via the formation of the corresponding acetals or aminals. This approach is highlighted by the stereoselective addition reactions of organometallics to aminal **47**, developed by Alexakis and co-workers, which was discussed in chapter 3.01.7.1.1 of <1995COFGT(3)1>, and this subject has since been reviewed <1995S1038>. In addition, the diastereoselective addition of Grignard reagents to chiral 1,3-oxazolidines **48** also leads, after cleavage, to enantiomerically enriched α-amino acetals (Scheme 58) <1994TL7489>. A useful class of *C*-protected α-amino aldehydes **49**, that employ the amino nitrile function as the *C*-protective group, can be readily accessed from the corresponding *N*-Fmoc-protected analogs under conditions that give only minimal racemization even with highly epimerization-prone substrates <2000OL3337>.



47

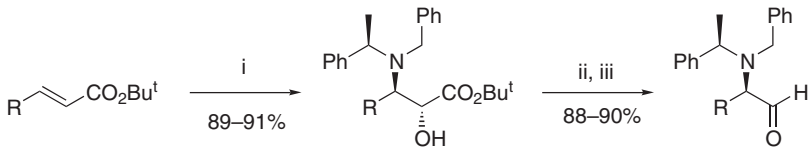


49



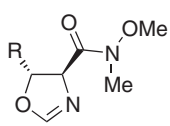
Scheme 58

A number of miscellaneous methods for the enantioselective synthesis of α-amino aldehydes have also appeared. Thus, a three-step procedure involving diastereoselective 1,4-addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzamide to α,β-unsaturated esters with subsequent enolate hydroxylation, ester reduction and finally oxidative cleavage can be used to generate *N*,*N*-protected α-amino aldehydes as shown in Scheme 59 <2001SL1599>. Gold(I)-catalyzed asymmetric aldol reactions have been used to produce *trans*-5-alkyl-2-oxazoline-4-(*N*-methoxy-*N*-methylcarboxamides) **50** that can be readily converted into the corresponding *N*-*t*-BOC-protected α-amino aldehydes <1995JOC1727>. Similar products are also accessible from *trans*-5-benzyloxy-4-methoxy-2-oxazolidinones **51** that can be used as electrophilic chiral α-methoxyglycinal derivatives. These compounds are available in either enantiomeric form (by resolution) and react regio- and stereoselectively with organocuperates in the presence of $BF_3{\cdot}Et_2O$ to give intermediates **52** that can be subsequently converted into the protected aminoaldehyde (Scheme 60) <2001OL897>. α,α-Disubstituted amino aldehydes may be formed by the asymmetric alkylation of the anion of the oxazolidinone imine **53** <1998JA12468>. *N*-Cbz-α-amino aldehydes have also been formed from the stereospecific rearrangement of homochiral allylic epoxides as was discussed in section 3.01.1.6 <1995JA7379>. Finally, racemic α-amino aldehydes have been synthesized using Weinreb resin <2000JCO172>.



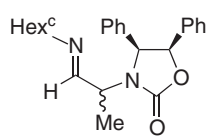
i. Lithium (*R*)-*N*-benzyl-*N*-α-methylbenzamide, –78 °C then (–)-(camphorsulfonyl) oxaziridine –78 °C to rt; ii. $LiAlH_4$, THF, –78 °C to rt; iii.H_5IO_6, CH_2Cl_2-H_2O, 0 °C 30 min

Scheme 59

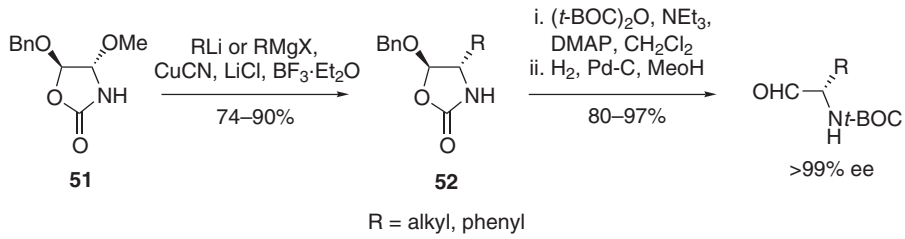


R = alkyl, vinyl, phenyl

50



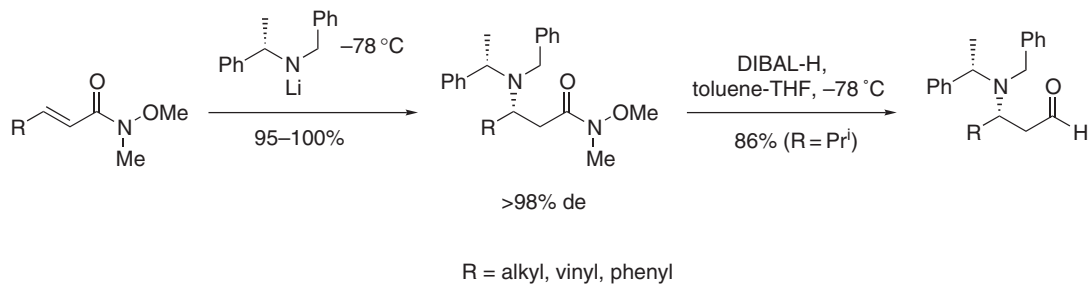
53



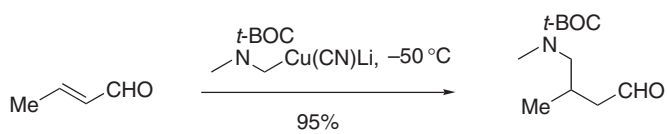
Scheme 60

3.01.7.1.2 β- and more remotely NH_2-, NHR-, and NR_2-functionalized aldehydes

The preparation of β- and more remotely nitrogen-functionalized aldehydes can, in general, be achieved by many of the methods outlined for nonfunctionalized aldehydes and therefore only specific methods for this class of compound will be discussed here. The conjugate addition of amines, or their anions, direct to α,β-enals is relatively rare and a more satisfactory approach is the use of α,β-unsaturated acid derivatives that may be subsequently transformed to the aldehyde functionality. Accordingly, Davies and co-workers have reported the stereoselective addition of lithium (*S*)-(α-methylbenzyl)benzylamide to α,β-unsaturated Weinreb amides to give, after a subsequent reduction step, homochiral β-amino aldehydes (Scheme 61) <1995SL700>. A similar conjugate addition reaction of α-aminoalkylcuprates can take place directly with α,β-enals and provides an efficient method for the synthesis of racemic γ-amino aldehydes (Equation (40)) <2000T2767>.



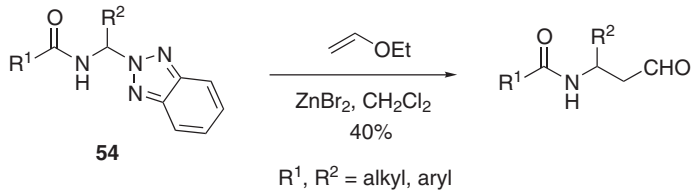
Scheme 61



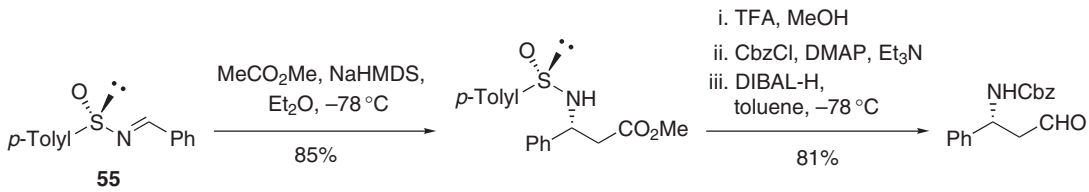
(40)

The use of imines and their equivalents in Mannich reactions can also lead directly to β-amino aldehydes. Thus, reaction of *N*-(1-benzotriazol-1-alkyl)amides **54** with ethyl vinyl ether in the presence of $ZnBr_2$ generates amino aldehydes albeit in modest yields (Scheme 62) <1999JOC7622>. The enantioselective synthesis of β-amino aldehydes has also been reported from the homchiral sulfinimine **55** by a four-step procedure as shown (Scheme 63) <1998TL5951>. The reaction of the α-carbanion derived from imines with *N*-tosylimines also provides a facile route to β-amino aldehydes (Scheme 64) <2002JCS(P1)1487>. Perhaps more significant is the first report of unmodified aldehydes as donors in proline-catalyzed asymmetric Mannich-type reactions (Scheme 65) <2002JA1866>. This approach employs readily available and inexpensive materials in a highly enantioselective reaction that is also diastereoselective (selectivity increases in the order R = Me < Et < *i*-Pr < *n*-C_5H_{11}) with preferential formation of the *syn*-isomer, although partial epimerisation to the *anti*-isomer can occur upon chromatography on silica gel.

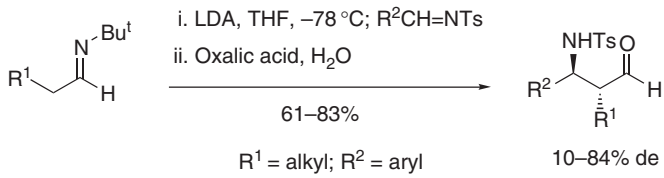
Amino aldehydes can also be prepared by a number of miscellaneous routes. These include synthesis of β-amino aldehydes from α-amino alcohols via the corresponding nitrile <1997BSF713>, of γ-amino aldehydes by the regioselective ozonolysis of tetrahydropyridines <1994SL675> and of γ- and more remotely functionalized *N*-acyl amino aldehydes by the samarium diiodide-mediated ring-opening of *N*-acyl lactams (Scheme 66) <2000TL7299>.



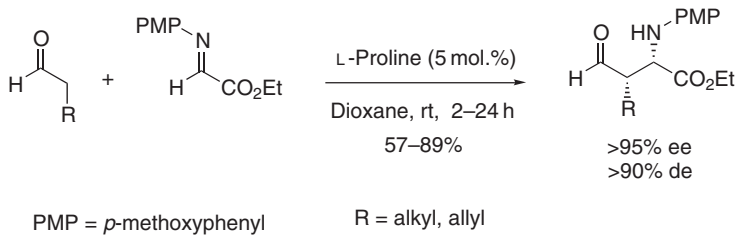
Scheme 62



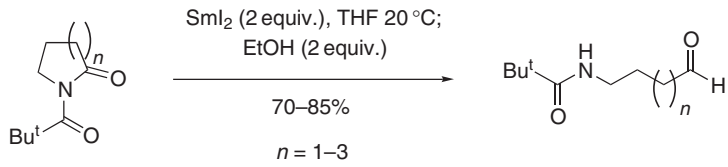
Scheme 63



Scheme 64



Scheme 65

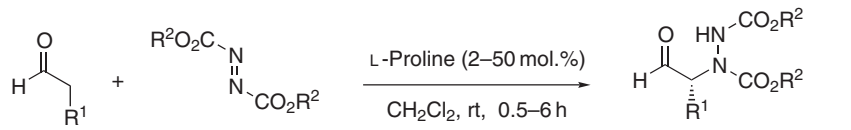


Scheme 66

3.01.7.2 NHX- and NX_2-Functionalized Aldehydes

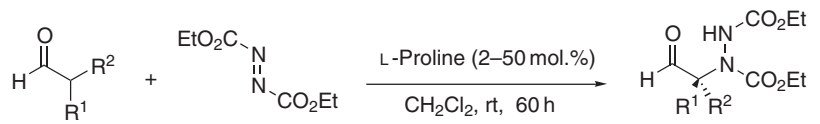
The direct proline-catalyzed asymmetric α-amination of aldehydes employing dialkyl azodicarboxylates to give α-hydrazino aldehydes has been reported independently by two groups <2002AG(E)1790, 2002JA5656>. This extremely simple procedure generates products in good-to-excellent yields and with excellent enantioselectivity after a straightforward aqueous work-up followed by evaporation of the excess aldehyde and solvent (Scheme 67). The product aldehydes readily undergo racemization and are therefore used immediately—in fact both groups suggest a direct reduction with sodium borohydride to give the corresponding α-hydrazino alcohols. This

method can also be employed using α,α-disubstituted aldehyde starting materials to generate compounds bearing quaternary chiral centers <2003CC2448>. However, the enantioselectivity of this reaction is generally lower and useful levels of stereoselectivity are only achieved with the presence of an α-aryl substituent (Scheme 68). Interestingly, this report also indictaes that the four-membered ring analog of proline L-2-azetidinecarboxylic acid also catalyzes the reaction but with significantly reduced stereoselectivity. β-Nitrone aldehydes can be prepared directly from the reaction of aldoximes with α,β-enals in the presence of a mixed Lewis acid catalyst <2001TL6719>.



R^1 = alkyl, allyl, Bn; R^2 = alkyl, Bn
77–99% (R^1 = Me, Et)

Scheme 67

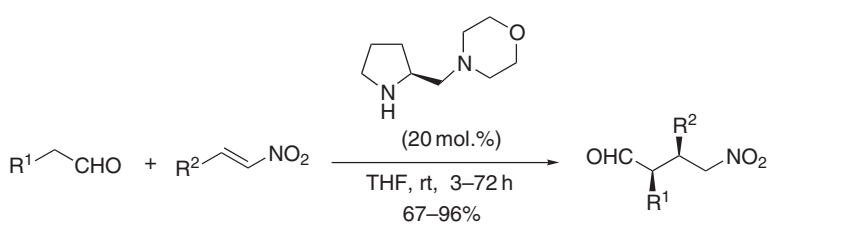


R^1 = alkyl; R^2 = alkyl, aryl

Scheme 68

3.01.7.3 NY-Functionalized Aldehydes

There have been few advances in the direct preparation of nitro aldehydes since the publication of chapter 3.01.7.3 in <1995COFGT(3)1>. Optically active γ-nitro aldehydes can be produced by the enantioselective Michael addition of silyl nitronates direct to α,β-unsaturated aldehydes using a chiral ammonium bifluoride catalyst <2003JA9022>. In an analogous fashion, the direct asymmetric Michael addition of unmodified aldehydes to aryl-substituted nitro alkenes using (*S*)-2-(morpholinomethyl)-pyrrolidine as catalyst gives γ-formyl nitro compounds in good yield, with excellent diastereoselectivity and moderate levels of enantioselectivity (Scheme 69) <2001OL3737>.



R^1 = alkyl; R^2 = aryl

Scheme 69

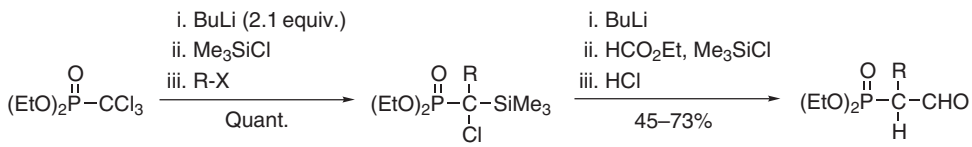
3.01.8 ALDEHYDES BEARING A PHOSPHORUS, ARSENIC, ANTIMONY, OR BISMUTH FUNCTION

3.01.8.1 XR_2, X^+R_3-Functionalized Aldehydes

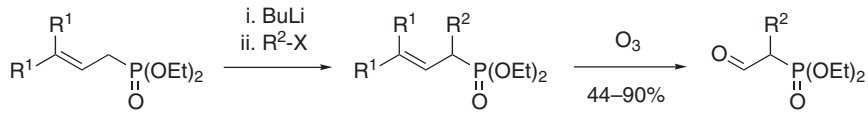
The formation of phosphonium and arsonium salts by treatment of appropriate halides with phosphines and arsines was discussed in chapter 3.01.8.1 of <1995COFGT(3)1> and no significant advances have occurred in this area since that time.

3.01.8.2 Higher-coordinated Phosphorus-, Arsenic-, Antimony-, or Bismuth-functionalized Aldehydes

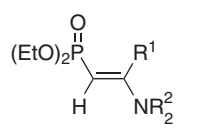
Phosphorylated aldehydes are important synthetic reagents especially for their use in Horner–Wadsworth–Emmons reactions. As a consequence, the preparation and reactions of this class of compounds has generated growing interest and progress in this area up to 1998 has been extensively reviewed <1998T14637>. The formylation of alkylphosphonate anions remains the most convenient method to generate 1-formylalkylphosphonates and a procedure based on diethyl trichloromethylphosphonate as a precursor and employing a sequential alkylation and Peterson reaction has been reported (Scheme 70) <1995JCS(P1)2835>. Alternatively, allylic phosphonates can be successively alkylated and cleaved by ozonolysis, to produce similar target compounds (Scheme 71) <2000SC789>. Unsaturated phosphonates can also be used as precursors to phosphorus-functionalized aldehydes. Thus, secondary amines add to alkynylphosphonates under copper(I) catalysis to generate (*E*)-2-(dialkylamino)alkenylphosphonates **56**, which can be regarded as precursors to α-formylphosphonates <2001TL4365>, whilst α-formylvinylphosphonates **57** can be prepared from β-(ethoxy)vinylphosphonate <2000JOC4326>. Carbohydrate-derived α-formylphosphonates have also been reported <1998T9859>. Finally, the diastereoselective phosphanylation of SAMP-hydrazones produces homochiral α-phosphanyl carbonyls (although the aldehydes have not been isolated but were directly reduced to the corresponding alcohols) <1997LA345>.



Scheme 70

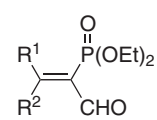


Scheme 71



R^1 = H, alkyl, aryl
R^2 = alkyl, cycloalkyl

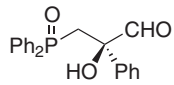
56



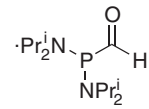
R^1, R^2 = H, alkyl, aryl

57

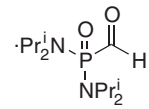
More remotely phosphorylated aldehydes can be produced by a variety of methods. Thus, triphenylphosphine undergoes direct 1,4-addition to acrolein to generate the corresponding phosphonium salt <2001JOC4673>, although this does not seem to be a widely applicable method. Alternatively, homochiral β-phosphinoyl hydroxy aldehydes **58** can be produced from methyldiphenylphosphine oxide using Mukaiyama's bicyclic aminal methodology <1996JCS(P1)2129>. γ-Functionalized aldehydes can also be produced from α-phosphonate anions <1996T1557> or by Michael addition of carbonyls to a phosphonoacrylate <1998SL1114>. Finally, two new types of stable aldehydes have been reported, the novel formylphosphane **59** and phosphane oxide **60** <1999AG(E)2201>.



58



59



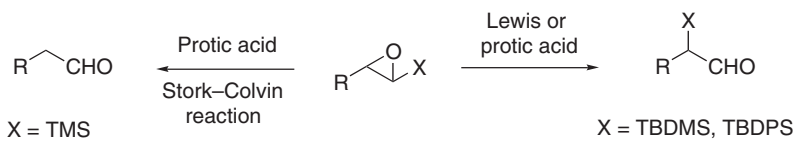
60

There have been no significant developments in the synthesis of arsenic, antimony, or bismuth functionalized aldehydes.

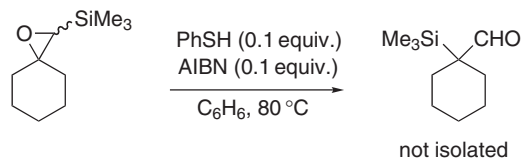
3.01.9 ALDEHYDES BEARING A METALLOID FUNCTION

3.01.9.1 Silicon-functionalized Aldehydes—α-Silyl Aldehydes

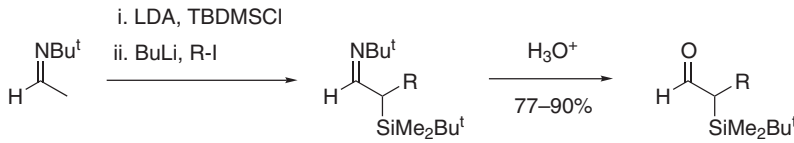
The formation of α-silyl aldehydes by sila-pinacol rearrangement was described previously in chapter 3.01.9 of <1995COFGT(3)1>. In addition to this method, this class of compounds can also be accessed by the selective rearrangement of epoxysilanes. Whilst epoxysilanes generally undergo the Stork–Colvin reaction when treated with acids to generate desilylated carbonyls, substrates having hindered silyl groups have been shown to generate α-silyl aldehydes when treated with sulfuric acid <1995JCS(P1)1525> or a bulky Lewis acid <1997CL519> (Scheme 72). Vinyl-substituted epoxysilanes undergo a similar rearrangement in the presence of catalytic palladium(0), generating α-trialkylsilyl-β,γ-unsaturated aldehydes in a stereoselective manner (see Section 3.01.2.1.3) <1996T7487>. Again, the transformation is only applicable to substrates having bulky silyl groups due to the competing 1,2-Brook rearrangement, which is the major reaction with less hindered precursors. This rearrangement of epoxysilanes can also be brought about in favorable cases with lithium phenylthiolate <2000TL1111>. Furthermore, although α-trimethylsilyl aldehydes have been reported as being unstable, they can be prepared (although not isolated) from the free-radical-induced rearrangement of cycloalkenyl epoxysilanes, a reaction that is thought to proceed by homolytic isomerization (Equation (41)) <1994TL3777>. Finally, α-silyl aldehydes can be synthesized by the silylation and alkylation of the acetaldehyde *t*-butylimine, in a one-pot procedure, followed by hydrolysis without purification (Scheme 73) <1995S1003>.



Scheme 72



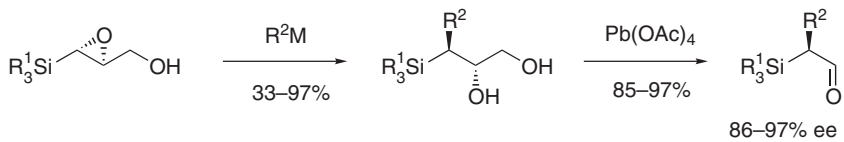
(41)



R = alkyl

Scheme 73

The use of SAMP- and RAMP-hydrazone methodology for the synthesis of homochiral α-silyl aldehydes was discussed in chapter 3.01.9 of <1995COFGT(3)1>. These compounds can also be synthesized using an asymmetric Claisen rearrangement <2002T8307> and from homochiral trialkylsilyl-substituted 2,3-epoxy alcohols prepared using Sharpless epoxidation methodology (Scheme 74) <1999TA3601>.

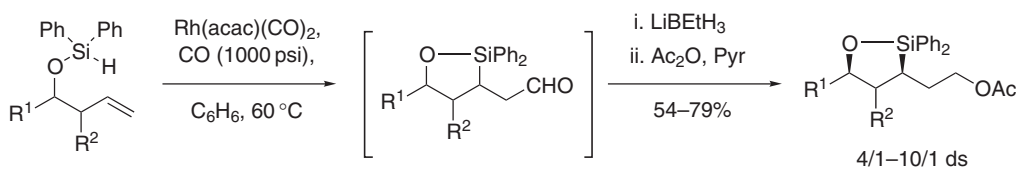


R^1 = alkyl, aryl; R^2 = alkyl, vinyl
M = $CuCNLi_2$, MgBr-CuI

Scheme 74

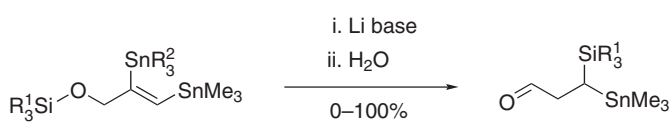
3.01.9.2 β-Silyl Aldehydes

β-Trialkylsilyl aldehydes can be prepared by the conjugate addition of silyl cuprates to α,β-enals and this methodology has been extended by the finding that the reaction can be carried out using a catalytic amount of copper(I) in conjunction with scandium triflate <1998JA4021>. These aldehydes can also be accessed by Claisen rearrangement <1995JA1165> and by a tandem [2,3]-Wittig-anionic oxy-Cope rearrangement <1997TL6445>. Rhodium-catalyzed intramolecular silylformylation of alkenes can also be used (Scheme 75) <1997JA12416>. Finally, a lithium amide-induced 1,4-silyl migration reaction also generates β-trialkylsilyl aldehydes (Scheme 76) <1999T1285>.



R^1, R^2 = H, alkyl

Scheme 75



R^1 = alkyl, aryl; R^2 = alkyl

Scheme 76

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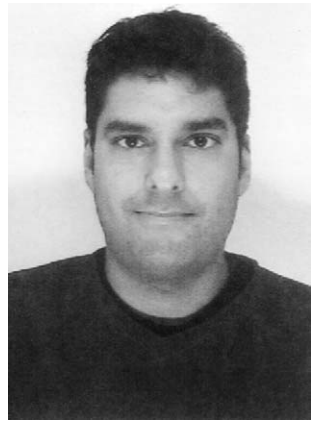
Biographical sketch



Sandeep Handa was born in London, studied at Cambridge University, where he obtained a B.A. in Natural Sciences in 1990 and his Ph.D. in 1994 under the direction of Dr. J. Staunton. After spending 18 months in the laboratories of Professor H. G. Floss at the University of Washington, Seattle, he returned to the UK for a further postdoctoral period at the University of Nottingham with Professor G. Pattenden. He was appointed to his current position as Lecturer in Chemistry at the University of Leicester in January 1998. His scientific interests include aspects of chemical biology especially the synthesis of novel enzyme inhibitors and biomimetic free-radical chemistry.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 1–58

3.02 Aldehydes: α,β-Unsaturated Aldehydes

P. R. MACKIE and C. E. FOSTER
Avecia Ltd., Manchester, UK

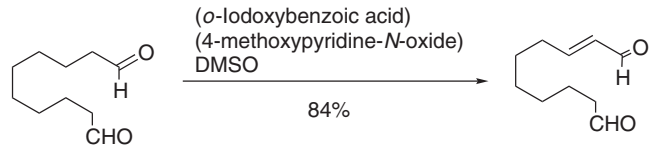
3.02.1 ALDEHYDES BEARING AN α,β-ALKENIC BOND

3.02.1.1 α,β-Unsaturated Aldehydes without Further Unsaturation

3.02.1.1.1 By elimination reactions

(i) By oxidative elimination of H_2

The palladium-promoted dehydrogenation of saturated aldehydes, the oxidation of silyl enol ethers with lead tetraacetate, and the oxidation of enols to α,β-unsaturated aldehydes with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) have been described previously <1995COFGT(3)53> as effective methods for effecting the oxidative elimination of H_2. Recently reported methods have described the use of 1:1 complexes of *o*-iodoxybenzoic acid (IBX) with ligands such as 4-methoxypyridine *N*-oxide <2002AG(E)993>. The use of such complexes has been reported to afford alkenals from aldehydes selectively and in high yield (Equation (1)). Related reagents have also been used to effect this transformation, with HIO_3 and I_2O_5 being described as mild and selective alternative reagents to IBX for the dehydrogenation of aldehydes <2002AG(E)1386>.



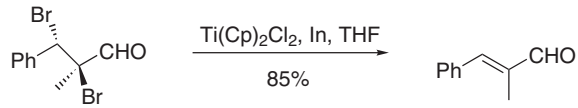
(1)

The regioselective catalytic dehydrogenation of aldehydes using allyldiethylphosphate with $NaHCO_3/Pd(OAc)_2$, has also been described recently <1998JOC5640>. This reaction proceeds slowly but selectively when DMF is used as solvent, to produce the desired alkenal with propylene and sodium diethylphosphate.

(ii) By elimination of halide from α-haloaldehydes and β-haloaldehydes

The treatment of α-haloaldehydes with a base yields α,β-unsaturated aldehydes. A variety of methods for effecting this transformation from both aldehydes and ketones (as part of a 1-carbon homologation sequence) have been described previously <1995COFGT(3)53>. The synthesis of α-haloaldehydes by direct halogenation of aldehydes was also detailed in the COFGT (1995). In addition, facile routes to enals such as chlorination of imines followed by elimination and hydrolysis, and bromination of enol acetates followed by elimination were outlined.

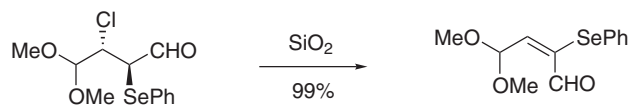
Recent examples of this reaction have included the reductive debromination of vicinal dibromides to yield alkenes, catalyzed by a bis(cyclopentadienyl)titanium(IV) dichloride–indium powder system <2001MI541> (Equation (2)).



(2)

Similarly, treatment of α,β-dibromoaldehydes with Bu_3SnH and a catalytic amount of nickelDPPE dichloride at room temperature rapidly yields unsaturated aldehydes <1998T1021>.

The elimination of a β-chloro-leaving group from a functionalized alkenal by reaction with silica (Equation (3)) has also been reported recently <1997T15843> as part of a regio- and stereocontrolled synthesis of highly functionalized C_4-building blocks.

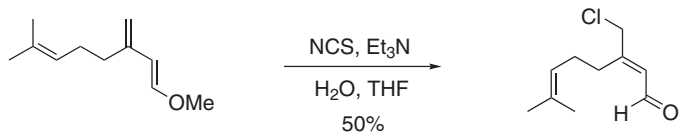


(3)

(iii) By elimination from alkoxyenol ethers and thioenol ethers

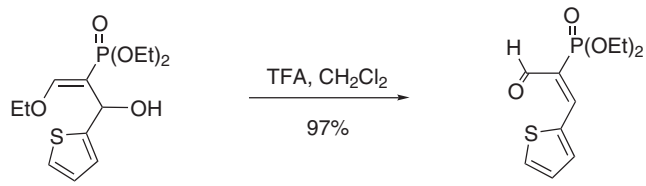
Transformations of this kind have been described <1995COFGT(3)53> where hydrolysis and elimination of thioether and thioenol ether groups by $HgCl_2$ in methanol/water yields alkenals. Similarly, hydrolysis of allylic alkoxy thioenol ethers and allylic thioenol alcohols, and addition of thiophenol to propargylic alcohol followed by hydrolysis of the resultant thioenol alcohol, produce unsaturated aldehydes. The hydrolysis of the corresponding enol ethers was also detailed in COFGT (1995) <1995COFGT(3)53>.

Recent examples of the synthesis of unsaturated aldehydes by elimination from enol ethers have utilized a variety of techniques and reagents, including the use of *N*-chlorosuccinimide with $Et_3N/H_2O/THF$ to prepare carbonyl-substituted allyl chlorides from unsaturated enol ethers <2000S1615> (Equation (4)).



(4)

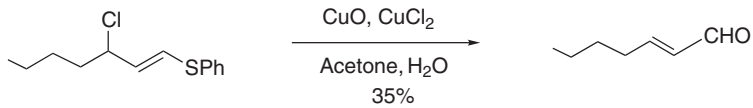
Similarly, α-formylvinylphosphonates have been prepared from their corresponding enol ethers by treatment with 5 equiv. of $TFAA/CH_2Cl_2$ <2000JOC4326> (Equation (5)). Other reagents that have been recently utilized for the hydrolysis of enol ethers to unsaturated aldehydes have included 1 M $HCl_{(aq.)}$ <1997JAN685> and trimethylsilyl triflate <1996BSF563>.



(5)

In addition, intermediate unsaturated aldehydes in the synthesis of highly oxygenated [4.4]spirononenes have been produced by oxidation of precursor enol ethers <1996JA9456>.

A recent example of elimination from a thioenol ether has been reported by the treatment of 3-chloro alkenic phenyl sulfides with $CuO/CuCl_2$ in acetone/H_2O (99:1) <1997SC3917> to yield α,β-unsaturated aldehydes (Equation (6)).

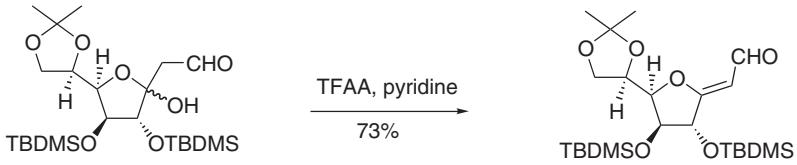


(6)

(iv) By elimination from β-hydroxy- and alkoxyaldehydes

The elimination of β-hydroxy and alkoxy groups has been widely used as a facile route to α,β-unsaturated aldehydes, with the aldehyde function commonly protected as an acetal. Reagents for direct elimination were described in COFGT (1995) <1995COFGT(3)53>, and these included H_3PO_4, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), formic acid, and 2% $HCl_{(aq.)}$, with the latter reagents frequently being used to effect a simultaneous deprotection of an aldehyde function. By protecting the aldehyde as an enol ether, the keto group of β-keto aldehydes may be reduced to a hydroxy function which may then be eliminated with deprotection of the aldehyde to yield an enal. In COFGT (1995) <1995COFGT(3)53> detailed eliminations of β-substituted aldehydes derived from epoxides, formation of β-mesylates followed by elimination, and a reaction sequence involving a rearrangement and hydrolysis reaction which results in a formal allylic elimination.

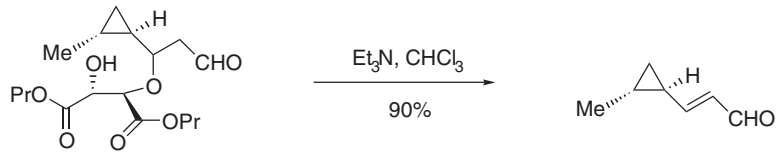
Recent examples of this elimination have included the synthesis of *C*-glycosal unsaturated aldehydes from sugar lactones by the reduction of a keto function to leave a β-hydroxyaldehyde, which may be dehydrated with TFAA/pyridine <2001TL4657> (Equation (7)).



(7)

A similar elimination has been achieved as part of the total synthesis of agaiastatin, where a functionalized β-hydroxyaldehyde was treated with $CuSO_4$ in toluene to yield the desired alkenal <2000H1051>. The synthesis of 3-(trifluoromethyl)-butenal from the corresponding β-hydroxyaldehyde has also been reported, using phosphorus pentoxide as the dehydrating agent <1995LA1587>.

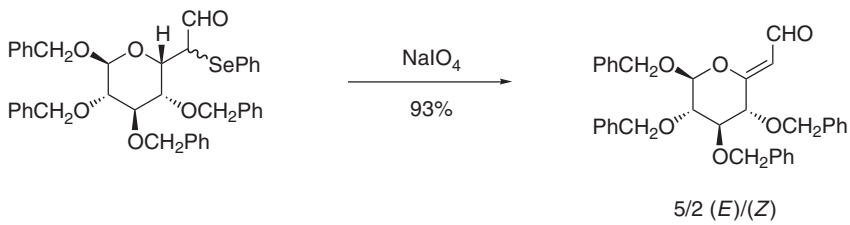
A particularly interesting example of an elimination from a β-alkoxyaldehyde has been recently reported, where the resultant alkenal is functionalized in the 3-position with a cyclopropane ring <1995TL357> (Equation (8)).



(8)

(v) By elimination of selenoxides

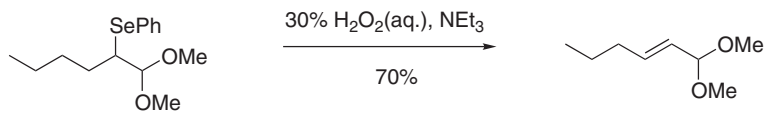
The α-selenation of aldehydes followed by oxidation and elimination of selenoxide has been described as a route to α,β-unsaturated aldehydes <1995COFGT(3)53>. Sigmatropic rearrangements of allylic selenium compounds to give alkenals were also described in COFGT (1995). The former strategy has been employed in the recent literature in the synthesis of conjugated *exo*-glycals, where the facile oxidation of the selenoether is carried out with $NaIO_4$ <2001TL6907> (Equation (9)).



(9)

5/2 (*E*)/(*Z*)

An analogous reaction of an acetal-protected aldehyde has also been reported recently <2000JOC2151> where oxidation and elimination are mediated by the use of 30% aqueous hydrogen peroxide and triethylamine (Equation (10)).

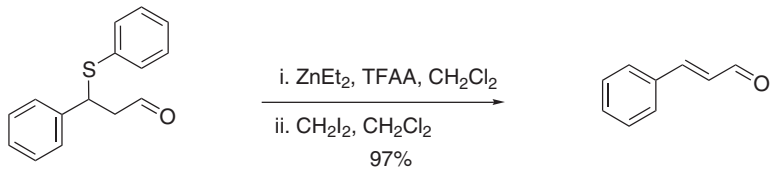


(10)

(vi) By elimination of sulfones

The synthesis of sulfones by oxidation of sulfides with $NaIO_4$ or ozone, which can be accompanied by ozonolysis of a double bond to produce an aldehyde group, has been discussed previously <1995COFGT(3)53>. Such β-sulfones may then be eliminated to yield the desired enals. Alkylation in the α-position of a β-sulfone acetal followed by elimination and deprotection to yield alkenals was also described in COFGT (1995) <1995COFGT(3)53>.

A particularly interesting recent report has described the Shi carbenoid-mediated elimination of sulfides as a mild and efficient route to alkenals <2002TL4959>. This method involved the *in situ* transformation of a sulfide into a sulfonium group, which can then generate a sulfur ylide that is able to facilitate elimination by acting as an internal base (Equation (11)).



(11)

(vii) Miscellaneous reactions

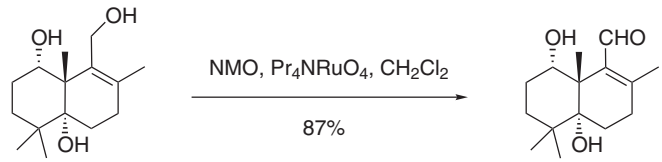
Of the classes of elimination reactions which yield α,β-unsaturated aldehydes that do not fall into the categories listed above, COFGT (1995) <1995COFGT(3)53> described an effective elimination from a β-epoxyaldehyde, an elimination of nitrous acid from β-nitro aldehydes, and synthesis of alkenals from ring opening and subsequent elimination from isoxazolidine derivatives.

A recent report <1996S621> has described the highly enantioselective alkenylation of aldehydes by aldol reaction of SAMP-hydrazones with 2-selenoether-derivatized aldehydes to yield the corresponding β-hydroxyhydrazones. Oxidative cleavage of the hydrazone followed by elimination of the hydroxy and phenylselenyl moieties yielded unsaturated aldehydes in good yields and in high enantiomeric excess.

3.02.1.1.2 By oxidations of alcohols and their equivalents

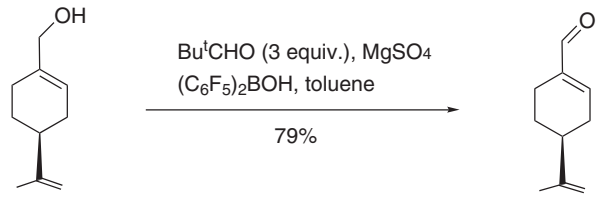
In COFGT (1995) the oxidation of primary allylic alcohol groups to α,β-unsaturated aldehydes <1995COFGT(3)53> was described as being one of the most common methods of preparing this functional group, and this remains the case. Indeed, with the growth in the utilization of supported reagents and with the development of novel homo- and heterogeneous catalysts, it could be argued that this method of preparing α,β-unsaturated aldehydes has broadened the scope of this technique.

Of the routes described previously, the use of manganese dioxide was reported as being one of the mildest techniques, and this reagent still finds favor in the recent literature <2001SC219> with this method producing high yields of α,β-unsaturated aldehydes from the corresponding alcohols. Other reagents described previously <1995COFGT(3)53> for effecting this transformation include pyridinium chlorochromate (PCC) and pyridinium sulfate with DMSO, and there are a number of recent examples of oxidation of allylic alcohols to α,β-unsaturated aldehydes using this class of materials. The use of poly(4-vinylpyridinium)perruthenate with tetrabutylammonium iodate/molecular sieves <2000TL3971>, and the use of PCC/molecular sieves in dichloromethane <1996RTC438> have been reported recently. Related methods have utilized transition metal-based oxidants such as tetra(*n*-propyl)ammonium perruthenate and *N*-methylmorpholine *N*-oxide/dichloromethane <2001JA1372, 2001JAN382> (Equation (12)) and catalytic pyridine/OsO_4/CuCl over molecular sieves with molecular oxygen <1999TL3723>.



(12)

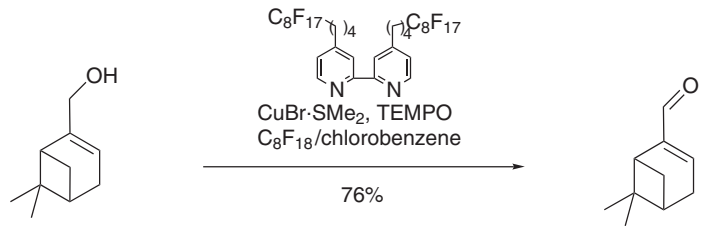
COFGT (1995) highlighted the use of oxalyl chloride with DMSO in the Swern oxidation for the synthesis of α,β-unsaturated aldehydes and indeed this chemistry is still in use <2000JCS(P1)2211>. A variety of other reagents have been discussed previously, including sodium dichromate, silver carbonate on Celite, and a range of nitroso compounds. Related reagents have been recently utilized for oxidation of allylic alcohols, such as *N*-chlorosuccinimide followed by potassium carbonate with PhSNH-*t*-Bu as catalyst <2001CL846>, 4-carboxy-*o*-iodoxybenzoic acid/water <2002TL569> and bis(pentafluorophenyl)boronic acid/toluene as a highly effective Oppenauer oxidation catalyst <1997JOC5664> (Equation (13)).



(13)

Transition metal-catalyzed transformations were described previously using, for example, Cp_2ZrH_2 and $RuH_2(PPh_3)_4$. A number of novel systems have since been developed, such as a system utilizing $Ru(CF_3CO_2)_3(Cn^*)\cdot H_2O$ as catalyst (where Cn* is *N*,*N*′,*N*′-trimethyl-1,4,7-triazacyclonane) with *t*-butyl hydroperoxide as oxidant <1998JOC2873>, and a system which uses molecular oxygen as oxidant with $RuCl_2(PPh_3)_2$/TEMPO (1:3) as the catalytic system in chlorobenzene <2001JA6826>.

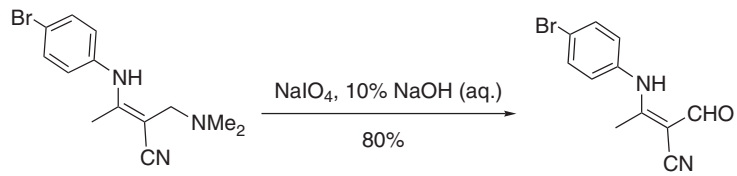
A number of other methods for synthesizing α,β-unsaturated aldehydes from a variety of substrates were described in COFGT (1995) <1995COFGT(3)53> including the oxidation of tertiary allylic alcohols to yield mixtures of (*E*)- and (*Z*)-alkenals, the hydrolysis of the conjugate bases of nitro compounds (Nef reaction), the oxidation of allylic thioamides, the Pummerer rearrangement of sulfoxides, and the oxidation of allylic iodides with a base and DMSO (Kornblum reaction). The oxidation of allylic halides is a well-utilized route to α,β-unsaturated aldehydes, with reagents such as potassium dichromate, *N*-ethyl morpholine oxide, and nitrocyclohexane being described previously <1995COFGT(3)53>. The copper-catalyzed aerobic oxidation of alcohols to aldehydes has been recently reported under fluorous biphasic conditions using a copper(I) bromide–dimethyl sulfide complex as catalyst with a 4,4-perfluorinated bipyridine as co-ligand and TEMPO as co-catalyst <2000TL4343> (Equation (14)).



(14)

Perhaps some of the most interesting recent developments in this transformation have arisen from the use of 1-(benzoylamino)-3-methylimidazolium chlorochromate (BAMICC) <1995TL8513>, and the related imidazolium fluorochromate (IFC) <1999IJC(B)99>, which are both selective and mild reagents for effecting the desired transformation.

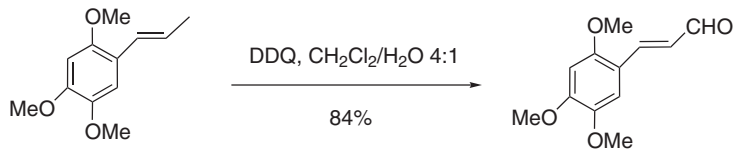
A recent report has also described the oxidation of an amine as an alcohol equivalent <1999MI253> with sodium periodate and 10% aqueous sodium hydroxide solution to yield an α,β-unsaturated aldehyde (Equation (15)).



(15)

3.02.1.1.3 Oxidation of allylic methyl groups

The oxidation of allylic methyl groups by selenium dioxide was described in COFGT (1995) <1995COFGT(3)53> with selectivity being derived from the preferential oxidation of the methyl group on the most electron-rich double bond. This reagent remains popular in the literature and may frequently be used in combination with another oxidant if the reaction proceeds via the allylic alcohol, for example, SeO_2 with PCC <2002IJC(B)635> or SeO_2 with *t*-butyl hydroperoxide <2001TL2205> although other reagents such as 2-iodo-5-nitrothiophene <1997G471> and most particularly 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) <1998TL2413> (Equation (16)) offer particularly useful alternatives to selenium dioxide.

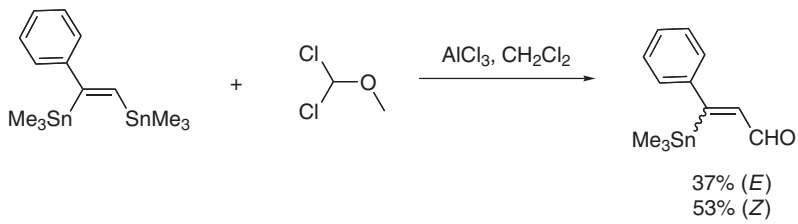


(16)

3.02.1.1.4 By formylations of alkenes

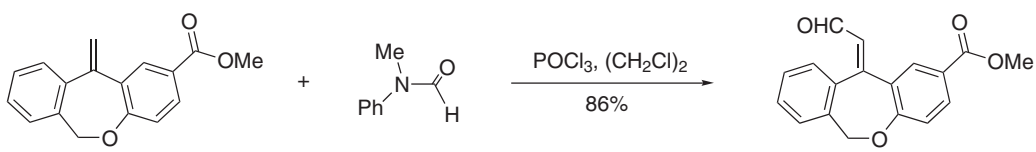
The synthesis of alkenals was described in COFGT (1995) <1995COFGT(3)53> by formylation of three related classes of substrates: vinyl silanes, vinyllithium or magnesium species, and vinyl iodides. The substrates were reacted with dichloromethyl methyl ether using a $TiCl_4$ catalyst, electrophiles such as DMF, methyl formate, or *N*-methyl-*N*-formyl-2-aminopyridine and with carbon monoxide and a palladium catalyst (followed by reduction), respectively. The first of these reactions was reported to proceed with retention of configuration, however the products isomerized to give (*E*)-enals, and this geometry appeared to be favored generally in such reactions.

An analogous electrophilic destannylation reaction between 1,2-bis(trimethylstannyl)-1-alkenes and dichloromethyl methyl ether using an $AlCl_3$ catalyst has recently been reported <1996JOM45> (Equation (17)).



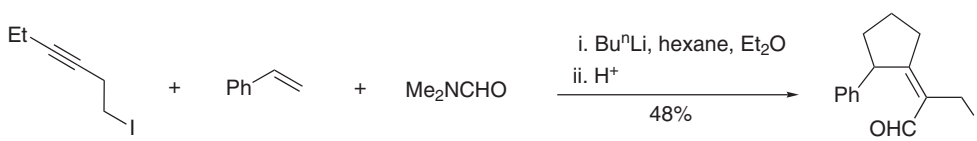
(17)

Formylations using Vilsmeier conditions have recently been reported, including the formylation of a benzylcyclohexanol <2000IJC(B)752> with DMF/$POCl_3$ and an analogous formylation of a functionalized alkene with *N*-phenyl-*N*-methylformamide/$POCl_3$ <1995S1257> (Equation (18)).



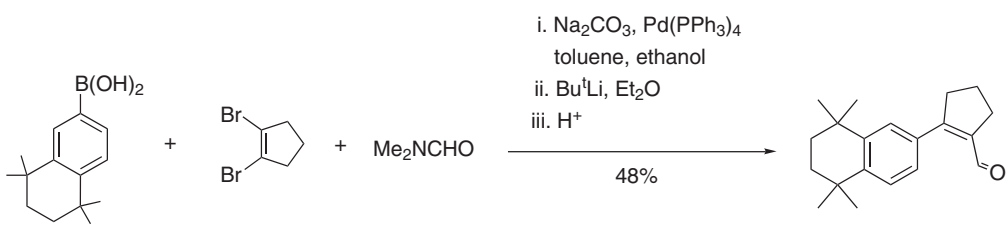
(18)

The formylation of vinyllithium species with DMF to produce alkenals has recently been reported as part of a tandem intermolecular–intramolecular carbolithiation strategy which yielded a cyclopentane-derivatized alkenal <2000AG(E)409> (Equation (19)), and also from acetal-protected cyclohexenones <1997TL309>.



(19)

Similarly, a Suzuki condensation reaction of 1,2-dibromo-1-cyclopentene with an aromatic boronic acid derivative followed by lithiation and formylation with DMF has recently been reported <1997BMCL2393> (Equation (20)).



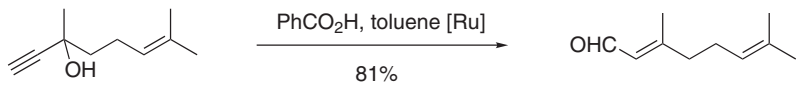
(20)

An analogous formylation of vinyllithium species generated from an unsaturated tosylhydrazone has also been reported recently <1995TL5479>.

The synthesis of alkenals by the industrially important hydroformylation of alkenes catalyzed by rhodium organobisphosphite catalysts <2002EUP1249445> and the analogous hydroformylation of unsaturated esters catalyzed by $Rh(acac)(CO)_2/PR_3$ systems <2001USP6307108> in carbon monoxide/hydrogen atmospheres has also been reported recently.

3.02.1.1.5 By rearrangements of α-acetylenic alcohols

COFGT (1995) <1995COFGT(3)53> described a route by which an alkyne was in effect hydrated in an anti-Markovnikov fashion to give an α,β-unsaturated aldehyde, instead of the Markovnikov product. The reagent for effecting this transformation was $(Ph_3SiO)_3VO$, the reaction proceeding via the vanadate ester. Recent reports of this reaction have described the isomerization of 2-methyl-3-butyn-2-ol into prenal in high yields using tricomponent catalytic systems based on $Ti(OR)_4$—CuCl—R′COOH <2000POL1693>, the rearrangement of dihydrodehydrolinalool to dihydrocitral in the presence of a catalytic system consisting of MoO_2X_2 (X = acetylacetonate, halogen), acrylic acid, and DMSO in toluene <1999EUP949237>, and the related isomerization of propargylic alcohols to alkenals catalyzed by *cis*-dioxomolybdenum(VI) complexes (Meyer–Schuster rearrangement) <1996TL853>. The selective isomerization of prop-2-yn-1-ols to unsaturated aldehydes (Equation (21)) catalyzed by $Ru(2\text{-}CH_2C(Me)CH_2)_2(Ph_2PCH_2CH_2PPh_2)$ <1997CC1201> in the presence of benzoic acid proceeds via (*Z*)-3-hydroxyprop-1-en-1-yl benzoates.



(21)

The transformation of propargylic alcohols to 2-silylmethyl-2-alkenals by formylation with CO and rearrangement in the presence of Me_2PhSiH, catalyzed by $Rh_4(CO)_{12}$ has also been reported recently <1999JOM133>. Additionally, the application of high temperature (<300 °C) and aqueous conditions to the rearrangement of propynols to alkenals in a pressurized microwave reactor or autoclave has recently been described <1997JOC2505>.

3.02.1.1.6 By displacements of β-leaving groups

COFGT (1995) <1995COFGT(3)53> outlined some examples of nucleophilic displacements of β-leaving groups such as alkoxy, silyloxy, and dialkylamino moieties from their respective α,β-unsaturated aldehydes. Such displacements feature frequently in the total syntheses of biologically relevant molecules and recent examples include the asymmetric syntheses of (3(*S*))-2,3,4,5-tetrahydropyridazine-3-carboxylic acid <1999JCS(P1)2591> and FR182877, a potent microtubule-stabilizing agent <2003JA5393>.

The displacement of chlorine from β-chloroenals by reduction with Zn/EtOH was also detailed in COFGT (1995) <1995COFGT(3)53>.

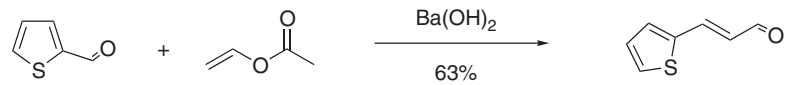
3.02.1.1.7 By aldol condensation reactions

The aldol condensation, where an aldehydic enol or enolate is reacted with a second carbonyl group, followed by dehydration of the β-hydroxyaldehyde intermediate so formed, is one of the most widely used approaches to α,β-unsaturated aldehydes. Recent reviews have highlighted the general applicability of aldol reactions to the synthesis of aldehydes <1998JCS(P1)1739> and the utility of the vinylogous aldol reaction in synthesis <2000CRV1929>.

The aldol reaction is important in the industrial synthesis of α,β-unsaturated aldehydes, with synthetic strategies including the stereoselective reaction of aldehydes over a heterogeneous Na/SiO_2 catalyst <2002GC392>, the use of phase-transfer catalysts in aldol cross-condensations <2001EUP1088811>, the contact of aldehydes in the vapor phase with particulate catalysts comprising basic alkali metal sites supported on inert substrates <2000MIP2000031011>, aldol condensations catalyzed by hydrated magnesium oxide <1997MIP9735825>, and the uniphase aldolizations of saturated C_6-aldehydes <1996MIP9634844>.

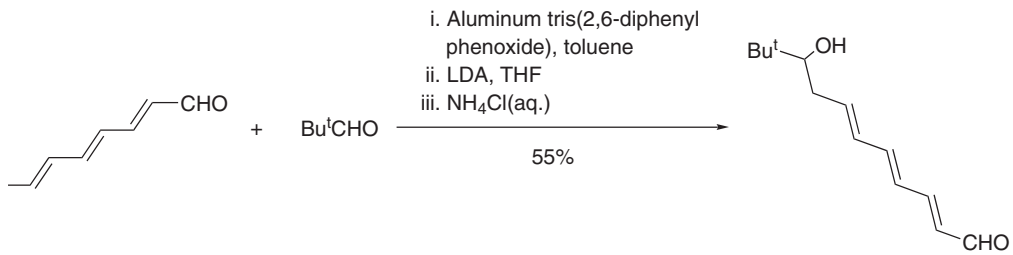
In addition, COFGT (1995) <1995COFGT(3)53> described both intramolecular aldol reactions where, for example, 1,6- or 1,7-dialdehyde systems react with regioselectivity through control of the reaction conditions or by use of enamines, and intermolecular aldol reactions, where control of regiochemistry is achieved by use of enamines, enol ethers, α-lithioimines, or α-lithiohydrazones. Indeed, the aldol reaction may be accomplished by a variety of reagents, with the use of NaOH <1998M89>, a combined $Ti(OBu)_4$/*t*-BuOK reagent <2000TL4415> and diethylaminotrimethylsilane <1999TL6627> providing effective routes to α,β-unsaturated aldehydes. Similarly, the self-condensation of aldehydes has been effected by the use of a *N*-methyl-3-aminopropylated silica catalyst in an ionic liquid <2003SL873, 2002TL9073>. This route is of particular interest as aldehydes having acid- or base-sensitive substituents can undergo aldol reactions to give alkenals in reasonable yields.

The formation of acetaldehyde enolate from vinyl acetate upon treatment with $Ba(OH)_2$ or Bu^tOK and subsequent aldol reaction with aromatic and heterocyclic aldehydes has recently been described <2000SL1345>. This procedure is useful as it allows the iterative synthesis of polyenals (Equation (22)).



(22)

A directed-aldol addition reaction mediated by aluminum tris(2,6-diphenylphenoxide) has recently been reported <1998JA813>, where regioselective reaction of conjugated carbonyl substrates with aldehydes proceeds upon precomplexation of the reactants with the bulky aluminum reagent (Equation (23)).

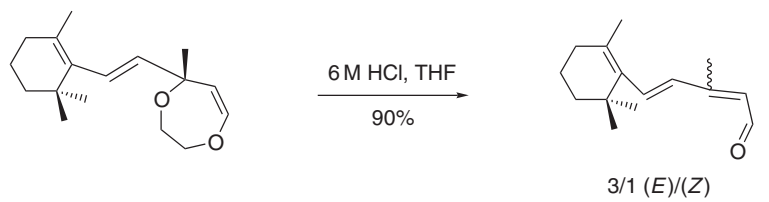


(23)

Similarly, an aldol-type reaction has recently been reported <2002JCS(P1)434> where trimethylsilyl-derived iodohydrins can react with, for example, aldehydes to produce alkenals.

A recent report has described the stereoselective synthesis of manganese–alkenylcarbene complexes of general formula $[(CH_3C_5H_4)(CO)_2Mn{:}C(OEt)CH{:}CHR]$, which were derived by aldol condensation of precursor carbene complexes with aromatic and unsaturated aldehydes <1999EJI739>. By protonation of the carbene complex at low temperature, followed by hydrolysis, the unsaturated aldehyde may be released from the complex by displacement with acetonitrile.

Reactions that are analogous to the aldol condensation have been described, and the Mannich reaction, where elimination of a β-amino group follows formation of an intermediate Mannich base to yield α-methylene aldehydes, was described previously <1995COFGT(3)53>. The synthesis of unsaturated aldehydes from 3-hydroxy-1-alkynes has recently been reported <1998MI1738> via an alternative to the aldol condensation (Equation (24)).

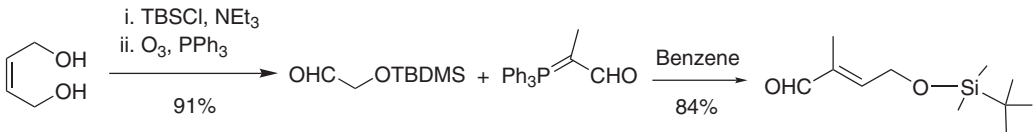


(24)

The method involves the conversion of 3-hydroxy-1-alkynes into their ethylene glycol monoethers, followed by base-catalyzed cyclization to give dihydro-1,4-dioxepins, which may be hydrolyzed under acidic conditions to yield alkenals.

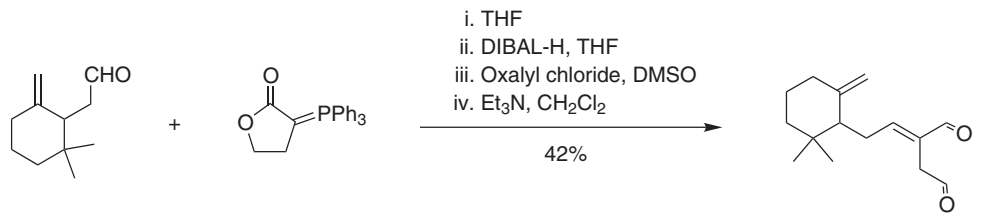
3.02.1.1.8 By Wittig reactions

The utility of the Wittig reaction for the synthesis of α,β-unsaturated aldehydes has burgeoned recently, and several examples of this methodology were described in COFGT (1995) <1995COFGT(3)53>. A major route to alkenals is the reaction between formyl phosphoranes and aldehydes, generally leading to alkenals in the (*E*)-configuration. Recent examples of this reaction include the reaction of formyl phosphoranes with β-aryl ethanals <1996JMC46>, δ-furyl-γ-methyl-γ-pentenals <1996T4245>, ω-ester-derivatized α-benzoyl pentanals <2001TL4445>, and α-silyl-oxypropanals <1999OL1475> as part of the synthetic routes to biologically relevant molecules. Similarly, formyl phosphoranes may react with functionalized alkenes, for example, in the syntheses of (+)-pseudophyrynaminol <1995T6379> and swinholide A <1995T9393>. Additionally, the reaction of formyl phosphoranes with allylic alcohols and *t*-butyldimethylsilylchloride to yield γ-silyloxy-α,β-unsaturated aldehydes has recently been reported <1995TL6033> (Equation (25)).



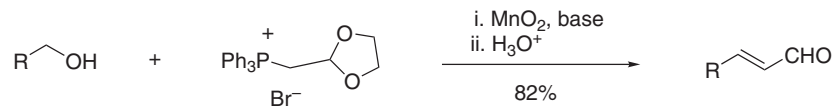
(25)

The utility of γ-lactone <1996TA3009> (Equation (26)) and ester-derivatized phosphoranes <1996CC21> in the Wittig-type synthesis of α,β-unsaturated aldehydes have also been described recently.



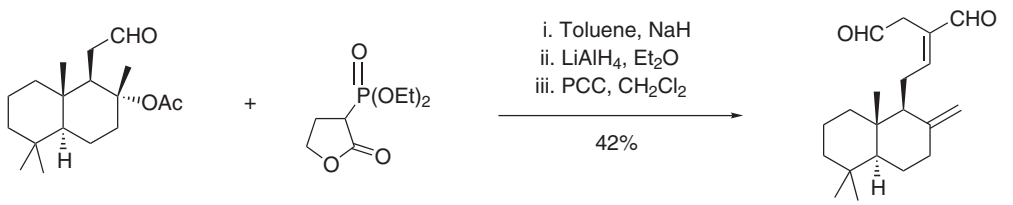
(26)

A facile route to α,β-unsaturated aldehydes from primary alcohols has been reported <2003CC2284>, which involves a one-pot combination of an oxidation of the alcohol with MnO_2 followed by a Wittig reaction of the intermediate aldehyde with a wide variety of reagents (Equation (27)). The reaction proceeds via α,β-unsaturated dioxolanes generated by reaction of the intermediate aldehyde with a dioxolane-derivatized phosphorane. An analogous methodology <2003TL115> has been utilized in the synthesis of 2-carbon-homologated α,β-unsaturated Weinreb amides, which may be readily reduced to yield α,β-unsaturated aldehydes.



(27)

The use of Horner–Wadsworth–Emmons diethylphosphonates with stable ketones that are unreactive with α-formyl phosphoranes was reported previously <1995COFGT(3)53>. Recent examples have described the synthesis of α,β-unsaturated aldehydes from formyl phosphonates and α-silyloxy-β-epoxy aldehydes <2002T2351>, ester-derivatized phosphonates with aliphatic <2001SC3219> and aromatic aldehydes <1999IJC(B)837>, and γ-lactone-derivatized phosphonates with aldehyde-derivatized diterpene derivatives <1998BMCL3295> (Equation (28)).



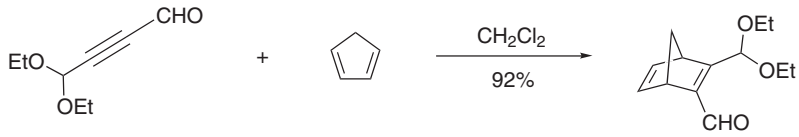
(28)

Peterson alkenylation reactions whereby lithiated α-silylimines react with aldehydes to yield the desired product were described previously <1995COFGT(3)53>, as was the use of stabilized arsonium ylides in Wittig-type reactions.

3.02.1.1.9 By Diels–Alder reactions

COFGT (1995) <1995COFGT(3)53> described the synthesis of cyclic α,β-unsaturated aldehydes from substituted-alkynic aldehydes. There are many examples in the recent literature where reactions of alkynic aldehydes result in the synthesis of heterocyclic aldehydes. By this method highly functionalized formylated furans <2002H35, 2000JA9324>, triazoles <2000JHC1597, 1995JAN1320>, selenofurans <1998SC301>, and 4,5-diformyl-1,3-dithiol-2-ylidene-substituted ethanals and ethanones <1995BSF975> have been synthesized.

The reaction of alkynic aldehydes with dienes such as cyclopentadiene to yield bicycloheptadienes derivatized with nitrobenzene <2001MI67> or diethyl acetals <1995BCJ3269> has been reported recently (Equation (29)). Chiral Lewis acid catalysts for effecting this transformation enantioselectively have been described such as (*R*)-HB(3,3′-bis(phenyl-2-oxy)-BINOL) <1997JOC3026> and tetraarylborate salts of cationic 1,3,2-oxazaborinanes <1997TL5755>.



(29)

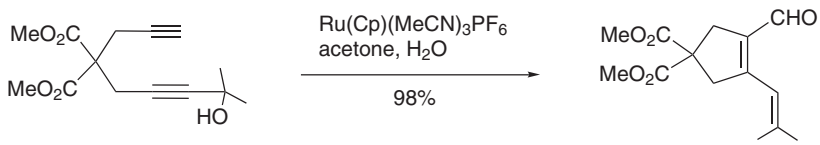
COFGT (1995) also described the reaction of formyl-substituted dienes with dieneophiles to yield cyclic α,β-unsaturated aldehydes <1995COFGT(3)53>. A recent example of such a reaction has been reported <1998TL7093> where the base-mediated reaction of a dienal with a 1-silyloxy-3-methyl diene results in a mixture of products.

3.02.1.1.10 By isomerizations

Isomerization of β,γ-unsaturated aldehydes under basic or acidic conditions and isomerization of propargylic ethers to allenic ethers followed by hydrolysis to yield α,β-unsaturated aldehydes were described in COFGT (1995) <1995COFGT(3)53>.

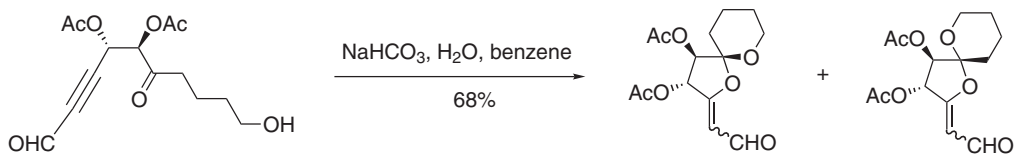
The synthesis of cyclic α,β,γ,δ-unsaturated aldehydes from mixtures of α,β- and β,γ-unsaturated aldehydes by treatment with Br_2/Ca_2CO_3 followed by Li_2CO_3 has recently been reported <1995T7555>. The synthesis of acyclic α,β,γ,δ-unsaturated aldehydes has been reported by isomerization of β-allene aldehydes <1995JOC1763> and β-methylene-γ-unsaturated aldehydes <2000T7211> under basic conditions.

The platinum-catalyzed isomerization of propargylic ethers to alkenals has recently been reported <2001AG(E)4754>, as has a [Rh(BINAP)][BF_4]-catalyzed isomerization of a formyl-derivatized alkyne to a 1,3-dienal with concomitant migration of a formyl group <2002CC684> and an unusual [Ru(Cp) $(MeCN)_3$][PF_6]-catalyzed cycloisomerization of an alkyne/propargylic alcohol to a α,β,γ,δ-unsaturated aldehyde <2002JA4178> (Equation (30)).



(30)

Other isomerization routes to alkenals include the synthesis of γ-hydroxy-α,β-unsaturated aldehydes by deprotection and hydroxy rearrangement of tertiary carbinols, which was also outlined previously <1995COFGT(3)53>, and the preparation of 3,4-diacetoxy-2-formylmethylene-1,6-dioxaspiro[4.5]decanes by intramolecular addition of keto alcohol to a propargylic aldehyde <1999TL3587> (Equation (31)).

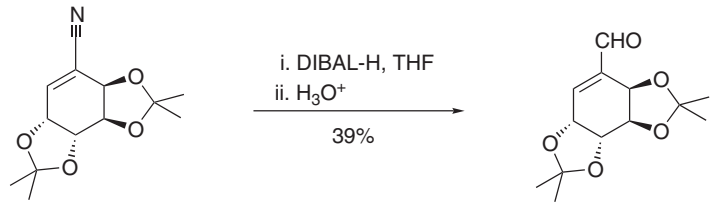


(*E*)/(*Z*) 2/1 (*E*)/(*Z*) 1.9/1.2

(31)

3.02.1.1.11 By reductions

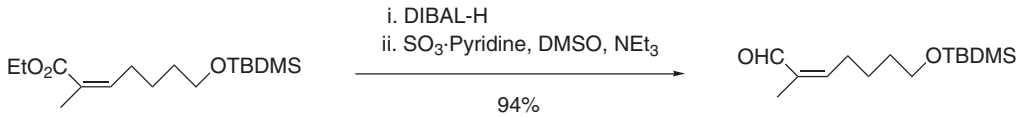
The reduction of α,β-unsaturated nitriles with DIBAL-H to yield α,β-unsaturated aldehydes was discussed in COFGT (1995) <1995COFGT(3)53>, and this method is still common in the literature <1999JFC115, 1996TA691, 1995SC3663> (Equation (32)). Recently, other reagents for effecting this transformation have been reported, including $LiAlH(OEt)_3$ <2001S2393>, formic acid with PtO_2 <2002TL1395> or Raney-nickel <2001S559>, and catecholalane <1996SL165>.



(32)

The reduction of α,β-unsaturated acid chlorides with weaker hydride-donor reductants such as $NaBH(OMe)_3$ was described in COFGT (1995) <1995COFGT(3)53>, and recent reports have described the use of reductive oxidation routes to α,β-unsaturated aldehydes using reductants such as sodium borohydride or lithium aluminum hydride <2000MI375> or aluminum hydride <1999OPP204>, followed by oxidation with PCC. Other reagents for reducing unsaturated acid chlorides to their corresponding aldehydes have included formic acid with ammonium hydroxide <1998TL8153> and $[Zn(DABCO)][BH_4]_2$ <1997BCJ155>.

Recent examples of the reduction of α,β-unsaturated esters with DIBAL-H to yield α,β-unsaturated aldehydes have been reported <2003OL599, 2002JOC9443> (Equation (33)).



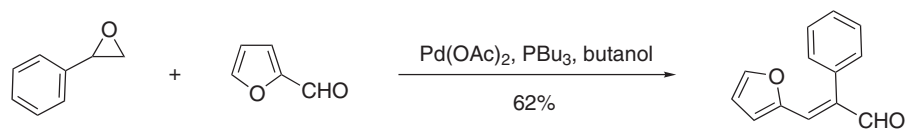
(33)

The reduction and hydrolysis of oxazines and benzoisothiazoles with sodium borohydride to yield α,β-unsaturated aldehydes was described previously <1995COFGT(3)53>.

3.02.1.1.12 From epoxides

The utility of epoxides as intermediates in the synthesis of α,β-unsaturated aldehydes was exemplified in COFGT (1995) <1995COFGT(3)53> by their application in the synthesis of vitamin A. The epoxide intermediate in this synthesis was formed by a Darzens–Claisen reaction and yielded an enal by hydrolysis and decarboxylation followed by rearrangement. Other examples included acid-catalyzed rearrangements of α-epoxynitriles and -silanes, the synthesis of enals from epoxides generated by pinacol rearrangements of α-hydroxyepoxides and the oxidation of terminal epoxides with sulfuryl chloride <1995COFGT(3)53>. A related reaction has recently been reported <2001JCS(P1)1942> where ring-opening of an epoxide with acetic anhydride/pyridine/DMAP followed by oxidation with periodic acid yielded a mixture of (*E*)- and (*Z*)-enals. The synthesis of enantiomerically pure α,β-unsaturated five-membered ring aldehydes has been achieved by ring-contraction of epoxypyranosides <1997JOC7972, 1997JOC7978>. The Li_3PO_4-catalyzed ring-opening of vinyloxiranes to give enals has been reported <1998ZOR1020>, as has a $Pd(PPh_3)_4$-catalyzed rearrangement of a functionalized vinyloxirane <1999SC3673>.

The amphoteric nature of vinyloxiranes has been investigated by the coupling with aldehydes with $Sc(OTf)_3$ catalysis <2000AG(E)4079>. Similarly, a tandem epoxide isomerization–aldol condensation reaction catalyzed by palladium acetate/tri(*n*-butyl)phosphine has recently been reported <1996JOC7656> whereby α,β-unsaturated aldehydes may be synthesized in good yield using mild conditions (Equation (34)).



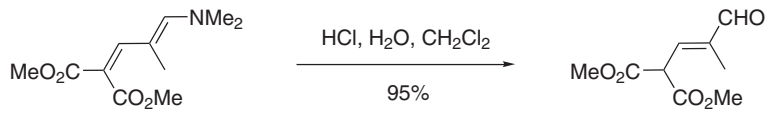
(34)

The radical addition of a triphenylgermane to (2,3-epoxy-4-pentenyloxy)trialkyl silanes promoted by $B(Et)_3$ has recently been described <2002SL569> in the synthesis of γ-germyl-substituted alkenals.

The deoxygenation of α,β-epoxyaldehydes with $NaOH/Bu_4NBr/HN{=}C(NH_2)SO_2H$ <1997TL745> and β,γ-epoxyaldehydes with NaO/MeOH <1995CJC2239> to give α,β-unsaturated aldehydes has also been reported recently.

3.02.1.1.13 Miscellaneous methods

Of the classes of reactions not covered by the headings above, COFGT (1995) <1995COFGT(3)53> discussed oxidative ring opening of furans with a variety of oxidizing agents, careful ozonolysis of dienes, and the use of oxy-substituted cyclopropanes in the synthesis of α,β-unsaturated aldehydes. The acid-mediated hydrolysis of an *N,N*-dimethylenamine to give a highly functionalized alkenal (Equation (35)) has recently been reported <2002PCT2002034710>.



(35)

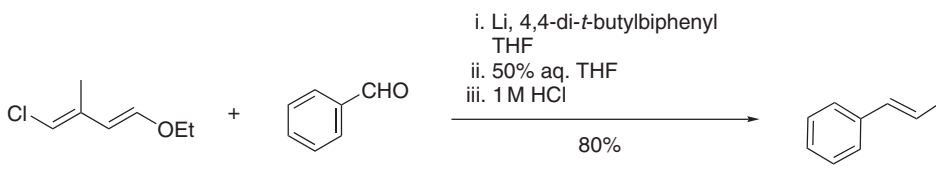
A recent report has described the synthesis of *threo*- and *erythro*-(*E*)-4,5-dihydroxydec-2-enals by reaction of a benzoyloxyheptanal with the Grignard reagent of 3,3-diethoxy-1-propyne followed by lithium aluminum hydride reduction <1995TL1347>. An olefin metathesis reaction has recently been described <2002AG(E)3171> where a formal vinyl-C—H activation and allylic oxidation occurs to yield α,β-unsaturated aldehydes in the presence of a ruthenium carbene complex. The olefin cross-metathesis reaction is reported to be both stereoselective and chemoselective, and provides an efficient route to functional alkenals from a variety of alkenes.

3.02.1.2 α,β-Unsaturated Aldehydes with Further Unsaturation

3.02.1.2.1 By elimination reactions

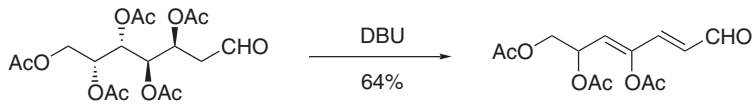
COFGT (1995) <1995COFGT(3)53> gave an overview of a variety of methods for synthesizing α,β-unsaturated aldehydes with further unsaturation by elimination reactions. These methods included eliminations of hydroxy and alkoxy groups β or δ to an aldehyde often under acidic conditions, where the intermediate to the polyenal may be formed by partial reduction of alkoxyalkynes followed by deprotection and elimination of a β-hydroxy or alkoxy group. An efficient dehydration of a hydroxy-substituted unsaturated aldehyde to yield a dienal using the Lewis acid $HfCl_4(THF)_2$ as catalyst has recently been reported <2001SL1690>.

The utility of 4-lithioalkoxydienes in, for example, 4-carbon homologation reactions featuring δ-hydroxy eliminations was detailed previously <1995COFGT(3)53> and a similar reaction has recently been reported, where benzaldehyde was treated with a 4-lithioalkoxydiene to afford a mixture of (2(*E*),4(*E*))- and (2(*Z*),4(*E*))-isomers <1998TL8975> with the former being favored (Equation (36)). Similarly, the treatment of a β-hydroxyalkoxyenol ether with $TFAA/CH_2Cl_2$ to yield a functionalized dienal has recently been reported <2000JOC4326>.



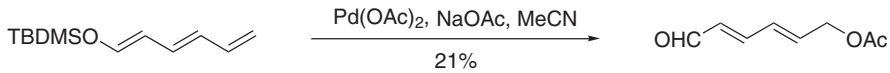
(36)

The elimination of δ-hydroxy and δ-methoxy groups under basic conditions using DBU and NaOMe was described previously <1995COFGT(3)53> and a recent report <2001JCS(P1)754> has described a related synthesis of a triacetylated dienal from an aldehydo-heptose derivative by treatment with DBU (Equation (37)).



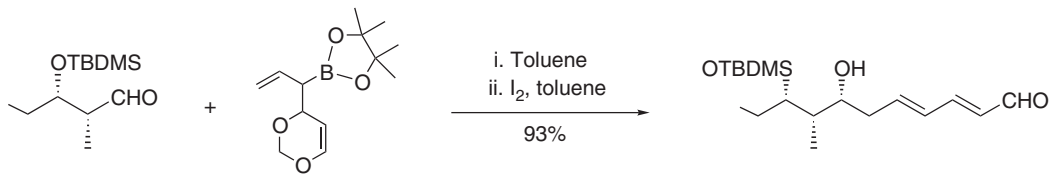
(37)

There are many examples in the recent literature of the cleavage of acetals to yield unsaturated aldehydes by elimination of, typically, alcohols or thiols as the final step in a synthetic strategy. Such reactions may occur in tandem with dehydration reactions, and are typically catalyzed by pyridine·HBr in acetone/water <2001S2463> or PTSA <2000MI951, 2001MI633>. The related cleavage of thioacetals may be achieved by treatment with $NH_4Br/H_2O_2/V_2O_5$ in water/dichloromethane <2002JCS(P1)1026>, *N*-bromosuccinimide in aqueous acetone <2000SL1798>, or using Amberlyst/H^+ <2001SL1251>. The cleavage of allylic ethers with DDQ/water/dichloromethane <2002JOC5176, 2000TL6945> and silyl ethers with palladium(II) salts <1998OM1069> (Equation (38)) also results in the synthesis of polyunsaturated aldehydes.



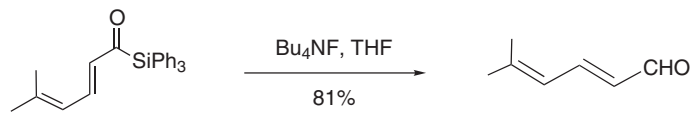
(38)

Other examples of this transformation which were detailed previously <1995COFGT(3)53> include elimination of β- and δ-sulfoxides and β-sulfones and formation and elimination of a β-mesylate group under weakly basic conditions. The efficient homologation of aldehydes to 2,4,6-alkatrienals by reaction with α-(1,3-dioxenylallyl)boronate (Equation (39)) has recently been reported <2000S2060>. This reaction features effective elimination of formaldehyde in addition to loss of the boronate group.



(39)

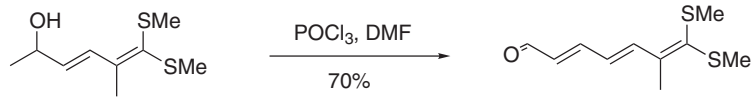
The facile cleavage of polyunsaturated acyl silanes with Bu_4NF/THF to yield the corresponding aldehydes has recently been reported <2001T6267> (Equation (40)).



(40)

3.02.1.2.2 By formylations of dienes

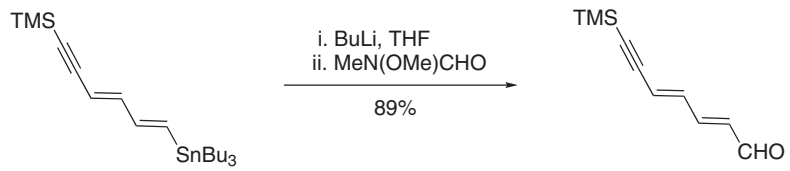
The direct Vilsmeier formylation of electronically activated or electron-rich dienes and trienes was presented in COFGT (1995) <1995COFGT(3)53>, and a 1,5- to 1,11-carbonyl transposition involving a ketene dithioacetal-derivatized unsaturated alcohol which proceeds by a Vilsmeier formylation with $POCl_3$/DMF (Equation (41)) has recently been reported <2001IJC(B)937>. The related formylations of a phenyl-substituted unsaturated alcohol <2000HAC303> and of a 1-iodo-functionalized diene <2002AG(E)3023> both under Vilsmeier conditions have also been reported recently.



(41)

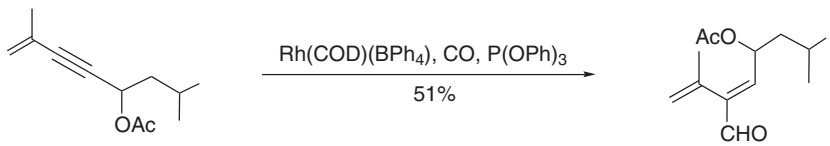
Chloroformylations using Vilsmeier conditions are discussed extensively in Sections 3.02.1.3.1 and 3.02.1.3.2, and particularly interesting examples of this reaction include the chloroformylation of spiro-ketones <2000IJC(B)334>, of diacetyl-derivatized heptatrienes <1995JCS(P1)2795>, and of 3β-acetoxyandrost-5-en-17-one to yield 3β-acetoxy-17-chloro-16-formylandrost-5,16-diene <1995JHC353>.

Formylation reactions involving β-methyl enones and lithio dienes were detailed previously <1995COFGT(3)53>, and the related formylation with a Weinreb *N*-methoxy-*N*-methylformamide of anions generated by the treatment of stannylated dienynes with *n*-BuLi has been reported <1999TL7889> (Equation (42)).



(42)

The use of $Rh_4(CO)_{12}$ as a catalyst to hydroformylate dienes was described previously <1995COFGT(3)53>, and regioselective hydroformylation of enynes <1999JOC3964> and acetylenic thiophenes <1999JOC9640> with carbon monoxide in the presence of a zwitterionic rhodium catalyst (Rh(COD) (η^6-$PhBPh_3$)) and triphenyl phosphite has been reported recently (Equation (43)).

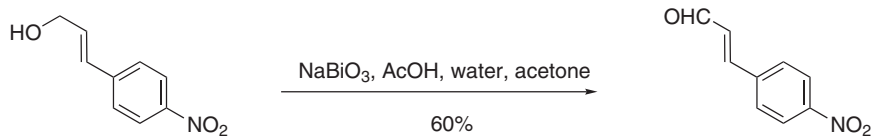


(43)

The formylation of a 1,1-dipyrrole-substituted alkene with a chloriminium ion and an analogous reaction with a trisubstituted pyrrole and a chloroformate ester have recently been reported <1996JOC8508>. A vinylogous formylation using β-dimethylaminopropenal or triformylmethane was also outlined in COFGT (1995) <1995COFGT(3)53>, and the related preparation of polyenic aldehydes from polyene dialkyl acetals and 1-alkoxy-1,3-dienes in the presence of a Lewis or Bronsted acid has recently been reported <1998EUP816334>.

3.02.1.2.3 By oxidations of alcohols and reductions of acids

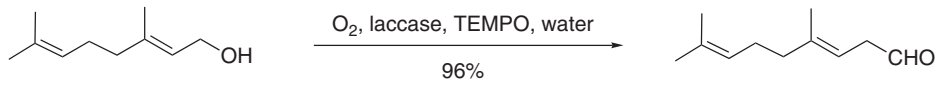
The oxidation of polyunsaturated alcohols proceeds by a similar mechanism to that described for α,β-unsaturated aldehydes without further unsaturation (see Section 3.02.1.1.2). COFGT (1995) described a number of reagents for achieving this transformation <1995COFGT(3)53> including MnO_2, pyridinium dichromate (PDC), Dess–Martin periodinane, and $RuCl_2(PPh_3)_3$ in the presence of molecular oxygen. The use of MnO_2 is still to be found in the recent literature <2001JOC1708, 2001SC3219, 2001SC117, 2001JOC3099>. The use of perruthenate-based oxidants such as $[NPr_4][RuO_4]$ with morpholine *N*-oxide <2000T479, 2000JOC3233> and poly(4-vinylpyridinium)perruthenate with PhIO <2000TL3971> have also been described recently, as has the use of the analogous OsO_4·quinuclidine with $Cu(OCOC_7H_{15})_2$ co-catalyst in the presence of molecular oxygen <2002OL1043>. A variety of Lewis acid catalysts have been employed to effect the oxidation of polyunsaturated alcohols, with the utility of chromium trioxide/zeolite H-ZSM 5 <1997JCR(S)462>, VO(2-(2-oxazolinyl)phenolato)$_2$/Bu^tOOH <1999TL8313>, bis[2-(2-pyridyl)phenyl]diselenide <2000JCS(P1)1429>, $NaBiO_3$/acetic acid <2000SC2701> (Equation (44)), bis(1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane) peroxodisulfate <1998BCJ2655>, and aqueous periodic acid/TEMPO <2002SL616> all being described in the recent literature.



(44)

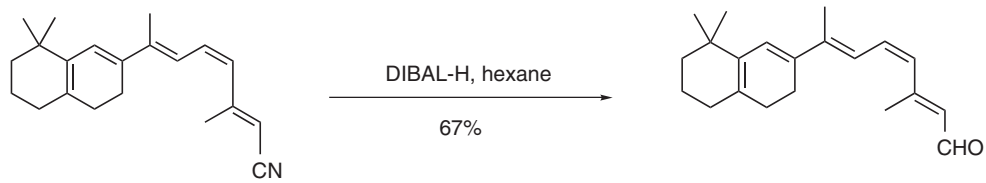
Transition metal-catalyzed oxidations of polyunsaturated alcohols have also been described recently, with ruthenium-based systems such as $RuCl_3$·nH_2O/$Ce(NO_3)_3$·$6H_2O$/$Co(NO_3)_2$·$6H_2O$ <2002TL7179> and $[RuCl_2(p\text{-cymene})]_2/Cs_2CO_3$ <2000TL7507> and palladium-based systems such as $Pd(OAc)_2$/hydrotalcite/pyridine/O_2 <2000CC1245>, and the highly selective palladium cluster catalysts $Pd_4(phen)_2(CO)(OAc)_4/O_2$ <1996JOC4502> and $Pd_{561}(phen)_{60}(OAc)_{180}/O_2$ <1997TL9023> being effective. A particularly interesting example of an oxidation of a

polyunsaturated alcohol to the corresponding aldehyde in high yield (Equation (45)) has recently been reported using an enzyme-based system, laccase (*Trametes villosa*) in the presence of molecular oxygen and TEMPO <2001TL7551>.



(45)

COFGT (1995) also described a method by which dienoic acid chlorides may be reacted with 3,5-dimethylpyrazole and subsequently reduced with $LiAlH_4$. The stereoselective reduction of polyunsaturated esters with DIBAL-H followed by oxidation of the resultant alcohols have been reported as key steps in biomimetic synthesis of biologically relevant molecules <2002OL2125, 2001AG(E)2063>. Reductions of polyunsaturated nitriles with the same reagent have also been reported recently (Equation (46)) <1997JOC3638, 2001JHC259, 2001JCS(P1)2430>.

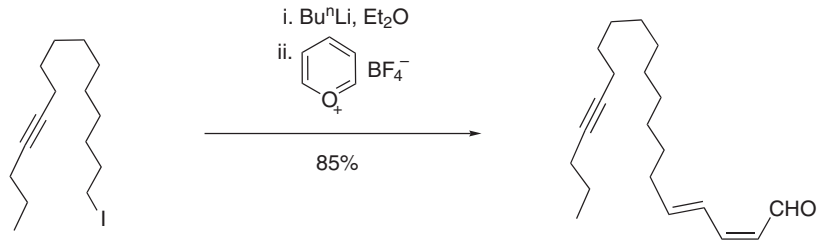


(46)

3.02.1.2.4 By ring-opening reactions of pyrylium salts and furans

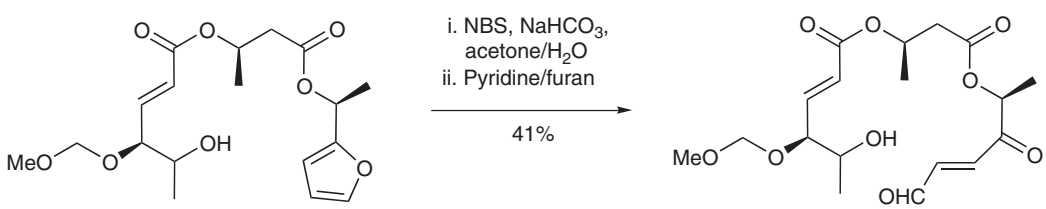
Examples of these types of reaction were presented in COFGT (1995) <1995COFGT(3)53> where pyrilium salts were ring-opened by the addition of nucleophiles such as phenyllithium, and where monosubstituted furans ring-opened upon α-deprotonation.

Recent examples of the former type of reaction have been reported in the literature, where, for example, 4-substituted pyrylium salts have been prepared and utilized in the synthesis of dienal compounds by reaction with carbon nucleophiles <1996JHC1083, 1995JCS(P1)2385>. Such reactions have been used in a stereocontrolled route to conjugated dienynals (Equation (47)) as intermediates in the synthesis of carduusyne A <1996TL1913>.



(47)

A number of reactions have been reported in the recent literature whereby furan rings are opened to yield α,β-unsaturated aldehydes, such as those presented in Section 3.02.1.2.6, which proceed via cyclopropanes formed by the addition of carbenoids to furans. Other routes have featured ring opening by the addition of a nitrosyl group to furan <2001JCS(P1)1908>, the synthesis of benz[*a*]azulenic enones from *o*-(2-furyl)cycloheptatrienylbenzenes by treatment with $[Ph_3C^+][BF_4^-]$ in dichloromethane <2000JCS(P1)3786>, and the addition of carbon nucleophiles to aldehyde tosylhydrazones of aromatic compounds <2000TL2667>. There have been a significant number of recent reports of efficient conversion of 2-substituted furans into 4-oxygenated α,β-unsaturated aldehydes <1998SL31> using NBS/pyridine/$NaHCO_3$ in acetone/water <2001JOC2011, 2001TA29, 2000JOC612, 1998JOC7505, 1997TL8883> (Equation (48)).

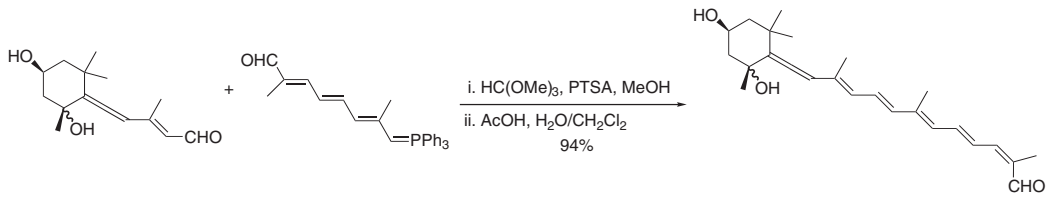


(48)

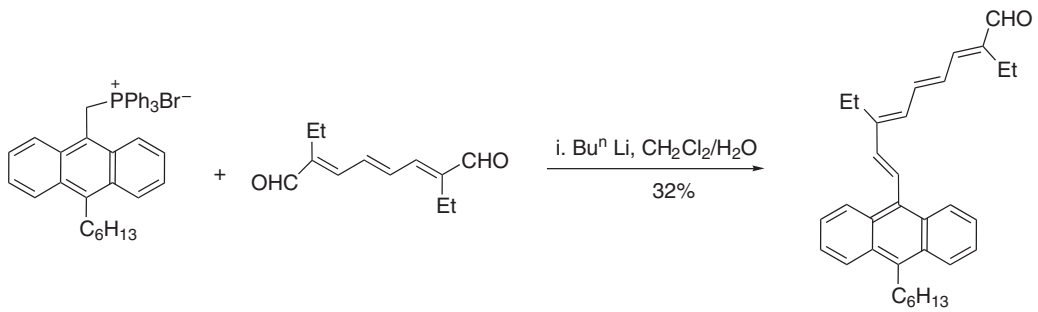
A similar reaction has also been reported using photochemical conditions, sensitized by methylene blue/O_2/acetone followed by treatment with Me_2S <1996CAR179>.

3.02.1.2.5 By Wittig reactions

Wittig reactions provide a straightforward and rewarding route for the synthesis of α,β-unsaturated aldehydes with further unsaturation <1995COFGT(3)53>. A number of methodologies have been described previously, including reaction of an aldehyde with 2 equiv. of formyl phosphorane and reaction of a protected formylphosphonium ylide with an unsaturated aldehyde followed by deprotection. There are many recent examples of the former type of reaction, including the synthesis of 3-thiazole-substituted alkenals synthesized from formyl thiazoles and formyl phosphoranes <2000TL8243>, and examples where highly functionalized alkenals are synthesized stereoselectively from chiral aldehydes and formyl phosphoranes as intermediates in total syntheses of biologically relevant molecules <2001T25, 2002JOC3615, 1996T4245>. The synthesis of retinal derivatives from polyunsaturated alkenals and phosphoranes (Equation (49)) has recently been reported <1996TL3887>, as has the synthesis of anthracene-derivatized polyenals from an anthracene-substituted phosphorane and a polyunsaturated aldehyde <1995S1115> (Equation (50)).

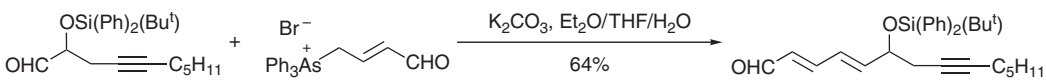


(49)



(50)

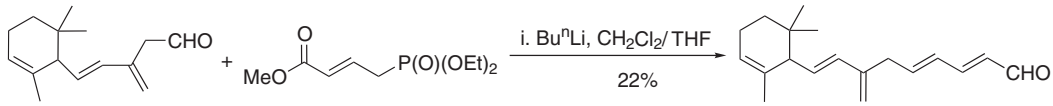
Reaction of an aldehyde with a vinylogous phosphorane or arsonium ylide to yield a mixture of ((*Z*),(*E*))- and ((*E*),(*E*))-isomers was reported previously <1995COFGT(3)53>, and the use of arsonium salts in the synthesis of (2(*E*),4(*E*))-dienals via double formyl olefination (Equation (51)) has recently been reported <1996JCS(P1)1057>.



(51)

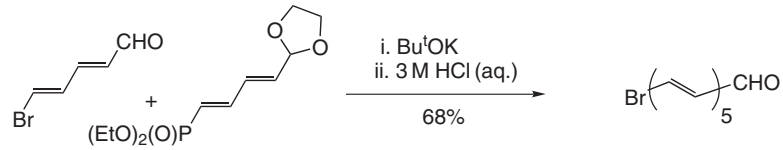
A review detailing the use of β-alkoxyalkenyllithium salts in many applications including Wittig-type reactions has recently been published <2002YGK847>. In this work, the electrophilic addition of β-alkoxyalkenyllithium salts to aldehydes and ketones and the subsequent hydrolysis of the allylic alcohol has been described.

The use of Horner–Wadsworth–Emmons methodology with protected aldehyde functionality on the phosphonate was described previously <1995COFGT(3)53>, and this methodology has grown in importance since COFGT (1995). This reaction has been utilized extensively in the synthesis of retinal derivatives, such as a four-component coupling approach to 9-fluororetinals featuring the key coupling of a 3-stannylated alkenal with an α-fluoro-α-(diethoxy)phosphonate-derivatized ester <1999T3675>. A related reaction between an unsaturated phosphonate and an unsaturated aldehyde yields a retinal analog <2001SC3219> (Equation (52)).



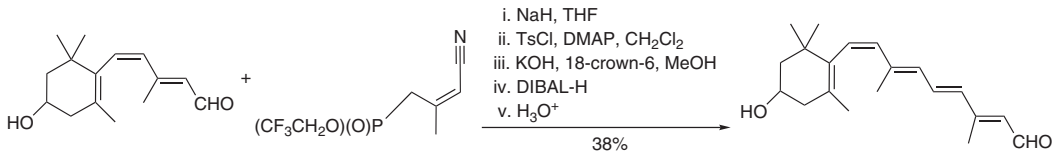
(52)

The synthesis of 9-halogenated retinal derivatives has been described from 3-halogen-substituted alkenals and unsaturated phosphonates <1996CPB264>, and ω-bromo-substituted polyenals have been synthesized in one-pot reactions (Equation (53)) from ω-bromo-substituted pentadienals and unsaturated acetal phosphonates <1997JCS(P1)1639>.



(53)

The synthesis of fluorine-substituted retinals has also been achieved by the reaction of fluorine-substituted unsaturated nitriles with phosphonate compounds <1997JOC3638>. Similarly, the reaction of an unsaturated aldehyde with a phosphonate-substituted unsaturated nitrile compound to yield retinal derivatives (Equation (54)) has recently been reported <1996T7809>.



(54)

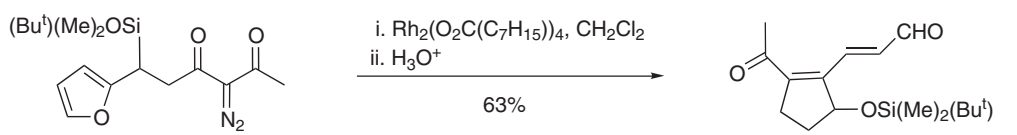
The synthesis of 11-(*Z*)-9-demethyl-9-((3-indolyl)methyl)retinal from a tricarbonyliron complex functionalized with a polyunsaturated aldehyde and a nitrile-derivatized phosphonate has also been reported recently <2001JHC259>. The utility of 4-diethoxyphosphonyl-2-methyl-1,3-dienolates and their *O*-acylated and *O*-silylated derivatives as efficient stereoselective polyvinylogation reagents has recently been reported <1999S1188>. These compounds afford (*E*)-stereoselective five-carbon polyvinylogation of aldehydes (Equation (55)).

(55)

Other examples of this reaction have included the efficient synthesis of polyunsaturated aldehydic precursors to raikovenal derivatives <1997SC1583> and polyenic analogs of tetrathiafulvalenes <1996BSF301>.

3.02.1.2.6 From cyclopropanes

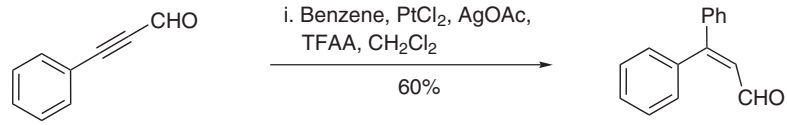
Cyclopropane systems were described in COFGT (1995) <1995COFGT(3)53> as intermediates in the reaction between α-keto carbenes and furans, where *in situ* electrophilic ring-opening yields dienals as predominantly ((*Z*),(*E*))-isomers. The thermolysis of isolated cyclopropanes was also described, as was the equivalent intramolecular reaction from which it was possible, under certain circumstances, to generate alkynals. Recent reports of syntheses of α,β-unsaturated aldehydes which proceed through cyclopropane intermediates have focused on the reaction between furans and $Rh_2(OAc)_4$-stabilized carbenoids <2000HCA755, 2000OL2393, 1999HCA511, 1999TL5171>. A particularly interesting intramolecular example of this reaction has recently been reported (Equation (56)) <1997TL5623>, where the products of this reaction were found to be dependent on the tether position.



(56)

3.02.1.2.7 Miscellaneous reactions

Some miscellaneous methods for the synthesis of α,β-unsaturated aldehydes with further unsaturation that were described in COFGT (1995) <1995COFGT(3)53> included an example of a vinylogous aldol reaction between α-cyclocitral and benzaldehyde, a hydrolytic ring-opening reaction of a pyridinium salt to produce a dienal, and related ring-opening reactions of pyridines with thiophosgene. Other reactions discussed were oxidative ring-openings, reaction of propargylic aldehydes with β-amino acrylates, and isomerizations of allylic propargylic tertiary alcohols under acidic conditions, all of which result in the synthesis of functionalized dienals. Recently, Pd(II)- and Pt(II)-catalyzed regio- and stereoselective *trans*-hydroarylations of alkynals to give the kinetically favored *cis*-alkenal have been reported (Equation (57)) <2000JA7252>. In contrast to previously reported Pd-catalyzed arylation reactions, the method reported also works with sterically hindered arenes.



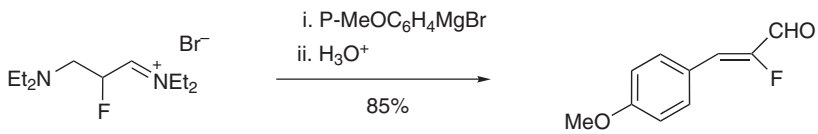
(57)

The manufacture of dimeric unsaturated aldehydes by oxidative coupling of unsaturated aldehydes has recently been reported <1995USP5382700>. Unsaturated aldehydes are reacted with an anhydrous copper(II) catalyst and a complexing amine catalyst in anhydrous conditions to yield dimeric unsaturated aldehydes in high yield, which are useful as intermediates in polymers and resins.

3.02.1.3 Halogenated α,β-Unsaturated Aldehydes

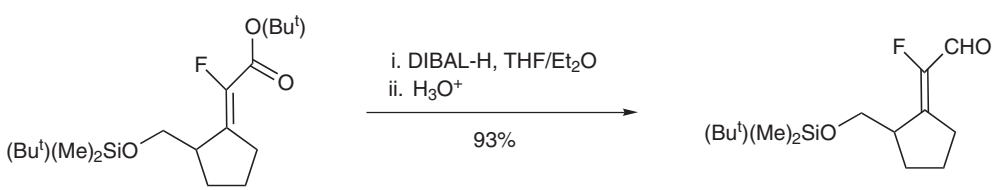
3.02.1.3.1 2-Halogenated α,β-unsaturated aldehydes

In COFGT (1995) <1995COFGT(3)53> a variety of methods were outlined for the synthesis of 2-halogenated α,β-unsaturated aldehydes. These included the ring-opening of methoxy-substituted cyclopropane systems derived from the reaction of enol ethers with carbenes, and the related addition of dihalocarbenes to silyl enol ethers. The addition of Grignard reagents to β-fluorovinylamidinium salts (Equation (58)) has recently been reported to provide a facile route to (*Z*)-α-fluoro-α,β-unsaturated aldehydes <1998TL6943>.



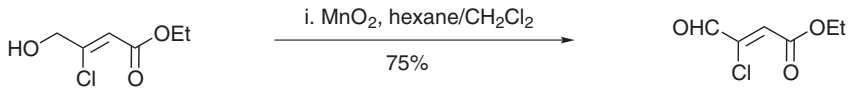
(58)

The reduction and rearrangement of tris-halogenated 3-hydroxyalkenes, prepared from the addition of, for example, trifluorovinyllithium to carbonyl compounds was also described previously, as was the synthesis of 2-bromo-α,β-unsaturated aldehydes by reaction of the 1-bromo-2-methoxyvinyllithium with, for example, acetone followed by rearrangement of the intermediate alcohol. A number of reductions have been reported in the recent literature, such as the reduction of 2-halogenated nitrosyl <2000TL2453> and ester <1996T291, 2002TA1589> functional groups (Equation (59)) to aldehydes with DIBAL-H in THF/Et_2O.



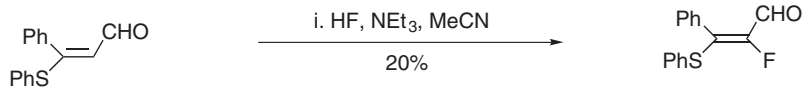
(59)

A procedure was described previously <1995COFGT(3)53> whereby oxidation of an iodine complex derived from an acetylenic alcohol yielded 2-iodo-α,β-unsaturated aldehydes. Oxidations of 2-halogenated allylic alcohols to alkenals have been reported recently, using reagents such as MnO_2/hexane <1996CPB264> (Equation (60)) and SO_3·pyridine/DMSO/(*i*-Pr)$_2$NEt <2000JA9036>.

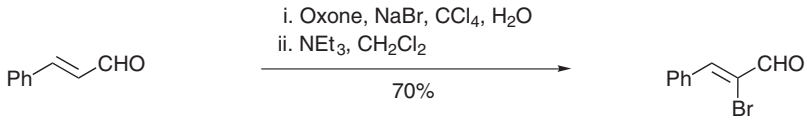


(60)

The substitution of α-hydrogens was featured extensively in COFGT (1995) and a variety of reagents for achieving this transformation were outlined. These included molecular halogen (addition–elimination mechanism where β-hydrogen is most acidic), hypohalous acid (where β-hydrogen is less acidic), and thionyl bromide (bromination via a radical mechanism). Recent reports of α-halogenations have included fluorination of alkenals with $HF/NEt_3/MeCN$ <1997T647> (Equation (61)), bromination and chlorination of alkenals with Oxone® and sodium halides <1996TL2377> (Equation (62)), and bromination with molecular bromine <1995TA2675> to yield 2-bromoalkenals.

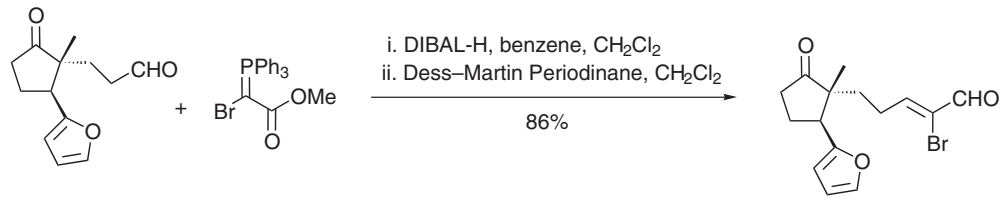


(61)



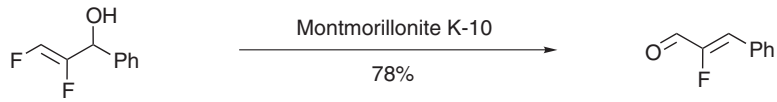
(62)

Wittig reactions were also described previously <1995COFGT(3)53>, where halogenated formyl phosphoranes react with aldehydes by the standard mechanism to yield 2-halogenated α,β-unsaturated aldehydes. A similar reaction of an ester with a halogen-substituted phosphorane (Equation (63)) followed by reduction with DIBAL-H and Dess–Martin oxidation yields the desired 2-halogenated product <2002JOC5669>. A related route featuring a formolysis and concomitant (*E*)- to (*Z*)-isomerization yielded a (*Z*)-2-bromoalkenal from (*E*)-bromoacetal was described previously.



(63)

An example of an elimination was also outlined in COFGT (1995) whereby the thermolysis of a 2,3-dichloro-pyran yielded 2-chloro-2,4-pentadienal. The montmorillonite K-10-catalyzed hydrolysis of aryl-substituted α,β-difluoroallyl alcohols to yield (*Z*)-α-fluoro-β-aryl-substituted acryl aldehydes (Equation (64)) has recently been reported <1999T4637, 1998TL1913>.



(64)

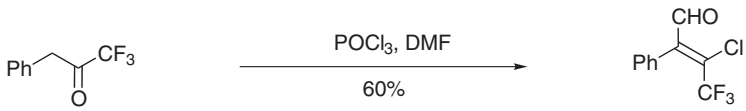
3.02.1.3.2 3-Halogenated α,β-unsaturated aldehydes

(i) By Vilsmeier–Haack–Arnold reaction with carbonyl compounds

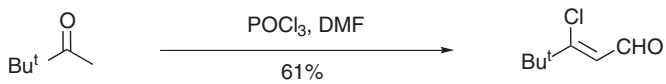
A major route to 3-halogenated α,β-unsaturated aldehydes is the Vilsmeier–Haack–Arnold reaction with carbonyl compounds <1995COFGT(3)53>. This is a very important reaction that is widely used for making β-halogenated α,β-unsaturated aldehydes from both aliphatic and aromatic carbonyl compounds, which are capable of forming enol ethers. The enol ether is formylated and halogenated by a mechanism described in COFGT (1995), commonly using DMF and $POCl_3$, PCl_3, PCl_5 PBr_3, or $POBr_3$ as reagents. Where symmetrical ketones are used as starting materials, regioselectivity is unimportant <2002EJM391>; however, where unsymmetrical carbonyl compounds with two enolizable sites are utilized as the substrate, mixtures of

regioisomers are produced, in addition to the mixtures of (*E*)- and (*Z*)-stereoisomers which are often possible. Recent examples of such unsymmetrical reactions include the synthesis of polyunsaturated systems <2000EJM797, 1998JHC1377>, β-aromatic systems <1999JHC703>, and an example where a lack of regiospecificity coupled with an excess of $POCl_3$ has resulted in multiple formylations <1997TL8391>.

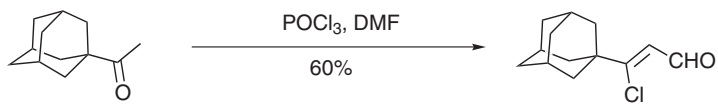
Regiospecificity can be introduced by effectively blocking one enolizable site although problems with this approach have been described, whereby unwanted by-products may be formed. A number of regioselective reactions using this strategy have been reported recently including the reaction of ketones bearing α-perfluorinated groups <1999JFC91, 1999S471> (Equation (65)) and *t*-butyl groups <2002S1096> (Equation (66)), and the reaction of 1-acetyladamantanes <2000MI999, 1999MI1773, 1999MI371> (Equation (67)) under Vilsmeier–Haack conditions.



(65)

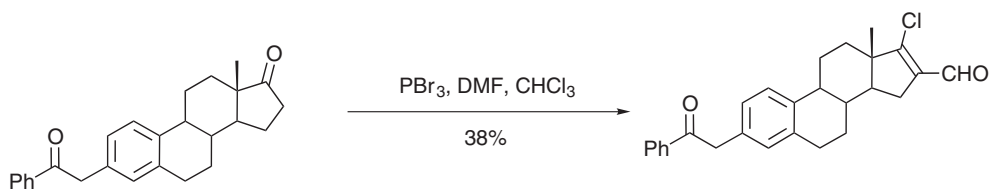


(66)



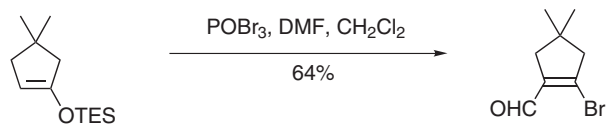
(67)

Similarly, the Vilsmeier–Haack bromoformylation of a fused tetracyclic system featuring a ketone with a bridgehead position α to the carbonyl (Equation (68)) produces only one product <1997JCR(S)248>.



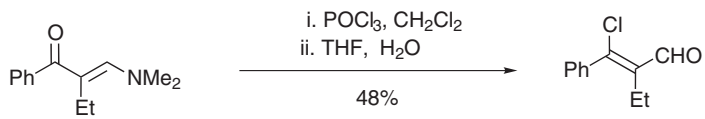
(68)

Ketones bearing α-phenyl groups <1999JCS(P1)1175, 2001IJC(B)1166> and naphthyl groups <1995SC1869> offer a similar regioselectivity as do acetyl-substituted benzocoumarin derivatives <2002MI610>. Other factors that influence regiochemistry include steric bulk of the carbonyl starting material and the relative thermodynamic or kinetic stabilities of intermediate enols. The use of triethylsilyl enol ethers to control the regiochemistry of the product (Equation (69)) has also been described recently <2001OL2611>.



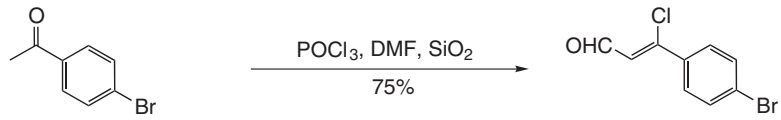
(69)

The utility of β-dimethylamino α,β-unsaturated carbonyl compounds was described previously <1995COFGT(3)53>. These are particularly useful synthons as they are formal intermediates in the Vilsmeier–Haack reaction. Similarly, the application of disubstituted vinylogous iminium salts in regiocontrolled chloroformylation reactions (Equation (70)) has recently been described <1998T5075>.



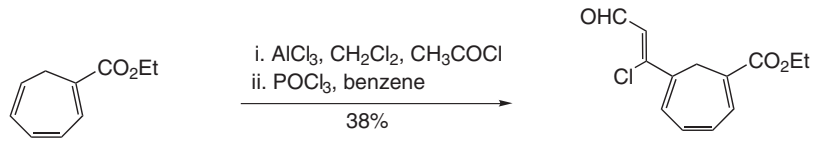
(70)

Vilsmeier–Haack formylations may be accelerated ultrasonically <2002SC1351> and may be carried out in solvent-free conditions using microwaves with silica-supported $POCl_3$ <2000SL1115> (Equation (71)) and with reaction times accelerated by approximately 270-fold <2000IJC(B)135>.



(71)

A combination of Friedel–Crafts acylation followed by Vilsmeier–Haack formylation of a cycloheptatriene derivative (Equation (72)) has also been described recently <1995BCJ3519>.

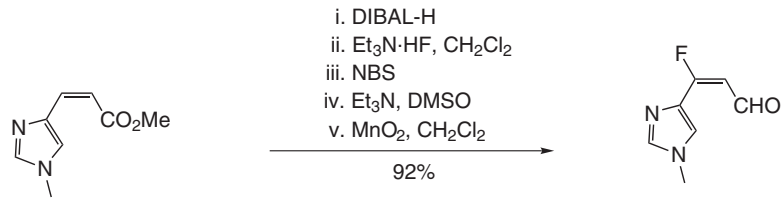


(72)

A related formylation reaction was also described previously <1995COFGT(3)53> whereby alkoxyacroleins were treated with thionyl chloride to give the desired product via allyl chloromethyl ether compounds.

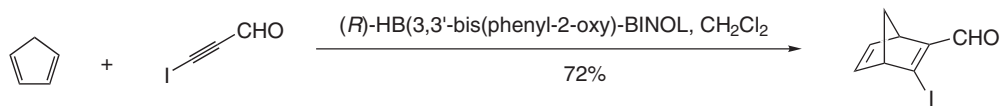
(ii) Miscellaneous

Of the methods to prepare 3-halogenated α,β-unsaturated aldehydes which do not fall into the above class, COFGT (1995) <1995COFGT(3)53> described the chloroformylation of dialkyl alkynes with dichloromethyl ether and boron trichloride, and the treatment of a trichloromethyl-substituted cyclohexadienal with sulfuric acid. The oxidation of 3-halogenated allylic alcohols to 3-halogenated α,β-unsaturated aldehydes has been reported extensively in the recent literature, using reagents such as chromium trioxide supported on silica gel <2003MI136>, potassium dichromate <2002TL8843, 1997JCR(S)206> and MnO_2 <2002TL6149, 1996SC433>. This transformation has also been reported using Swern oxidation conditions <1998TL8857> and by methylene blue-sensitized photooxidation <2002TL9129>. The preparation of 3-fluoro-3-imidazolyl-propenals has been reported by the addition of an "FBr" equivalent to a double bond followed by HBr elimination <2002JOC3468>. Tritylation of the imidazole nitrogen was necessary for the successful addition of "FBr" to the double bond, and prior reduction of the carboxyl group to the alcohol was required to provide chemoselectivity in the elimination of HBr. Reoxidation provided the desired 3-fluoro-3-imidazolyl-propenal (Equation (73)).



(73)

A stereospecific Diels–Alder reaction between cyclopentadiene and a 3-iodopropynal (Equation (74)) has been reported to yield a 3-iodo-alkenal with (*R*)-HB(3,3,-bis(phenyl-2-oxy)-BINOL) catalyst <1997JOC3026>. The same product is obtained when a 3-stannylated alkenal is treated with *N*-iodosuccinimide/THF <1997TL5755>.



(74)

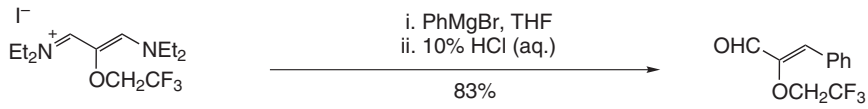
A [3,3]-sigmatropic rearrangement route to β-fluoro-α,β-unsaturated aldehydes, catalyzed by $Hg(OAc)_2$ has also been described recently <1995T11327>.

3.02.1.4 Oxygen-substituted α,β-Unsaturated Aldehydes

3.02.1.4.1 2-Oxygen substitution

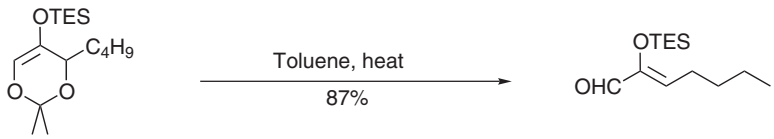
In COFGT (1995) <1995COFGT(3)53>, relatively few routes to α-oxygen-substituted alkenals were discussed. The Swern oxidation of alcohols followed by β-elimination to yield 2-oxygenated alkenals was described previously and this method has been reported recently in the synthesis of formylated dihydrofuran β-lactam-fused bicyclic systems <2000PJC1243>. The oxidation of an alcohol with PCC/toluene followed by β-elimination has also been reported recently <1997IJC(B)808>. The oxidation of 2-alkoxy allylic alcohols was also described in COFGT (1995) and similar reactions with *o*-iodoxybenzoic acid/DMSO <2002S869> and $NaBiO_3$/CH_3COOH in water/acetone <2000SC2701> have recently been reported.

The reaction of dimethoxyvinyllithium species with aldehydes was detailed in COFGT (1995) and a related reaction of β-trifluoroethoxyvinamidinium salts with carbon nucleophiles such as Grignard reagents or those generated by treatment of ketones and nitriles with LDA to yield 2-trifluoroethoxy-derivatized alkenals (Equation (75)) has recently been described <2000JFC225, 2003JFC33>.



(75)

The stereoselective synthesis of (*Z*)-2-(trialkylsilyloxy)-2-alkenals by retrocycloaddition reactions of 4*H*-4-alkyl-5-(trialkylsilyloxy)-1,3-dioxins (Equation (76)) has recently been reported <2001OL3553> as has the base-mediated ring opening of a D-glucose-derived eight-membered ring carbocycle <2001OL731> to yield highly functional 2-benzyloxy-substituted alkenals.

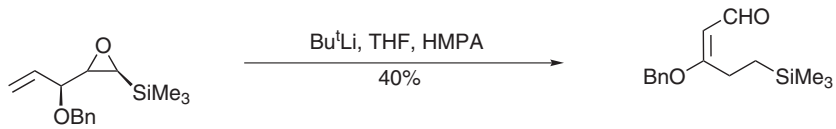


(76)

Other routes to 2-oxygen-substituted alkenals include the rearrangement of propargylic esters which was described in COFGT (1995), the base-mediated elimination of 2 equiv. of acetic acid from aldopentose tetraacetate by treatment with DBU or NEt_3 <1998JAP10287615>, a related reaction featuring elimination of benzoic acid <1995TL7811>, and the treatment of an α-brominated ketone with $AgNO_3$/MeCN and sodium acetate/DMSO to yield an α-hydroxyacrolein <1997CC323>.

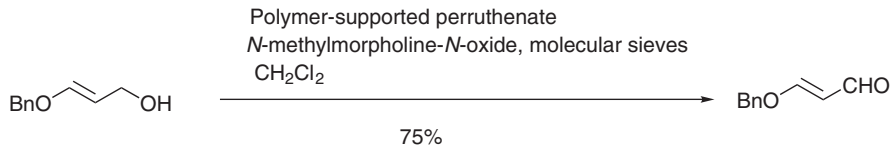
3.02.1.4.2 3-Oxygen substitution

A number of routes to β-alkoxyacroleins were described in COFGT (1995) <1995COFGT(3)53> and these included the β-formylation of enol ethers, which may be achieved using Vilsmeier conditions ($POCl_3$/DMF) or with triethyl orthoformate/BF_3. A related formylation of a β-keto epoxide-functionalized steroid with $BF_3{\cdot}OEt_2$/benzene has recently been reported <2001IJC(B)510>. Methods to prepare 3-oxygenated alkenals were also described <1995COFGT(3)53> from dihydropyrans via [2 + 1]-cycloaddition followed by ring-expansion and -contraction reactions. Ring-closure reactions have been reported recently where reaction of α-formylated ketones with LDA/THF and 1,4-dibromobut-2-ene yields formylated 2-vinyl-2,3,3a,4,5,6-hexahydro-2,3-benzofurans <2002MI917>. A ring-closure reaction of an functionalized alkynal yields optically active 3,4-diacetoxy-2-formylmethylene-1,6-dioxaspiro[4.5]decanes <1999TL3587>. Conversely, the ring opening of an optically active trimethylsilyl epoxide bearing both an allylic and a benzylic ether with excess *t*-butyllithium/THF/HMPA has been reported to yield (*E*)-3-phenylmethoxy-5-trimethylsilyl-2-pentenal <1996JOC9065> (Equation (77)).



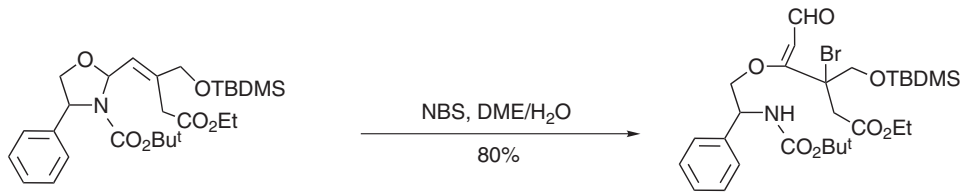
(77)

Oxidative routes to 3-oxygen-substituted alkenals were described previously <1995COFGT(3)53>, including addition of alcohols to propargylic esters followed by the reduction to the allylic alcohol and subsequent oxidation, oxidation of 3-alkoxy allylic alcohols by reagents such as PCC, and Pd-catalyzed oxidation of α-silyl-substituted allylic tosylates. Recent examples of this type of reaction have included oxidation of β-silyloxy-substituted allylic alcohols to aldehydes with Dess–Martin periodinane/[Cr(salen)]Cl <2000OL2773> and oxidation of 3-benzyloxy-substituted allylic alcohols with polymer-supported perruthenate/*N*-methylmorpholine *N*-oxide <1997JCS(P1)1907> (Equation (78)).



(78)

Other routes that were discussed in COFGT (1995) <1995COFGT(3)53> include cycloaddition of vinyl ethers with malonaldehyde derivatives and reaction of 3-halogenated (or ammonium) acroleins with alcohols. The synthesis of β-methoxy-substituted alkenals has been reported <1999CPB1115> by Michael-type additions of sodium methoxide to alkynals. The elimination of water to yield *C*-glycosyl-conjugated aldehydes from sugar lactones with trifluoroacetic acid/pyridine has recently been reported <2001TL4657> as has a Claisen rearrangement of allylic and propargylic alcohols with NBS/DME/water <2002EJO29, 2000T367> (Equation (79)).



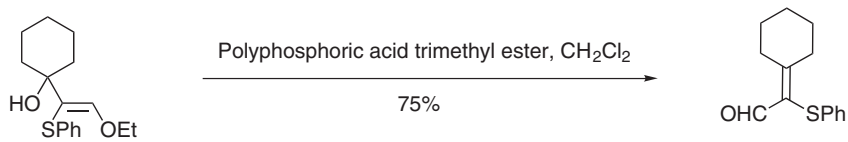
(79)

A variety of routes to 3-oxygenated alkenals as intermediates to viridenomycin have been described recently <2001TL4301, 2001TL4305> as have facile routes to 11-chloro-3-methoxy-2-undecenal from 8-bromooctanol <2001CPB18>.

3.02.1.5 α,β-Alkenic Aldehydes with Sulfur Substituents

3.02.1.5.1 2-Thio α,β-unsaturated aldehydes

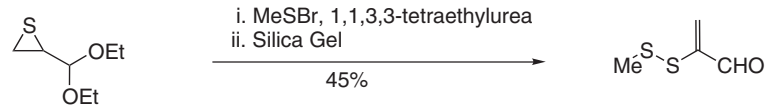
Previously, three methods were described for the synthesis of 2-thio α,β-unsaturated aldehydes <1995COFGT(3)53>. These included the hydrolytic ring opening of an alkoxybromothiocyclopropane derived from a dibromoalkoxycyclopropane, the cleavage of a thiol-substituted enol ether under mild nonacidic conditions, and the use of TFA acid to produce an α-sulfonyl alkenal from a 3-hydroxy-2-sulfonyl enol ether. Similarly, a recent example describes the 1-chalcogen-substituted formylolefination of ketones and aldehydes using 1-lithio-2-ethoxyvinyl chalocogenides to give 2-thio α,β-unsaturated aldehydes, <1998JOC4475> after elimination of ethanol from the resultant thio-substituted enol ethers (Equation (80)) with polyphosphoric acid or trimethylsilyl triflate.



(80)

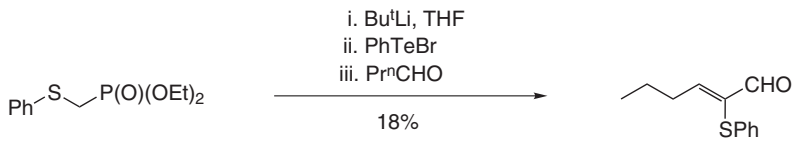
A number of examples may be found in the literature of sulfur-substituted unsaturated ring systems featuring formyl groups; see for example aldehydic dithiine systems <1997JOC9369> synthesized from their respective enol ethers using DDQ, the photooxidation of methyldithiepins <1999OL937> in the presence of molecular oxygen, and an oxidative ring closure with concomitant oxidation of an allylic alcohol to yield formylated 1,2-benzodithiins <1995TL1421>.

Ring-opening reactions as methods for the synthesis of 2-thio-α,β-unsaturated aldehydes have also been reported, including the ring opening of thiiranes such as acrolein diethyl acetal sulfide with methanesulfenyl bromide to yield a halodisulfide, which may undergo dehydrohalogenation with silica gel to give a disulfide-substituted acrolein (Equation (81)) <2001JOC910>.



(81)

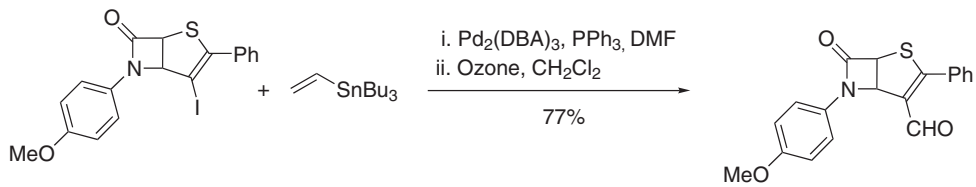
The ring opening by photooxidation of enantiomerically pure (*S*)-*p*-tolylsulfinylfurans in the presence of methylene blue <2000TA1183> yields (*S*)-1,4-dicarbonyl-2-(*p*-tolylsulfinyl)-2-alkenes. The lithiation of thiomethylphosphonates followed by stepwise reaction with tellurenyl bromide and an aldehyde yields ketene (S,Te) acetals <1999T7421>, which may undergo transmetallation with *n*-BuLi followed by quenching with electrophiles to yield (*Z*)-α-phenylthio-α,β-unsaturated aldehydes (Equation (82)).



(82)

3.02.1.5.2 3-Thio α,β-unsaturated aldehydes

The synthesis of β-thio-alkenals has been achieved by a variety of routes <1995COFGT(3)53>. Methods described previously include the displacement of a halogen-leaving group by a sulfur nucleophile in an activated 3-chloro-alkenal and an analogous reaction utilizing an ammonium-leaving group. Examples of the former reaction may also be found in the recent literature with the treatment of 3-formyl-4-bromo-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl radicals with thioethane in the presence of DBU <1998S1476>, and an analogous synthesis of a thio-substituted formylated benzofuran derivative <1996JOC4842> in the presence of potassium carbonate. A novel approach to β-thio alkenals has also been described <1998JOC8898>, whereby a halogen-substituted penicillin derivative was effectively formylated by Heck coupling of an vinylstannane reagent followed by ozonolysis (Equation (83)).

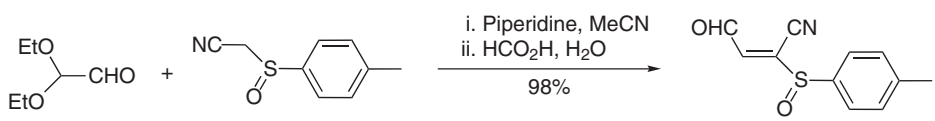


(83)

COFGT (1995) <1995COFGT(3)53> further described a Wittig condensation between glyoxal- and a thiol-substituted ylide and a ring-opening reaction of a thiopyran. The Pummerer-based ring opening of 2-alkyl-substituted 1-[(2-methoxyethoxy)methoxy]-2-(phenylsulfinyl)cyclopropanes with trifluoroacetic anhydride and $(i\text{-Pr})_2$NEt <2001TL4389> to yield β-thiophenyl alkenals has recently been described (Equation (84)).

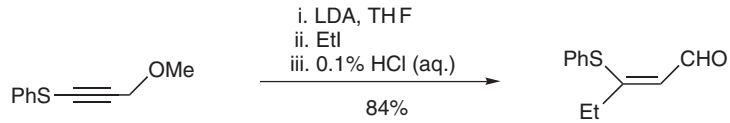
(84)

An aldol-type reaction (Equation (85)) has been described where the synthesis of (*E*)-3-formyl-2-sulfinylacrylonitriles has been achieved from 2-sulfinyl acetonitriles in the presence of piperidine and formic acid <2002TA2003>.



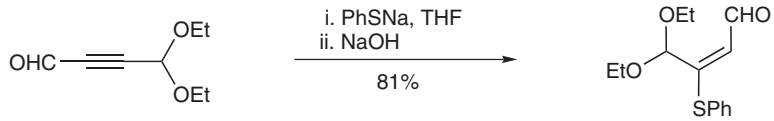
(85)

A facile preparation of β-alkyl-β-phenylthio-α,β-unsaturated aldehydes (Equation (86)) has been described by conjugate addition of alkyl synthons to a 3-methoxy-1-phenylthio-1-propyne <1995H13>.



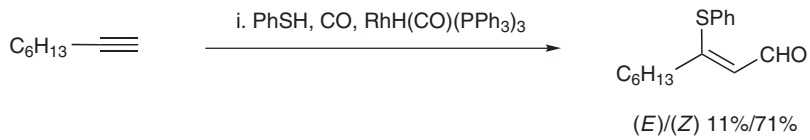
(86)

A related reaction has been described as a model system for a traceless linker for solid-phase reactions <2000TL7875>, whereby a retro-Diels–Alder reaction is effected by Michael addition of thiophenol to the adduct between resin-bound furan and a propargylic aldehyde to yield a β-thiophenyl alkenal (Equation (87)).



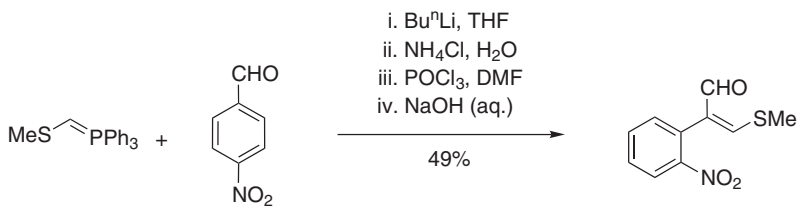
(87)

A number of formylation reactions were presented in COFGT (1995) <1995COFGT(3)53>, including the Vilsmeier formylation (oxalyl chloride or $POCl_3$ with DMF or similar) of activated thiol-substituted alkenes such as 1,4-benzooxathiins or 1,4-benzodithiins, and a related formylation of a lithiated tetrathiafulvalene with DMF. Formylations remain a popular route to β-thio alkenals, with the Rh(CO) $(PPh_3)_3$-catalyzed thioformylation of acetylenes with aromatic thiols and carbon monoxide <1995JA7564> (Equation (88)), the synthesis of β-methylsulfanylacroleins from alkenyl sulfides by the Vilsmeier reaction <2002H2081> (Equation (89)) and the thioformylations of 4-acetylanisole <1996JCS(P2)731> (Equation (90)) and α-trifluoromethylbenzylketones <1995JFC1> (Equation (91)) under Vilsmeier conditions being recently reported.

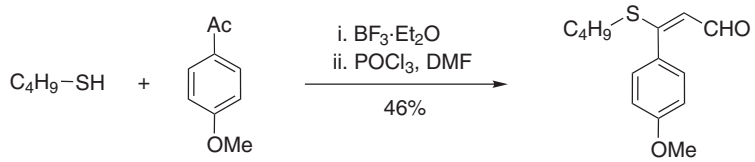


(*E*)/(*Z*) 11%/71%

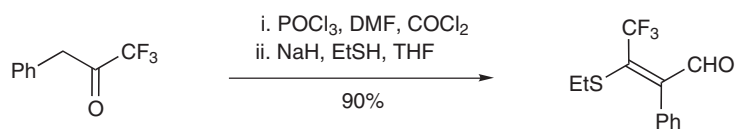
(88)



(89)



(90)

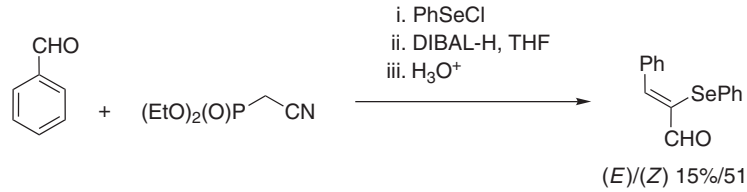


(91)

3.02.1.6 Selenium-substituted α,β-Unsaturated Aldehydes

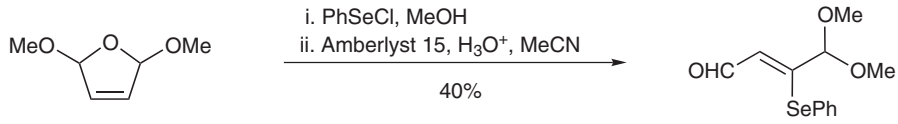
Previously, three methods of preparing α-selenium-derivatized alkenals had been described <1995COFGT(3)53> and these were reaction of alkenals with morpholino–benzoselenamide, transmetallation and formylation of vinyl diselenides, and rearrangement reactions starting from allylic alcohols. Recent methods for synthesizing these compounds have included the

formylation of telluro-substituted enol ethers with DMF <2000JOC61>, oxidation of 2-selenium-substituted allylic alcohols with Dess–Martin periodinane <1997JOC6974>, elimination of HCl from a 3-chloro-2-phenylselenated aldehyde <1997TL15843>, and effective elimination of ethanol from a 3-hydroxy-2-phenylseleno-functionalized enol ether <1998JOC4475>. A particularly interesting example has been reported <2001T5953> where α-selenium-substituted alkenals were synthesized using Wadsworth–Emmons reactions from precursor phenylselenoacrylonitriles and phosphonates (Equation (92)).



(92)

In COFGT (1995) <1995COFGT(3)53>, three methods of preparing β-selenium-derivatized alkenals were described, namely, nucleophilic displacement of chlorine from β-chloro alkenals with a selenol, hydroselenation of propynal, and oxidation of selenium-substituted allylic alcohols. Recently reported methods have described the stereoselective *trans*-addition of phenyl selenyl chloride to 2,5-dihydro-2,5-dimethoxyfuran followed by regioselective acetal group hydrolysis under acidic conditions with Amberlyst 15 resin (Equation (93)).

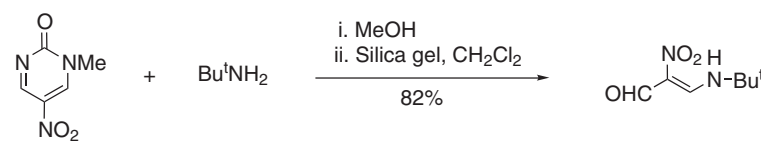


(93)

3.02.1.7 Nitrogen-substituted α,β-Unsaturated Aldehydes

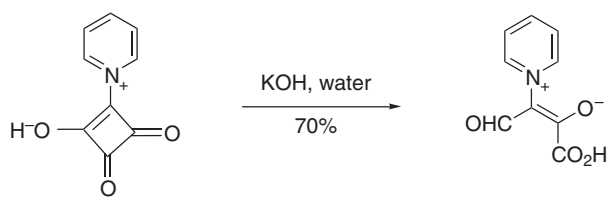
3.02.1.7.1 α-Nitrogen-substituted α,β-unsaturated aldehydes

At the time of writing COFGT (1995) <1995COFGT(3)53>, α-nitrogen-substituted α,β-unsaturated aldehydes were not widely reported; indeed only two methods were described. The first was the Vilsmeier–Haack–Arnold reaction of ene-diamines, dipiperidino derivatives, and α-amino-substituted ketones with $POCl_3$ or oxalyl chloride in DMF; the second being an oxidative amino-mercuration of propynol which yielded bis(2,3-*N*-alkylamino)propenals. The recent literature abounds with examples of α-nitrogen-substituted α,β-unsaturated aldehydes as part of heterocyclic systems, which will not be discussed in this chapter. However, the synthesis of 2-nitro-3-amino-propenals may be accomplished by aminolysis of a heterocycle, 1-methyl-5-nitropyrimidin-2(1*H*)-one, in the presence of a primary amine and silica gel <1996BCJ1997> (Equation (94)).



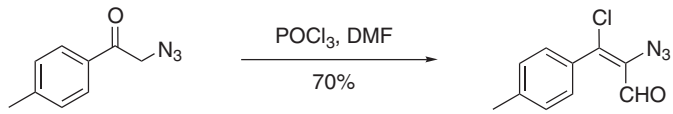
(94)

Other ring-opening reactions have been described which result in the synthesis of 2-aminated enals, including the ring-opening reactions of pyridinium and phosphonium betaines of squaric acid in alkaline media <1996JPR718> (Equation (95)) and a deprotection/elimination sequence of an acetal-protected β-lactam with a perfluorinated periodinane ($PhI(O_2CCF_3)_2$ and $NaHCO_3$ to yield an α,β-unsaturated aldehydes bearing a lactam group in the α-position <2002JOC8243>.



(95)

The Vilsmeier formylation reaction with $POCl_3$ in DMF has recently been used in the synthesis of α-azido-β-chloro-α,β-unsaturated aldehydes from 2-azidoacetophenones (Equation (96)) <1998JOC7136, 1997TL6889> and as intermediates in the synthesis of 5-aryloxazole-4-carboxaldehydes. It is interesting to note that the chloroformylation reaction proceeded at room temperature without affecting the azide function.

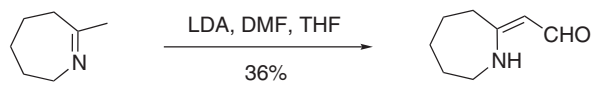


(96)

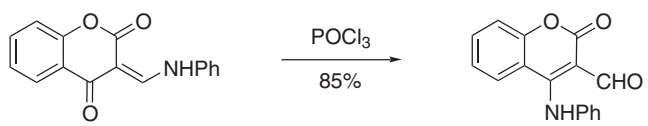
3.02.1.7.2 β-Nitrogen-substituted α,β-unsaturated aldehydes

A number of methods for producing β-nitrogen-substituted α,β-unsaturated aldehydes were described in COFGT (1995) <1995COFGT(3)53>. These methods included the reaction of 1,3-dicarbonyl compounds (e.g., malonaldehydes) and alkoxyacroleins with nitrogen nucleophiles such as acetamides or amines and anilines. A second method described previously was the Vilsmeier–Haack–Arnold reaction of amides (e.g., azepines) and α-amino-substituted ketones with $POCl_3$ or oxalyl chloride in DMF. Related reactions were described whereby vinyl ethers were aminated and subsequently partially hydrolyzed and where lithium salts of alkanoic acids react with an aminomethyleneating reagent via a decarboxylative double formylation to yield the desired products. An alternative formylation reaction was also described whereby β-lithioenamines were reacted with DMF to yield the desired enaminoaldehyde. A third synthetic route described previously was the oxidative addition of amines to propargylic alcohols to yield β-amino acroleins and the complementary addition of alcohols to 3-amino propynals. Other routes outlined included the photolysis of isoxazolines and the reaction of sodium azide with chlorinated cycloalkenals to yield β-aminated-α,β-unsaturated aldehydes.

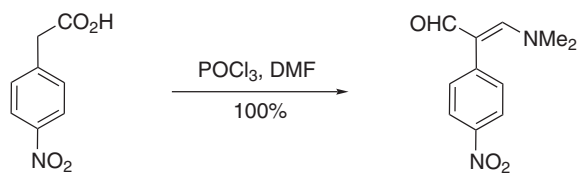
The synthesis of β-aminated-α,β-unsaturated aldehydes by formylation remains popular in the recent literature, with particularly interesting examples being the deprotonation and alkylation of 2-methyl-4,5,6,7-tetrahydro-3*H*-azepine with LDA/DMF <1999AJC965> (Equation (97)), an intramolecular reaction of 3-(arylaminomethylene)chroman-2,4-dione with $POCl_3$ to yield 2-arylamino coumarin derivatives <2000T3583> (Equation (98)), Vilsmeier-type formylations of alkenones <1998JHC1377, 2000EJM797> and 4-nitrophenylacetic acid <1995MI489> (Equation (99)), and the synthesis of β-formylsteroidal enamides under Vilsmeier conditions <1999IJC(B)274> (Equation (100)).



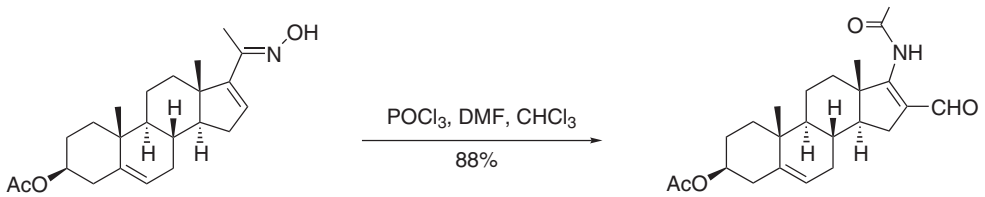
(97)



(98)

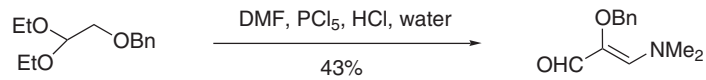


(99)



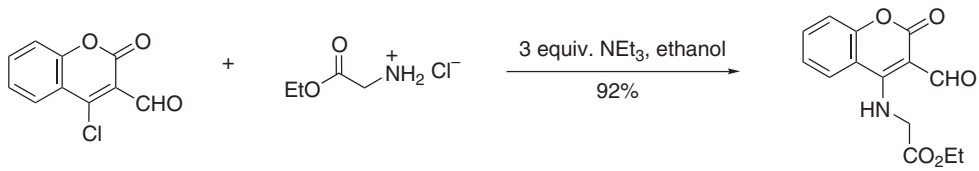
(100)

Similarly, acetals may be formylated with DMF in the presence of PCl_5/HCl <1999TL4073> (Equation (101)), and α,β-unsaturated *N*,*N*-dimethylimines may be formylated with sodium carbonate <2000CHE1206>.

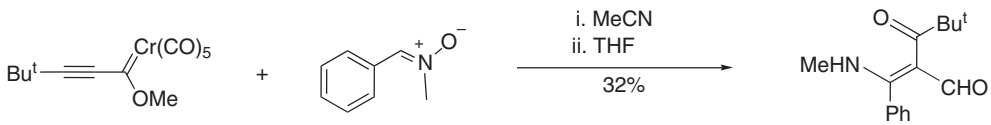


(101)

The synthesis of 2-alkylamino coumarin derivatives may also be achieved by the substitution of their 3-chloro analogs <2001S1941> (Equation (102)). The reaction of α,β-unsaturated Fischer carbene chromium complexes with 1,3-dipolar materials such as nitrones and nitrilimines (Equation (103)) also affords 3-nitrogen-substituted alkenals <2000EJO1773>.

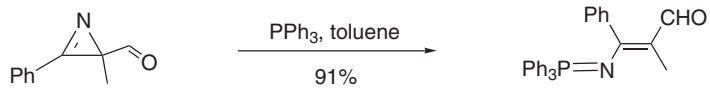


(102)

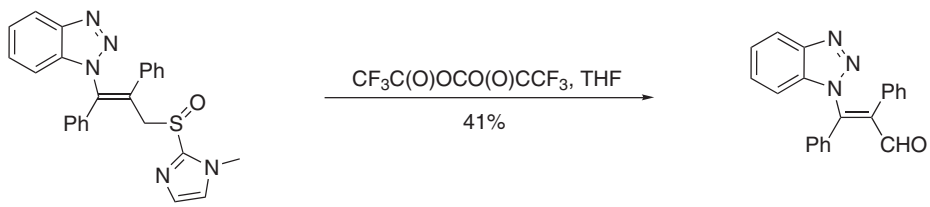


(103)

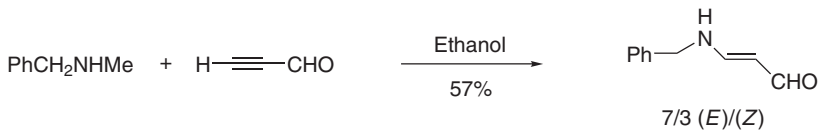
Reactive intermediates such as 2-(phosphoranylideneamino)acryl aldehydes (Equation (104)) may be synthesized by the reaction of 2-formylazirines with triphenylphosphine <1998H2551>. A Pummerer-type reaction (Equation (105)) of γ-benzatriazolyl-substituted allylic sulfoxides with $O(COCF_3)_2$ yields β-benzatriazolyl alkenals <2002EJO493> and the formation of enamino-aldehydes from *t*-propargylamine *N*-oxides in protic solvents by a prototropic rearrangement (Equation (106)) <2001JOC7219> has also been reported.



(104)

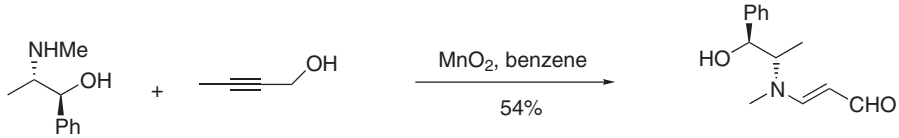


(105)



(106)

The treatment of diformylchloromethane with ammonium hydroxide in propan-2-ol to yield β-amino alkenals has been reported <2000JOC8415>, as has the oxidative addition of ephedrine alkaloids with propargyl alcohols (Equation (107)) in the presence of manganese dioxide <1997MI1946>.



(107)

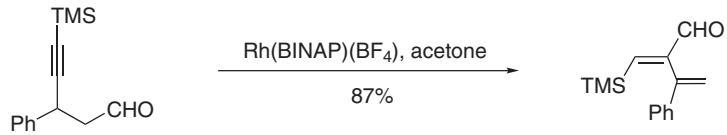
A route to 2-cyano-3-amino alkenals has been reported <1998TL4013> from 3,3-dimethoxy-2-formylpropanenitrile. The synthesis of building blocks for heterocyclic systems such as 2-formylated 1-amino-4-(*p*-tolylsulfinyl)-1,3-butadienes <1999TA3473> and 3-(alk-2-enyl)amino-2-cyanoacrolein derivatives <2000EJO1489> has also been reported in the recent literature.

3.02.1.8 α,β-Alkenic Aldehydes with P-, As-, Sb-, or Bi-based Substituents

In COFGT (1995), no examples of compounds of this type had been reported in the literature, and this remains the case for As-, Sb-, and Bi-substituted alkenals. Phosphorus-substituted α,β-alkenic aldehydes such as 2-diethoxyphosphonyl alkenals <1995S1401> and 4-diethoxyphophonyl-2-methyl-2-butenal <1995TL393> have, however, been reported in the literature, as these are important building blocks in retinoid chemistry.

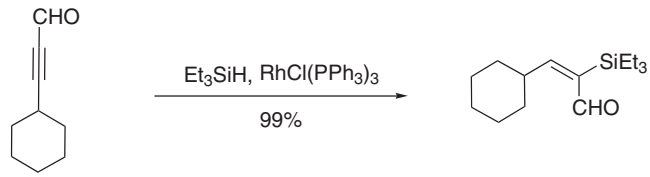
3.02.1.9 α,β-Alkenic Aldehydes with Si-based Substituents

COFGT (1995) <1995COFGT(3)53> outlined four routes to β-silyl-α,β-unsaturated aldehydes, namely the (formal) silylformylation of alkynes in the presence of $Rh_4(CO)_{12}$ catalyst and dimethylphenyl silane, a selective hydroformylation of a silyl alkyne via nickel-catalyzed hydrocyanation followed by DIBAL-H reduction, the treatment of an allylic sulfide (a homoenolate dianion equivalent) with aqueous sodium periodate, and the PCC oxidation of a silyl-substituted allylic alcohol to yield the silyl aldehyde. Of these methods, rhodium-catalyzed silylformylation of acetylenic bonds is commonly found in the literature with catalysts such as $Rh_4(CO)_{12}$ <1997OM4327>, rhodium/mesitylene co-condensate <2001EJO4321>, Rh(acac) $(CO)_2$ <2001OL1303>, [Rh(COD)][BPh_4] <2001CL650>, zwitterionic [Rh(C_7H_8)][BPh_4] <1999JOC9711>, and dirhodium perfluorobutyrate, $Rh_2(OCOC_3F_7)_4$ <1995TL8723>. A related [Rh(BINAP)][BF_4]-catalyzed rearrangement of an alkyne to a 1,3-diene with concomitant migration of a formyl moiety yielded a 3-silyl-substituted dienal <2002CC684> (Equation (108)). A synthesis of a β-silyl-α,β-unsaturated aldehyde has also been reported where, in effect, an oxidative ring-opening reaction occurs and an allylic methylene group is oxidized with SeO_2 to yield the desired product <2000TL225>.



(108)

There are comparatively few examples of α-silylated alkenals, although recent routes have included hydrosilylation of an alkynal in the presence of a $RhCl(PPh_3)_3$ catalyst <2001TL2605> (Equation (109)), Dess–Martin periodinane oxidation of 2-silylated allenic alcohols, and formylation of silyl-substituted alkynes <2002OL2437>.

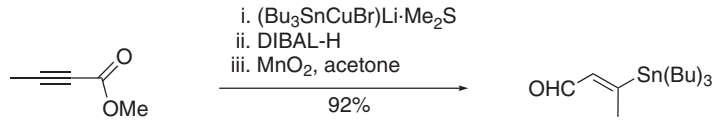


(109)

3.02.1.10 α,β-Alkenic Aldehydes with Metal Substituents

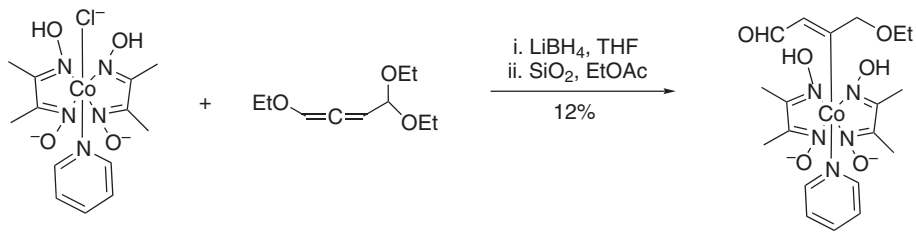
Previously, methods were described whereby alkynyl aldehydes may be hydrostannylated using hexmethyldistannane in the presence of a Pd-catalyst <1995COFGT(3)53> to yield the corresponding β-stannyl enals. Recent approaches to stannylated aldehydes have included the stereoselective addition of tributyltin cuprate to methyl-but-2-ynoate followed by reduction to yield the 3-stannylated alkenal <2001TL1247> (Equation (110)). Similarly, oxidation of 3-stannylated alcohols with manganese dioxide <2000JOC5917> or with Pr_4NRuO_4 <1997JCS(P1)3291> has yielded 3-stannylated alkenals. Diels–Alder cycloaddition of cyclopentadiene and 3-stannylated

alkynals in the presence of chiral tetraarylborate salts of cationic 1,3,2-oxazaborinanes <1997TL5755> and reduction of 3-stannylated alkenic esters also yield the corresponding alkenals <1998T10609>.



(110)

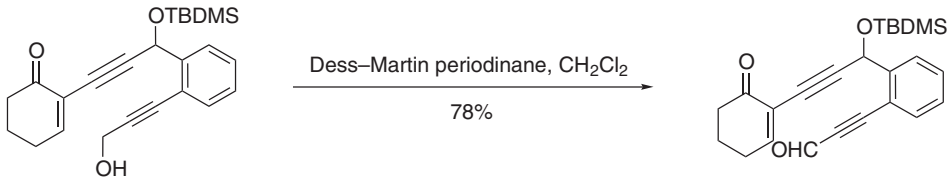
A method was described previously <1995COFGT(3)53> by which pentacarbonyl manganese centers may be added to alkynyl aldehydes to give the β-substituted adduct in low yield. Similarly, cobaloxime [(pyridine) (dimethylglyoxime)$_2$cobalt] complexes react with *o*-substituted allenic and propargyl electrophiles to produce 3-cobaloxime-substituted α,β-unsaturated aldehydes <2000OM2730> (Equation (111)), and dimethyliminium-substituted 3-chloroalkenals react with [(cyclopentadiene) (CO)$_2$Fe] complexes to yield alkenals substituted in the 3-position with iron complexes <1997AG(E)509>.



(111)

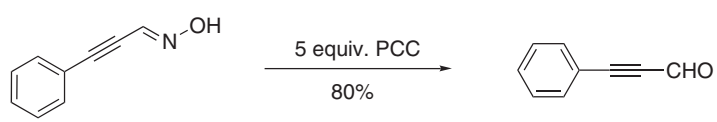
3.02.2 ALDEHYDES BEARING AN α,β-TRIPLE BOND

A number of routes to alkynals were discussed in COFGT (1995) <1995COFGT(3)53>, including the oxidation of propargylic alcohols in much the same way as for allylic alcohols, for example, using MnO_2, chromium trioxide/pyridine or nickel oxides. Such methods are still to be found in the literature; see for example the use of CrO_3 in reference <1995JCR(S)8> and the use of MnO_2 in a combined palladium-catalyzed coupling of an propargylic alcohol with a bromoalkene derivative followed by oxidation <1996TL2433>. The use of a Swern oxidation to yield alkynals has also been reported <2001TA53>. More recent examples of propargylic alcohol oxidations have included the use of reagents such as an oxovanadium complex catalyst with molecular oxygen <2001TL8877>, *N*-*t*-butylbenzenesulfinimidoyl chloride with DBU <2002BCJ223>, $TiCl_4$ with Et_3N <2001SL1421>, and oxidation with Dess–Martin periodinane <2000EJO939, 1998NJC531, 1997TL7353> (Equation (112)). An example of a polymer-supported oxidation of an alkynic alcohol to the corresponding aldehyde was described in reference <2002CL250> where the oxidant was sulfinimidoyl chloride-derivatized polystyrene.



(112)

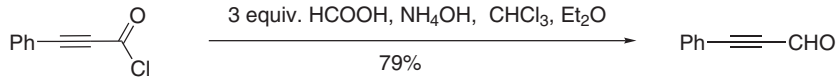
A number of related deprotections starting from acetals and ketals to yield alkynic aldehydes have been reported; see for example the use of reagents such as bismuth triflate <2002JOC1027> or bismuth nitrate <2000JOC8399>, formic acid <2001JOC3146, 1998JOM279>, 85% aqueous phosphoric acid with hydroquinone <1999CPB1115>, and DDQ <1995TL401>. Oxidation of acetals, alcohols, and oximes with PCC has also been reported <2001S2273> (Equation (113)).



(113)

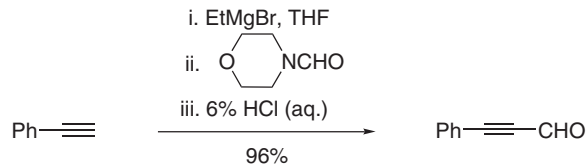
Similarly the deprotection of a siloxy-derivatized alkyne with Bu_4NF followed by oxidation with $BaMnO_4$ yields the alkynic aldehyde <1998AG(E)320>. A route to propynal by oxidative deamination of propargylamine using bisdiphenylphosphorinyl peroxide was also discussed previously <1995COFGT(3)53>, but no recent examples have been reported.

By way of a contrast, the reduction of alkynic acid chlorides to alkynals has been reported <1998TL8153> using formic acid as a hydride donor in the presence of NH_4OH (Equation (114)).



(114)

The synthesis of alkynals by formylation of acetylide anions with DMF or formate esters and of terminal alkynes with *o*-esters in the presence of Lewis acid catalyst was also described previously, and such methods are still to be found in the literature; see for example formylations of terminal alkynes with DMF <2001MI4378, 2001JOC3146, 1998JCS(P1)1607, 1998TL6427> and with *N*-formyl morpholine <2000OPRD46> (Equation (115)).



(115)

Eliminations of HBr from dibromoaldehydes and of triphenylphosphine oxide from the product of formyl phosphorane with acid chlorides to yield alkynals were reported previously <1995COFGT(3)53>. Whilst no new examples of these eliminations have been reported, a recent review has discussed the utility of phosphorus elimination in alkyne synthesis <2000S185>.

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Biographical sketch

Philip R. Mackie was born in Aberdeen, studied at the University of Glasgow where he obtained a B.Sc. in 1995 and a Ph.D. in supramolecular chemistry in 1998 under the direction of Drs. Andrew Benniston and Robert Peacock. From 1998 until 2000 he worked as a Research Fellow at Trinity College, University of Dublin under the direction of Dr. Paul Kruger and Professor John Kelly as part of an EU project focusing on coordination complexes with novel magnetic and photophysical properties. In 2001 he moved to the Electrophotography and Displays business of Avecia Ltd., based in Manchester, where he is currently employed as a Research Chemist within the Organic Semiconductors team.

Clive E. Foster was born in Derby in 1971 and studied from 1990 to 1996 at Durham University, England. He obtained his Ph.D. under the supervision of Professor David Parker. Following a year as a Royal Society ESEP Research Fellow with Professor Manfred T. Reetz at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany, he took up his current position at Avecia. He currently works in the Ink Jet Printing Materials Research Group and has interests in conjugated molecules for applications as colorants and as advanced materials.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 59–97

3.03
Aldehydes: Aryl and Heteroaryl Aldehydes

F. ALDABBAGH
National University of Ireland, Galway, Republic of Ireland

3.03.1 GENERAL METHODS FOR THE SYNTHESIS OF ARYL ALDEHYDES

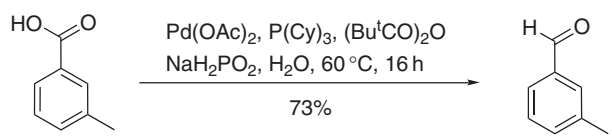
General methods are divided into the same main categories used by Hollingworth <1995COFGT(3)81>. A brief introduction is given to each method; however, the focus is on new methods and techniques introduced since 1995.

3.03.1.1 Reduction of Aromatic Carboxylic Acids and Their Derivatives

3.03.1.1.1 Reduction of benzoic acids

The reduction of benzoic acids into the corresponding aldehydes is traditionally considered to be problematic. Many organic chemists still rely on the lithium aluminium hydride (LAH) or borane reduction of the benzoic acid to the benzylic alcohol with subsequent re-oxidation to the aldehyde. Hollingworth <1995COFGT(3)81> reviewed derivatives of LAH, borane, and silanes used to accomplish reduction to the aromatic aldehyde, but generally reductions of aromatic carboxylic acids are slower than their aliphatic counterparts <1991COS(8)259, 1991COS(8)283>.

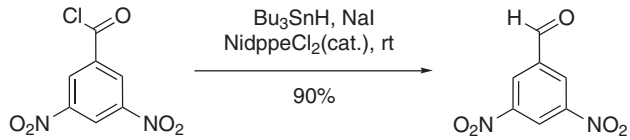
Newly introduced mild direct methods generally involve protecting the acid *in situ* prior to reduction to the aldehyde. The carboxylic acid has been converted *in situ* to the TMS ester, which was subsequently reduced by DIBAL-H in a one-pot reaction <1998TL909>. Using the latter procedure, aromatic aldehydes were isolated in 60–70% yield along with traces of the respective alcohols. Yamamoto and co-workers carried out the hydrogenation of carboxylic acids to aldehydes by using pivalic anhydride to convert the acid *in situ* into the mixed anhydride, and reducing with high hydrogen gas pressure in the presence of a Pd(0) catalyst <2001BCJ1803, 2002MI(15)90>. A more convenient method was later developed by Gooßen and Ghosh, in which a catalyst generated *in situ* from palladium acetate and tricyclohexylphosphine efficiently catalyzed the reduction of carboxylic acids to aldehydes with sodium hydrogenphosphite in the presence of pivalic anhydride, as represented by the example in Equation (1) <2002CC836>.



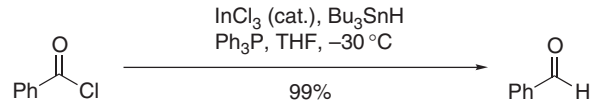
(1)

3.03.1.1.2 Reduction of benzoyl halides

This transformation is traditionally carried out using hydrogenolysis with Pd-$BaSO_4$: the so-called Rosenmund reaction. Many reducing hydrides have been tested <1991COS(8)259>, but most of them are too reactive to stop the reduction at the aldehyde stage. The reagent introduced by H. C. Brown in the 1950s, lithium tri-*t*-butoxyaluminium hydride, is probably still the most convenient reagent <1995COFGT(3)81>. Recently, benzoyl chlorides have been converted into aldehydes in the presence of stoichiometric amounts of tributyltin hydride (Bu_3SnH), sodium iodide, and a catalytic amount of $NidppeCl_2$ at rt, as represented by the example in Equation (2) <1997TL8093>. Nickel hydride (Ar-CO-NiL_2-H) can be considered as an intermediate in this reaction. Similarly, indium hydride ($HInCl_2$) generated from the reaction of tributyltin hydride with indium trichloride in the presence of coordinating phosphine was shown to efficiently reduce benzoyl chlorides to the corresponding aldehydes, as represented by the example in Equation (3) <2000TL113>.

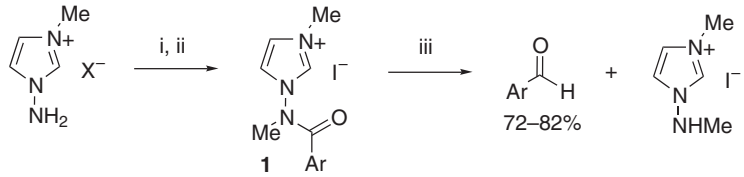


(2)



(3)

Alternatively, the acyl halide may be converted into an acyl heterocycle, prior to reduction to the aldehyde. The reaction of acyl chlorides with 1-amino-3-methylimidazolium salts followed by *N*-methylation of the resulting *N*-amides afforded 1-(acylmethylamino)-3-methylimidazolium salts **1**, which were reduced by DIBAL-H to the aldehydes (Scheme 1). Aromatic aldehydes containing methyl, chloro, and nitro substituents were prepared in yields of 72–82% <1995TL455>.

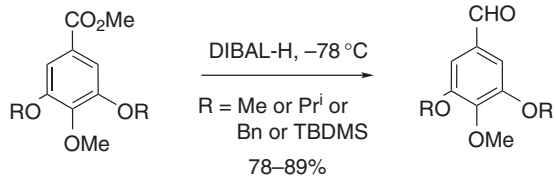


i. ArCOCl, K_2CO_3; ii. MeI, acetone; iii. DIBAL-H

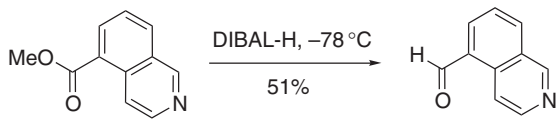
Scheme 1

3.03.1.1.3 Reduction of aromatic esters

DIBAL-H is the best known reducing agent for conversion of aromatic esters into aldehydes. A recent example is shown in Equation (4); however, careful monitoring of the reaction mixture was necessary in order to avoid over-reduction, since aldehyde formation was complete in 15–20 min <1998JOC1981>. Other examples use longer reaction times, e.g., 4 h was required for the DIBAL-H reduction shown in Equation (5) <2000JMC3878>. Many other reducing agents have been used, but none have succeeded in superseding DIBAL-H <1995COFGT(3)81>.

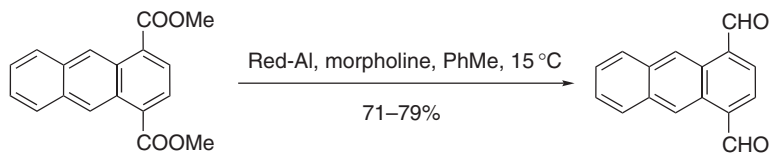


(4)



(5)

Reduction of anthracene-1,4-dicarboxylic acid methyl ester to the dialdehyde was reported using Red-Al {$NaAlH_2(OEtOMe)_2$} deactivated with morpholine, as shown in Equation (6) <1998BMCL121>. Direct reductions of this type are improvements on two-step procedures involving reduction of the carboxylic acid to the alcohol followed by oxidation to the aldehyde.



(6)

3.03.1.1.4 Reduction of anhydrides

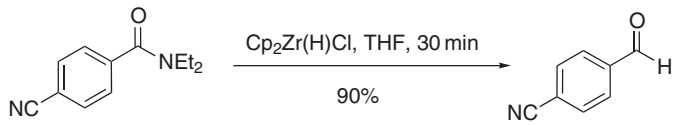
Recent research interest has focused on converting carboxylic acids directly into aldehydes usually via the mixed anhydride intermediate (see Section 3.03.1.1.1), rather than the direct reduction of the anhydride. However, several older examples exist, as reviewed by Hollingworth <1995COFGT(3)81>.

3.03.1.1.5 Reduction of thiol esters

No further synthetically useful methods have been introduced since the review by Hollingworth <1995COFGT(3)81>.

3.03.1.1.6 Reduction of amides

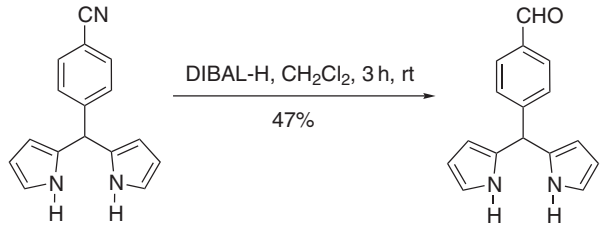
Traditionally aluminum hydrides are used to facilitate this transformation <1995COFGT(3)81>. However, there are alternatives, the reduction of a variety of amides to aldehydes has been reported using $Cp_2Zr(H)Cl$ <2000JA11995>. The cyano functionality, which is known to be reduced after extended time in the presence of $Cp_2Zr(H)Cl$, remained intact (Equation (7)), presumably due to the kinetically slower rate of reduction of the cyano as compared to the amide <1991COS(8)667>.



(7)

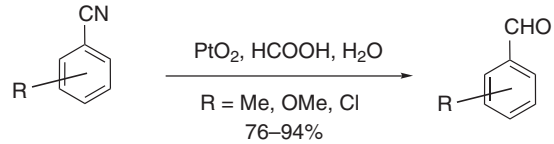
3.03.1.1.7 Reduction of aromatic nitriles

DIBAL-H is commonly used to reduce nitriles to aldehydes, as represented by the recent example in Equation (8) <2000JOC7323> (also see Equation (83), Section 3.03.4.2.1).



(8)

A newly introduced method is the reduction of aromatic nitriles using platinum(IV) oxide in aqueous formic acid giving the aldehydes in 76–94% yield (Equation (9)) <2002TL1395>. The latter procedure was less effective in the reduction of aliphatic nitriles, which may be useful in making this selective.



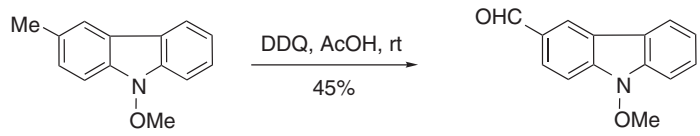
(9)

3.03.1.2 Oxidation of Aromatic Methyl Groups and Benzyl Alcohols, Halides, Amines, Ethers, and Carbamates

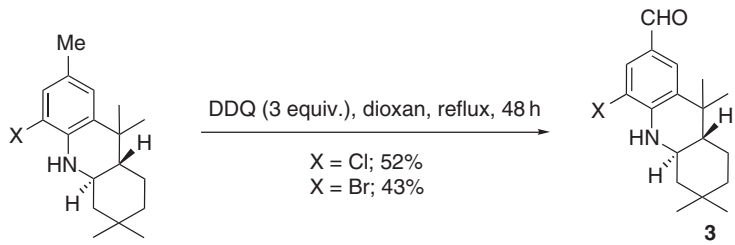
Oxidations are classified as in the review by Hollingworth <1995COFGT(3)81>, apart from the addition of Section 3.03.1.2.6 on the oxidation of ethers and carbamates into aromatic aldehydes.

3.03.1.2.1 Oxidation of toluenes to benzaldehydes

Hollingworth reviewed the oxidizing reagents used for this transformation <1995COFGT(3)81>, the most commonly used being DDQ. Recent examples are shown in Equations (10) <2003TL7071> and (11) <1998JPR(340)341> for the respective formation of 9-methoxycarbazole-3-carbaldehyde **2** and acridine-carbaldehyde derivative **3**. CAN is recommended as a mild oxidant, because the oxidation normally stops at the monoaldehyde stage, as highlighted by the oxidation of mesitylene to 3,5-dimethylbenzaldehyde in 100% yield <1992CRV29, 1994SC(24)2011> (also see Equation (86), Section 3.03.4.3.1).

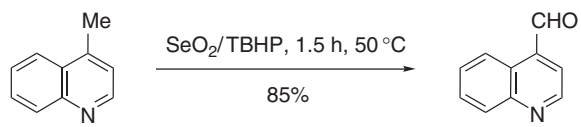


2 (10)



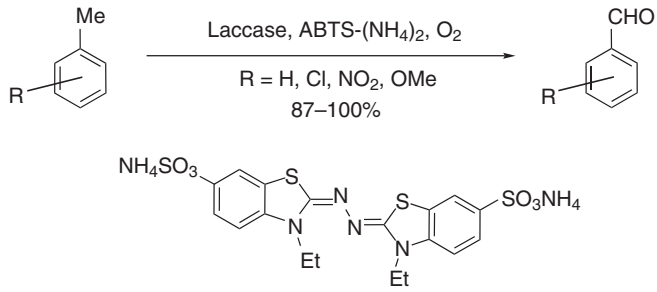
3 (11)

Another traditionally used oxidant is selenium dioxide (see Equation (95), Section 3.03.4.3.2 and Equation (97), Section 3.03.4.3.3), and recently it has been shown that the oxidation can be improved upon by the formation of a complex between selenium dioxide and TBHP prior to addition to the substrate. This allowed the oxidation of activated methyl groups of *N*-heterocyclic compounds to occur under milder conditions without the formation of the over-oxidized carboxylic acid, as illustrated in Equation (12) for the oxidation of lepidine <2003H953>.

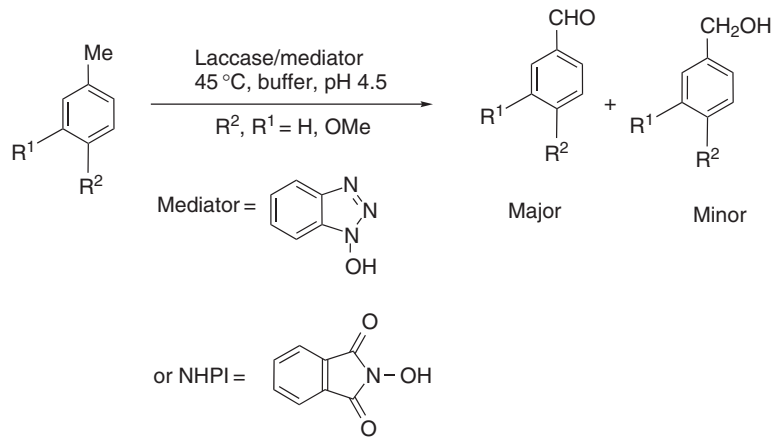


(12)

However, the oxidation of toluenes to aldehydes in the presence of other oxidizable groups is most often troublesome. Perhaps the most selective reagent introduced till now is the laccase enzyme (benzenediol:oxygen oxidoreductase; EC 1.10.3.10). Laccase acts as a catalyst to accomplish four-electron transfer from the substrate to molecular oxygen, which is reduced to water. Since laccase alone shows no reactivity towards nonphenolic substrates, it is commonly applied together with a cosubstrate or "mediator." Chen and co-workers converted a number of toluenes into the corresponding aldehydes in about 90% yield using 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid, ABTS-$(NH_4)_2$ as the mediator (Equation (13)). The mediator acts as a single-electron donor and activator of the enzyme, but does not function as an oxidant of the substrate. The reaction proceeded under physiological conditions at atmospheric pressure and rt <1995JOC4320>. Laccase-mediated oxidations in the presence of catalytic amounts of *N*-hydroxy compounds were also reported, as shown in Equation (14). The benzyl alcohols are intermediates in the laccase oxidation, and only traces of the benzoic acids were formed <1998TL5955>.

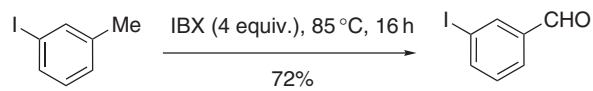


(13)

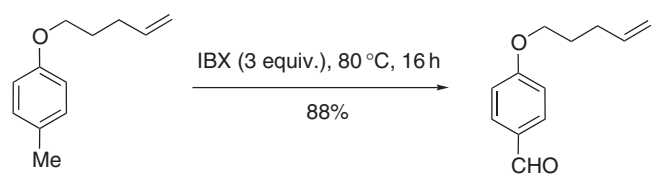


(14)

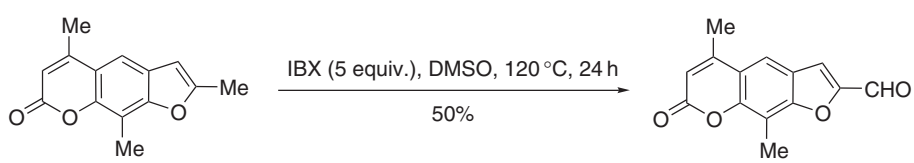
Nicolaou and co-workers used *ortho*-iodoxybenzoic acid (IBX) to oxidize various benzylic C-centers to benzylic carbonyls, particularly toluenes into aldehydes, as shown in Equations (15) and (16) <2002JA2245>. Mechanistic investigations by this group demonstrated that these reactions were initiated by a single electron transfer (SET) from the substrate to IBX to form a radical cation, which reacted further to give the final products. Accordingly methyl groups adjacent to electron-donating substituents (with higher oxidation potentials) could be oxidized faster than those adjacant to electron- withdrawing substituents (with lower oxidation potentials) or those with no free *ortho* positions, and this was used to achieve selective mono-aldehyde formation, as demonstrated by the oxidation in Equation (17).



(15)



(16)

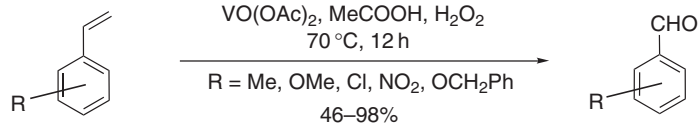


(17)

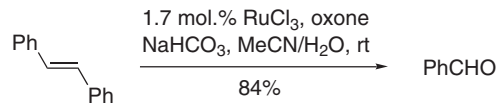
3.03.1.2.2 Oxidation of aryl ethylenes

Hollingworth gave examples of $OsO_4/NaIO_4$ as the oxidizing system used to facilitate this transformation <1995COFGT(3)81>. New oxidizing systems introduced include the use of

peroxo vanadium complexes with hydrogen peroxide, which were used by Choudary and Reddy to transform various substituted styrenes to the respective aldehydes, as represented by the examples in Equation (18) <1995JMOC-A(103)L1>. Ruthenium-catalyzed cleavage of olefins to aldehydes has also been reported, as shown in Equation (19). While RuO_2 performed very well in the cleavage of *trans*-stilbene giving 89% yield of benzaldehyde at room temperature, $RuCl_3$ was the preferred Ru source on the basis of cost consideration. Only 1.7 mol. % of $RuCl_3$ was required to efficiently breakdown *trans*-stilbene to benzaldehyde in 84% yield <2001JOC4814>.

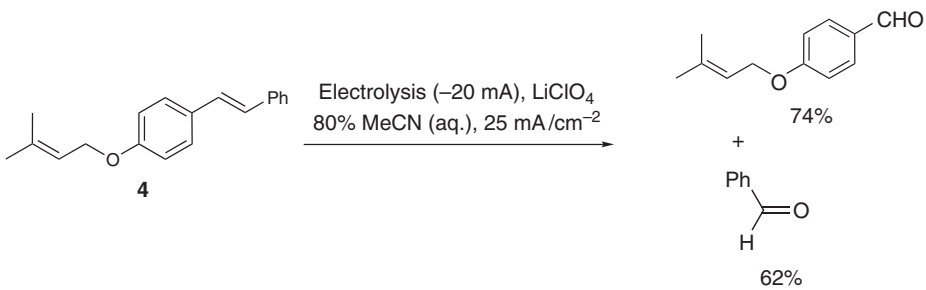


(18)



(19)

A facile electrochemical cleavage of styryl olefins was described by Maki and co-workers to form aromatic aldehydes and ketones (see also Chapter 3.06) <1997SL1385>. Under these conditions *trans*-stilbene was oxidized to benzaldehyde in 71% yield, and nonconjugated double bonds, for example in compound **4**, were unaffected, as shown in Equation (20).



(20)

Enzymatic oxidative cleavage of alkenes are rare, although laccase-hydroxybenzotriazole oxidation of cinnamyl alcohol to cinnamaldehyde and benzaldehyde in 40% and 43% yield, respectively, was reported <2000JMOC-B(10)435>. The latter oxidizing system is more effective in the oxidation of toluenes to the corresponding benzaldehydes (see Section 3.03.1.2.1).

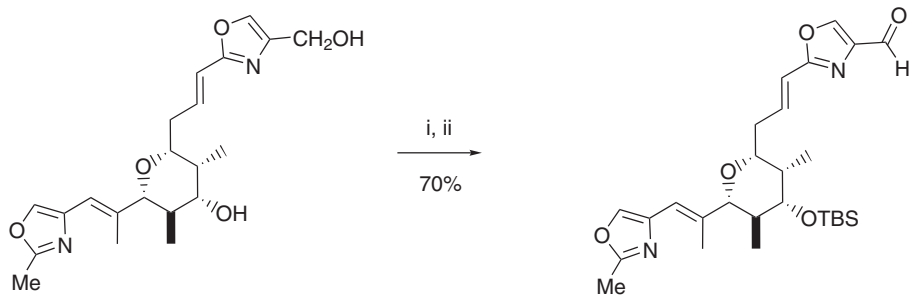
3.03.1.2.3 Oxidation of benzylic alcohols

The oxidation of activated benzylic alcohols to aldehydes is a facile process. Many of the reagents reviewed in Chapter 3.06, which oxidize secondary benzylic alcohols to ketones, can also be used to convert primary benzylic alcohols into aldehydes. The reagent should be mild, and only convert the alcohol into the aldehyde, and not over-oxidize to the carboxylic acid. Some reagents are selective, i.e., they convert the benzylic alcohol into aldehyde in the presence of other oxidizable functional groups including other alcohols. The following section briefly reviews newly introduced mild reagents, and also discusses some recent examples of selective oxidation.

The TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxyl)/[bis(acetoxy)iodo]benzene (BAIB) system is one such mild oxidizing system, which performed the impressive selective oxidation shown in Scheme 2 <2003TL3749>.

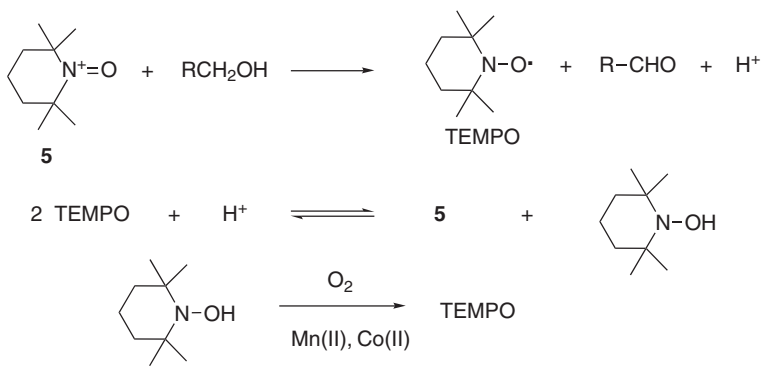
Catalytic TEMPO-based systems have received enormous research attention as selective oxidizing systems for the conversion of alcohols into aldehydes and ketones <1996S1153>. Recent developments include the introduction of catalytic polymer-supported TEMPO reagents <2001JOC8154> and TEMPO–CuCl-catalyzed aerobic oxidations of primary and secondary alcohols into aldehydes and ketones using a recyclable ionic liquid reaction medium <2002OL1507>. TEMPO has also been used to mediate rt oxidations of various benzylic alcohols into aldehydes by oxygen in the presence of laccase enzyme <2001TL7551>. Other developments include: Minisci and co-workers reported a room temperature oxidation, where a number of alcohols were converted into aldehydes and ketones using oxygen in the presence of

catalytic amounts of Mn(II)–Co(II) or Mn(II)–Cu(II) nitrates in combination with TEMPO in an acetic acid medium <2001TL6651>. In such systems, TEMPO has a dual role forming the oxoammonium salt oxidant **5** and inhibiting any further oxidation of the aldehydes and ketones, which would otherwise occur in the absence of TEMPO. Scheme 3 shows the general TEMPO-mediated oxidation cycle.



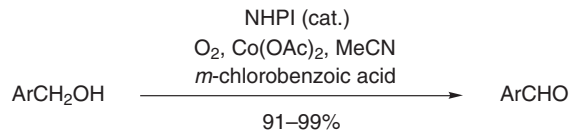
i. TEMPO (cat.), BAIB, CH_2Cl_2, 20 °C, 30 min
ii. TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C

Scheme 2



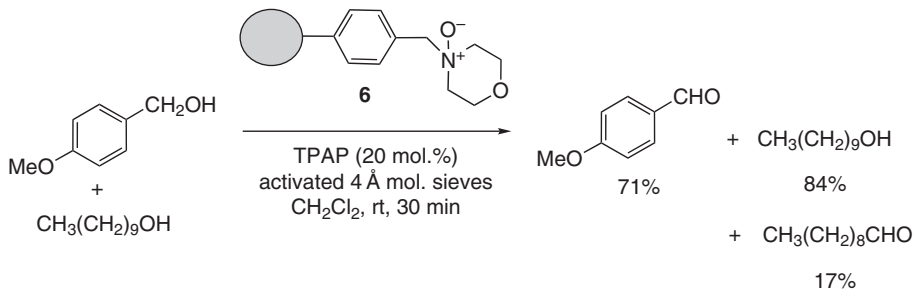
Scheme 3

The oxidation can be limited to the conversion of benzylic alcohols into aldehydes by replacing TEMPO by *N*-hydroxyphthalimide (NHPI) combined with cobalt(II) salts (Equation (21)) <2002CC688>. The NHPI catalyst can be obtained from the reaction of phthalic anhydride with NH_2OH.



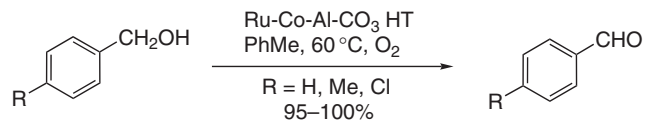
(21)

The mild oxidant, TPAP (tetrapropylammonium perruthenate, $(CH_3CH_2CH_2)_4NRuO_4$)) can be used in catalytic quantities, in the presence of stoichiometric quantities of a co-oxidant, usually NMO. Aerobic oxidations (TPAP-O_2) have also been reported <1997JA12661> with a rt oxidation by Lenz and Ley converting benzyl alcohol into benzaldehyde in less than 40 min in 95% yield <1997JCS(P1)3291>. The polymer-supported perruthenate (PSP)-O_2 system also proved effective as a mild oxidizing system <1998S977, 1999JCS(P1)1251>. A more recent modification to this technique was introduced by Kerr and co-workers using polymer-supported NMO **6**, which was demonstrated to be a mild and recyclable co-oxidant for TPAP oxidations <2001SL1257>. Equation (22) shows the oxidation of the highly-activated alcohol, *para*-methoxybenzyl alcohol, carried out in the presence of one equiv. of 1-decanol giving mostly *para*-methoxybenzaldehyde with most of the 1-decanol recovered.



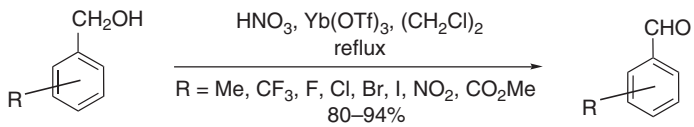
(22)

Ruthenium hydrotalcite catalysts have also received much recent research attention, as alternative oxidants. Hydrotalcites (HT) are layered mineral materials consisting of cationic Brucite layers separated by layers of anionic species. Various metals can be introduced into the Brucite layer via isomorphic substitution of Mg^{2+} and Al^{3+} to become active sites for catalysts. The catalyst introduced by Kaneda and co-workers contained Ru and Co cations and was shown to be particularly effective for the mild oxidation of benzylic and allylic alcohols in the presence of molecular oxygen <1999CC265>. Examples of the latter Ru-Co-Al-CO_3 HT catalyst oxidations are given in Equation (23). Ru-Cu-Al HT catalyst was shown to be more effective with tetrabutylammoium periodate (TBAP) as a co-oxidant, but could oxidize both aliphatic and aromatic alcohols <2001SL869>. Pd(II)-hydrotalcite was also reported to convert a number of benzylic alcohols into aldehydes in high yield under very mild ambient conditions <2001JOC6620>.



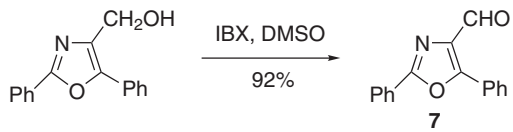
(23)

Ytterbium(III) triflate (10 mol.%) was found to catalyze the selective oxidation of a range of simple benzylic alcohols into benzaldehydes in excellent yield using stoichiometric quantities of 69% nitric oxide with water as the oxidant and oxides of nitrogen being the only by-products (Equation (24)) <1998SL1489>.



(24)

Periodinanes (iodoxo, iodine(V) reagents) are widely employed in the oxidation of sensitive and complex alcohols, e.g., IBX <2002JA2245> or its acetylated product, the Dess–Martin reagent. A recent example of an IBX-oxidation is shown in Equation (25) in which oxazole aldehyde **7** was prepared on multi-gram scale <2000TL2253>. A water-soluble derivative of IBX **8** was recently shown to selectively oxidize benzylic alcohols into the aldehydes and ketones, as represented by the example in Equation (26) <2002TL569>. Polymer-supported IBX reagents have also been reported, and shown to convert several benzylic alcohols into aldehydes at rt <2001AG(E)4393, 2001AG(E)4395>.



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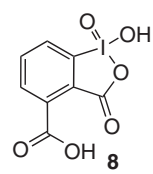
(25)



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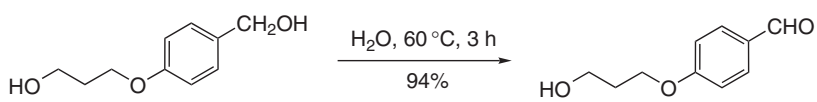
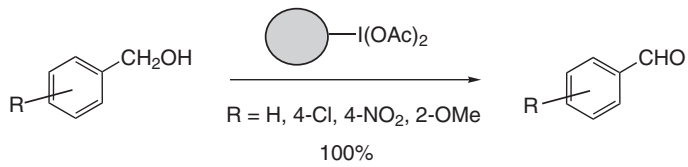


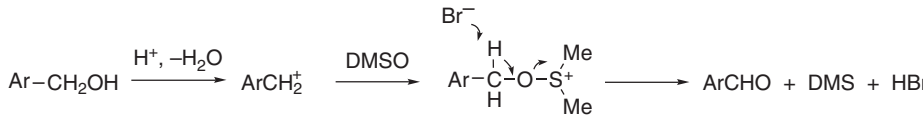
(26)

A polymer-supported hypervalent iodine(III) reagent was reported by Ley and co-workers, and used to convert a variety of substituted benzylic alcohols into aldehydes in quantitative yield, as shown in Equation (27) <1999JCS(P1)669>.



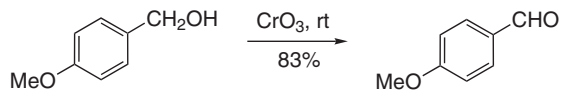
(27)

A promising cheap and stable oxidizing reagent is benzyltriphenylphosphonium periodate ($Ph_3P^+CH_2Ph\ IO_4^-$), which can be readily prepared by the reaction of an aqueous solution of benzyltriphenylphosphonium chloride ($Ph_3P^+CH_2Ph\ Cl^-$) with sodium periodate ($NaIO_4$). This oxidizing agent was shown to convert a variety of benzylic alcohols into aldehydes in excellent yield in the presence of $AlCl_3$ catalyst in refluxing acetonitrile, and was shown to be less reactive towards aliphatic alcohols <2001SL1735>. Another new oxidizing system uses catalytic HBr in DMSO. The mechanism is given in Equation (28) with electron-donating groups such as OH and OR on the aromatic moiety providing higher yields of aromatic aldehydes <2002SL2041>.



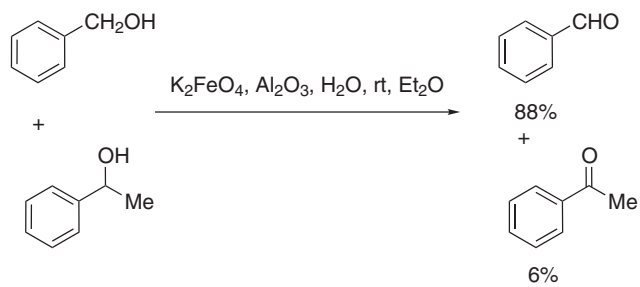
(28)

The traditional oxidant chromium trioxide has been reported to oxidize benzylic alcohols to aldehydes at rt in 3–4 h in the absence of a solvent. This is one of many reported solutions to over-oxidation problems associated with this oxidant. Here the commercial oxidant (1.5 equiv.) is simply added to the substrate, and the mixture stirred until TLC indicated a complete transformation, as represented by Equation (29) <2002TL6095>.



(29)

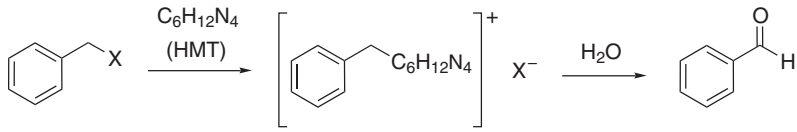
Potassium ferrate with wet alumina was shown to oxidize benzyl alcohol to benzaldehyde at room temperature in the presence of *s*-phenylethyl alcohol, with almost exclusive oxidation of the former to the aldehyde observed, as demonstrated by Equation (30) <2000T9365>.



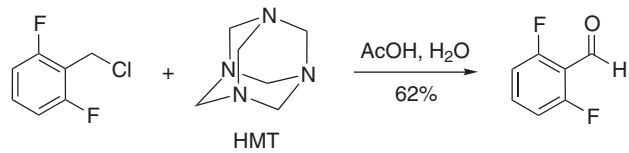
(30)

3.03.1.2.4 Oxidation of benzyl halides

The Sommelet reaction uses hexamethylenetetramine (HMT) to convert benzylic halides into aldehydes, as outlined in Scheme 4 <B-2001MI001>. The reaction requires mild acidic conditions, and halo, nitro, alkyl, alkoxy, and ester groups are unaffected. *Ortho*-substituents usually give lower yields, and 2,6-disubstituted benzyl halides usually fail to react. A recent exception was reported by Malykhin and Shteingarts, who used the reaction to prepare 2,6-difluorobenzaldehyde in 62% yield, as shown in Equation (31) <1998JFC(91)19>. A further example is shown in Equation (102) (Section 3.03.4.4).



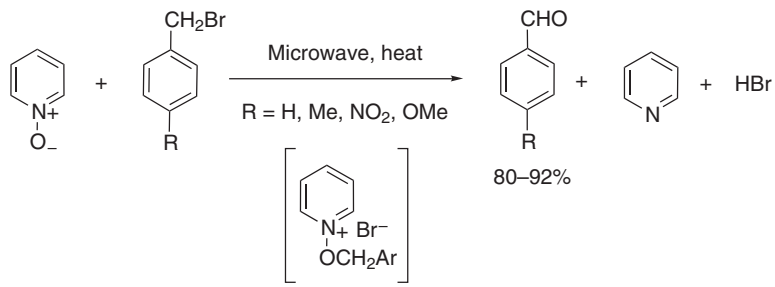
Scheme 4



(31)

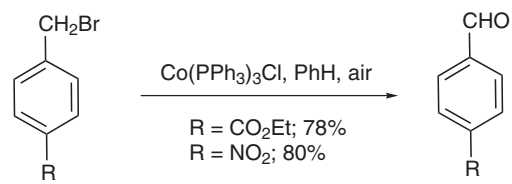
Other traditional methods include the Kornblum reaction, which involves the refluxing of a silver salt and sodium carbonate in DMSO solution of the benzyl halide, which facilitates a direct conversion to the aldehyde. Other oxidants operating under similar conditions have also been reported <1995COFGT(3)81>.

More recent methods include the formation of a variety of aromatic aldehydes in high yields via the reaction of pyridine *N*-oxide with benzylic halides under microwave irradiation conditions, as shown in Equation (32) <1996TL7725>.



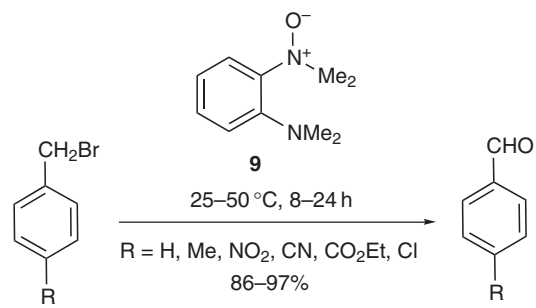
(32)

Goswami and Mahapatra reported a Co(I)-mediated oxidation of benzyl bromides to aldehydes, which probably proceeds via the trapping of benzylic radical intermediates by molecular oxygen (Equation (33)) <1998TL1981>.



(33)

Chandrasekhar and Sridhar used 2-dimethylamino-*N*,*N*-dimethylaniline-*N*-oxide **9** to facilitate a very mild oxidation of benzyl bromides to aldehydes in good yields, as shown in Equation (34) <2000TL5423>. In this reaction, reagent **9** had a dual role, acting as an *O*-centered nucleophile to displace the bromide, and as a base in the final step to form the aldehyde.

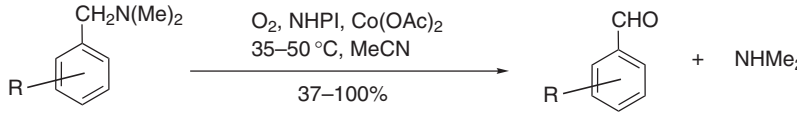


(34)

Chromate-based oxidizing agents can also facilitate the transformation of benzylic bromides to aldehydes (Equation (77), Section 3.03.3), and polymer-bound chromate oxidizing agents have also been reported to selectively convert benzylchlorides into benzaldehydes <1997MI187>.

3.03.1.2.5 Oxidation of benzylamines

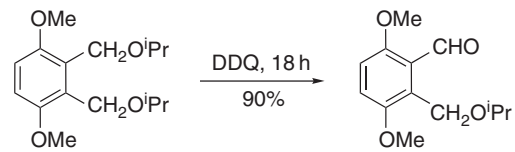
The Sommelet reaction conditions can be used for this transformation (see Section 3.03.1.2.4). New methods include the efficient oxidation of various benzyldimethylamines to aromatic aldehydes with oxygen catalysed by *N*-hydroxyamides (e.g., (NHPI)) and Co(II), as shown in Equation (35) <2002TL3605>. A similar redox radical chain reaction was effective with benzyl alcohols (see Section 3.03.1.2.3).



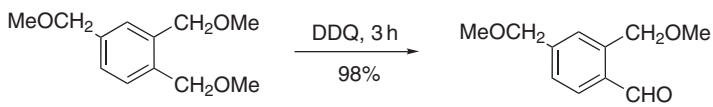
(35)

3.03.1.2.6 Oxidation of benzyl ethers and benzyl carbamates

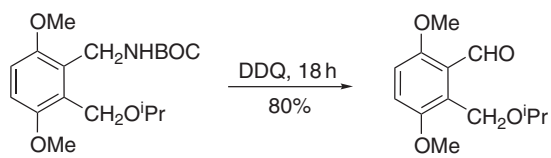
The oxidation of benzyl ethers to aromatic aldehydes is typically accomplished using hydride-transfer agents such as trityl tetrafluoroborate and DDQ. It is well documented that the reaction involves the hydride transfer from an electron-rich system to form an electron-deficient charge-transfer complex. Wang and co-workers reported remarkable selectivity in DDQ oxidations of bis-benzyl ethers to the mono-aldehydes under mild conditions, represented by the examples in Equations (36) and (37) <1997JOC6598>. The authors achieved this selectivity by taking advantage of the inertness of the electron-deficient aldehyde product, and the selectivity was usually not lost by using 2 equiv. of DDQ. The method was also extended to the selective oxidation of benzyl carbamate moiety in the presence of aromatic benzyl ethers, as shown in Equation (38).



(36)



(37)



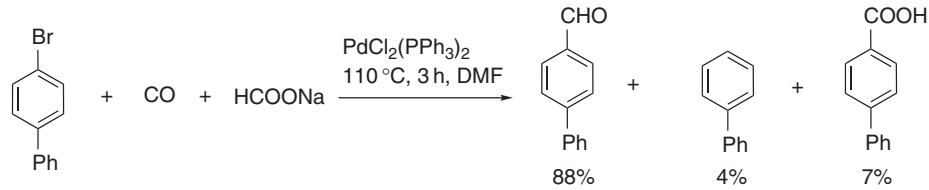
(38)

3.03.1.3 Synthesis of Benzaldehydes from Aryl Organometallic Reagents

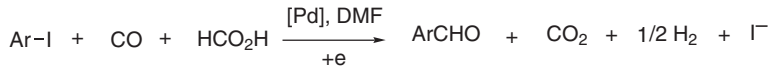
3.03.1.3.1 Aryl palladium reagents

Stille first reported the palladium-catalyzed synthesis of benzaldehydes from aryliodides, carbon monoxide, and tributylstannane <1995COFGT(3)81>. Okano and co-workers reported a palladium-catalyzed formylation of aryl bromides or iodides with sodium formate under a CO atmosphere (Equation (39)) <1994BCJ2329>. A modification to the latter procedure was recently reported using an alternative catalyst, silica-supported poly-γ-(*p*-diphenylphosphinophenyl) propylsiloxane palladium complex ("Si"-P-Pd). The formylation was carried out by stirring a suspension of iodo or bromobenzene, powdered sodium formate and 2 mol.% "Si"-P-Pd in DMF at

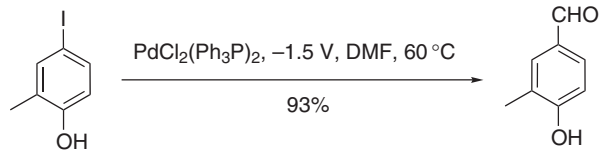
90–110 °C for 8–15 h under a CO atmosphere resulting in 45–80% yields of methyl-, methoxy; and chloro-substituted benzaldehydes <2002SC(32)923>. A further modification to the Okano and co-workers procedure was reported using a palladium-catalyzed reductive electrocarbonylation of aryl iodides in the presence of formic acid under a CO atmosphere to give aromatic aldehydes in good-to-high yields, as represented by Equation (40), and the example in Equation (41) <1999EJO1471>.



(39)



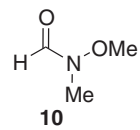
(40)



(41)

3.03.1.3.2 Aryllithium and aryl Grignard reagents

This is one of the most popular methods of making benzaldehydes involving halogen–metal exchange, from aryl halides or deprotonation of acidic hydrogens or hydrogens activated by *ortho*-directing groups, with subsequent quenching of the carbanion by an electrophilic formylating reagent. The most common formylating reagent is DMF; however *N*-methoxy-*N*-methylformamide **10** (the formyl derivative of the Weinreb carboxylic acid amide) was reported to be an effective alternative <1999TL7889>. Lithium bases in combination with DMF are the most popular, although the older method using Grignard reagent to facilitate halogen–metal exchange followed by quenching with DMF was recently used to prepare 5-formyl derivatives of benzofuran and benzothiophene, as shown in Equations (42) and (43) <1998CPB22>. Several recent reports have also used hindered magnesium ate complexes (Equation (93), Section 3.03.4.3.2) <2003TL2033> or amide bases (Equation (101), Section 3.03.4.4) <1996JCS(P1)2331, 2001JCS(P1)442>, which tend to be more selective, and allow hydrogen/halogen–metal exchanges to occur under milder conditions than the most popular organometallic, *n*-BuLi.



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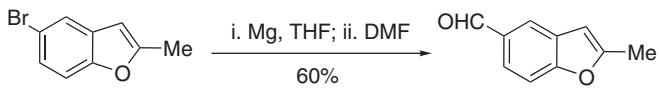
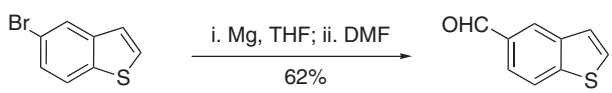


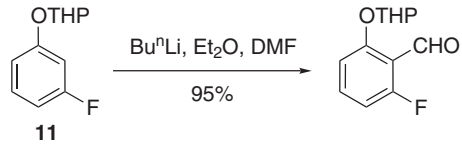
(42)



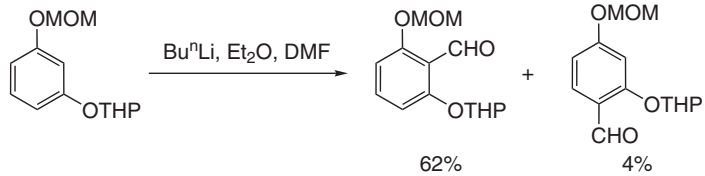
(43)

The factors which control the regioselectivity and efficiency of lithiation of aromatic substrates have been reviewed <1990CRV879>. Numerous functional groups are known to promote *ortho*-lithiation of 1,3-di-OMe or 1,3-di-OTHP benzenes giving selective metallation at the common *ortho*-site <1982JOC2101>. More recently, lithiation of compound **11** was shown to occur between the two *ortho*-directing groups in high selectivity (Equation (44)). This methodology

was extended to form a general synthesis of 2-hydroxy-6-alkoxy substituted benzaldehydes, with the critical step being the highly regioselective *ortho*-2-lithiation in 1,3-disubstiuted benzenes, as shown in Equation (45). Selective hydrolysis of the THP group in the presence of the MOM protecting group makes this procedure attractive for functionalization of polysubstituted aromatic compounds <1997JCS(P1)2925>.

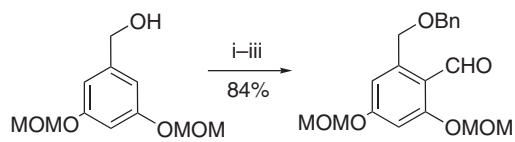


(44)



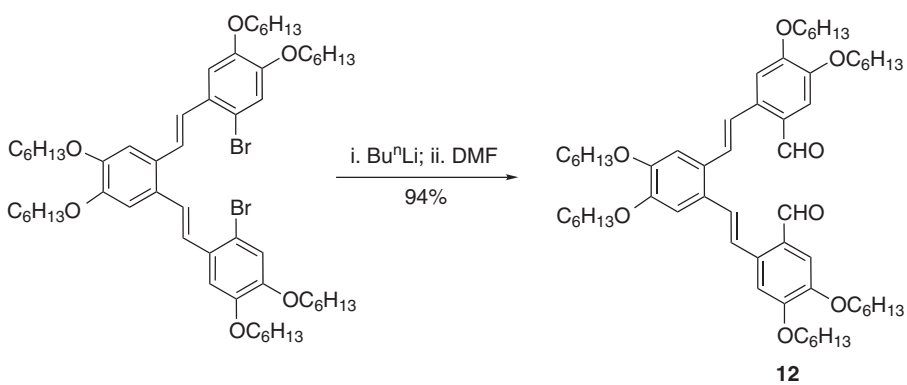
(45)

Alternatively selective formylation can be achieved by regioselective bromination followed by bromine–lithium exchange, as shown in Scheme 5 <2002T1289>. A further effective bromine–lithium exchange followed by quenching with DMF is given in Equation (46), which produced dialdehyde **12**, a precursor for McMurry cyclization <2000TL1535>. The preparation of aromatic dialdehydes by aromatic lithiation, and quenching with DMF was recently extensively studied by Kuhnert and co-workers, and an example is shown in Scheme 7 (Section 3.03.2.7) <2003OBC1157>.



i. NBS, DMF, 0 °C; ii. BnBr, NaH, DMF, rt;
iii. Bu^{n}Li, Et$_2$O, DMF, –78 °C to rt

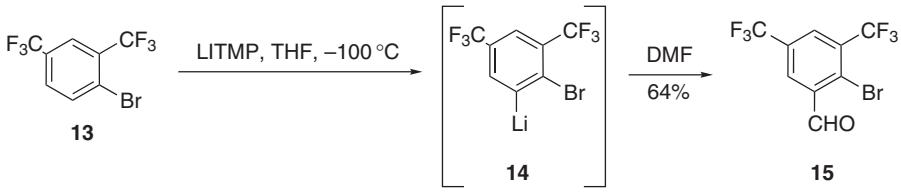
Scheme 5



12

(46)

The bromine–lithium exchange can be deliberately avoided by use of hindered lithium bases, such as LITMP. This facilitated deprotonation of compound **13** at the sterically least hindered position adjacent to bromine followed by quenching of lithiated species **14** with DMF to provide aldehyde **15** in overall yield of 64%, as shown in Equation (47) <2002JFC(117)167>.



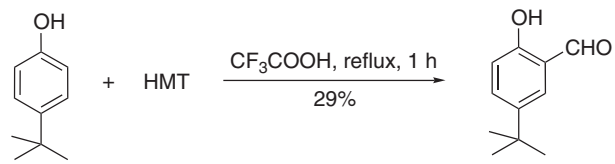
(47)

3.03.1.4 Electrophilic Formylation Reactions of Arenes

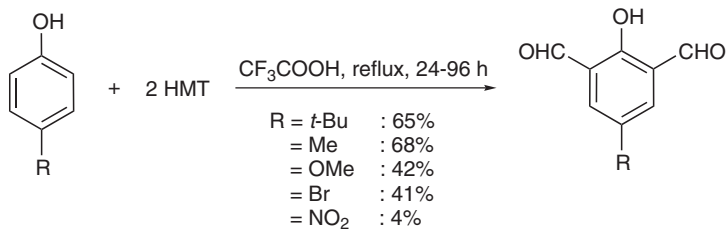
The following section reviews electrophilic aromatic substitutions that usually introduce a functionality that is converted into the formyl group either upon work-up or some additional synthetic step. The difference between these reagents lies primarily in: (i) reactivity; *O*-based reagents are more reactive than *N*-based; and (ii) steric bulk. From a regioselectivity viewpoint the more reactive systems would be expected to be less selective, while bulky reagents should favor the least hindered site of reaction (and vice versa). The polyformamides (Section 3.03.1.4.7) represent a new class of electrophilic formylating reagent introduced since the review by Hollingworth <1995COFGT(3)81>.

3.03.1.4.1 The Duff reaction

This reaction uses HMT (Section 3.03.1.2.4) in an acidic medium, usually trifluoroacetic acid. The Duff reaction is traditionally used to give *ortho*-carboxaldehydes of phenols and aromatic amines in moderate yields. A modified Duff reaction at high pressure was reported to successfully formylate haloarenes, although in many cases mixtures of isomers and considerable amounts of *N*-(haloarylmethyl)trifluoroacetamides were produced <1995MI2127>. The utility of the reaction in preparing mono- and diformyl 4-substituted phenols was elegantly demonstrated by Svenstrup and co-workers <1998S1029>. Monoformylation of 4-*t*-butylphenol was achieved in 1 h using 1 equiv. of HMT in refluxing anhydrous trifluoroacetic acid, as shown in Equation (48). When 2 equiv. of HMT was used and the reaction time suitably extended 4-*t*-butyl-2,6-diformylphenol was formed, and the procedure was further extended to other 4-substituted phenols, as shown in Equation (49). The reactions generally proceeded in moderate-to-good yield, apart from the diformylation of the nitro derivative. The nitro group was too electron withdrawing and gave more of the monoformylation product, 5-nitrosalicylaldehyde.

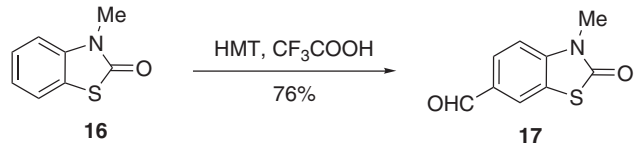


(48)



(49)

The Duff reaction can also be used to replace other electrophilic reagents, e.g., using dichloromethyl methyl ether (Cl_2CHOMe) under typical Friedel–Crafts conditions failed to give the desired conversion of the benzothiazole **16** into its 6-carboxaldehyde derivative **17**, whereas Duff reaction conditions proved successful, as shown in Equation (50) <1997CCC494>.



(50)

3.03.1.4.2 The Reimer–Tiemann reaction

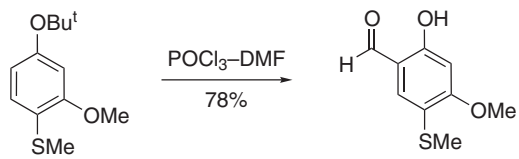
The reaction involves the formylation of phenols by means of dichlorocarbene (Cl_2C:), generated through a base-induced HCl elimination from chloroform (Equation (51)). It is used to prepare *o*- and *p*-hydroxybenzaldehydes. Upon the addition of β-cyclodextrin improved regioselectivity towards 2,4-dihydroxybenzaldehyde (70%) and 2-hydroxy-4-methoxybenzaldehyde (48%) was reported for the respective reaction on resorcinol (1,3-dihydroxybenzene) and one-pot Reimer–Tiemann and methylation of resorcinol <2001JMOC-A(169)185>.

(51)

A modification of this reaction is the photo-Reimer–Tiemann reaction in which a mixture of phenol and diethylamine in chloroform is irradiated with UV-light. The mechanism probably involves electron transfer from the excited phenol to chloroform giving a dichloromethyl radical ($Cl_2HC^{\cdot}$) instead of the dichlorocarbene as the key intermediate. Dichloromethyl phenyl ethers were confirmed as major products of the photo-Reimer–Tiemann reaction conducted in the absence of base <1995T5825>.

3.03.1.4.3 The Vilsmeier–Haack reaction

This is the most common formylation procedure using electrophilic chloromethylene iminium intermediates ($CH(Cl)=NRR^{+}$) formed by the reaction of a dialkyl formamide with an acid chloride, usually DMF and $POCl_3$, respectively <1991COS(2)777>. Electrophilic aromatic substitution gives an iminium salt, which is hydrolyzed in water (see Equations (66) and (67), Section 3.03.2.4) or with base work-up to give the aromatic aldehyde. Aromatics activated by electron-donating substituents, such as amino, alkylthio, and alkoxy groups, are most amenable to this reaction. Equation (52) gives a typical example <2000TL3997>.



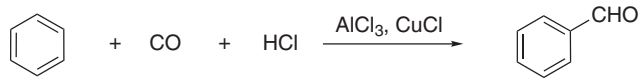
(52)

The reaction is normally carried out with $POCl_3$ and DMF acting as the solvent although microwave-assisted solventless methodology was reported for the formylation of a variety of aromatics <2000SL1115>. Examples of the latter are given in Equations (75), (76) (Section 3.03.3), and (87) (Section 3.03.4.3.1); optimized conditions used 2–3 mmol of Vilsmeier reagent per mmol of substrate on silica gel affording efficient transformations to the respective aromatic aldehydes in 1–2.5 min.

3.03.1.4.4 The Gattermann–Koch reaction

This formylation uses carbon monoxide with a Lewis acid in an acidic medium, and can be carried out on benzene, alkyl benzenes, or polycyclic aromatics. Addition of cuprous chloride to the Gattermann–Koch reaction using HCl and $AlCl_3$ enables CO to be used at atmospheric pressure, as represented by the general reaction shown in Equation (53). Numerous other combinations of acid medium–Lewis acid have been employed, and the most recent are

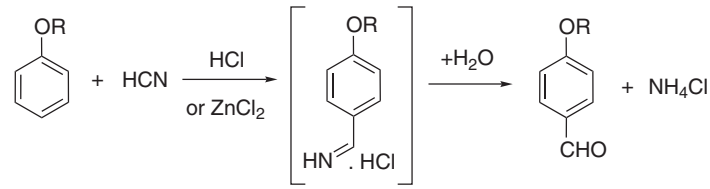
CF_3SO_3H-SbF_5 <1995JOC2106>, HF-SbF_5 <1996CC159, 1998JOC4408>. However, there are no new synthetic uses for this reaction, and the reaction fails for highly activated aromatics such as phenols or alkoxy- and amino-substituted benzenes.



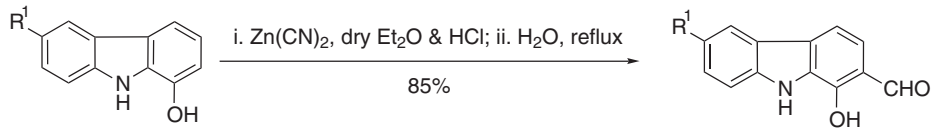
(53)

3.03.1.4.5 The Gattermann reaction

The reaction involves the formylation of phenol ethers or heterocyclic compounds by treatment of the aromatic substrate with hydrogen cyanide and hydrogen chloride in the presence of a Lewis acid catalyst, as demonstrated by the general reaction (Equation (54)). The active electrophile is *N*,*N*-diprotonated hydrogen cyanide, $HC^{+}{=}N^{+}H_2$ <1995JA3037>. The formylation generally occurs *para* to an activating substituent; however a recent example of a *ortho*-formylation is shown in Equation (55) <1999H2163>.



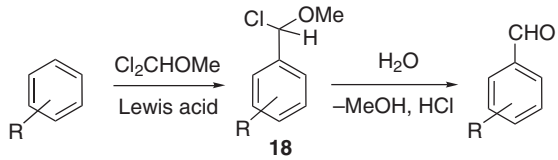
(54)



(55)

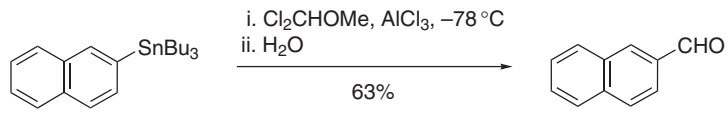
3.03.1.4.6 Dichloromethyl methyl ether as formylating reagent

This established procedure has the widest scope allowing the formylation of both activated and nonactivated arenes. In the reaction, 1,1-dichloromethyl methyl ether (Cl_2CHOMe) undergoes electrophilic aromatic substitution onto arenes in the presence of Lewis acids to afford 1-methoxy-1-arylmethyl chloride **18**, which is hydrolyzed to the corresponding aldehyde, as depicted in Equation (56).

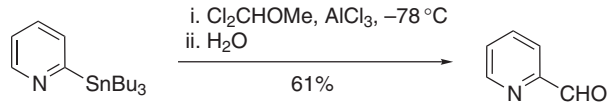


(56)

Niestroj and Neumann reported formylations in which aryl tributylstanannes underwent *ipso*-destannylation by the electrophile, as represented by the examples in Equations (57) and (58) to give the respective aromatic and heteroaromatic aldehydes in moderate-to-good yield <1996CBR(129)45>. This methodology is an improvement on the previously discussed electrophilic formylations as regioisomers are not formed.

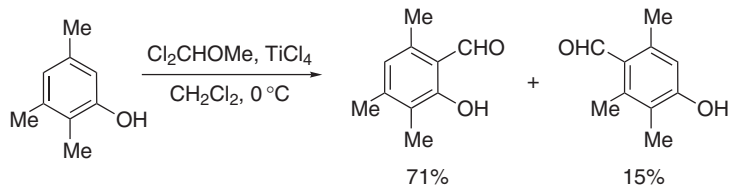


(57)



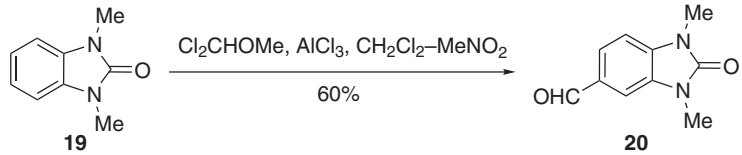
(58)

Very recently, highly selective *ortho*-formylations of electron-rich phenols with Cl_2CHOMe were reported in the presence of $TiCl_4$, as represented by the example in Equation (59). The regioselectivity of this reaction can be interpreted in terms of coordination of the Ti to the oxygen of the phenol <2003TL4961>.

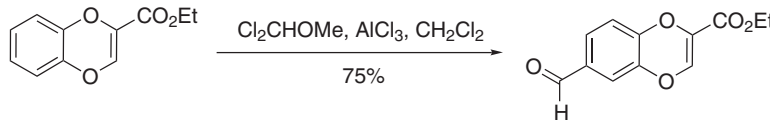


(59)

The formylation of benzimidazolone **19** under typical Friedel–Crafts conditions was reported to give 5-carboxaldehyde **20**, as shown in Equation (60) <1997CCC494>. The Vilsmeier–Haack formylation was reported to be unsuccessful on 1,4-benzodioxin-2-carboxylic acid ethyl ester, but $Cl_2CHOMe/AlCl_3$ was successful, as shown in Equation (61) <1997SC(27)431>.



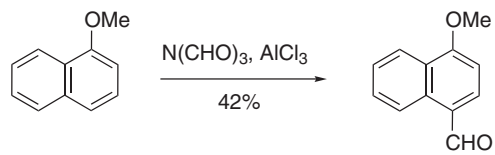
(60)



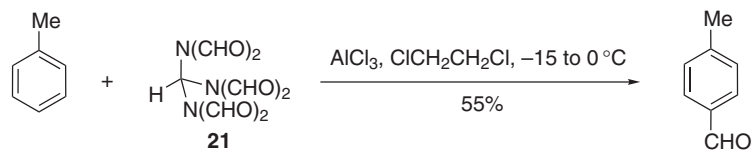
(61)

3.03.1.4.7 Polyformamides as formylating reagents

This is the most recent method. A mixture of diformamide ($HN(CHO)_2$), P_4H_{10}, and $AlCl_3$ was reported to formylate toluene as well as anisole. Lewis acids, $AlCl_3$ or BCl_3, and triformamide were also reported to formylate a number of activated aromatics, as represented by the preparation of 1-formyl-4-methoxynaphthalene in Equation (62) <2000JPR(342)297>. Improved yields of benzaldehydes were achieved by using the more powerful formylating agent, tris(diformylamino)methane **21**. With $AlCl_3$ as the Lewis acid, yields were highest with **21**:$AlCl_3$ ratios of 1:6 to 1:8. Although only moderate yields of benzaldehyde were obtained in most cases; the *para*-substituted product was always the only isomer formed, and weakly activated aromatics such as alkyl benzenes were successfully formylated, as represented by the formylation of toluene in Equation (63) <2001EJO2947>.



(62)



(63)

3.03.2 BENZALDEHYDE AND SUBSTITUTED BENZALDEHYDES

This is a group of aromatics that are weakly activated towards electrophilic aromatic substitution, and using Duff, Vilsmeier–Haack, Reimer–Tiemann and Gattermann reactions only poor yields of aldehydes are achieved. However, dichloromethyl methyl ether under Friedel–Crafts conditions, Gattermann–Koch and new polyformamide formylation methods have been reported to produce

respectable to excellent amounts of these aldehydes <1995COFGT(3)81>. However, reduction, oxidation, and metallation methods are still the most popular routes for the preparation of aldehydes of weakly activated aromatics.

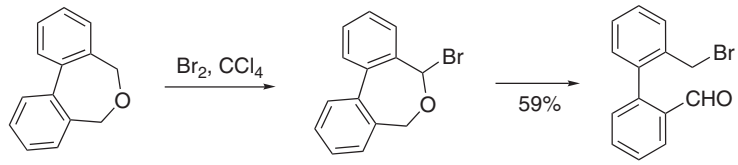
Section 3.03.2 follows the same structure as the review by Hollingworth <1995COFGT(3)81>, except for the addition of a new section on the preparation of dicarbaldehydes (see Section 3.03.2.7).

3.03.2.1 Benzaldehyde

Hollingworth reviewed classical preparations of benzaldehyde <1995COFGT(3)81>.

3.03.2.2 Alkyl and Phenyl Benzaldehydes

The ring opening of dibenzoxepine **22** by bromination gave *ortho*-phenyl-substituted benzaldehyde **23** in 59% yield (Equation (64)) <2002SL580>.



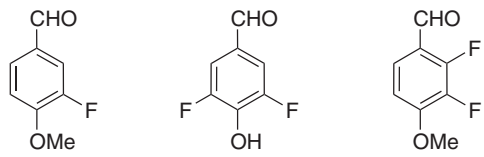
22 **23** (64)

3.03.2.3 Halobenzaldehydes

Aryl halides are readily reduced by hydrogenolysis with the process becoming more facile in the presence of electron-withdrawing groups; thus, caution is recommended for the reduction of halo benzoic acid derivatives to their corresponding aldehydes. Nevertheless, many deactivated borane and aluminum hydride reagents are applicable <1995COFGT(3)81>. Oxidations with PCC are common and chromium trioxide oxidation of di- and tribromotoluenes to the corresponding aldehydes has recently been carried out <2000SC(22)4039, 2001EJO293>.

Several selective halogen–lithium exchange reactions of one halogen substituent in the presence of another have been reported recently, and are shown in Equations (47) (Section 3.03.1.3.2), (91) and (92) (Section 3.03.4.3.2). Actually, a single bromine–lithium exchange followed by quenching with DMF to convert 1,3,5-tribromobenzene into 3,5-dibromobenzaldehyde was reported in the 1980s <1981JOM(215)281>.

Electrophilic formylations are difficult, since the aromatic ring of halobenzenes is deactivated in comparison to benzene; however, electrophilic substitution will occur in the presence of other strongly activating groups. Lawrence and co-workers reported the use of the Duff reaction (HMT, CF_3CO_2H, 18 h, reflux) to facilitate the formylation of 2-fluoroanisole and 2,6-difluorophenol to aldehydes **24** and **25** in good yields of 54% and 67%, respectively. However, the Duff reaction failed to give aldehyde **26** by the formylation of 2,3-difluoroanisole, although the latter underwent an rt reaction with $TiCl_4$ and Cl_2CHOMe to yield aldehyde **26** in 71% yield <2003JFC(123)101>.

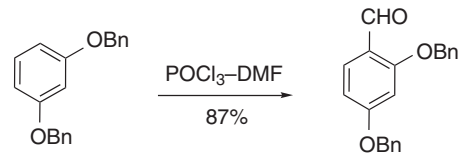


24 **25** **26**

3.03.2.4 Oxygen-substituted Benzaldehydes

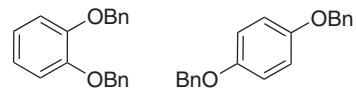
Vilsmeier–Haack formylation of anisole has been reported to give 89:11 ratio (58%) of 4- to 2-isomers with $POCl_3$–DMF, but 94:6 (75%) when bulkier pyrophosphoryl chloride ($Cl_2PO_2POCl_2$) is used, with this rising to >98:2 (72%) when *N*-methylformanilide (PhNMeCHO) replaced the DMF

<1993T4015>. The combination of $POCl_3$–DMF was reported to facilitate the formylation of 1,3-dibenzyloxybenzene **27** to give **28** (Equation (65)) but not the formylation of isomers **29** and **30**. This is explained in terms of the directing effects of the *meta*-benzyloxy groups in **27** reinforcing each other, while the directing effects oppose each other in **29** and **30** <1997T215>. Lewis acids (e.g., $MgBr_2$ or BCl_3) can be used to selectively deprotect the aromatic benzyloxy group adjacent to the carbonyl functionality to provide the required 2-hydroxybenzaldehyde <1997T215>.



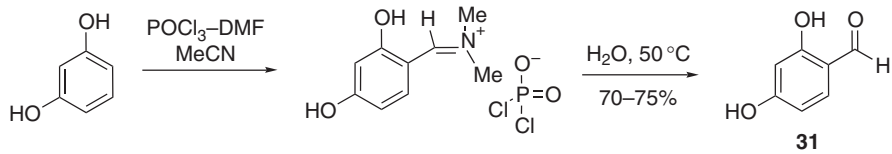
(65)

27 **28**



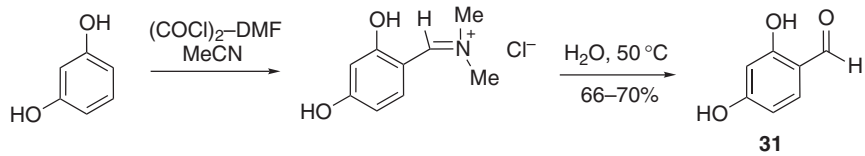
29 **30**

The Vilsmeier–Haack reaction was also used to prepare 2,4-dihydroxybenzaldehyde **31** from resorcinol. Equations (66) and (67) show that either $POCl_3$–DMF or $(COCl)_2$–DMF can be used to prepare **31** on multi-gram scale in 66–75% overall yield. The intermediate formamidinium salts were also characterized <1996SC(26)603>.



(66)

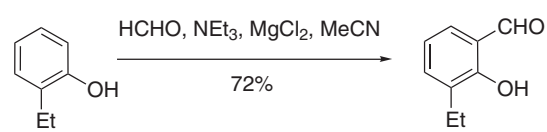
31



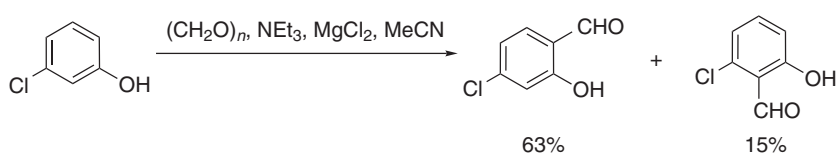
(67)

31

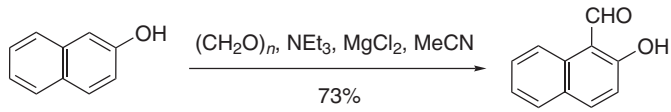
2-Hydroxybenzaldehydes can be prepared by the reaction of phenols with formaldehyde with control towards *ortho*-selectivity being achieved by the addition of a magnesium salt, which coordinates to the oxygens of the hydroxyl group and formaldehyde. The formation of this aryloxymagnesium bromide complex activates the formaldehyde towards electrophilic attack, and specifically substitution at the *ortho*-position of phenol <1978JCS(P1)318>. The reaction facilitated the formylation of a variety of alkyl- and chloro-substituted phenols, and 3- and 4-methoxyphenols, but 2-methoxyphenol was unreactive <1999ACS258, 1994SC(24)1757>. Recent examples are given in Equations (68) <2003TA1659>, (69) <1999ACS258>, and (70) <1999ACS258>.



(68)

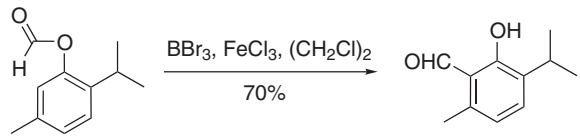


(69)

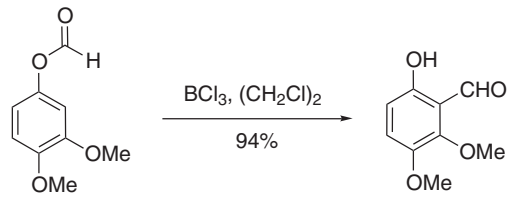


(70)

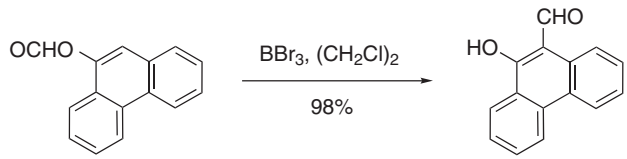
The Fries rearrangement (see Chapter 3.06) can be used to convert aryl formates into 2-hydroxybenzaldehydes, as described by Zeigler and co-workers. Stoichiometric amounts of Lewis acids, BCl_3, BBr_3, or trifluoromethanesulfonic acid were used. BBr_3 in combination with stoichiometric amount of $FeCl_3$ was found to be the most effective towards weakly activated aromatics (Equation (71)). Further examples of this reaction are provided in Equations (72) and (73) <2001ZN1178>.



(71)



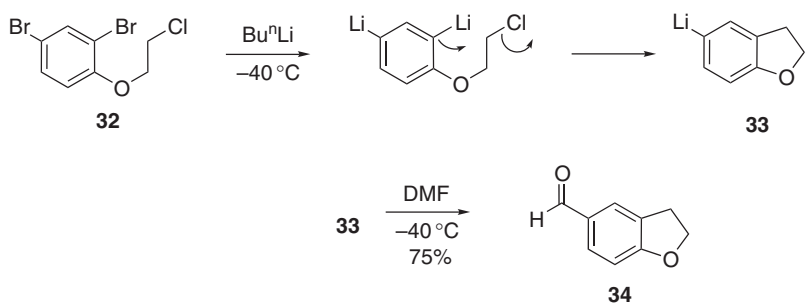
(72)



(73)

Alternatively, Duff, Reimer–Tiemann, and Cl_2CHOMe/Lewis acid reactions can be used to prepare 2-hydroxybenzaldehydes.

Selective lithiation with subsequent electrophilic formylation is widely used with ether-substituted benzenes (see Section 3.03.1.3.2), with such groups often possessing considerable *ortho*-directing ability. Lithium–bromine exchange reactions have been used in the formylation of benzoate esters containing OBn and OMe substituents *ortho* to the lithiation site giving benzaldehyde in yields of 14–58% <1999SC(29)3401>. The preparation of functionalized benzodihydrofurans (e.g., **34**) was achieved by sequential treatment of ether dibromides (e.g., **32**) with 3 equiv. of *n*-BuLi followed by DMF resulting in a Parham cyclization followed by intermolecular reaction with DMF, as shown in Equation (74) <2000TL2269>.



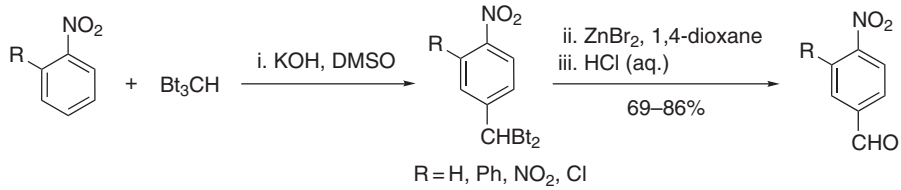
(74)

3.03.2.5 Sulfur-substituted Benzaldehydes

Sulfanyl-substituted benzaldehydes are difficult to prepare by oxidation reactions owing to the susceptibility of the S to oxidation. Higher oxidation states of S may also be readily reduced. Many electrophilic methods have proved largely unsuccessful; however, a recent efficient Vilsmeier-Haack reaction is shown in Equation (52) (Section 3.03.1.4.3). Perhaps the most reliable method is *ortho*-lithiation, as S substituents are strongly *ortho*-directing <1995COFGT(3)81>.

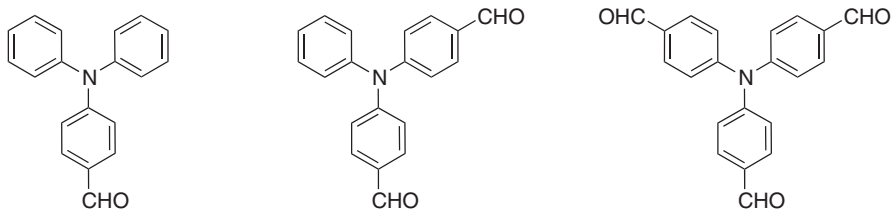
3.03.2.6 Nitrogen-substituted Benzaldehydes

The electrophilic formylation of highly deactivated nitrobenzenes is not possible, and thus, it is not surprising that oxidation–reduction techniques are most often used. Exceptions include the introduction of the bis(benzotriazol-1-yl)methyl group by a vicarious nucleophilic substitution into the *para*-position of nitrobenzenes followed by hydrolysis providing *para*-nitrobenzaldehydes in 69–86% overall yield, as shown in Scheme 6 <1996TL347>.



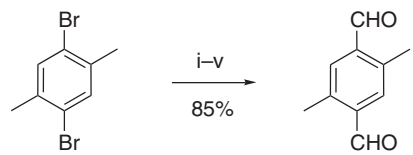
Scheme 6

On the other hand, aromatic amines are highly activated towards electrophilic formylation. The Vilsmeier–Haack formylation of triphenylamine was reported to give the monoformylation product **35** in 90–94% yield, when equal equivalents of $POCl_3$ in DMF were used at 100 °C for 20 h <1997SL1275, 2002TL3521>. When Ph_3N was treated with a large excess of $POCl_3$ (10.5 equiv.) in DMF for 6 h, dialdehyde **36** was produced in 71% yield with monoaldehyde **35** obtained in 3% yield. However, trialdehyde **37** could not be prepared in high yield with only optimum isolated yield of 18% achieved, when Ph_3N was treated with 40 equiv. of $POCl_3$ in DMF at 100 °C for 48 h. In the latter reaction, compound **36** was the major product being isolated in 40% yield. This inferred that the intermediate(s) leading to **36** after work-up may not be sufficiently electron-rich, thus retarding any further electrophilic formylation <1997SL1275>.



3.03.2.7 Aromatic Dicarbaldehydes

Aromatic dicarbaldehydes can be prepared by double oxidation of benzylic alcohols, double reduction of aromatic diesters (Equation (6), Section 3.03.1.1.3) or dinitriles (Equation (83), Section 3.03.4.2.1). The Duff reaction was effectively used for the preparation of 2,6-diformylphenols, as shown in Equation (49) (Section 3.03.1.4.1). However, there are an increasing number of examples that use halogen–lithium exchange reactions, as shown in Equations (46) (Section 3.03.1.3.2), (78) (Section 3.03.3), and (89) (Section 3.03.4.3.1). However, the direct double bromine–lithium exchange, and quenching with DMF failed in the case of alkylbenzenes, and a sequential dilithiation procedure was found more effective as represented by Scheme 7 <2003OBC1157>.

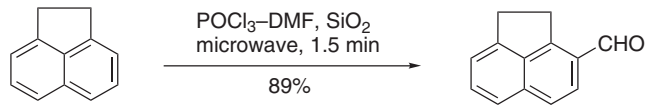


i. Bu^sLi (1.1 equiv.), THF, –78 °C; ii. DMF
iii. Bu^sLi (4.3 equiv.), THF, –78 °C; iv. DMF; v. 6 M HCl

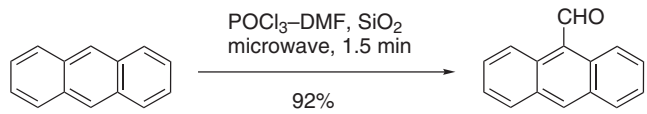
Scheme 7

3.03.3 POLYAROMATIC ALDEHYDES

Naphthalene has not been reported to undergo formylation with the usual Vilsmeier–Haack ($POCl_3$–DMF) mixture but with the more potent combination of DMF and trifluoromethanesulfonic anhydride, naphthalene-1-carbaldehyde was produced in 50% yield <1991COS(2)777>. $POCl_3$–DMF can facilitate the formylation of naphthalene with electron-donating ether substituents at the 2-position to give the 1-formyl derivative <1997T215>. The Vilsmeier–Haack formylation of naphthalene with electron-donating substituents at the 1-position and anthracene is known to occur regioselectively at the 2- and 9-positions respectively, and has been recently reported using microwave irradiation conditions, as shown in Equations (75) and (76) <2000SL1115>. 1- and 2-Naphthalene carbaldehydes were also prepared via electrophilic Cl_2CHOMe *ipso*-substitutions of the respective 1- and 2-tributyl stannanes in yields of 80% and 63% respectively (Equation (57), Section 3.03.1.4.6) <1996CBR(129)45>.

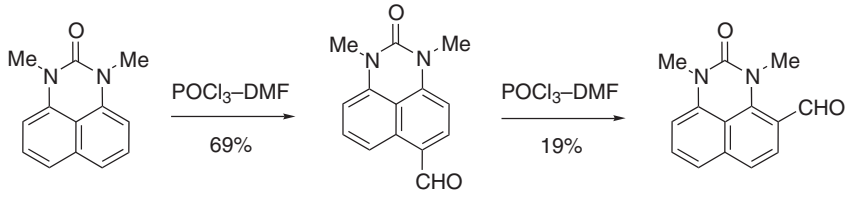


(75)



(76)

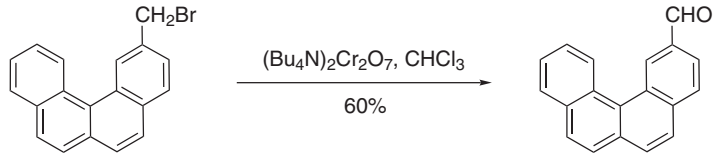
It was reported that 1,3-dimethylperimidone **38** underwent the Vilsmeier–Haack reaction at 80–90 °C to form perimidon-6-carbaldehyde **39** in 69% yield. However, treatment of **39** with excess $POCl_3$–DMF led to the formation of isomer **40** in 19% yield (Scheme 8) <1999CHE319>.



38 **39** **40**

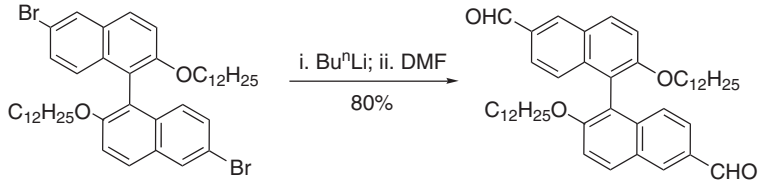
Scheme 8

Reduction and oxidation methods are widespread in the preparation of polyaromatic carbaldehydes. A recent example of the reduction of carboxylic esters is shown in Equation (6), Section 3.03.1.1.3. The preparation of 2-formyl-benzo[*c*]phenanthrene was reported via the oxidation of the 2-bromomethyl derivative, as shown in Equation (77) <1997TL2145>.



(77)

Halogen–lithium exchange reactions are sometimes used. Chiral binaphthyl derivative **41** was reported to undergo efficient double bromine–lithium exchange to give dialdehyde **42** in excellent yield, as shown in Equation (78) <2000JOC7501>.



41 **42**

(78)

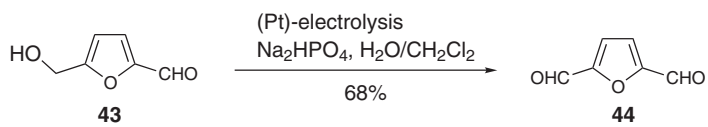
A new method specific to the formylation of polycyclic aromatic hydrocarbons was devised by Periasamy and co-workers <1999SC(29)677>. This method involved the treatment of a dry THF solution of aromatic substrate and *N*,*N*-dialkylformamide (or ethyl formate) with 2 equiv. of sodium metal to simultaneously form the highly conjugated aromatic radical anion and the radical anion of the amide or ester, which presumably couple. Subsequent quenching of the colored reaction mixture with hydrochloric acid gave the desired aldehydes: 1-naphthalenecarbaldehyde, 9-anthracenecarbaldehyde, 9-phenanthrenecarbaldehyde, and 4-biphenylcarbaldehyde in yields of 56%, 49%, 68%, and 69% respectively.

3.03.4 HETEROCYCLIC ARYL ALDEHYDES

3.03.4.1 *O*-Heterocyclic Aldehydes

3.03.4.1.1 Furan and benzofuran carboxaldehydes

The furan and benzofuran rings are unaffected by many oxidizing (e.g., PCC, MnO_2, Swern, HMT) and reducing agents (e.g., DIBAL-H), which makes these methods a popular means of preparing them <1995COFGT(3)81>. Electrochemical oxidation of primary alcohols generally yields carboxylic acids making the preparation of aldehydes difficult. However, the room temperature electrochemical ($8\,mA\,cm^{-2}$) biphasic oxidation of 5-hydroxymethylfurfural **43** to dialdehyde **44** was reported with no traces of furan-2,5-dicarboxylic acid formed, as shown in Equation (79) <1996S1291>.



43 **44** (79)

Lithiation of furan and benzofuran occurs preferentially at the 2-position, and the carbanion is readily quenched with DMF to give 2-carboxaldehydes <1995COFGT(3)81>. The preparation of benzofuran-5-carbaldehyde via a Grignard reaction is shown in Equation (42) (Section 3.03.1.3.2).

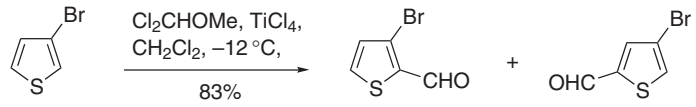
Furan undergoes electrophilic formylation preferentially at the 2- or 5-positions, and benzofuran at the 2-position <1995COFGT(3)81>. Regioselectivity is improved using the Friedel–Crafts-like electrophilic *ipso*-destannylation procedure with Cl_2CHOMe to give furan-2-carbaldehyde in 76% yield with 100% regioselectivity, as described in Section 3.03.1.4.6.

3.03.4.2 *S*-Heterocyclic Aldehydes

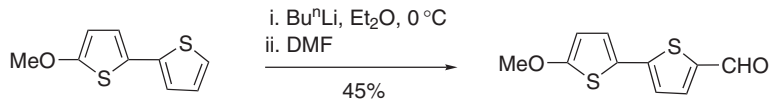
3.03.4.2.1 Thiophene and benzothiophene carboxaldehydes

Like furan and pyrrole, thiophene undergoes electrophilic formylation preferentially at the 2- and 5-positions. Section 3.03.1.4.6 described how the regioselectivity of such formylations was improved by using *ipso*-destannylation with Cl_2CHOMe-$AlCl_3$ at $-78\,^{\circ}C$, which allowed the selective synthesis of thiophene-2-carboxaldehyde in 76% yield, although this procedure was unsuccessful in the preparation of thiophene-3-carbaldehyde <1996CBR(129)45>. The $POCl_3$–DMF formylation of 3-alkylthiophenes was reported to predominately occur at the 2-position; however, bulky 3-alkyl substituents encourage greater levels of substitution at the 5-position <1995H925>. Furthermore, utilizing large planar aromatic Vilsmeier reagents (e.g., PhNMeCHO) can encourage greater substitution at the less hindered 5-position, while still maintaining good overall yield of aldehyde <1995H925, 2000TL2749>. Good regioselectivity for the 2-position of the less active 3-bromothiophene has been reported using more reactive *O*-containing electrophilic reagents (see Section 3.03.1.4.6), as shown in Equation (80) <2000TL2749>. When formylation by Vilsmeier–Haack methods failed to give formylation at the 5-position, metallation with *n*-BuLi followed by quenching with DMF was found to be successful for the preparation of 5-formylbisthiophenes shown in Equation (81) <2003T4891, 1995BCJ2363>. Selective hydrogen–metal exchange reactions on thiophene and ethyl thiophene-2-carboxylate have been shown to proceed at room temperature using the magnesium amide base, *i*-Pr_2NMgCl, to give thiophene-2-carbaldehyde and ethyl

5-formylthiophene-2-carboxylate, respectively, in yields of 52% and 84% on quenching the carbanion with *N*-formyl-piperidine <2001JCS(P1)442>. Applications of this methodology for the synthesis of thiazole-2-carboxaldehyde are given in Equation (101) (Section 3.03.4.4).

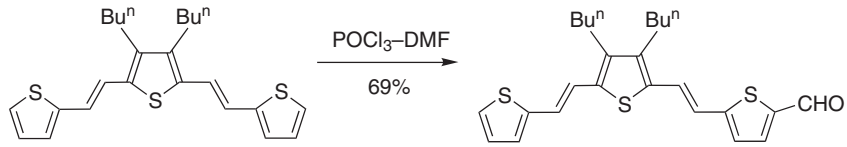


(80)



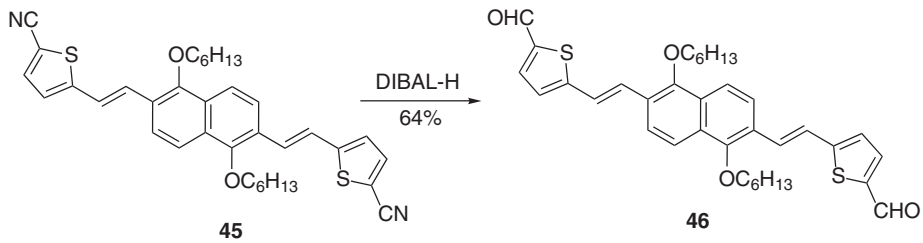
(81)

The chain extension technique of thienylenevinylene oligomers involves the stepwise formation of α-thiophene carboxaldehyde upon treatment with *n*-BuLi/DMF or Vilsmeier–Haack formylation followed by coupling with α-substituted thiophene phosphonium ylid in a Wittig reaction. Roncali and co-workers reported the synthesis of the longest such oligomers, which contained alkyl substituents at thiophene ring β-positions. These substituents gave enhanced solubility and electronic properties compared to previously reported oligomers with substituents at the α-positions. The mono-formylation of the trimer is shown in Equation (82) <1997JA10774>.



(82)

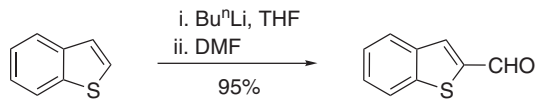
DIBAL-H is an effective reducing agent for converting aromatic nitriles into aldehydes, as described in Section 3.03.1.1.7. In the twofold reduction shown in Equation (83), DIBAL-H (2 equiv., 1 M) was refluxed with substrate **45** for 5 h in dry dichloromethane to afford dialdehyde **46** in 64% yield <2000JOC7501>.



45 **46**

(83)

Benzothiophene is less reactive towards electrophiles than thiophene, but still undergoes Vilsmeier–Haack formylation with preference towards substitution at the 3-position <1995COFGT(3)81>. There have been several reports of the preparation of benzothiophene-2-carbaldehyde including the selective lithiation of benzothiophene at the 2-position followed by quenching with DMF (Equation (84)) <1996ACS71>, and the oxidation of the benzothiophene-2-methanol with potassium ferrate on wet alumina in a low yield of 34% <2000T9365>. The preparation of benzothiophene-5-carboxaldehyde via a Grignard reaction is shown in Equation (43) (Section 3.03.1.3.2).



(84)

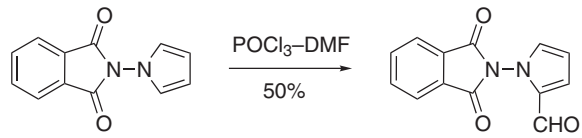
3.03.4.2.2 *Se and Te heterocyclic aldehydes*

Since 1995, there have been no reports of Se and Te heterocyclic aryl aldehydes <1995COFGT(3)81>.

3.03.4.3 *N*-Heterocyclic Aldehydes

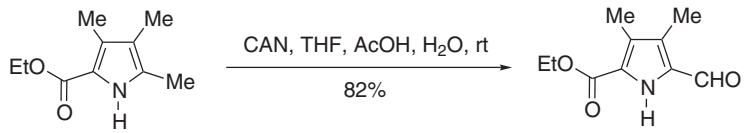
3.03.4.3.1 Pyrrole and indole carboxaldehydes

The Vilsmeier–Haack formylation occurs easily at the most nucleophilic 2-position of pyrrole, and is still the most popular method of preparing pyrrole-2-carbaldehydes <1995OPP236>. Recently the Vilsmeier–Haack formylation on 1-phthalimidopyrrole was reported, as shown in Equation (85) <2001JHC(38)1441>. Electrophilic formylation at the pyrrole-3-position can be facilitated by using pyrroles *N*-substituted with electron-withdrawing or bulky protecting groups <1990JOC6317, 1998TL3927>. These groups may be cleaved to give pyrrole-3-carbaldehyde using multistep procedures <1992CPB2338, 1995OPP503>.



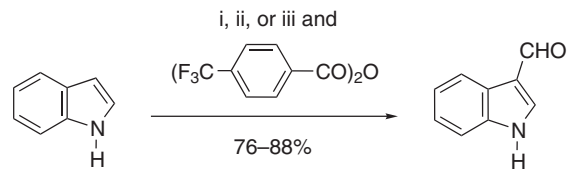
(85)

CAN was shown to selectively oxidize the α-methyl in the presence of other methyl substituents in pyrrole with the presence of α'-carboxylic esters apparently activating this process (Equation (86)). The room temperature oxidation to the formyl group required 4 equiv. of CAN, and water was necessary to form the intermediate alcohol <1995TL4345>.



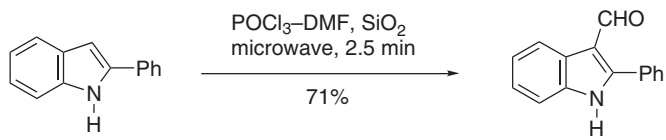
(86)

In the presence of a stoichiometric quantity of 4-trifluoromethylbenzoic anhydride, formic acid formylates the nucleophilic indole-3-position using catalytic amounts (10 mol. %) of $TiCl_4$–AgOTf or $Yb(OTf)_3$, as shown in Scheme 9 <1995H141>. However, formylations under Friedel–Crafts-type conditions with formic acid or its derivatives as the electrophile are rare, and the Vilsmeier–Haack formylation is routinely used. Rapid Vilsmeier–Haack formylation of the indole-3-position was reported under solventless-microwave irradiation conditions, as shown in Equation (87) <2000SL1115>.



i. HCOOH, $TiCl_4$:AgOTf (1:2), CH_2Cl_2:TMS_2O (1:1), rt, 40 h
ii. HCOOH, $Yb(OTf)_3$, CH_2Cl_2, reflux, 12 h
iii. HCOOH, $TiCl_4$:AgOTf (1:2), TMSCl (3 equiv.), rt, 20 h

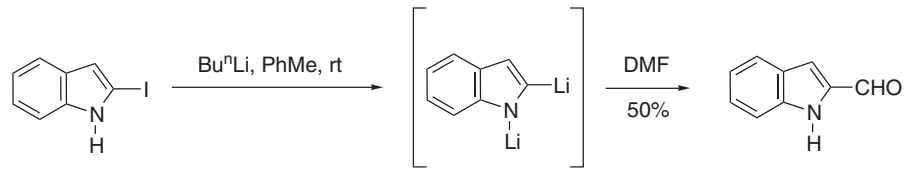
Scheme 9



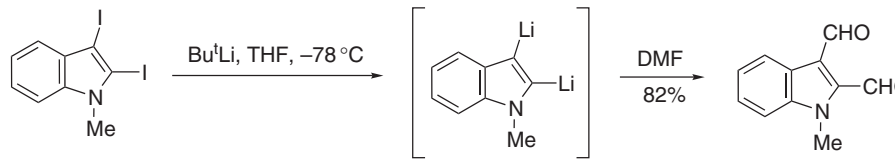
(87)

The generation of 1,2-dilithioindole from 2-iodoindole, and the quenching of the carbanionic center with various electrophiles was used to prepare a range of 2-substituted indoles, including 2-formyl indole in 50% overall yield, as shown in Equation (88) <2001SC(31)947>. Generation of 2,3-dilithioindole from 2,3-diiodo-*N*-methylindole using the stronger base *t*-BuLi, and quenching with excess DMF (10 equiv.) was reported to give

2,3-diformyl-*N*-methylindole in 82% overall yield, as shown in Equation (89) <2001TL2949>. Selective bromine–lithium exchange of 2,3-dibromo-*N*-methylindole using *t*-BuLi at −78 °C was more recently reported to give 3-bromo-2-lithio-1-methyl indole, which was quenched with DMF to give the 2-formyl indole in 86% yield <2002TL7135>. The indole-2-carbanion generated by reaction of *t*-BuLi with 3-ethynyl-1-(phenylsulfonyl)indoles has alternatively been quenched with ethyl formate to give the corresponding indole-2-carbaldehyde in 59–84% yield <1999CPB1740>. Vilsmeier–Haack formylation is also possible at the indole-2-position if the 3-position is blocked <1995COFGT(3)81>.



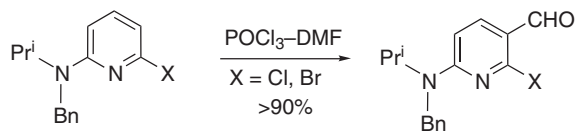
(88)



(89)

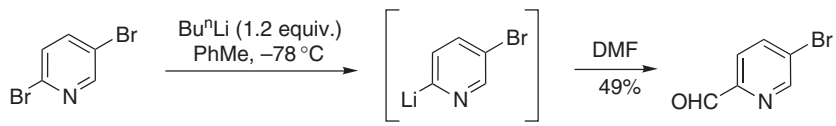
3.03.4.3.2 Pyridine and quinoline carboxaldehydes

Although pyridine is generally considered not activated enough to undergo classical electrophilic formylations, regioselective Vilsmeier formylations were recently reported with pyridines activated by 2-amino substituents, as shown in Equation (90) <2002T3409>. *ipso*-Substitution of 2- and 3-tributylstannyl groups by Cl_2CHOMe electrophile in the presence of $AlCl_3$ provided 2- and 3-pyridinecarbaldehydes in 61% (Equation (58), Section 3.03.1.4.6) and 53% yield, respectively, with 100% regioselectivity <1996CBR(129)45>.



(90)

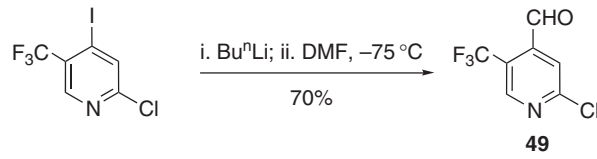
The selective monolithiation of 2,5-dibromopyridine was reported to give 2-lithiated species **47**, which was quenched with various electrophiles including DMF to give 2-formyl-5-bromopyridine **48** in 49% overall yield (Equation (91)) <2000TL4335>. This selective lithiation was favored in noncoordinating solvents, such as toluene, and with low concentrations of substrate. Similarly, it was found that 3-pyridyllithium was generated more easily by bromine–lithium exchange in toluene rather than THF, and the yellow solid of 3-pyridyllithium could be dissolved by adding THF, and conveniently reacted with a variety of electrophiles including DMF to give 3-formyl pyridine in 90% isolated yield <2002TL4285>.



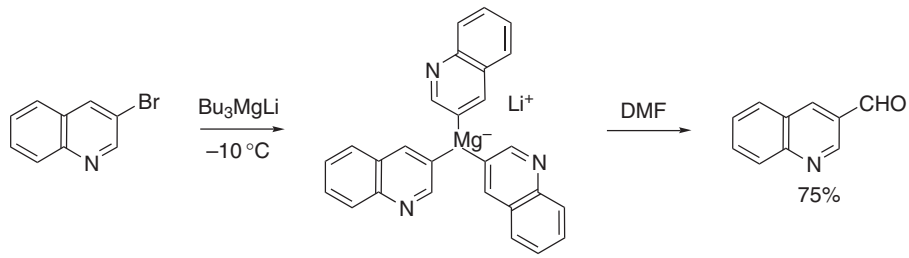
47 **48**

(91)

The formation of the pyridine-4-carbaldehyde **49** was reported in 70% yield by lithium–iodine exchange followed by quenching with DMF, as shown in Equation (92) <2002JFC(117)167>. *n*-BuLi is not always used; for instance the treatment of 3-bromoquinoline with 0.35 equiv. of Bu_3MgLi in toluene gave the corresponding lithium tri(quinolyl)magnesate, which was quenched with DMF to give quinoline-3-carbaldehyde in 75% overall yield (Equation (93)) <2003TL2033>.

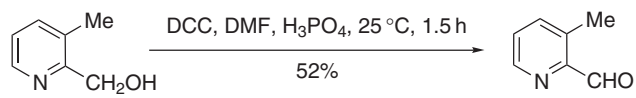


49 (92)

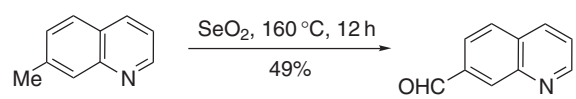


(93)

Pyridinecarbaldehydes can also be obtained by various oxidation reactions of activated aromatic methyl groups or alcohols. Oxidation of 2-(hydroxymethyl)-3-(or 6)-substituted pyridines with either DCC–H_3PO_4 (e.g., Equation (94)) or activated MnO_2 was used to give the required 2-formyl derivatives <1998JMC1827>. A particularly useful oxidant is selenium dioxide, which is known to have a strong preference for the oxidation of 2- and 4-methyl groups of lutidines (dimethylpyridines). Optimized conditions used wet dioxane solutions containing less than 1 equiv. of the oxidant <1999OPP120>. Selenium dioxide was reported to oxidize 7-methylquinoline to quinoline-7-carbaldehyde in 49% yield, as shown in Equation (95) <2000JMC3878>. The addition of TBHP allowed the selenium dioxide oxidation to occur under mild conditions, as shown in Equation (12) (Section 3.03.1.2.1).



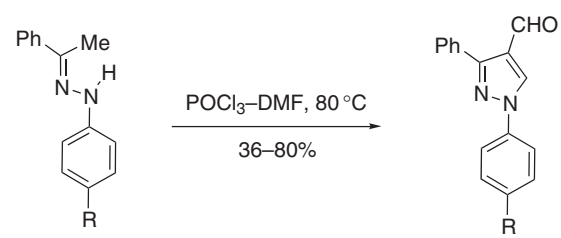
(94)



(95)

3.03.4.3.3 Aromatic diazole carboxaldehydes

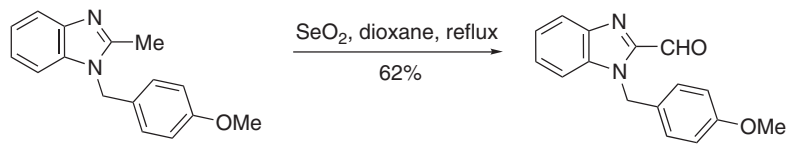
N-Alkylpyrazole is activated enough to undergo Vilsmeier–Haack reactions in reasonable yields to give 4-formyl-1-alkylpyrazoles <1995T4779>. Alternatively, hydrazone derivatives **50** can be cyclized to pyrazoles, which are subsequently formylated in a one-pot reaction under Vilsmeier–Haack conditions to give 4-formyl-1-aryl-pyrazoles **51** (Equation (96)) <1969TL109, 2002EJM671>. 5-Formyl-1-methylpyrazole can be obtained by regioselective lithiation of 1-methylpyrazole with *n*-BuLi followed by quenching with DMF <1997BMCL1409>.



50 **51** (96)

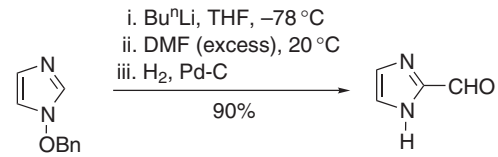
2-Formylimidazoles are usually obtained by lithiation of the most acidic imidazole-2-position followed by quenching with DMF. A more straightforward method of obtaining 2-formylbenzimidazole was reported involving the oxidation of 1-(benzyl-4-methoxy)-2-methylbenzimidazole with selenium dioxide, as shown in Equation (97) <1995T4779>. Improvements to selenium dioxide oxidations of activated *N*-heterocyclic methyl groups have been achieved by addition of TBHP <2003H953>. Alternatively, oxidation of the imidazole-2-methyl group can be accomplished using

CrO_3/pyridine to give the corresponding aldehyde in 44% yield <1997JMC4199> or oxidation of imidazole-2-methanols with activated manganese dioxide will also give 2-formylimidazoles in good yields <2002T4445>.



(97)

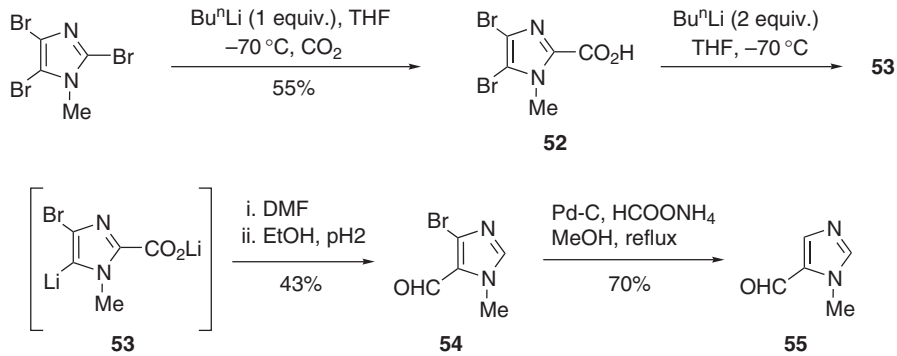
Begtrup and co-workers lithiated *N*-(benzyloxy)imidazole, and quenched with various electrophiles including DMF with subsequent removal of the *N*-benzyloxy group achieved by catalytic hydrogenation giving 2-formylimidazole in excellent overall yield, as shown in Scheme 10 <1998JOC12>.



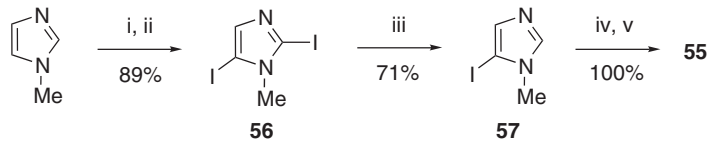
Scheme 10

4-Formylimidazole (imidazole-4-carbaldehyde) is commercially available and 4-formyl-*N*-alkylimidazole products are readily obtainable by alkylation under basic conditions <1999T8111>. However, the preparation of 5-formyl isomers in reasonable yields is difficult, even under neutral or slightly acidic conditions. However, this synthetic problem may be alleviated by selective lithiation procedures, since the most acidic position on the imidazole ring is the 2-position, followed by the 5-position with the 4-position being the least acidic. Shapiro and Gomez-Lor used regioselective bromine–lithium exchange followed by quenching with carbon dioxide to obtain the imidazole-5-carboxylic acid **52** (Scheme 11). The addition of excess *n*-BuLi resulted in the formation of dilithium species **53**, which was stable at low temperatures. Quenching of the imidazol-5-yl anion of **53** with DMF followed by de-carboxylation gave 5-formyl-imidazole **54**. The presence of a 4-bromo-substituent in **54** allowed subsequent elaboration by Suzuki couplings. Alternatively, catalytic hydrogenation gave 5-formyl-1-methylimidazole **55** in reasonable yield <1994JOC5524>.

Scheme 12 shows a more recent, shorter synthesis of 5-isomer **55** with a selective deiodination of 2,5-diiodo-derivative **56** giving the desired 5-iodo-1-methylimidazole **57**. The latter was treated with EtMgBr to give an intermediate heterocyclic Grignard reagent, which produced **55** upon reaction with DMF <1997T14481, 2002JOC5913>. LITMP has also been used in the selective lithiation of the imidazole-5-position for various *N*-substituted imidazoles with the 2-position blocked to give 5-formylimidazoles <2002TL4377>. Alternatively, *N*-alkyl-5-formylimidazoles can be obtained by oxidation of the 5-methanol derivative with activated manganese dioxide <1996JHC(33)1345>.



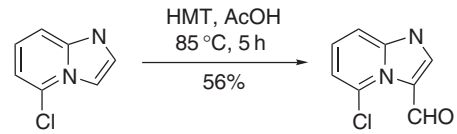
Scheme 11



i. Bu^nLi (2.4 equiv.), TMEDA, hexane, –20–22 °C
ii. I_2 (2.5 equiv.), THF, –65 °C
iii. Bu^nLi, THF, 0 °C; work-up
iv. CH_2Cl_2, $EtMgBr$ in Et_2O
v. DMF, 0 °C

Scheme 12

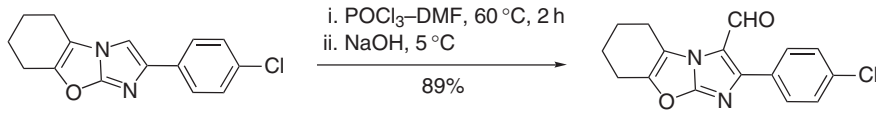
The Duff reaction was reported to give better yields of 5-chloro-3-formylimidazo[1,2-*a*]pyridine **58** compared to $POCl_3$–DMF and dichloromethyl methyl ether-$TiCl_4$ procedures (Equation (98)) <2002T489>.



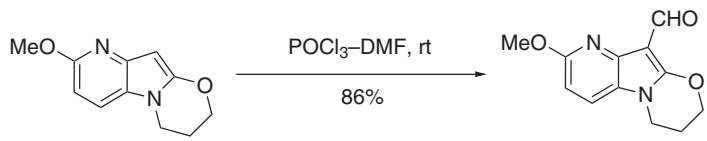
(98)

3.03.4.4 Miscellaneous Heterocyclic Aryl Aldehydes

Mekonnen and Crank showed that the electrophilic aromatic substitution of imidazo[1,2-*a*]oxazoles occurred preferentially at the 5-position when the positions on the benzene ring were suitably deactivated by a chlorine substituent, as illustrated in Equation (99) by the Vilsmeier–Haack formylation <1997T6959>. Viaud–Massuard and co-workers reported the analogous formylation of tricyclic heterocycle **59**, which occurred selectively in 86% yield in an analogous manner to neutral indole derivatives, as shown in Equation (100) <2002TL1205>.

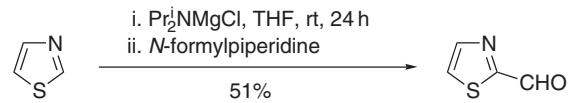


(99)



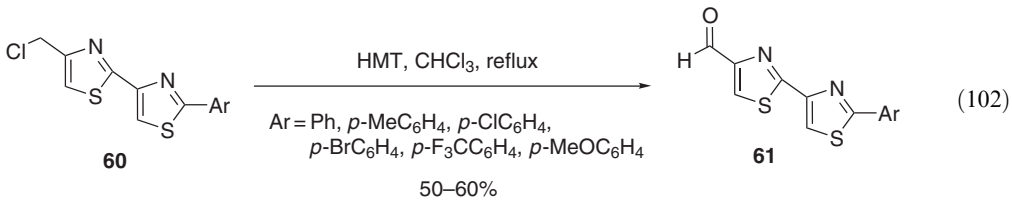
(100)

The selective metallation of thiazole at the 2-position has been recently reported using the magnesium amide base, *i*-Pr_2NMgCl, which on addition of the electrophile, *N*-formylpiperidine, gave thiazole-2-carbaldehyde in good yield, as shown in Equation (101) <2001JCS(P1)442>. These mild magnesium bases allowed the metallation to occur at rt, unlike previous preparations of thiazole-2-carbaldehyde using *n*-BuLi, which required temperatures of −78 °C because of the susceptibility of the organolithium to further reactions <1987S998>.



(101)

Simiti and Oniga described the use of the Sommelet reaction to convert 2,4′-bisthiazole benzyl chlorides **60** into the respective 4-formyl derivatives **61** in 50–60% yield (Equation (102)) <1996M(127)733>.



(102)

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Biographical sketch

Fawaz Aldabbagh was born in Baghdad, Iraq in 1971. He studied in the UK at Brunel University for B.Sc, in 1994 and Ph.D. at Loughborough University, in 1997 under the direction of Professor W. R. Bowman. He spent two years working as a postdoctoral research fellow with Professors I. D. Jenkins and W. K. Busfield at Griffith University, Brisbane, Australia, before taking his current position as a lecturer in organic chemistry at National University of Ireland, Galway in April 2000. Fawaz has diverse research interests, currently including controlled/living nitroxide-mediated free radical polymerizations. The synthesis of biologically active heterocyclic systems using free radical chemistry, as well as research interests in other areas of organic and polymer chemistry. Fawaz is the author of Chapters 3.03, 3.06, and 5.01.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 99–133

3.04
Ketones: Dialkyl Ketones

V. CAPRIO
University of Auckland, Auckland, New Zealand

3.04.1 SATURATED UNSUBSTITUTED KETONES

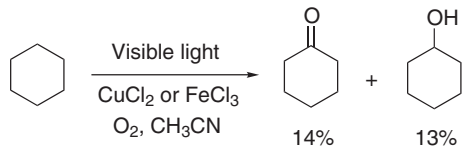
This chapter provides an account of the variety of methods for the synthesis of saturated unsubstituted dialkyl ketones developed since the publication of COFGT (1995). Some progress has been made in a number of the areas detailed in the relevant chapter in COFGT (1995) and major advances have been made in the synthesis of saturated ketones from α,β-unsaturated precursors. The most popular approach to the synthesis of saturated ketones is by the oxidation of secondary alcohols, and this chapter details the modifications that have been made to existing oxidation processes and the range of new oxidizing reagents available.

3.04.1.1 From Alkanes

While major advances have been made in the area of C—H bond activation, the selective oxidation of unactivated hydrocarbons continues to be a challenging subject of research. Investigations in this area have mainly focused on the use of transition metal catalysts in combination with either hydrogen peroxide or *t*-butyl hydroperoxide (TBHP) to oxidize secondary and tertiary C—H bonds of alkanes. To date, such oxidations have been performed on relatively simple alkanes and, in general, conversion and selectivity is moderate to low. Ruthenium(II) complexes have

been used in stoichiometric and catalytic quantities to oxidize C—H bonds in high yield but low selectivity <2000JOC7996>. Better selectivity, in favor of the dialkyl ketone product, has been obtained using ruthenium on carbon in the presence of peracetic acid <2000JOC9186>. Osmium(III) chloride has also been found to act as an efficient alkane oxidation catalyst in the presence of pyridine and hydrogen peroxide <2000CC1131>. Other transition metal catalyst/oxidant combinations used include vanadium(V) salts/H_2O_2 <1997T3603> and manganese(IV) salts/H_2O_2/O_2 <1999T5345>. The latter system utilizes oxygen as the true oxidant and proceeds under very mild conditions to give dialkyl ketones as a mixture with other oxygenates.

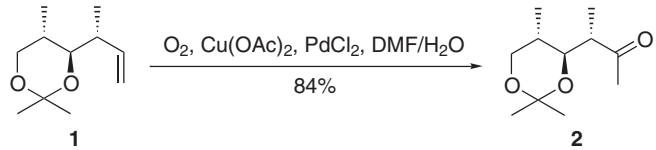
Aerobic oxidation of unactivated hydrocarbons has been achieved using copper(II) acetate as catalyst in the presence of acetaldehyde <2001PAC311> and cyclohexane is oxidized to cyclohexanone and cyclohexanol under mild conditions using copper(II) chloride or iron(III) chloride under visible light irradiation (Equation (1)) <2003BCJ393>.



(1)

3.04.1.2 From Alkenes

The Wacker oxidation is still the most commonly used procedure for the conversion of terminal alkenes into methyl ketones. Recent research in this area has focused on the use of alternate reoxidants and/or solvents to overcome the limitations associated with this procedure. The use of propan-2-ol as a reductant in combination with palladium(II) acetate and molecular oxygen allows the aerobic oxidation of terminal alkenes to methyl ketones to take place in toluene under mild conditions <2000JCS(P1)1915>. In another mild alternative to the standard Wacker oxidation, TBHP and a palladium(II) catalyst bearing perfluorinated ligands is used to oxidize a number of functionalized alkenes in a fluorous biphasic solvent system <1998TL6667>. This method also allows for the convenient separation and reuse of the catalyst. The selective oxidation of long-chain alkenes is achieved by slow addition of the alkene to a solution of palladium(II) acetate and a molybdovanadophosphate reoxidant <2002TL8887> and by the use of cyclodextrins and a biphasic reaction medium <1995TL387>. The Wacker oxidation has also been modified to tolerate the presence of acid-labile functional groups by the use of copper(II) acetate as reoxidant <1998TL8765>. In this operationally simple procedure, alkene **1** is converted into methyl ketone **2** in high yield with no evidence of acetonide hydrolysis (Equation (2)).



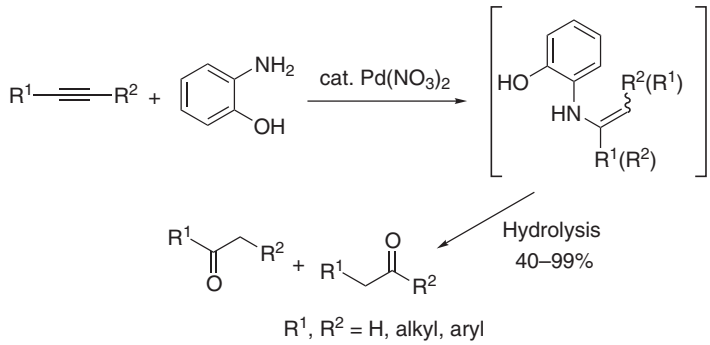
(2)

The oxidative cleavage of C—C double bonds to give methyl ketones is commonly achieved using sodium periodate in the presence of osmium tetroxide and only a few examples of a catalytic oxidative cleavage of alkenes using other oxidants have been reported. A variety of alkenes are selectively oxidized to the corresponding methyl ketone using a combination of manganese, cobalt, or vanadium catalysts and a thiophenol in the presence of molecular oxygen <2001JOC4504>. This transformation may also be achieved using hydrogen peroxide in combination with heteropolyacids adsorbed onto magnesium, aluminum, or zinc oxides <1999CC37>.

3.04.1.3 From Alkynes

A number of stoichiometric and catalytic reagents have been investigated as replacements for toxic mercury(II) salts in alkyne hydrations. Treatment of terminal and internal alkynes with platinum tetrachloride in the presence of carbon monoxide leads to the formation of dialkyl ketones in high yields <1997JOC669>. Gold(I) complexes are highly efficient at catalyzing the hydrolysis of terminal alkynes <2002AC(E)4563>. While this procedure is tolerant of a variety of

functional groups, the reaction proceeds poorly using internal alkynes. The hydration of internal alkynes to give a mixture of regioisomeric ketones is conveniently achieved by hydroamination using *o*-aminophenol in the presence of palladium(II) nitrate catalyst followed by hydrolysis of the enamine intermediate <2002JA12670> (Scheme 1).



Scheme 1

3.04.1.4 From Halides

The oxidation of secondary bromides to dialkyl ketones is achieved in good yield using sodium metaperiodate in dimethyl formamide under mild conditions <2003TL1375>.

A variety of secondary β-bromoalcohols are converted into alkyl ketones in high yield by free-radical elimination of hydrogen bromide using di-*t*-butyl peroxyoxalate <2002JOC312>. Tertiary β-bromoalcohols may be converted into alkyl ketones using a modification of the Kornblum oxidation using DMSO in the presence of zinc sulfide to activate the C—Br bond <2003JOC2460>.

3.04.1.5 From Alcohols and Their Derivatives

3.04.1.5.1 By oxidation of secondary alcohols

The conversion of secondary alcohols into ketones is one of the most common transformations in organic synthesis regularly performed on an industrial scale. Consequently, while the oxidation reagents discussed in COFGT (1995) are still routinely employed <1995COFGT(3)111>, recent attention has focused on modifying traditional reagents and developing oxidative catalysts in the search for mild and environmentally friendly oxidation systems. Research in this area has also been driven by the advent of combinatorial methods and a wide variety of polymer-supported oxidants for use in automated parallel syntheses are now available. The development of selective oxidants is also an active area of research. In general, secondary alcohols are oxidized at faster rates than primary alcohols, and an extensive survey of those reagents that selectively oxidize secondary alcohols in the presence of primary alcohols has been published recently <2001T9765>.

The reagents covered in this section are divided into seven classes: (i) metal-based oxidants; (ii) activated dimethyl sulfoxide reagents; (iii) halogen-based oxidants; (iv) nitrosyl radical/oxoammonium salt catalyzed oxidations; (v) Oppenauer and related oxidants; (vi) electrochemical and photochemical oxidants; and (vii) miscellaneous oxidants.

(i) Using metal-based oxidants

(a) Chromium reagents. Chromium reagents continue to see widespread use as oxidants in organic synthesis despite the problems associated with product isolation and the disposal of toxic chromium waste. Recent research has focused on the development of solid-supported chromium reagents and the use of catalytic quantities of soluble chromium complexes in order to circumvent the problems associated with the use of more traditional chromium-based oxidants.

Chromium dioxide (Magtrieve^{TM}) in chloroform has been shown to be a mild oxidant readily removed by magnetic separation <1997TL3857>. Chromium trioxide has been immobilized on silica gel <1996SC205, 2003T4997> and on wet alumina <1998TL1481> to give oxidizing agents readily removed by filtration and bis(trimethylsilyl) chromate supported on silica gel oxidizes a wide variety of alcohols in very high yield under mild conditions <1996SC543>.

Chromium(III) complexes have been found to catalyze the oxidation of alcohols to aldehydes and ketones in the presence of co-oxidants, but to date this methodology has been largely limited to the oxidation of allylic and benzylic alcohols. Chromium(III)(salen) complexes selectively oxidize a variety of benzylic and allylic ketones in the presence of iodosobenzene diacetate <2000OL2773> and iodosobenzene <2003SL1391> under mild conditions but the oxidation of unactivated alcohols requires more forcing conditions. Similar transformations have been achieved in high yield using chromium(III) acetylacetonate and periodic acid in acetonitrile <2003TL2553>.

(b) Manganese reagents. Manganese dioxide is a valuable oxidizing reagent but its use is limited to the oxidation of benzylic and allylic alcohols and by the large excesses often required. It has recently been discovered that the use of MnO_2 can be extended to effect the oxidation of secondary alcohols to saturated ketones under solvent-free conditions <2002TL6149>. A more economic and environmentally friendly manganese oxide-based oxidant is represented by microporous mixed-valency manganese oxides. These octahedral molecular sieve (OMS) materials are readily prepared from potassium permanganate and have been shown to be efficient and reusable catalysts for the aerobic oxidation of a variety of alcohols under mild conditions <2001AC(E)4280>.

A number of homogenous manganese(II)- and manganese(III)-based catalysts have also been developed to effect the oxidation of alcohols. Manganese(II) acetate or sulfate in the presence of 1,4,7-trimethyl-1,4,7-triazacyclononane (TMTACN) and ascorbic acid catalyzes the oxidation of secondary alcohols in acetonitrile using hydrogen peroxide as reoxidant <1999TL7965>. Manganese-catalyzed oxidations have also been performed under aqueous conditions. Water-soluble manganese(III)(salen) complexes have been found to be effective catalysts for the oxidation of secondary alcohols. A number of chiral Mn(salen) complexes have been used to catalyze the oxidation of alcohols using iodosobenzene diacetate as co-oxidant in water, and this procedure has been used to effect the kinetic resolution of secondary alcohols <2003AC(E)1042>.

(c) Ruthenium reagents. The use of ruthenium complexes to catalyze oxidations has been known for sometime. The major drawback in the use of these oxidation systems is the need for a large excess of co-oxidant. The main subject of current research has been in the development of novel homogenous catalysts, that efficiently utilize inexpensive and more environmentally benign co-oxidants, and in readily prepared heterogeneous catalysts that may be easily recycled.

Bis(triphenylphosphine)ruthenium(II) chloride in combination with 2,2′,6,6′-tetramethylpiperidine *N*-oxyl (TEMPO) has been found to be an efficient catalyst for the aerobic oxidation of a variety of secondary alcohols in chlorobenzene <2001JA6826>. A ruthenium(III) complex with *N*,*N*′,*N*″-triazacyclononane using *t*-butyl hydroperoxide as terminal oxidant is also an effective oxidation catalyst in dichloromethane <1998JOC2873> and a recyclable silica gel immobilized version of this catalyst is now available <2002JOC7716>. Another example of a heterogenous ruthenium-based catalyst is ruthenium(III) combined with microcrystals of cobalt hydroxide and cerium oxide <2002TL7179>. This system is an efficient catalyst for the oxidation of secondary alcohols in trifluoromethylbenzene under 1 atm of oxygen. A more environmentally friendly stable and reusable catalyst composed of ruthenium dioxide nanoparticles confined in a zeolite has been recently developed <2003JA2195>. The catalyst is prepared in one step from ruthenium trichloride and an aluminosilicate gel and catalyzes the oxidation of secondary alcohols in air without the need for any secondary oxidant.

Tetrapropylammonium perruthenate (TPAP) is the most popular ruthenium-based oxidant available. The reagent is generally used in catalytic quantities in combination with a stoichiometric excess of *N*-methylmorpholine-*N*-oxide (NMO). Recent research has focused on modifying this system to provide a more ecological and economical process. A novel approach to the recycling and reuse of the oxidation catalyst is through the use of an ionic liquid as solvent. TPAP smoothly oxidizes a variety of secondary alcohols in 1*H*-imidazolium hexafluorophosphate ([emim][PF_6]). The catalyst is sequestered in the ionic liquid on addition of diethyl ether and readily isolated for reuse <2001CC2278>.

The most popular approach to the isolation and reuse of TPAP is by immobilizing this reagent on a solid support. A polymer-supported TPAP has been synthesized using Amberlyst anion exchange resin (IR 27) <1997JCS(P1)1907>. The resulting reagent resin still requires NMO as

co-oxidant but the catalyst is readily isolated by filtration. Sol–gel-encapsulated TPAP, readily prepared by a one-step sol–gel process, is a heterogenous form of TPAP that catalyzes the aerobic oxidation of alcohols. This catalyst has been found to be more active than unsupported TPAP and recyclable <2003CEJ5067>. Alternative co-oxidants for this process have been investigated. Homogeneously catalyzed TPAP oxidations can be performed using oxygen as co-oxidant <1997JCS(P1)3291> and polymer-supported NMO has also been investigated as a recyclable co-oxidant <2001SL1257>.

(d) Miscellaneous metal oxidants. A wide variety of palladium(II) and palladium(0)-based catalytic systems have been used to good effect in the oxidative dehydrogenation of secondary alcohols to give ketones and this area has been the subject of a recent review <2003T5789>. Both homogeneous and heterogeneous catalyst systems have been investigated and a wide variety of co-oxidants, including oxygen, peroxides, and organic halides are tolerated.

Polyoxometalates have seen increasing use as mild oxidation catalysts <1998CRV171>. A vanadium-containing polyoxomolybdate has been found to catalyze the nitrous-oxide-activated oxidation of primary and secondary alcohols <2003AC(E)92>. A readily prepared water soluble zinc/tungsten-containing polyoxometalate catalyzes the aqueous hydrogen peroxide oxidation of secondary alcohols. Another example of an oxidation process with aqueous hydrogen peroxide utilizes sodium tungstate as catalyst <1997JA12386>. This economic and environmentally friendly process can be used to oxidize a wide variety of secondary alcohols in toluene or under solvent free conditions and is highly amenable to scaleup. An example of an iron-catalyzed oxidation is an iron(II) nitrate–iron tribromide-catalyzed aerobic oxidation performed in acetonitrile at room temperature <2002TL4475>. This mild reaction does not require any co-oxidant and selectively oxidizes secondary alcohols in the presence of primary alcohols.

The use of fluorous biphasic systems in oxidations has been extended to copper-catalyzed processes. Copper bromide as the dimethyl sulfide complex catalyzes the oxidation of secondary alcohols in the presence of fluorous bipyridine ligands using TEMPO and oxygen in a mixture of chlorobenzene/perfluorooctyl bromide <2002T3985>. The perfluorinated phase could be reused for further runs after separation.

(ii) Using activated dimethyl sulfoxide reagents

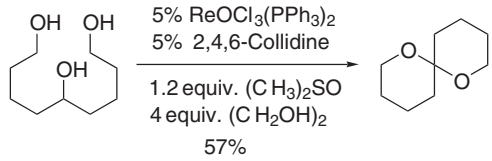
The Swern oxidation procedure is a widely used method for the oxidation of secondary alcohols but cannot be considered as an environmentally friendly process owing to the production of large quantities of malodorous dimethyl sulfide as a by-product. Much recent research has been directed toward the development of modified Swern oxidations using polymer-bound dimethyl sulfoxide or long-chain sulfoxides that lead to the formation of odorless sulfides.

Sulfoxides have been attached to polyethylene glycol (PEG) to give soluble polymer-bound oxidizing reagents <1998JOC2407>. These reagents are used in a typical Swern procedure and are easily separated and recycled. Sulfoxides bound to noncrosslinked polystyrene (NCPS) are another example of a soluble, polymer-bound sulfoxide <2003T7171>. These reagents were also used to good effect in the Swern oxidation and are again readily isolated and recyclable.

Another approach to the development of odorless Swern oxidations is the use of fluorous sulfoxides <2001JA7449>. Continuous extraction of the product residue with fluorous hydrocarbons allows isolation of the resulting sulfide for recycling. Dodecyl methyl sulfoxide is a readily prepared reagent that also may be used in the Swern oxidation to give odorless by-products <2003T8393>.

A number of different activators have also been investigated to avoid the use of the toxic, irritant oxalyl chloride. Both triphenylphosphine dibromide and triphenylphosphine dichloride effectively activate DMSO at $-78\,^{\circ}C$ and may be used in the Swern oxidation to give ketones in high yield <2002TL8355>. 2,4,6-Trichloro[1,3,5]triazine has also been used as a mild and very cheap activator of DMSO allowing the Swern procedure to be performed at $-30\,^{\circ}C$ in THF <2001JOC7907>.

An oxidation procedure of much synthetic potential is provided by the rhenium-activated DMSO oxidation of secondary alcohols in the presence of ethylene glycol <1999OL769>. This procedure is performed using a rhenium complex as catalyst in toluene and conveniently supplies the corresponding ethylene ketal as the major product. This system oxidizes secondary alcohols in the presence of primary alcohols and has been successfully applied to the direct conversion of 1,5,9-nonanetriol to the corresponding [6.6]-spiroacetal (Equation (3)).



(3)

(iii) Using halogen-based oxidants

Secondary alcohols are smoothly oxidized to ketones using elemental bromine in the presence of a catalytic quantity of *N*-*t*-butyl-nitrobenzenesulfenamide, potassium carbonate, and molecular sieves <2003CL182>. Bromine adsorbed on neutral alumina has also been found to be an effective reagent for the oxidation of secondary alcohols <2000SC963>.

Sodium hypochlorite (bleach) provides a cheap oxidizing reagent that converts secondary alcohols into ketones in high yield under mild conditions <1998TL7263>. A variety of secondary alcohols are oxidized in high yield using aqueous sodium hypochlorite in ethyl acetate:water in the presence of a phase-transfer catalyst at room temperature. An example of a bromine(I) oxidizing reagent is bis(collidine)bromine(I) hexafluorophosphate <2000TL8881>. This compound oxidizes a wide variety of secondary alcohols using an operationally simple procedure but is not compatible with the presence of *p*-methoxybenzyl ethers.

A number of higher-oxidation-state halogen-based oxidants are available. The most important of these is undoubtedly Dess–Martin periodinane. Although this reagent is a popular nonacidic, mild oxidant early preparations resulted in the generation of large amounts of bromine and often resulted in the isolation of poor quality product. A number of modified preparations of Dess–Martin periodinane from 2-iodobenzoic acid have now been developed, notably that by Boeckman and co-workers <2000OS141> using potassium bromate as oxidant and that by Frigerio and co-workers <1999JOC4537> that avoids the hazardous generation of bromine by the use of Oxone® as oxidant. The Dess–Martin oxidation has been modified for use in solution-phase chemical library synthesis <1999T6785>. The oxidation is performed under mild conditions and treatment with a thiosulfate resin followed by a base-functionalized resin results in sequestration and ready removal of reagent by-products.

Other iodine(V) compounds have been investigated as oxidizing agents. 2-Iodoxybenzoic acid (IBX) is the initial product formed during the synthesis of Dess–Martin periodinane and this compound also readily oxidizes secondary alcohols <1995JOC7272>. The reagent is tolerant of moisture but the insolubility of IBX requires the use of highly polar solvents such as DMSO. A polymer-bound version of IBX has been synthesized and investigated as an oxidant for use in chemical library construction <2001AC(E)4395>. Polystyrene-bound 2-iodobenzoic acid is treated with tetrabutylammonium oxone to give an immobilized version of IBX, stable to air and moisture, that oxidized a variety of alcohols.

Iodine(V) reagents are potentially explosive and unstable, and some research has been directed toward the use of more stable derivatives. 2-Iodoxybenzamides, readily prepared by dimethyl dioxirane oxidation of the corresponding 2-iodobenzamide, display similar oxidizing properties to IBX but are of greater stability and more soluble in organic solvents <2003AC(E)2194>. Iodine(III) reagents are also beginning to be investigated as oxidants. Iodosobenzene oxidizes a variety of secondary alcohols to ketones in water in the presence of potassium bromide <2000AC(E)1306>. Polymer-bound (diacetoxyiodo)benzene also effects the same transformation in the presence of potassium bromide.

(iv) Using nitrosyl radical/oxoammonium salt catalyzed oxidations

The nitrosyl radical TEMPO has become one of the most important metal-free oxidizing reagents available <1996S1153>. The reactive intermediate in TEMPO oxidations is thought to be an oxoammonium salt that is reduced to a hydroxylamine. While TEMPO may be used stoichiometrically, it is most often utilized as a catalyst in the presence of a co-oxidant. A wide variety of cooxidants have been used. Recent examples of TEMPO/co-oxidant combinations include 10% TEMPO/iodosobenzene diacetate in dichloromethane <1997JOC6974> and 1% TEMPO/MCPBA <1999JOC310>. The oxidation of secondary alcohols may also be achieved using Oxone® as co-oxidant, and this procedure is tolerant of silyl ethers <2000OL1173>. Research

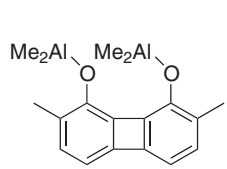
has also been conducted into the use of oxygen in combination with TEMPO. Alcohols are oxidized to aldehydes and ketones in good yield using TEMPO in combination with manganese(II) and cobalt(II) nitrate in acetic acid under oxygen <2001TL6651>. Aerobic oxidation is also achieved using TEMPO in combination with a polyoxometalate co-catalyst in acetone under 2 atm of oxygen <2001JOC8650>. Polymer-bound co-oxidants have also been used in combination with TEMPO. A polystyrene-bound bromite complex has been shown to be an efficient cooxidant in TEMPO-catalyzed oxidations and is isolated for reuse by filtration at the end of the reaction <2000OL3781>.

Expensive TEMPO may be converted into a heterogenous catalyst that may be isolated and recycled. This reagent has been anchored to silica gel <1999CC1795> and also entrapped in a sol–gel system <2000CC1441>. Oxidation of Chimassorb 944, an oligomeric, hindered amine, with sodium tungstate gives a polymer-immobilized form of TEMPO that catalyzes the oxidation of alcohols using aqueous sodium hypochlorite <2001SL102>. Insoluble polystyrene-bound oxoammonium halides have been synthesized and shown to be effective oxidizing reagents at stoichiometric levels with potential for use in a variety of polymer-assisted, solution-phase operations including automated parallel synthesis <2001AC(E)1436>.

(v) Oppenauer and related oxidations

The classical Oppenauer oxidation is a highly chemoselective oxidation process but disadvantages of this method include the use of high temperatures, large quantities of ketone hydride acceptors and the production of aldol condensation products with the hydride acceptors. Research has focused on the development of more efficient Oppenauer-type oxidations that may be performed under milder conditions.

Diisopropoxyaluminum trifluoroacetate efficiently catalyzes the oxidation of a variety of secondary alcohols in benzene at room temperature using 4-nitrobenzaldehyde as hydride acceptor <1997TL6925>. Other examples of aluminum-based Oppenauer catalysts include the bidentate complex **3**, used in tandem with pivaldehyde in dichloromethane <2002S279> and complex **4**, used in combination with pivaldehyde or acetone in toluene <2002OL2669>. Both complexes catalyze the oxidation of a number of secondary alcohols in high yield at room temperature.



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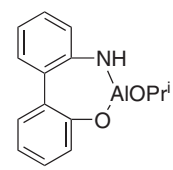

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The Oppenauer oxidation can also be performed with transition metal-based catalysts. Zirconium(IV) alkoxides catalyze the quantitative conversion of a number of nonhindered secondary alcohols into ketones using potassium *t*-butoxide as hydride acceptor in toluene in the presence of molecular sieves <1996JOC1467>, and ruthenium(II) complexes catalyze the Oppenauer oxidation of hydroxysteroids in acetone under reflux <1996JOC6587>.

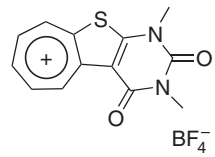
(vi) Electrochemical and photochemical oxidants

The electrochemical oxidation of secondary alcohols represents an attractive, environmentally benign method for synthesizing ketones as it could, in principle, proceed without the requirement for chemical oxidants. In practice, the oxidation potential of alcohols is high and intermediary species, that are reoxidized at the anode, are required to oxidize alcohols.

Electrooxidations using chiral nonracemic mediators have been used in the kinetic resolution of secondary alcohols <1999TL6469, 2000TL8131>. In an operationally simple procedure, an aqueous silica gel disperse system is used to oxidize secondary alcohols in an undivided beaker-type cell with platinum foil electrodes. The use of optically pure *N*-oxyl radicals as mediators

leads to the isolation of optically pure secondary alcohols in moderate-to-good enantiomeric excess <2001TL445>. Polyethylene-bound *N*-oxyl mediators have also been used as the disperse phase in this procedure <2003SL951>.

The photochemical oxidation of secondary alcohols is an area that has received little attention. Tetrafluoroborate salt **5** catalyzes the photo-induced aerobic oxidation of cyclohexanol in acetonitrile but the scope of this process has not been investigated <2003T4929>.



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(Nitroso)(salen)ruthenium(II) chloride has also been found to be an efficient catalyst for the photo-induced aerobic oxidation of secondary alcohols <2000TL5119>. The use of optically active ruthenium complex leads to the kinetic resolution of secondary alcohols under these conditions. Photochemical and electrochemical processes have been coupled to provide a novel oxidizing catalyst cycle <2003JA10133>. In this example, sulfo-polyoxometallates, activated photochemically, oxidize a variety of alcohols. These catalysts are then regenerated by application of an external potential.

(vii) Miscellaneous oxidants

Peroxides are potentially ideal oxidants for the conversion of secondary alcohols into ketones. A variety of secondary alcohols are converted into ketones in high yield using aqueous hydrogen peroxide in the presence of catalytic sodium tungstate <1997JA12386>. This oxidizing reagent has also been used in combination with methyltrioxorhenium and bromide ion as catalysts to effect the same transformation.

The oxidation of secondary alcohols has been achieved in high yield using the sodium salt of *N*-chloro-4-chlorobenzenesulfonamide as catalyst and dimethyl-2,2′-diselenodibenzoate as co-catalyst in 1,2-dichloroethane <1996BCJ3601>.

The oxidation of alcohols proceeds in moderate-to-good yield under the same conditions as a Swern oxidation using dimethyl(trifluoromethanesulfonyl)sulfonium triflate prepared *in situ* from dimethyl sulfide and triflic anhydride <1997JOC2483>.

3.04.1.5.2 From diols

The conversion of 1,2-diols into ketones is an increasingly attractive transformation owing to the recent progress made in the syntheses of pinacols. The traditional pinacol–pinacolone rearrangement suffers from a number of drawbacks such as the formation of dehydration products and the incompatibility of the reaction conditions with acid-labile functionality. Research has focused on developing modified pinacol rearrangements to alleviate some of these problems. A recent study into the effects of various acids on this rearrangment has indicated that the levels of dehydration by-products increases with decreasing acid concentration <2002TL9307>. A pinacol rearrangement of potentially broad synthetic scope has been performed using trialkyl orthoformates in the presence of catalytic amounts of Lewis acids, and this procedure is compatible with diols bearing acid-labile functionality <1998T14689>. This rearrangment has also been catalyzed by phosphonic acid-functionalized microporous silicas <2001CC67> and proceeds in the absence of catalyst in supercritical water <1999AC(E)2910>.

Little attention has been directed toward the development of new reagents for the oxidative cleavage of tertiary 1,2-diols to give ketones. A conveniently prepared silica gel-supported sodium periodate effects the cleavage of a range of diols in high yield without the need for chromatography <1997JOC2622> and pyridinium dichromate has also been found to oxidatively cleave vicinal tertiary alcohols under mild conditions <2000JIC651>.

3.04.1.5.3 By oxidation of derivatives of alcohols

(i) Ethers

Only a small number of new reagents have been applied to the oxidative cleavage of alkyl ethers to give ketones. Most recent attention in this area has been directed toward the development of new methods for converting silyl and tetrahydropyranyl ethers into ketones in one pot using oxidative deprotection strategies.

A number of alkyl ethers are oxidized to ketones in high yield using perfluoro-*cis*-2,3-dialkyloxaziridines in Freon-11 at room temperature <1995JOC2314>. Methyl ethers are also directly converted into carbonyl compounds under mild conditions using nitrogen dioxide in dichloromethane or hexafluoro-2-propanol with added water <1997BCJ3111>. This transformation may also be carried out using nitrogen dioxide and ozone in the absence of water but proceeds at a slower rate. A one-pot, deprotective oxidation strategy has been applied to the conversion of a wide variety of secondary *O*-allyl ethers into ketones <1999SL1063>. This transformation is achieved using catalytic amounts of chromium trioxide in the presence of *t*-butyl hydroperoxide in dichloromethane and is tolerant of a variety of acid-labile protecting groups including THP, TBDMS, and MOM ethers.

The use of oxidative deprotections has become the most common method for the conversion of tetrahydropyranyl and silyl ethers into ketones. A number of reagent systems used to effect this transformation utilize chromium(VI)-based oxidants. 3-Carboxypyridinium chlorochromate in acetonitrile under reflux converts a variety of secondary THP and TMS ethers into ketones <1997S756>. Both types of ether have also been cleaved to ketones in a solvent-free system using chromium trioxide supported on wet alumina <1999S393>. The readily prepared coordination polymer of oxodiperoxochromium(VI) with pyrazine can be used to oxidize a variety of organic compounds and converts trimethylsilyl ethers into ketones under mild conditions in high yield <1997T7889>.

A variety of other reagents have also been developed to oxidatively cleave tetrahydropyranyl and silyl ethers. Butyltriphenylphosphonium peroxodisulfate effectively cleaves both types of ether in acetonitrile under reflux and also effects the cleavage of acetals in high yield <2002SC1311>. The same spectrum of reactivity is exhibited by potassium permanganate supported on alumina, and this method may be performed under solvent-free conditions <2002SC771>. This oxidative deprotection may also be performed under aerobic conditions using easily recovered, catalytic amounts of manganese or cobalt salts of 4-aminobenzoic acid supported on silica gel <2000SC1857>. While the above methods are restricted to the cleavage of trimethylsilyl ethers, a method has been developed for the conversion of *t*-butyldimethylsilyl ethers into ketones. Bis(acetonitrile)dichloropalladium(II) in DMF/acetone/water catalyzes the conversion of a number of *t*-butyldimethylsilyl ethers to ketones <1996JOC2918>. This method also cleaves trimethylsilyl ethers but does not remove triisopropyl or *t*-butyldiphenylsilyl ethers.

(ii) Esters

Benzoylformate esters are converted into aldehydes and ketones via photochemical hydrogen transfer and have been investigated as photochemically labile protecting groups <1995JOC2461>. Cyclododecylbenzoylformates are readily prepared from the corresponding benzoylformic acid and cyclododecanol. Irradiation of the benzoylformate in acetonitrile at 350 nm gave cyclododecanone in high yield (Scheme 2).

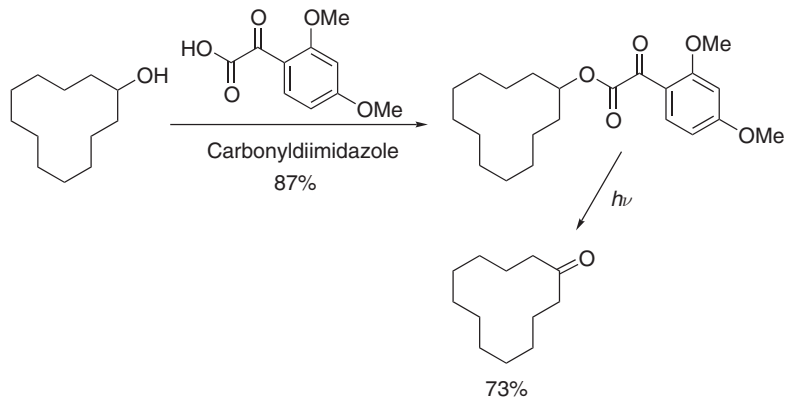
(iii) Carbonates

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(3)111>.

3.04.1.5.4 Isomerization of allylic alcohols

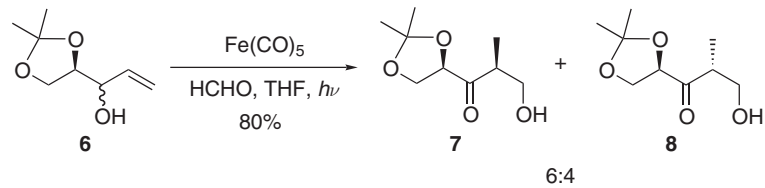
A range of allylic alcohols are isomerized to ketones in high yield in THF using a variety of novel rhodium and ruthenium catalysts readily prepared *in situ* from commercially available starting materials <2001EJOC3141>. This method does not proceed with propargylic or

primary alcohols. Catalytic quantities of TPAP can also be used to isomerize allylic alcohols <1999AC(E)1960>. In the presence of 2-undecanol and the absence of oxygen, TPAP is reduced to a Ru(III) intermediate that effects the isomerization of secondary alcohols in good yield in degassed fluorobenzene. This isomerization has also been performed in an aqueous biphasic medium of water:*n*-octanol using a rhodium(I) complex as catalyst <2001NJC11>.



Scheme 2

Iron pentacarbonyl catalyzes the isomerization of a broad range of allyl alcohols to ketones in pentane under UV light irradiation <2001T2379>. This transformation proceeds via the formation of a metal enolate that maybe trapped out with aldehydes in a tandem isomerization–aldol sequence <2003TL6187>. As an example, allyl alcohol **6**, readily available from D-mannitol, gives aldol products **7** and **8** in good yield upon irradiation with a mixture of iron pentacarbonyl and formaldehyde (Equation (4)) <2003JOC6392>.

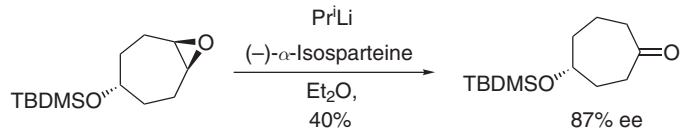


(4)

3.04.1.6 From Epoxides

Epoxides rearrange to carbonyl compounds in the presence of a variety of Lewis acids. This transformation is limited by the stoichiometric amounts of harsh Lewis acid often required and by the formation of mixtures. Indium(III) chloride catalyzes the rearrangement of a variety of substituted epoxides in THF under mild conditions. The isomerization of benzylic epoxides occurs with high regioselectivity in high yield <1998JOC8212>. Bismuth(III) oxide perchlorate is a commercially available air-insensitive Lewis acid that smoothly catalyzes the rearrangement of benzylic and aliphatic epoxides containing a tertiary carbon to ketones in dichloromethane <2000TL1527>.

Certain epoxides will undergo base-induced rearrangement to ketones via α-deprotonation, and this process has been achieved in an enantioselective manner using chiral lithium amide bases or organolithiums in the presence of (−)-sparteine. A number of bicycloalkene-derived epoxides are converted into ketones in moderate ee using lithium (*S*),(*S*)-bis(1-phenyl)-ethylamide as base <1997TA519>. Cycloheptene oxides are also rearranged to ketones in an enantioselective manner. *Trans*- and *cis*-5-silyloxycyclopentene oxides gave 4-silyloxycycloheptanones in high ee upon treatment with *iso*-propyllithium and (−)-α-isosparteine in diethyl ether at −98 °C (Equation (5)) <1999TL8637>.



(5)

3.04.1.7 From Acetals

A wide variety of acetals may be used to protect carbonyl compounds and a range of conditions and reagents have been used to regenerate the carbonyl group. This section will concentrate on reagents recently developed to deprotect acetals. Readers requiring a comprehensive review of the use of acetals in organic synthesis are advised to consult the specialist texts on the subject of protecting groups such as Greene and Wuts <B-99MI001> and Kocienski <B-03MI002>.

Cyclic and acyclic acetals are commonly deprotected by acid-catalyzed hydrolysis. Recent research has focused on developing new methods that are milder and more chemoselective than those traditionally used. Bismuth(III) nitrate pentahydrate is an inexpensive reagent that may be used to deprotect acetals <2000JOC8399>. Use of 25 mol.% bismuth nitrate in dichloromethane effects the deprotection of a variety of dimethyl acetals and this reagent is selective for dimethyl acetals over ethylene ketals and is also tolerant of THP ethers and TBDMS ethers. Bismuth(III) triflate in THF/water exhibits a similar reactivity profile and this reagent may be used in catalytic quantities <2002JOC1027>. Magnetically retrievable chromium dioxide (Magtrieve^{TM}) is a deprotection reagent that is also selective for dimethyl acetals over ethylene ketals <1999TL6025>.

Both cyclic and acyclic ketals are hydrolyzed using catalytic amounts of carbon tetrabromide in acetonitrile:water under ultrasonication <1997T14255>. This method is selective for the hydrolysis of ethylene ketals over 1,3-dioxanes. Cerium(III) chloride in acetonitrile in the presence of catalytic quantities of sodium iodide can also be used to hydrolyze ethylene ketals <1997JOC4183>. This method deprotects ketals of conjugated enone systems at a faster rate than those of saturated systems and also hydrolyzes ethylene ketals of ketones over those of aldehydes. Catalytic quantities of polymer-supported dicyanoketene acetal (DCKA) can be used to deprotect acetals and ethylene ketals in acetonitrile:water under neutral conditions <1999SL1960>. This method is tolerant of primary MOM and TBDPS ethers and the catalyst is easily recovered and reused without loss of activity.

3.04.1.8 From Aldehydes or Ketones

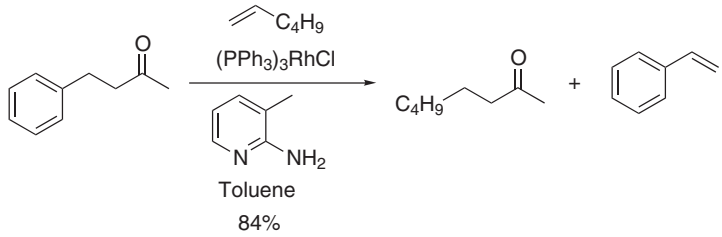
3.04.1.8.1 From saturated aldehydes or ketones

(i) Alkylation

The alkylation of ketones is a fundamental C—C bond-forming process and a wide variety of methods for the synthesis of alkyl ketones, in a regio- and stereoselective manner, from enolates now exist. Only the most recent methods developed for the formation of alkyl ketones, directly from ketones, will be discussed in this section. Readers seeking a comprehensive introduction to this subject are advised to consult the relevant section in COFGT (1995) <1995COFGT(3)111>.

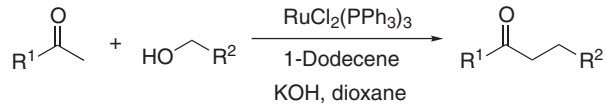
While the deprotonation of unsymmetrical ketones under thermodynamic control usually leads to formation of the more highly substituted enolate selectivity is often only moderate. It has been found that prior complexation of unsymmetrical ketones with the bulky Lewis acid aluminum tris(2,6-diphenylphenoxide) (ATPH) results in α-deprotonation, using LDA, at the more hindered site to give the more highly substituted ketone enolate with high selectivity <1997JA611>. Quenching of these enolates with a variety of alkylating agents leads to the formation of α-alkylated products, regioselectively in high yield.

The α-alkylation of ketones may also be achieved using homogeneous transition metal catalysts. [Chlorotris(triphenylphosphine)rhodium(I)] catalyzes the exchange of an alkyl group in a ketone with an alkene via C—C bond activation and cleavage <1999JA880>. As an example, benzylacetone reacts with 1-hexene in the presence of the catalyst and 2-amino-3-picoline to give 2-octanone and styrene (Equation (6)). A variety of unstrained ketones may be used as substrates.



(6)

Ruthenium(III) complexes catalyze the transfer of alkyl groups from a range of imines and trialkylamines to the α-carbon of a variety of ketones <2001AC(E)958> and ruthenium(II) complexes catalyze the regioselective alkylation of ketones with a range of primary alcohols in the presence of 1-dodecene as hydrogen acceptor and KOH in dioxane <2002TL7987> (Equation (7)). The latter process proceeds by a ruthenium-catalyzed transfer hydrogenation using the alcohol as a hydrogen donor to give an aldehyde followed by C—C bond formation via a crossed aldol reaction.

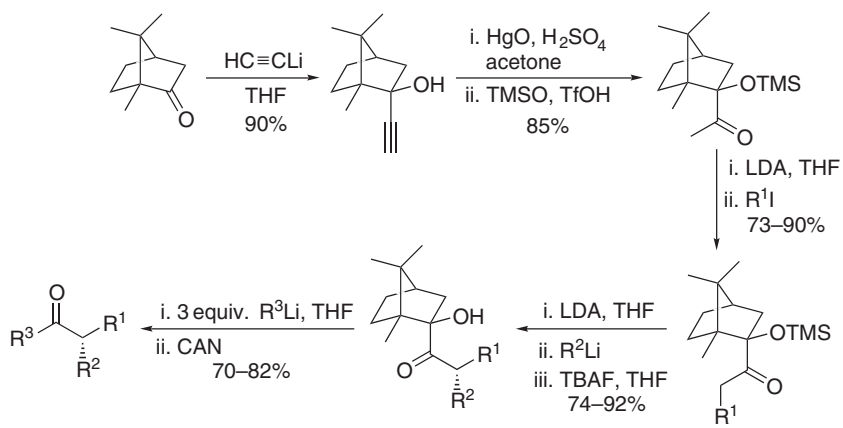


(7)

The generation of α-keto carbon radicals and their addition to alkenes is a potentially useful process for alkyl ketone construction that has only recently received attention. The α-keto radical of acetone is generated by reaction with manganese(III) acetate generated *in situ* using potassium permanganate and manganese(II) acetate <1995T9917>. Acetone reacts with a variety of alkenes in the presence of glacial acetic acid, potassium permanganate, and manganese(II) acetate to give α-alkylated products in moderate yields. The radical addition of ketones to alkenes is also mediated by catalytic quantities of manganese(II) acetate and cobalt(II) acetate in acetic acid under 1 atm of oxygen <2000CC2317>.

Asymmetric alkylation of achiral ketone enolates with alkyl halides has been achieved using catalytic quantities of chiral tetradentate amine ligands in the presence of achiral bidentate amines <2000T179>. Enantioselectivity in this reaction is thought to arise from the formation of a chiral complex of the enolate with the tetradentate amine.

The alkylation of α-hydroxyketones derived from (1(*R*))-(+)-camphor is an example of an auxiliary-controlled, asymmetric alkylation that proceeds via formation of a ketone enolate <1999JOC8193, 2001OL3249>. In this process, an acetylide anion is added to (1(*R*))-(+)-camphor. Hydration of the alkyne followed by sequential alkylation and oxidative cleavage of the auxiliary gives α-branched ketones in high ee (Scheme 3). The overall process may be thought of as an asymmetric alkyne hydration.

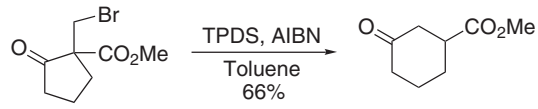


Scheme 3

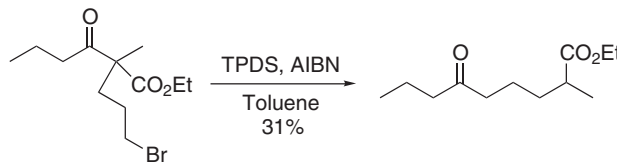
(ii) Homologation

A range of dialkyl ketones undergo regioselective one-carbon homologation with the introduction of a methoxy group in high yield on treatment with the lithium salt of [(methoxymethyl)sulfonyl]benzene in THF followed by zirconium or hafnium tetrachloride <1997JCS(P1)2821>. Carbon-insertion processes can also be used to access a wide variety of α-aryl- and α-heteroaryl-substituted ketones. Treatment of cyclic and acyclic ketones with the lithium anion of a variety of 1-(arylmethyl)- and 1-(heteroarylmethyl)-benzotriazoles in THF followed by *in situ* rearrangement in the presence of zinc bromide gives one-carbon chain-extended or ring-expanded α-functionalized ketones in good yield <1996JOC7571>. This procedure can also be used to effect the homologation of aldehydes.

Carbon homologation can also be achieved using radical processes. Treatment of α-bromomethyl cyclic β-keto esters with samarium diiodide in THF provided the one-carbon homologated γ-keto ester in good yield <1998TL4059>. A wider variety of acyclic and cyclic α-haloalkyl γ-keto esters undergo one-carbon homologation using tetraphenyldisilane (TPDS) as the radical reagent in the presence of AIBN in toluene <2002T3171> (Equation (8)). Three-carbon homologation of acyclic α-haloalkyl β-keto esters can also be achieved using this procedure (Equation (9)).



(8)

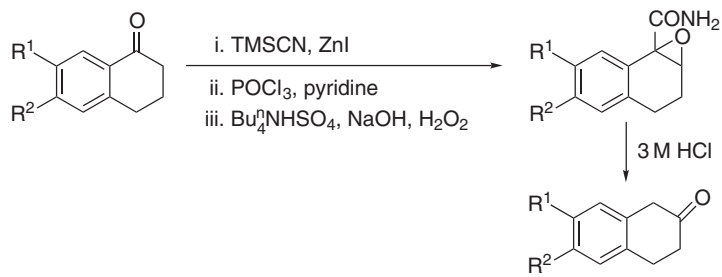


(9)

Cyclic α-bromomethyl β-keto esters also undergo ring expansion using photochemical methods. Irradiation of a mixture of the keto ester, 1,3-dimethyl-2-phenylbenzimidazole (DMPBI) in the presence of 1,6-bis(dimethylamino)pyrene (BDMAP) as sensitizer in DMF gives the ring-expanded product in moderate yield <1999T12957>.

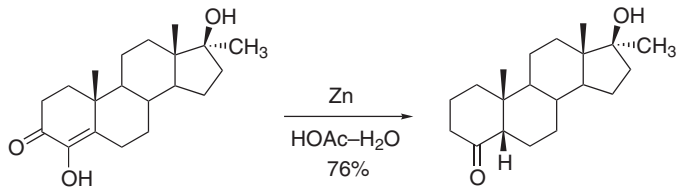
(iii) Transposition

The synthesis of 2-tetralones may be achieved by 1,2-carbonyl transposition of 1-tetralones. Epoxyamides, readily accessed from 1-tetralones in three steps, are converted into 2-tetralones in good yield upon treatment with 3 M HCl (Scheme 4) <1996TL3243>.



Scheme 4

Steroidal 5α- and 5β-ketones can be synthesized from the corresponding steroidal 4-en-3-one by 1,2-carbonyl transposition using zinc–acetic acid <1999T3717>. In this example, treatment of the diosphenol **9** with zinc dust in acetic acid and water at room temperature gives the 5β-4-one **10** as the major product (Equation (10)).



9 10 (10)

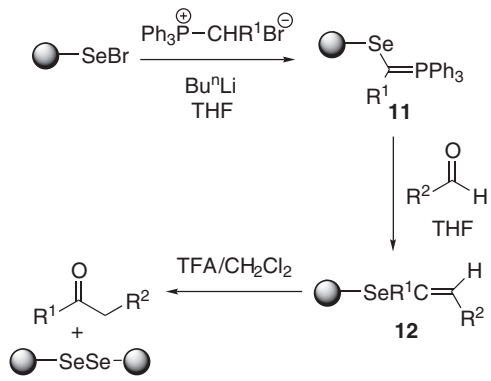
(iv) From aldehydes

The homologation of an aldehyde to give an alkyl ketone may be achieved in one step using diazoalkanes in the presence of Lewis acids. The limitations associated with handling diazoalkanes are avoided by the use of benzaldehyde tosylhydrazone salts, which generate phenyl diazomethane *in situ* upon heating. A variety of aldehydes are converted into benzylic ketones using this reagent. This reaction may be performed using sodium hydroxide or sodium alkoxides in alcohol solvents <2000JOC6458> or in THF/H_2O <2000TL10327>. The latter procedure can be used to generate the tosylhydrazine *in situ* from the appropriate aldehyde and tosylhydrazine.

The one-carbon homologation of aldehydes to give methyl ketones may be achieved using a two-step procedure. The reaction of an aldehyde with carbon tetrabromide/triphenylphosphine and treatment of the resulting 1,1-dibromo-1-alkene with zinc in near-critical water using a high-pressure steel reactor affords a variety of methyl ketones in good yield <2003TL4685>.

Hydroacylation of alkenes to give methyl ketones may be achieved using a rhodium(I) complex as catalyst to activate the aldehydic C—H bond <1997JOC1200>. A range of aldehydes react with a variety of alkenes in the presence of the catalyst and 2-amino-3-picoline in toluene to give ketones in moderate-to-high yields. Simple alkenes also undergo hydroacylation in the presence of acyl radicals <2001CC2352>. Various aldehydes form acyl radicals, in the presence of *N*-hydroxyphthalimide (NHPI) and dibenzoyl peroxide. These acyl radicals add to a number of alkenes in toluene to give ketones in high yield.

Aldehyde homologation can also be performed using polymer-supported reagents. Polymer-bound selenium bromide undergoes transylidation with alkylidinetriphenylphosphoranes to give polymer-supported selenophosphoranes **11**. These reagents undergo Wittig reaction with aldehydes to give vinylic selenides **12** that are cleaved to ketones using TFA (Scheme 5) <2001TL9035>. A variety of alkyl ketones are obtained in high yield using this method and the diselenide resin is readily separated and recycled by treatment with bromine in chloroform.



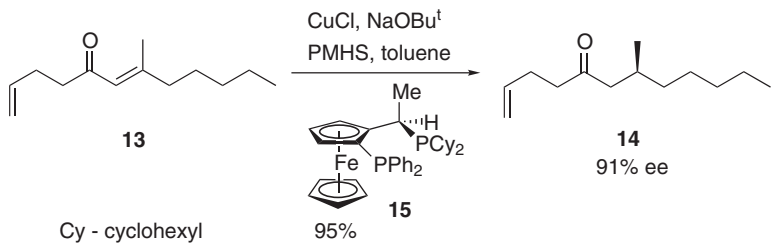
Scheme 5

3.04.1.8.2 From unsaturated ketones

(i) Conjugate reduction

Highly chemoselective 1,4-reduction of α,β-unsaturated ketones may be achieved using a combination of bulky Lewis acids and tetracoordinated aluminate complexes <1996JOC2928>. Prior coordination of the α,β-unsaturated ketones with aluminum tris(2,6-diphenylphenoxide) (ATPH) followed by addition of diisobutylaluminum hydride-butyllithium leads to the formation of the conjugate reduction product in high yield. The generated enolate undergoes reaction with methyl triflate to give α-methyl ketones in good yield.

Copper hydrides are commonly employed to effect the conjugate reduction of α,β-unsaturated ketones. These reagents may be used in catalytic quantities in the presence of stoichiometric amounts of hydride donors. Stryker's reagent $[(Ph_3P)CuH]_6$ may be used catalytically in the presence of tributyltin hydride or phenyl silane in toluene to reduce a number of cyclic ketones in a conjugate sense <1998TL4627>. More economical silyl hydrides such as dimethylphenylsilane and polymethylhydrosiloxane (PMHS) may be used in combination with Stryker's reagent in a tandem 1,4-reduction/alkylation process <2000T2779>. Use of PMHS leads to an enhancement in reaction rate and catalytic efficiency. Catalytic quantities of copper(I) chloride in combination with dimethylphenylsilane in 1,3-dimethylimidazolidinone (DMI) or DMF also reduces α,β-unsaturated ketones in a 1,4-manner. A range of substituted cyclopentenones undergo conjugate reduction in the presence of catalytic amounts of a copper carbene complex generated *in situ* from 1,3-bis(2,6-di-*iso*-propylphenyl)imidazolium chloride, copper(I) chloride, sodium *t*-butoxide and PMHS <2003OL2417>. Asymmetric conjugate reductions of β,β-disubstituted enones is achieved using catalytic quantities of copper(I) chloride and sodium *t*-butoxide in the presence of PMHS and a chiral ligand in toluene <2003AC(E)4789>. For example, enone **13** is reduced to ketone **14** using ligand **15** in high yield and ee (Equation (11)).



(11)

The asymmetric conjugate reduction of β-substituted cyclopentenones has been achieved in high ee using copper(I) chloride, sodium *t*-butoxide and PMHS in the presence of chiral bis-phosphine ligands <2000JA6797>. Reaction of the intermediate silyl enol ethers formed in this process with alkylating agents gives *trans*-2,3-disubstituted cyclopentanones in high de and ee <2001OL1129>.

Other metal-based catalysts are also effective in the conjugate reduction of enones. Catalytic quantities of manganese(III) complexes in combination with phenyl silane and isopropanol effect the 1,4-reduction of β-substituted enones <2000TL9731> and indium hydride, generated *in situ* from indium(III) chloride and sodium borohydride, reduces a variety of conjugated alkenes including α,β-unsaturated ketones in a conjugate sense <2002TL7405>. Tributyltin hydride may also be used in catalytic amounts, in the presence of phenyl silane as hydride donor, to conjugatively reduce α,β-unsaturated ketones and stoichiometric quantities of low-valent titanocenes, produced *in situ* by the reduction of bis(cyclopentadienyl)titanium dichloride with zinc, reduce α,β-unsaturated ketones under mild conditions via a single-electron transfer process <2002TL2013>.

Sodium dithionite is utilized on a commercial scale to reduce a variety of functional groups. It has now been reported that this reagent will conjugatively reduce a range of α,β-unsaturated ketones and aldehydes in good yield in H_2O/dioxane at 50 °C <1995TL1107>.

(ii) Conjugate addition of carbon nucleophiles

The 1,4-addition of carbon nucleophiles to α,β-unsaturated ketones is an important method for C—C bond formation and is usually achieved using organocuprate reagents. The selectivity and efficiency of organocuprate additions is improved by the incorporation of nontransferable dummy ligands. Lithium alkyl selenolates and alkyl tellurolates, readily prepared from the corresponding

alkyllithium and elemental selenium or tellurium, have been found to be efficient nontransferable ligands in the 1,4-addition of cyanocuprates to enones <2001TL2415>. The use of a dummy ligand often results in cuprates of reduced reactivity. A solution to this problem takes advantage of the trimethylsilyl chloride acceleration of cuprate additions and utilizes nontranferable groups with a β-silicon atom <1996JA10906>. This novel class of cuprates exhibits the high reactivity of homocuprates with the thermal stability and efficiency of mixed cuprate species.

Enantioselective organocuprate additions are now also available. Recently, the 1,4-addition of alkyl and phenyl groups to β-substituted enones has been achieved in high yield and ee by using organocuprates in the presence of optically active amidophosphine ligands as an external source of chirality <1999T3831>. Moderate-to-good enantioselectivities have also been obtained using mixed lower-order cuprates incorporating chiral thiophenes as dummy ligands <2003TA3281>.

Other organometallic compounds also add to α,β-unsaturated ketones in a conjugate sense under certain reaction conditions. Simple trialkylaluminum reagents undergo conjugate addition onto α,β-unsaturated ketones in the presence of catalytic amounts of copper(I) bromide <1995T743>. Trialkylindium compounds, readily prepared from the corresponding organolithium and indium(III) chloride, transfer one ligand to the β-position of α,β-unsaturated ketones in the presence of nickel(II) catalysts <1998JOC10074>. While primary diorganozinc compounds do not add to enones in the absence of copper(I)-based catalysts in THF, these reagents undergo efficient conjugate addition to unsaturated nitriles, nitroalkenes, and enones using *N*-methylpyrrolidinone (NMP) as co-solvent in the presence of iodotrimethylsilane <1996TL4495>. Secondary and tertiary alkylzinc bromides undergo 1,4-addition with enones in the presence of iodotrimethylsilane and boron trifluoride etherate in pentane:THF without the need for copper(I) catalysts <1995JA10775>.

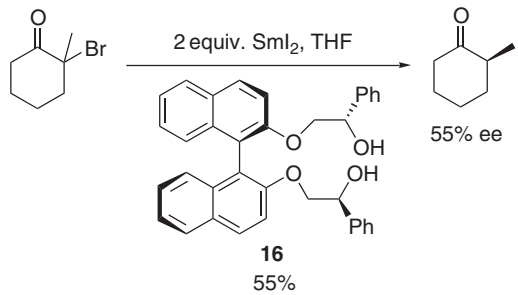
Much progress has been made in the copper-catalyzed asymmetric 1,4-additions of organozinc compounds to α,β-unsaturated ketones in the presence of chiral ligands. While a variety of methods have been investigated <2000T2847>, phosphorus(III)-based compounds have been the most popular choice of ligand in combination with copper(I) triflate. In particular, biaryl phosphoramidites <2000ACR346>, phosphonites <2001TA2497>, and phosphites <2000TA3161> have shown much promise as soft chiral nonracemic ligands for copper(I) in this enantioselective addition. Peptidic phosphines have been found to act as efficient catalysts for the asymmetric conjugate addition of diethylzinc and other alkylzinc compounds to α,β-unsaturated ketones giving access to the 1,4-addition products in high yield and ee <2002JA779>. Chiral diaminocarbenes, generated *in situ* by deprotonation of chiral imidazolium salts in toluene, allow the 1,4-addition of diethylzinc to proceed in low-to-moderate ee <2001TA2083>. Thiourethane and thioether binaphthyl-based ligands form active chiral copper(I) complexes in the presence of copper(I) salts that catalyze the 1,4-addition of trialkylaluminum compounds, Grignard reagents, and diethylzinc to enones in moderate ee <1999TL1767, 2001EJOC2435>. Grignard reagents also add to cycloalkenones in high yield and ee in the presence of copper(I) iodide and a chiral bidentate phosphine ligand derived from L-proline <1999T3843> and trimethylaluminum adds to 2-cyclohexenone in high ee using chiral bidenate phosphites as ligands in the presence of copper(I) triflate <2002TA1393>.

3.04.1.8.3 From α-functionalized ketones

A number of new reagents have been developed for the reduction of α-haloketones. Bis(triphenylstannyl) selenide and bis(*t*-butyldimethylsilyl)telluride, readily prepared from selenium and tellurium respectively, promote the dehalogenation of α-chloro and α-bromoketones in the presence of potassium fluoride in acetonitrile under mild conditions <1998S1137>. The reduction of α-haloketones is also effected by indium metal in water. A variety of α-bromo- and α-chloroketones are reduced to the parent ketone using powdered indium in the presence of catalytic quantities of sodium dodecyl sulfate in water at 60 °C <2000JCS(P1)4462>. Both α-bromo- and α-iodoketones undergo reduction using elemental indium as the sole reagent in water under sonication <1999JCS(P1)1139>. The reductive dehalogenation of α-haloketones often results in the formation of a metal–enolate that can react further with electrophiles. Treatment of α-bromoketones with gallium triiodide, readily prepared *in situ* from gallium and iodine, or methylgallium iodide, led to the formation of a gallium enolate <1998TL7751>. These enolates undergo addition reactions with carbonyls or imines present in the reaction mixture and in the absence of an electrophile give the corresponding ketone.

New methods for the deoxygenation of α-oxygenated ketones have also been developed. Treatment of *O*-acyl derivatives of a variety of acyloins with TBAF in the presence of propane-1,2-dithiol and *N*-methylmorpholine in THF leads to the formation of the ketone in high yield <1995TL7467>. Acyloin silyl ethers are reduced to silyl enol ethers and hence ketones using phenyldimethylsilyllithium in THF at −78 °C <1998JCS(P1)1215>.

A variety of α-oxygenated and α-halogenated ketones are reduced to regiodefined manganese enolates using manganese(II) ate complexes. The enolates undergo aldol reactions and alkylations in the presence of the appropriate electrophile <1997JA5459>. This process can also be performed enantioselectively. Treatment of a variety of α-hetero α-substituted ketones with samarium iodide results in the formation of a thermodynamic samarium enolate that undergoes enantioselective protonation in the presence of chiral C_2-symmetric diols such as **16** to give the corresponding α-substituted ketone in good-to-moderate ee (Equation (12)) <1999T4595>.



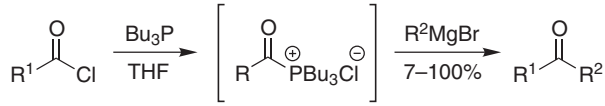
(12)

3.04.1.9 From Carboxylic Acids and Their Derivatives

3.04.1.9.1 Reaction of carbon nucleophiles with acids and their derivatives

Dialkyl ketones may be synthesized directly from carboxylic acids and alkyl halides under Barbier-type conditions <1996JOC6058>. Addition of a THF solution of the halide and acid to a solution of lithium naphthalenide in THF at 0 °C gave the coupled ketone product in moderate-to-good yields.

Organomanganese compounds undergo acylation with aliphatic acid chlorides to give dialkyl ketones. The classical transmetallation route from manganese halides and organolithiums is not tolerant of the presence of functional groups and a new method, amenable to scaleup, has been devised that centers on the production of activated manganese metal from manganese(II) chloride using lithium in the presence of 2-phenylpyridine as an easily removable electron carrier <1999TL6407>. Addition of an alkyl halide to the activated magnesium gives an organomanganese halide that readily undergoes addition with a variety of acid chlorides to give alkyl ketones in high yield. Acyl chlorides undergo coupling with a variety of alkylaluminum and dialkylzinc species <1997JOC4327>. While dimethylaluminum chloride and methylaluminum dichloride add to acid chlorides in dichloromethane to give alkyl ketones in high yield, the addition of trimethylaluminum or diethylzinc requires the presence of a Lewis acid such as aluminum trichloride. The reaction of Grignard reagents with acid chlorides does not provide a useful route to ketones but alkylmagnesium halides react smoothly with acyltributylphosphonium salts, prepared *in situ* from the corresponding acid chloride and tributylphosphine, to give the dialkyl ketone product in high yield <1996TL5381> (Equation (13)).



R^1, R^2 = alkyl, aryl

(13)

Acyl chlorides undergo cross-coupling with a variety of trialkylboranes under Suzuki–Miyaura conditions in the presence of tetrakis(triphenylphosphine)palladium and potassium acetate in THF to give access to a range of dialkyl ketones <2000TL999>.

The conversion of esters into dialkyl ketones without the formation of over-addition products is possible using organoaluminum complexes formed from a trialkylaluminum and a diamine <1998JOC7590>. Addition of an ester to a toluene solution of a trialkylaluminum

and *N*,*N*′-dimethylethylenediamine gave the methyl ketone in moderate-to-high yield. While organomanganese compounds undergo addition reactions with a variety of acyl chlorides, the corresponding reaction with mixed anhydrides is slow and proceeds in low yield. It has been found that organomanganese compounds prepared from the ate complexes $MnX_2{\cdot}2LiBr$ and $MnCl_2{\cdot}R_4NX$ and Grignard reagents add to mixed anhydrides quickly and in high yield <1998TL849>. This method was successfully applied to the addition of the normally unstable *s*- and *t*-alkylmanganese halides to anhydrides.

3.04.1.10 From Sulfur or Other Lower Chalcogen-containing Precursors

Thioacetals play an important role in total synthesis owing to their function as both acyl anion equivalents and protecting groups for the carbonyl moiety. Consequently, there is much interest in the development of methods for the selective deprotection of thioacetals to the parent ketone.

A variety of 1,3-dithiolanes are oxidatively deprotected to ketones under neutral conditions using *t*-butylhydroperoxide in methanol <2002TL6031>. This method gives the corresponding ketone in high yield and is tolerant of the presence of esters. Dithioacetals are oxidatively cleaved under mild conditions using DDQ in acetonitrile <1995JCS(P1)453>. This method may be used to effect the selective deprotection of 1,3-dithianes in the presence of 1,3-dithiolanes. Selenium dioxide in acetic acid also mediates the oxidative deprotection of 1,3-dithianes in high yield, and this method is tolerant of esters and ethers <1995S39>. A very mild, novel method for the deprotection of thioacetals using elemental fluorine is now available <1996JCS(P1)1941>. Passage of dilute fluorine through aqueous acetonitrile solutions of thioacetals gave the parent ketone in high yield.

Dithioacetals are also deprotected using solid-supported reagents. A variety of thioacetals and dithianes are converted into the parent ketone using clay-supported ammonium nitrate in dichloromethane <1997TL8891>. The removed sulfur functionality is adsorbed onto the support and this is removed by filtration at the end of the reaction. Dethioacetalization is also effected using clay-supported iron(III) nitrate in combination with microwave irradiation under solvent-free conditions <1997TL2623>. 1,3-Dithianes and 1,3-dithiolanes are also effectively deprotected using silica-gel-supported copper(II) nitrate in carbon tetrachloride <1995CL507>. This method is also effective for the generation of carbonyl groups from oximes and tosylhydrazones.

3.04.1.11 From Nitrogen-containing Precursors

3.04.1.11.1 From amines

Primary amines may be oxidized to ketones using potassium permanganate. This harsh oxidant becomes more selective when adsorbed onto a solid support and amines may now be converted into ketones in high yield using heterogeneous sources of potassium permanganate. Permanganate supported on copper(II) sulfate pentahydrate oxidizes a number of primary amines to ketones in high yield in dichloromethane <1999S939>, and the same transformation is achieved using potassium permanganate supported on iron(II) sulfate heptahydrate <2002SC3407>.

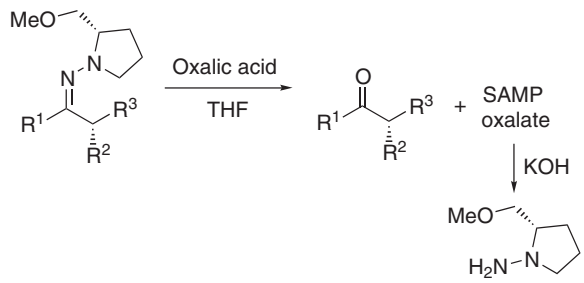
Amines also undergo oxidative deamination using *N*-*t*-butylphenylsulfinimidoyl chloride <2001CL712>. This one-pot oxidation requires prior conversion of the amine into the *N*-mesylated derivative and proceeds through formation of the corresponding imine. Addition of the oxidant to a solution of *N*-mesyl amine and DBU in dichloromethane gives the imine which is hydrolyzed upon work-up with 1 M HCl to give the ketone in high yield. Amines are also oxidized to carbonyls via formation of the corresponding acetamides <2001CC523>. Addition of aqueous hydrogen peroxide to a 1,2-dichloroethane:water solution of the acetamide and bromine gives the ketones in moderate yield along with the small amounts of α-bromoketone.

3.04.1.11.2 From oximes, hydrazones, and their derivatives

Hydrazones are useful synthetic intermediates serving as both carbanion equivalents and as protecting groups for the carbonyl functionality. A variety of methods have been developed for their deprotection to ketones with recent efforts focused on developing more mild and selective

cleavage reagents. Hydrazones may be cleaved by hydrolysis or under reductive or oxidative conditions. A novel oxidative cleavage of *N*,*N*-dimethylhydrazones involves the use of hydrogen peroxide and catalytic amounts of methyltrioxorhenium in acetonitrile–acetic acid <2000JOC2218>. Hydrazones are also deprotected under aerobic conditions. Stirring a range of *N*,*N*-dimethylhydrazones in fluorobenzene in the presence of a nickel(II) catalyst, pivaldehyde, and *N*-methylimidazole under 1 atm of oxygen leads to formation of the ketone <2000S403>. This method is also applicable to the deprotection of oximes and tosylhydrazones. *N*,*N*-Dimethylhydrazones are rapidly deprotected to ketones using cerium trichloride heptahydrate supported on silica gel under microwave irradiation <2001SL1134>. This method is tolerant of a variety of functional groups including alkenes, ethers, and halides. Transition metal catalysts have found use in the regeneration of ketones from *N*,*N*-dimethylhydrazones. The deprotection has been achieved using catalytic amounts of nickel, mercury, and manganese complexes in chloroform <2000SL1482>. A variety of dialkylhydrazones undergo deprotection using catalytic quantities of palladium(II) acetate and tin(II) chloride in water.

SAMP/RAMP hydrazones are important chiral auxiliaries for the asymmetric alkylation of ketones. These auxiliaries are commonly cleaved by ozonolysis and are thus not compatible with functionality that is sensitive to ozone. Both auxiliaries may be cleaved under racemization-free conditions using aqueous oxalic acid in diethyl ether or hexane <1998SL721>. Base-treatment of the aqueous layer on work-up leads to recovery of SAMP/RAMP in sufficient optical purity for reuse (Scheme 6). SAMP/RAMP hydrazones are also cleaved to ketones using ammonium dihydrogen phosphate buffer in THF <2000EJOC3971>. Both these cleavage methods are compatible with the presence of acid-labile functionality such as acetals and acetonides.



R^1 = alkyl, benzyl, aryl
R^2 = H, alkyl
R^3 = alkyl, allyl
yield = 84–98%

Scheme 6

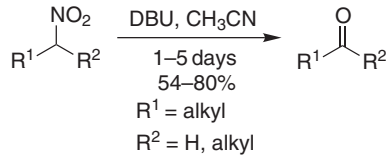
As with hydrazones, oximes may be cleaved under hydrolytic, reductive, or oxidative conditions. Ketones may be immobilized on solid supports in the form of their piperazine hydrazones <2002SL1931>. These piperazine hydrazones may then be alkylated using LDA followed by an alkyl halide, and the resulting alkylated products are readily cleaved from the solid support using 10% TFA. Oximes may be oxidatively cleaved using a combination of pyridinium fluorochromate in combination with 30% aqueous hydrogen peroxide <2001SC1607>. The Dess–Martin periodinane in dichloromethane can also be used to regenerate ketones from ketoximes under mild conditions <1998TL3209>. Solid-supported oxidants have found application in the oxidative deprotection of oximes. Alumina-supported potassium permanganate in diethyl ether effects the deprotection of a range of oximes and this method is tolerant of alkenes <2001TL4775>. This process is also possible under solvent-free conditions. Microwave irradiation of oximes in the presence of silica-supported chromium trioxide effects the regeneration of the ketone in the absence of solvent <1998TL5867>. Ketones are regenerated from oximes under mild conditions in carbon tetrachloride using poly[4-vinyl-*N*,*N*-dichlorobenzenesulphonamide] <2002TL3073>. This polymer is readily prepared from *p*-styrenesulfonate and recovered and regenerated.

Nontoxic, water-stable bismuth compounds find utility in the deprotection of oximes. Ketoximes undergo hydrolysis in acetone:water using 0.5 equiv. of bismuth(III) nitrate pentahydrate <2001S1010>, and ketones are regenerated from oximes under solvent-free conditions using wet silica-supported sodium bismuthate under solvent-free conditions <1998SL1345>.

Oximes are also cleaved using a photosensitized electron-transfer method <2002OL2325>. Photolysis of the oxime in acetonitrile in the presence of chloranil gives the corresponding ketone in moderate yield.

3.04.1.11.3 From nitroalkanes

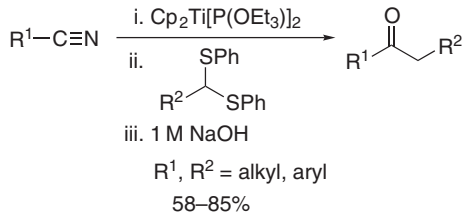
The conversion of nitroalkanes into carbonyl groups, also known as the Nef reaction, proceeds mildly and selectively under homogeneous basic conditions using DBU in acetonitrile <2002TL5233> (Equation (14)). A variety of functionalized nitroalkanes are converted into the corresponding ketones in good yield and this method is selective for secondary over primary nitroalkanes. Secondary nitroalkanes are also converted into ketones using bis(trimethylsilyl)peroxide in the presence of sodium hydride <1999SC4321>.



(14)

3.04.1.11.4 From nitriles

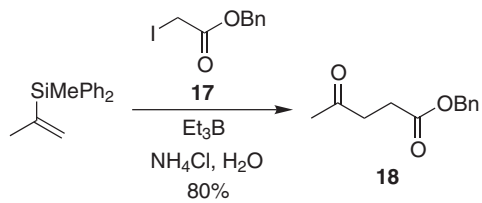
Alkanenitriles react with alkylidene titanocenes, formed from the corresponding thioacetal and *in situ* generated low-valent titanium reagents, to give a variety of acyclic alkyl ketones in good yield <2000TL65> (Equation (15)).



(15)

3.04.1.12 From Organosilanes

Vinyl silanes may be oxidatively cleaved to ketones using molecular oxygen via a tandem radical addition–oxidation sequence <2003AC(E)825>. A variety of vinyl silanes couple with iodides in the presence of triethylborane in air to give silylhydroperoxy radicals, which undergo conversion into ketones under the reaction conditions. For example, 2-(diphenylmethylsilyl)propene is converted into ketone **18** using iodide **17** and triethylborane in water (Equation (16)).

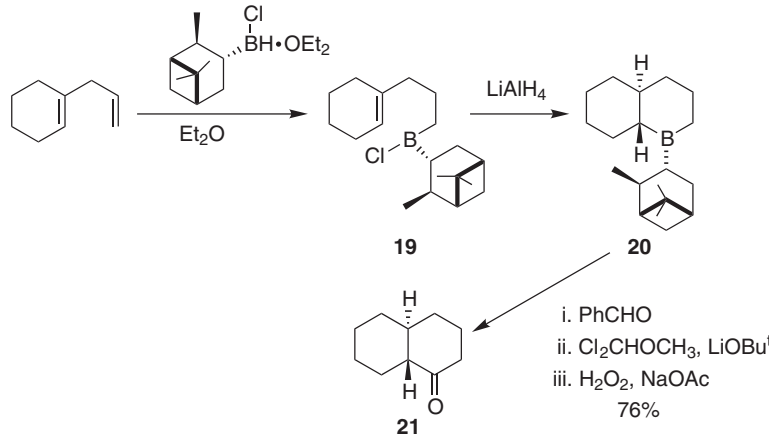


(16)

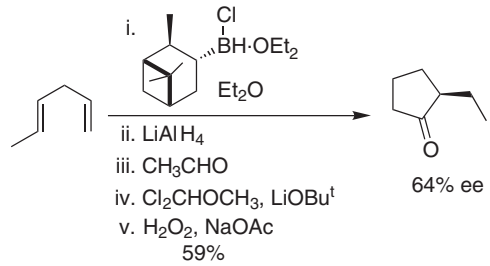
3.04.1.13 From Organoboranes

The hydroboration–carbonylation of organoboranes provides access to an array of dialkyl ketones. This methodology may be performed in an enantioselective manner using optically pure organoboranes. Stepwise hydroboration of dienes using enantiomerically pure isopinocampheylchloroboranes followed by carbonylation provides a convenient route to a variety of

optically pure *trans*-fused bicyclic and cyclic ketones <1998JOC8276>. As an example, 1-allyl-1-cyclohexene undergoes hydroboration with isopinocampheylchloroborane to give chloroborane **19**. Treatment with lithium aluminum hydride leads to the formation of cyclic trialkylborane **20**. Elimination of (+)-α-pinene using benzaldehyde followed by carbonylation with α,α-dichloromethyl ether and oxidative work-up gives (+)-*trans*-1-decalone **21** in good ee (Scheme 7). α-Substituted cyclopentenones are also available using this methodology. Treatment of *trans*-1,4-hexadiene with isopinocampheylchloroborane followed by reduction and carbonylation gives optically active 2-ethylcyclopentanone in 64% ee (Equation (17)).

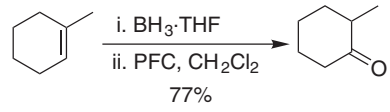


Scheme 7



(17)

Organoboranes may also be oxidized directly to ketones using chromium(VI)-based oxidizing agents. This transformation may now be conveniently achieved using pyridinium fluorochromate (PFC) <1997JCR(S)64>. As an example, 1-methylcyclohexene is converted into 2-methylcyclohexanone in good yield by regioselective hydroboration followed by oxidation of the resulting alkylborane with PFC in dichloromethane (Equation (18)).



(18)

PFC - Pyridinium fluorochromate

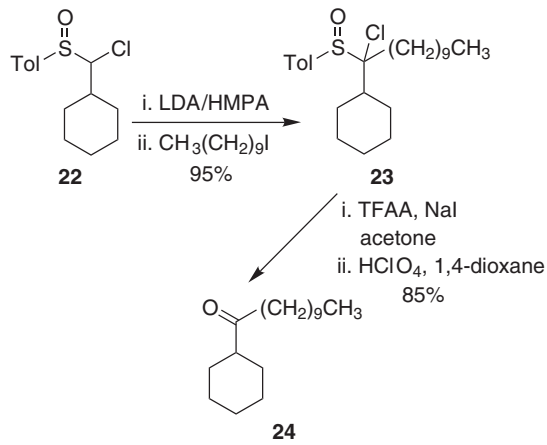
3.04.1.14 Methods Involving Umpolung

The introduction of a carbonyl group by addition of an acyl anion or other umpolung reagents is a useful transformation in organic synthesis and a variety of such reagents have been developed. This section will only cover the use of acyl anions and other anion equivalents in the synthesis of unsubstituted dialkyl ketones. In many instances, these reagents are used to contruct α-hydroxy ketones and the application of this methodology toward such targets will be discussed in detail in Section 3.04.4.1.1.

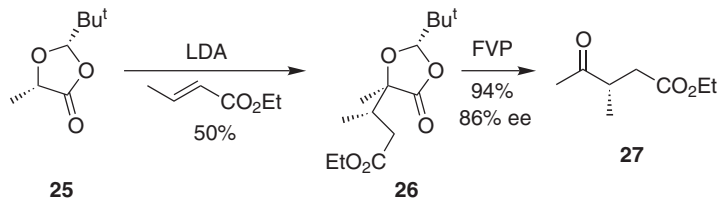
3.04.1.14.1 Acyl anions and their equivalents

1,3-Dithianes continue to play a pivotal role as acyl anion equivalents, and their use in the total synthesis of natural products has recently been reviewed <2003T6147>. One drawback associated with the use of 1,3-dithianes is the unpleasant smell of the thioacetals used in their synthesis. This problem may be overcome by the use of 1,3-dithiane polymers. Polymeric thioacetals, prepared from 4-chloromethylstyrene, may be converted into supported 1,3-dithianes using a variety of aldehydes <1998TL9263>. Deprotonation of the polymer-bound dithianes using *n*-butyllithium followed by alkylation with alkyl iodides occurs readily in THF. The resulting disubstituted dithianes are cleaved to ketones using mercury(II) perchlorate.

Carbanions of aryl-1-chloroalkyl sulfoxides also act as acyl anion equivalents <2001T493>. For example, treatment of chloro(cyclohexyl)methyl *p*-tolyl sulphoxide **22** with LDA/HMPA followed by 1-iododecane gives adduct **23**. Treatment of **23** with TFAA followed by perchloric acid gives ketone **24** (Scheme 8). Enantiopure 1,3-dioxolan-4-ones, prepared from α-hydroxyacids, readily undergo deprotonation followed by alkylation or 1,4-addition and are cleaved to ketones using flash vacuum pyrolysis (FVP). Hence, these reagents may act as chiral acyl anion equivalents <1998SL102>. The lithium anion of dioxolanone **25** adds to ethyl crotonate in a conjugate sense to give 1,4-adduct **26** that yields ketone **27** on FVP at 550 °C (Scheme 9).



Scheme 8

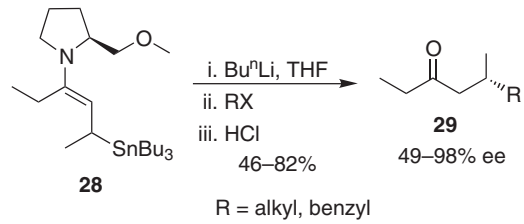


Scheme 9

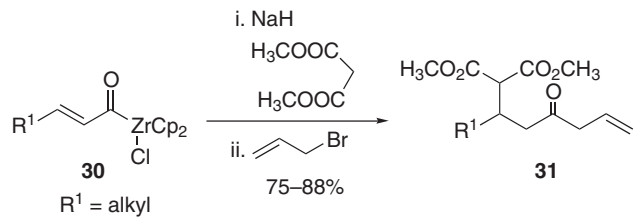
3.04.1.14.2 Other anion equivalents

Lithiated 3-[(*S*)-(methoxymethyl)pyrrolidino]hex-3-ene, readily prepared from the corresponding 3-stannyl derivative **28** by tin–lithium exchange, is a chiral homoenolate equivalent that has utility in the synthesis of β-methylated ketones <1998EJOC1371>. Lithiation of this reagent using *n*-butyllithium followed by alkylation of the anion and acidic hydrolysis gives a range of ketones **29** in high ee (Equation (19)). α,β-Unsaturated acylzirconocene chlorides **30** are useful reagents for the synthesis of substituted ketones. The reaction of these reagents with nucleophiles gives intermediates displaying either a nucleophilic or electrophilic character at the acyl and β-positions. The nature of the intermediate synthon depends on the nucleophile initially used <2000TL7525>. Addition of stabilized anions such as malonates occurs in a 1,4-manner to

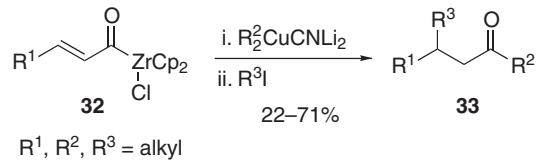
give an intermediate that reacts as an acyl anion with electrophiles such as allyl bromide to give ketones such as **31** (Equation (20)). Addition of higher-order cyanocuprates to **32** followed by treatment with alkyl halides gives ketones such as **33** arising from initial 1,2-addition of the cuprate followed by alkylation of an intermediate β-anion (Equation (21)).



(19)



(20)



(21)

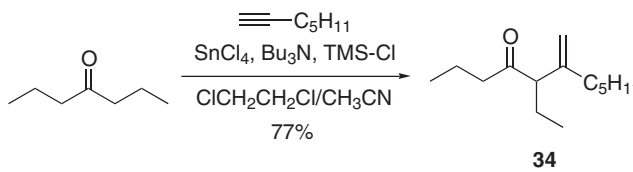
3.04.2 β-UNSATURATED AND MORE REMOTELY UNSATURATED KETONES

3.04.2.1 Dialkyl Ketones with One Double Bond

3.04.2.1.1 From ketones

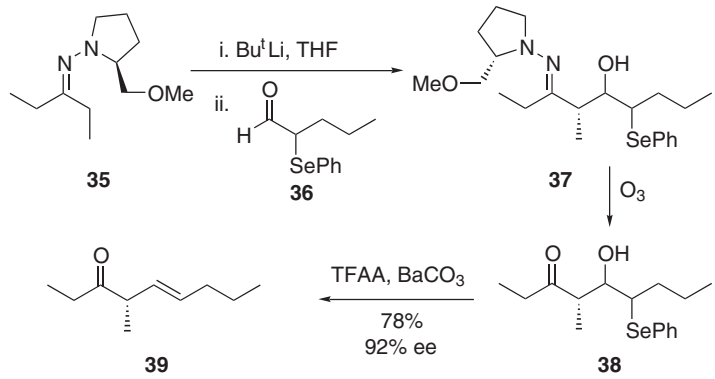
(i) Vinylation of saturated ketones

Few examples of the direct ethenylation of ketones are known, and these reactions often result in the formation of conjugated α-enone products. Direct α-alkenylation of ketones to give the β,γ-unsaturated product is possible with 1-alkynes via formation of the α-trichlorostannylketone <1995SL51>. For example, heptan-4-one reacts with hept-1-yne in the presence of tin(IV) chloride, tributylamine, and trimethylsilyl chloride to give the corresponding β-enone **34** in good yield (Equation (22)). Silyl enol ethers undergo α-ethenylation with trimethylsilylethyne in the presence of gallium trichloride to give α-alkenylated ketones <1999JA4074>. While a variety of cyclic and acyclic silyl enol ethers undergo conversion into the β,γ-unsaturated ketones in good yield in methylcyclohexane/THF, medium ring silyl enol ethers give varying amounts of conjugated α-enones.



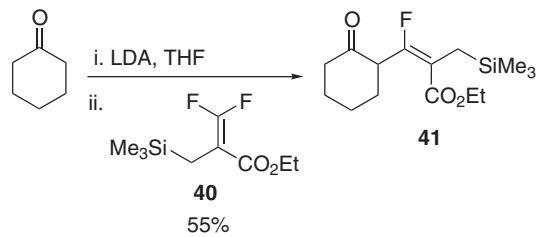
(22)

Optically pure β,γ-unsaturated ketones may be accessed with high ee in four steps by the aldol reaction of SAMP-hydrazones with α-phenylselenyl aldehydes <1996S621>. For example, treatment of the aza-enolate of ketone SAMP-hydrazone **35**, prepared using *t*-butyllithium in THF, with phenylselenyl aldehyde **36** gives α-phenylselenyl-β-hydroxyhydrazone **37**. The aldol product was converted into the α-ethenylated product **39** by oxidative cleavage of the chiral auxiliary followed by elimination of the resulting β-hydroxyketone **38** (Scheme 10).



Scheme 10

Highly functionalized β,γ-unsaturated ketones may be accessed by reaction of ketone enolates with difluoroacrylate **40** <2000JOC627>. For example, the lithium enolate of cyclohexanone reacts with acrylate **40** to give the ethenylated product **41** as a single stereoisomer (Equation (23)).



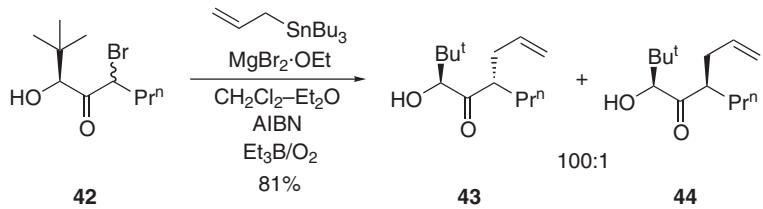
(23)

(ii) Allylation of saturated ketones

The addition of stabilized nucleophiles to π-allyl palladium complexes is a well-known reaction. The scope of this process has now been extended to the use of nonstabilized ketone enolates and this addition may be performed in enantioselective fashion. Tetralone and cyclohexanone-based tin enolates undergo asymmetric alkylation in high yield and ee with allyl acetates in the presence of a palladium complexes and chiral nonracemic ligands <1999JA6759, 2001OL149>.

Ketone enolates undergo regioselective and stereospecific allylic alkylation with rhodium catalysis. Treatment of the copper enolate of acetophenone with a variety of enantioenriched secondary allylic carbonates in the presence of trimethyl phosphite-modified Wilkinson's catalyst gives the alkylation product in high yield and ee <2003JA8974>.

The formation of δ,ε-unsaturated ketones is also possible by radical allylation of α-bromoketones <2003TL531>. An α-hydroxy group has been found to exert a high degree of 1,3-diastereocontrol in this process in the presence of Lewis acids. Bromide **42** undergoes diastereoselective allylation with allyltributyltin in the presence of AIBN, triethylborane, and oxygen using magnesium dibromide or zinc chloride as Lewis acid to give allylated product **43** as the major product (Equation (24)).

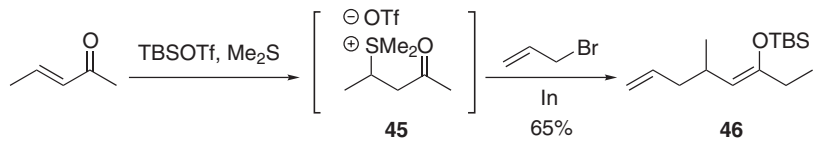


(24)

(iii) Conjugate addition of unsaturated nucleophiles to α,β-unsaturated ketones

A range of vinylzirconocene reagents add to a variety of cyclic and acyclic enones in a conjugate manner in the presence of catalytic amounts of copper(I) iodide:0.75 dimethyl sulfide complex. Treatment of an alkyne with Schwartz reagent in THF followed by addition of catalyst and enone gives the γ,δ-unsaturated ketone in good yield <2004OL107>.

Formal Michael addition of allylindium reagents is achieved by prior conversion of the enone substrate to the corresponding 3-*t*-butyldimethylsilyloxyalk-2-enylsulfonium salt <2003JA9682>. For example, reaction of pent-3-en-2-one with trimethylsilyl triflate and dimethyl sulfide gives sulfonium salt **45**, which undergoes nucleophilic substitution with allylindium, generated from allylbromide and indium, to give the allylated silyl enol ether **46** (Scheme 11).



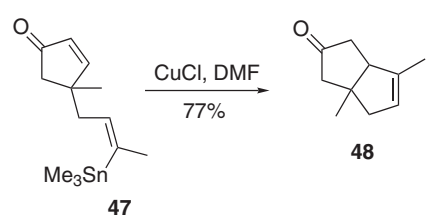
Scheme 11

Trialkylsilyl triflates have been found to be efficient promotors for the conjugate addition of allyl and vinyl aluminates to enones <1995SL163>. The aluminates are readily prepared *in situ* by the addition of trimethylaluminum to the corresponding organolithium reagent and undergo 1,4-addition to a variety of cyclic enones to give the substituted silyl enol ether as the product in good yield.

The 1,4-addition of allyltrimethylsilane to conjugated enones in the presence of Lewis acids, known as the Sakurai reaction, is an important C—C bond forming process. While stoichiometric quantities of Lewis acid are usually required, the Sakurai reaction has been shown to proceed using catalytic quantities of indium trichloride <2001JOC8646>. A range of cyclic and acyclic α,β-unsaturated ketones undergo conjugate addition with allyltrimethylsilane in the presence of 0.1 equiv. of indium(III) chloride and 5 equiv. of trimethylsilyl chloride. The Sakurai reaction also proceeds diastereoselectively in high yield in the presence of catalytic quantities of bistrifluoromethanesulphonimide <1998TL3215>.

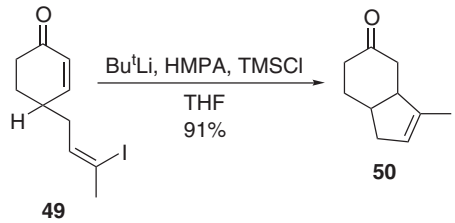
A range of rhodium(I) complexes catalyze the conjugate addition of unsaturated organometallic reagents to enones. (3-Trimethylsilyl-1-propenyl)boronates add to enones in a conjugate sense to give trimethylsilyl-substituted γ,δ-unsaturated ketones in the presence of 1.5% of a rhodium(I) complex in methanol/water <2002SL767>. The rhodium-catalyzed conjugate addition proceeds in an enantioselective manner using optically pure rhodium catalysts. 2-Alkenyl-1,3,2-benzodioxoboroles, accessed by hydroboration of alkynes with catecholborane, add to enones in high yield to give γ,δ-unsaturated ketones in high ee using a rhodium/(*S*)-BINAP catalyst <1998TL8479>. A range of alkenyltrialkoxysilanes also undergo conjugate addition to cyclic and acyclic ketones in a highly enantioselective manner in the presence of catalytic quantities of a BINAP–rhodium complex <2003OL97>.

The conjugate addition of vinyl organometallic reagents also occurs readily in an intramolecular sense under certain reaction conditions. Treatment of a variety of vinylstannyl-substituted enones with 2.5 equiv. of copper(I) chloride effects intramolecular conjugate addition to give bicyclic unsaturated ketone products <2000T2753>. For example, vinnylstannane **47** gives bicyclic ketone **48** on treatment with copper(I) chloride in DMF (Equation (25)).



(25)

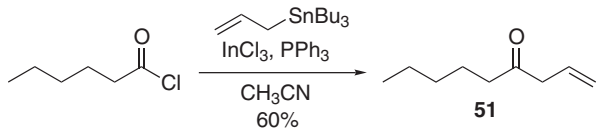
Vinyllithium reagents also undergo intramolecular conjugate addition under carefully controlled conditions. A variety of alkenyl iodides such as **49** undergo intramolecular conjugate addition to give bicyclic ketones such as **50** on treatment with *t*-butyllithium in the presence of HMPA and TMSCl in THF at −78 °C <2001OL3245> (Equation (26)).



(26)

3.04.2.1.2 From carboxylic acids and carboxylic acid derivatives

A range of aryl and aliphatic acyl chlorides undergo coupling with allyl tributyltin reagents in the presence of catalytic amounts of indium(III) chloride to give β,γ-unsubstituted ketones <2001SL1659>. For example, hexanoyl chloride reacts with allyltributylstannane in the presence of 0.1 equiv. of indium(III) chloride and 0.2 equiv. of triphenylphosphine in acetonitrile to give ketone **51** (Equation (27)).



(27)

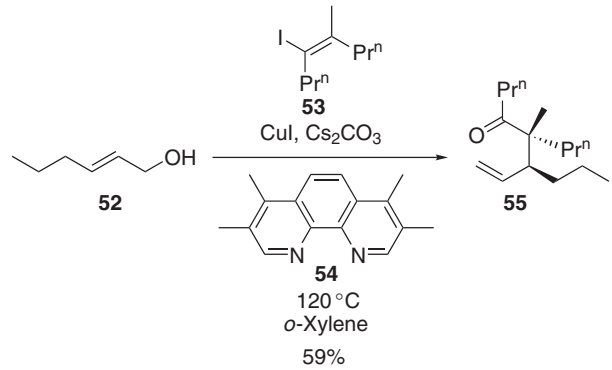
A variety of acid chlorides undergo coupling with allyl bromide in the presence of zinc dust under mild conditions to give β,γ-unsaturated ketones <1996TL1109>. Sonication of a mixture of acid chloride, allyl bromide and zinc dust in diethyl ether gives the corresponding β,γ-enone in high yield.

3.04.2.1.3 Preparations involving rearrangements

(i) Claisen rearrangements

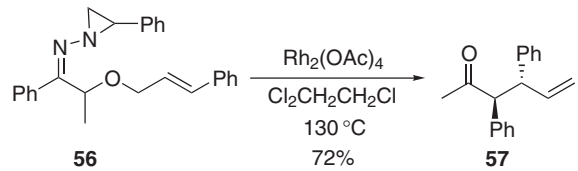
The [3.3] sigmatropic rearrangement of allyl vinyl ethers, known as the Claisen rearrangement, remains a powerful method for the construction of δ,γ-unsaturated ketones. Recent efforts have focused on investigating the substrate-controlled enantioselective variant of this rearrangement and this area of study has been recently reviewed <1996TA1847, 1999CSR43>. The utility of this procedure is often limited by the high reaction temperatures required. This limitation has now been largely overcome by the use of Lewis acid catalysts that allow the rearrangement to occur at room temperature or below. It has also been found that Lewis acids can significantly enhance the diastereoselectivity of the Claisen rearrangement <1995TL803>, and stoichiometric quantities of chiral Lewis acids have been used to effect enantioselective Claisen rearrangements <2001JA2911>. A catalytic enantioselective variant has been recently developed using chiral bis(oxazoline)copper(II)-based Lewis acids but this strategy is so far limited to the use of alkoxycarbonyl-substituted allyl vinyl ethers <2002EJOC1461>.

Another limitation associated with the Claisen rearrangement of allyl vinyl ethers is the difficulty in preparing the precursors as single stereoisomers. A number of new methods have been developed to overcome this problem. A novel domino copper-catalyzed coupling-Claisen rearrangement has been developed recently that may be used to access aldehydes and ketones with quaternary stereocenters as single diastereoisomers directly from simple precursors <2003JA4978>. Vinyl halides couple to allylic alcohols in a stereospecific manner in the presence of a copper(I) catalyst to give allyl vinyl ethers as single stereoisomers. These precursors undergo *in situ* diastereoselective rearrangement under the coupling reaction conditions give γ,δ-unsaturated aldehydes and ketones. For example, allyl alcohol **52** is converted into ketone **55** with vinyl iodide **53** in the presence of 1,10-phenanthroline **54**, copper(I) iodide and caesium carbonate in *o*-xylene at 120 °C (Equation (28)).



(28)

A tandem Bamford–Stevens/Claisen rearrangement has been developed that provides a route to a range of γ-alkenyl aldehydes and ketones from α-allyloxyhydrazones <2002JA12426>. The (*Z*)-isomers of allyl enol ethers, that undergo *in situ* Claisen rearrangement, are readily accessed by rhodium-catalyzed elimination of diazoalkanes derived from hydrazone precursors. Hydrazone **56** is converted into γ,δ-unsaturated ketone **57** using rhodium(II) acetate as catalyst in 1,2-dichloroethane at 130 °C (Equation (29)).

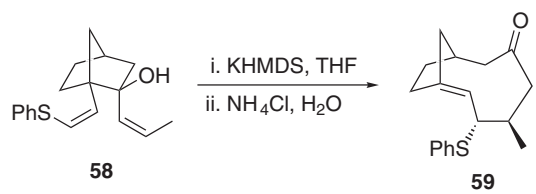


(29)

(ii) Oxy-Cope rearrangements

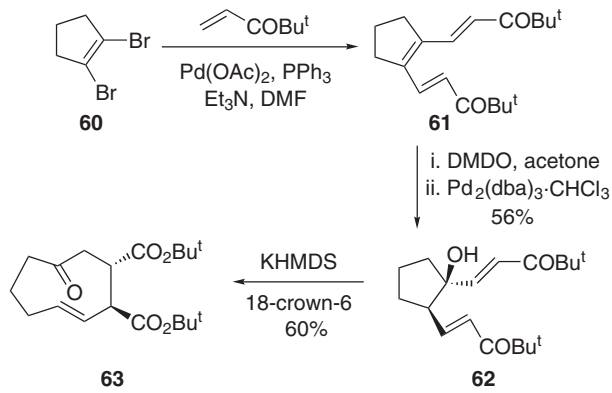
A variety of hexa-1,5-dien-3-ol systems undergo the thermal [3.3]-sigmatropic rearrangement to form δ,ε-unsaturated ketones, known as the oxy-Cope rearrangement. The rate of this process is vastly enhanced by prior conversion of the precursor into the corresponding potassium alkoxide, and the discovery of the anionic oxy-Cope rearrangment has transformed the utility of this rearrangement. As the anionic oxy-Cope rearrangement plays a major role in total synthesis, the discovery of new variants of this process and the development of novel routes to the precursors remains an active area of investigation.

It has been observed that the presence of a thiophenyl group at the terminal carbon of a bridgehead vinyl group in *exo*-norbornanols such as **58** causes the rearrangement to proceed at a greater rate <2000JA10788> (Equation (30)).



(30)

The precursors for this rearrangement are generally obtained by 1,2-addition of vinyl organometallic reagents to β,γ-unsaturated ketones or by addition of allyl anions to α,β-unsaturated carbonyls. A novel and attractive approach to oxy-Cope rearrangement precursors, that may be used in the synthesis of medium-sized rings, is by double Heck reaction of 1,2-dibromocycloalkenes followed by epoxidation and reductive ring-opening of the epoxide <2000S1327>. These transformations may be performed on a variety of dibromocycloalkenes and anionic oxy-Cope rearrangement of the resulting cyclic alcohols provides access to a variety of highly functionalized medium-sized rings. The stereochemical outcome of the rearrangement was found to depend on ring-size, and it is rationalized that this process is the first example of a reversible anionic oxy-Cope rearrangement. For example, 1,2-dibromocyclopentene undergoes twofold Heck reaction with *t*-butyl acrylate to triene **61** that is converted into alcohol **62**. Anionic oxy-Cope rearrangement gives functionalized cyclononenone **63** as a single isomer (Scheme 12).

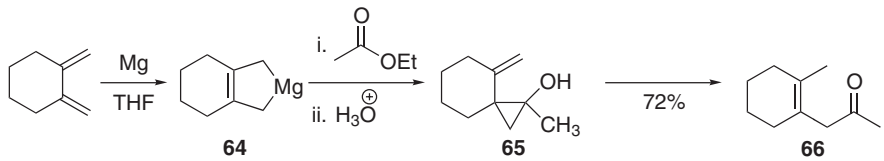


Scheme 12

This rearrangement is limited to precursors with proximal double bonds. To overcome this limitation, a radical alternative to the anionic oxy-Cope rearrangment has been developed based on the formation of an alkoxy radical from 1,5-dien-3-ols derived from norbornenones <2002AC(E)4321>. Fragmentation of the alkoxy radical to a carbon-centered radical followed by a 6-*endo*-cyclization gives the desired δ,ε-unsaturated ketone.

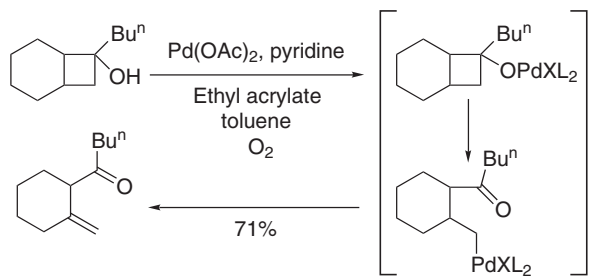
(iii) Other rearrangements

A variety of substituted (2-butene-1,4-diyl)magnesium complexes, formed by treatment of 1,3-conjugated dienes with Rieke magnesium, react with esters to give β,γ-unsaturated ketones via rearrangement of an intermediate magnesium salt of a cyclopropanol <1995JA5430>. Treatment of 1,2-bis(methylene)cyclohexane with Rieke magnesium gives magnesium complex **64**. Reaction with ethyl acetate and protonation at $-10\,^{\circ}C$ gives cyclopropanol **65** that undergoes rearrangement on warming to room temperature to give β,γ-unsaturated ketone **66** (Scheme 13).



Scheme 13

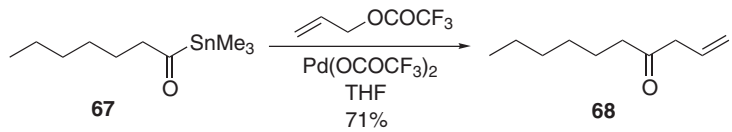
t-Cyclobutanols are transformed into β,γ-unsaturated ketones in high yield in the presence of catalytic amounts of palladium(II) acetate and ethyl acrylate under an atmosphere of oxygen. The reaction mechanism is thought to proceed via formation of a palladium(II) alkoxide that undergoes β-carbon elimination followed by β-hydrogen elimination <2001JOC1455> (Scheme 14).



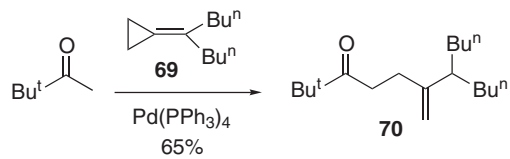
Scheme 14

3.04.2.1.4 Miscellaneous preparations

Unsaturated dialkyl ketones may be accessed using a number of transition metal-catalyzed procedures. The palladium(0)-catalyzed nucleophilic attack of stabilized carbanions onto allylic acetates is a well-known process and the palladium-catalyzed addition of nucleophilic acyl species to allylic esters to give β,γ-unsaturated ketones is now also possible. The acylation of a range of allylic trifluoroacetates with acyl silanes gives β-ethenylated ketones in good yield although unsubstituted allyl trifluoracetates provide the α,β-unsaturated ketone as the major product <2001JA10489>. This problem has been overcome by the use of acylstannanes that react with substituted and unsubstituted allyl trifluoroacetates to give β,γ-unsaturated ketones in good yield without isomerization <2002JOC5835>. For example, acylstannane **67** reacts with allyl trifluoroacetate in the presence of the palladium catalyst in THF at room temperature to give the unsaturated ketone **68** in good yield (Equation (31)). Acylzirconocene chlorides also act as acyl anion donors and react with allylic halides to give β,γ-unsaturated ketones <2002T10429>. These reagents, readily prepared by hydrozirconation of alkenes and alkynes with the Schwartz reagent and subsequent carbon monoxide insertion, undergo coupling with allyl bromide and iodide in the presence of catalytic quantities of copper(I) iodide in DMF to give β-alkenylated ketones in good yield. Alkylidene cyclopropanes undergo hydrocarbonation with methyl ketones in the presence of tetrakis(triphenylphosphine)palladium(0) to give α-allylated ketones in good yields <2002TL2903>. For example 3,3-dimethylbutan-2-one adds to alkylidene cylopropane **69** in the presence of the palladium catalyst in neat solution or THF to give γ,δ-unsaturated ketone **70** (Equation (32)).



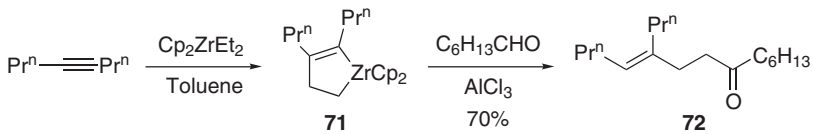
(31)



(32)

Allyl bromides react with a range of nitriles under Lewis acid-promoted Barbier conditions to give a variety of allyl ketones <2000TL8803>. A mixture of allyl halide, nitrile, zinc powder, and aluminum trichloride in THF at 0 °C gives the allyl ketone in good yield. The reaction with crotyl bromides proceeds via an S_E2' pathway to give 2-methyl allyl ketones.

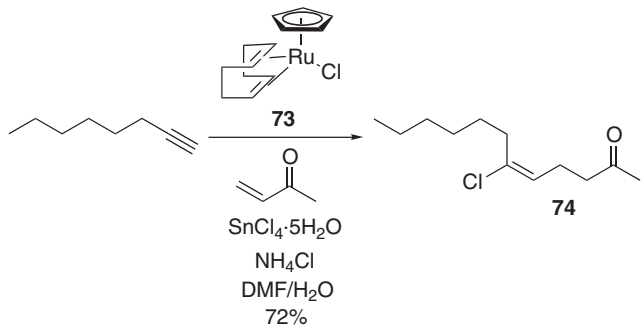
Lewis acids also promote the addition of zirconacyclopentenes to aldehydes to give homoallyl ketones <2002CC142>. Alkynes couple with zirconocene–ethylene complexes, generated from Cp_2ZrEt_2 *in situ*, to give zirconacyclopentenes that undergo reaction with aromatic and aliphatic aldehydes in the presence of aluminum trichloride to give homoallyl ketones in good yield. For example, oct-4-yne reacts with Cp_2ZrEt_2 in toluene to give zirconacyclopentene **71**. This intermediate reacts with heptanal at −78 °C to room temperature to give homoallylic ketone **72** (Scheme 15).



Scheme 15

1,2-Allenyl ketones undergo hydrohalogenation with sodium or lithium halides in acetic acid under mild conditions to give β,γ-unsaturated β-haloketones <1999JOC5325>. Unsubstituted allenyl ketones give the β,γ-unsaturated product along with the formation of some α,β-unsaturated isomer while 3,3-disubstituted 1,2-allenyl ketones undergo hydrohalogenation in high yield to give the β,γ-unsaturated ketone exclusively in high yield. Hydrohalogenation of 3-substituted 1,2-allenyl ketones gives the (*Z*)-β,γ-unsaturated ketone as the major product. A wide range of

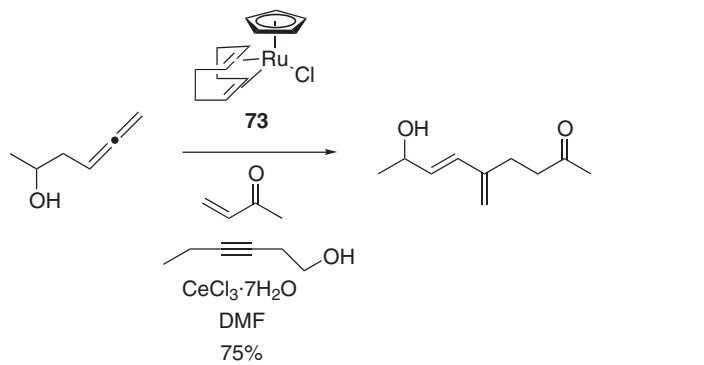
both (*E*)- and (*Z*)-δ-halo-γ,δ-unsaturated ketones are available by a ruthenium-catalyzed three component coupling of an alkyne, an enone, and halide ion <2002JA7376>. For example, oct-1-yne couples with methyl vinyl ketone in the presence of the ruthenium catalyst **73**, tin(IV) chloride and ammonium chloride in DMF/H_2O to give (*E*)-chloro-enone **74** (Equation (33)). The stereochemistry of the resulting vinyl halide depends on the reaction conditions used. More polar solvents favor the formation of the (*E*)-isomer, whereas less polar solvents such as acetone favor formation of the (*Z*)-isomer. Vinyl bromides are also accessible using this methodology with ammonium bromide or lithium bromide as halide source.



(33)

3.04.2.2 Dialkyl Ketones with More Than One Double Bond

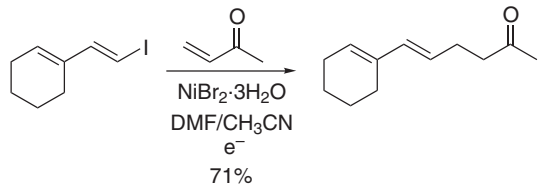
A range of dienones may be accessed using ruthenium-catalyzed coupling procedures. Allenes couple to a variety of activated alkenes including enones to give dienone products under ruthenium(II) catalysis <2001JA12466>. The reaction is highly chemoselective and tolerates a variety of substituents on the allene and in some cases, when using disubstituted allenes, shows high regioselectivity. The reaction proceeds in the presence of ruthenium catalyst, cerium trichloride, and hex-3-yn-1-ol as additive in DMF to give a wide range of functionalized dienone products in good-to-high yield (Equation (34)). A wide range of alkynes couple to alkenes in the presence of a ruthenium(II) catalyst to give diene products and this process has been used to synthesize dienone <2001JA12504>. Hex-5-yn-2-one couples with methyl undec-10-enoate to give the dieneone product **76** in good yield in the presence of cyclopentadienylruthenium (tris(acetonitrile) hexafluorophosphate **75** in DMF at room temperature (Equation (35)).



(34)

(35)

Conjugated iododienes and enones undergo coupling in the presence of a nickel complex generated *in situ* by electroreduction of a nickel(II) salt <2000JOC4575>. Electrolysis of a mixture of alkenyl halide and enone in the presence of nickel(II) bromide using a nickel grid cathode gives access to the coupled product in good yield (Equation (36)).



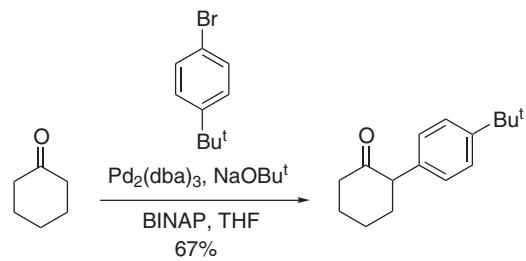
(36)

3.04.2.3 Dialkyl Ketones with Aryl or Heteroaryl Substituents

3.04.2.3.1 From ketones

(i) Arylation of saturated ketones

A number of methods have been developed to effect the α-arylation of ketones over the last few decades, but many of these use stoichiometric quantities of reagents and require the generation of tin enolates and/or silyl enol ethers <1995COFGT(3)111>. Much recent research in this area has focused on developing the direct arylation of ketones using catalytic quantities of palladium complexes. A wide variety of ketones undergo regioselective α-arylation with aryl bromides in the presence of 1.5 mol.% tris(dibenzylideneacetone)dipalladium(0), BINAP, and sodium *t*-butoxide in THF under mild conditions <1997JA11108> (Equation (37)).



(37)

A range of functionality is tolerated and the α-aryl ketone product is formed with good regioselectivity in high yield. This process can also be used to effect the asymmetric arylation of ketones <1998JA1918>. α-Tetralone is arylated in good yield and ee with aryl bromides using 5 mol.% $Pd(OAc)_2$/12 mol.% BINAP in toluene. Further studies in this area have revealed that the sterically hindered phosphines such as tri-*t*-butylphosphine and 1,1′-bis-(di-*t*-butylphosphino)ferrocene accelerate the α-arylation process <1999JA1473>. Electron-rich phosphines with a biphenyl backbone such as 2-methyl-2′-dicyclohexylphosphinobiphenyl are also highly active catalysts for the α-arylation of ketones, while palladium-catalyzed arylation with certain combinations of aryl bromide and ketone proceed in good yield in the absence of ligand <2000JA1360>. It has also been discovered that catalytic quantities of 4-methoxyphenol has a beneficial effect in the arylation of ketones with electron-deficient arenes especially *o*-halonitroarenes. Palladium(0) complexes with *N*-heterocyclic carbenes have also shown much promise as air-stable active catalysts for the α-arylation of ketones <2002OL4053>.

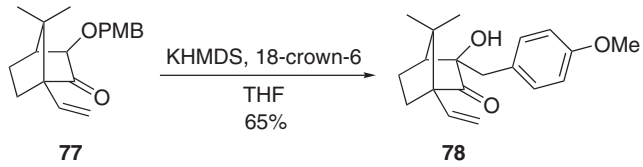
Dialkyl ketones are also directly arylated in moderate yield with *m*-dinitrobenzene in the presence of TBAF under irradiation with UV light <1996TL7591>.

(ii) Benzylation of saturated ketones

In general, α-benzyl ketones may be accessed from saturated ketones using the akylation methodology outlined in Section 3.04.1.8.1. This section will only cover methods developed specifically for the benzylation of ketones and methods with a scope that has been little extended beyond that of benzylation.

Conjugated α,β-unsaturated ketones undergo regioselective α'-benzylation with benzyl bromide in the presence of manganese(III) acetate <2003TL7311>. The reaction, which is thought to proceed via formation of an α'-keto radical, proceeds in benzene at 80 °C to give cyclic, α'-benzylated ketones in moderate yield.

Some α-(*p*-methoxybenzyl)ketones undergo 1,2-anionic rearrangement under mild conditions upon treatment with potassium hexamethyldisilazide to give α-benzylated α-hydroxy ketones <1999TL3823>. Treatment of α-(*p*-methoxybenzyl)ketone **77** with KHMDS and 18-crown-6 in THF at room temperature gave α-benzyl ketone **78** in moderate yield (Equation (38)).

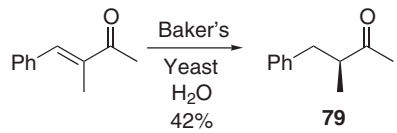


77 **78** (38)

(iii) Conjugate reduction of aryl-containing α,β-unsaturated ketones

Indium metal functions as a chemoselective reductant of C—C double bonds in highly activated ethenes <2001OL2603>. A variety of β-aryl α,β-unsaturated ketones are reduced to the saturated β-aryl ketone in moderate-to-high yield in the presence of indium metal in aqueous ethanolic ammonium chloride under reflux.

The asymmetric reduction of α-methyl β-aryl α,β-unsaturated ketones in moderate-to-good yield is achieved using bakers yeast in water <1995TA2143, 1996T4041>. For example, 3-methyl-4-phenyl-butan-2-one is reduced to the corresponding (3*S*)-ketone **79** in moderate yield and good ee (Equation (39)).

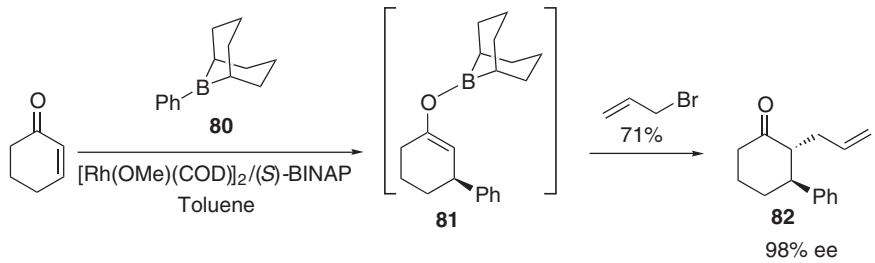


79
71% ee (39)

(iv) Conjugate addition of aryl nucleophiles to α,β-unsaturated ketones

While the conjugate addition of aryl groups to enones is traditionally limited to the use of organocopper reagents, these transformations may now be achieved using a variety of aryl halides and aromatic organometallic reagents using transition metal catalysts. Aryl substitution and conjugate addition are two competing paths under standard Heck arylation conditions with enones. It has been found that simply changing the base used in this reaction can have a profound influence on its selectivity <1998TL4055>. The use of triethylamine as base in DMF leads predominantly to the isolation of the conjugate addition product in moderate yields. The hydroarylation of a variety of acyclic enones occurs in excellent yield using supercritical carbon dioxide as solvent, using triethylamine and palladium(II) acetate as catalyst <2000SL650>.

Arylboron compounds undergo asymmetric 1,4-addition to enones in the presence of rhodium catalysts and optically pure ligands. Much recent research has focused on the development of novel organoboron compounds that are convenient to prepare and transmetallate to rhodium with ease. Potassium organotrifluoroborates, readily prepared from the corresponding organolithium reagents, undergo conjugate additon to cyclic and acyclic enones in high yield and ee in the presence of an *in situ* generated rhodium(I) complex and (*S*)-BINAP in toluene/water <2002TL6155, 2002EJOC3552>. This rhodium-catalyzed asymmetric addition also proceeds in high yield and ee using arylborates prepared *in situ* by reaction of the corresponding organolithium with trimethoxyborane <1999TL6957>. The catalytic cycle of the asymmetric rhodium-catalyzed addition has been determined to proceed via the formation of an oxa-π-allylrhodium, the hydrolysis of which requires the presence of water in the reaction medium <2002JA5052>. This reaction has now been developed to obtain chiral boron and titanium enolates that may be utilized in other transformations. Conjugate addition of 9-aryl-9-borabicyclo[3.3.1]nonanes such as **80** to cyclohexenone in the presence of a rhodium(I) catalyst and (*S*)-BINAP gives a chiral boron enolate **81** that maybe trapped with a variety of electrophiles such as allyl bromide to give the alkylated product **82** in good yield and high ee (Scheme 16).



Scheme 16

Use of aryltitanium triisopropoxides in the addition results in the formation of chiral titanium enolates that undergo asymmetric alkylation and may also be trapped as chiral silyl enol ethers on treatment with trimethylsilyl chloride <2002JA12102>.

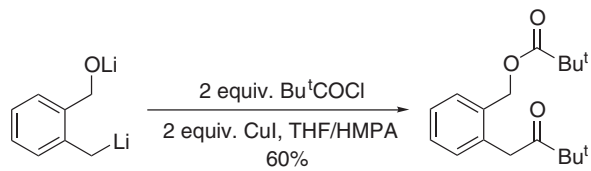
Aryltrimethylstannanes also add to enones in a conjugate sense in moderate-to-high yield in the presence of rhodium(I) catalysts in THF/water <2002T91> and aryl silanes react with a variety of cyclic and acyclic enones in water in the presence of bis(cyclooctadienyl)rhodium(I) tetrafluoroborate <2001CC2348>.

Anisoles undergo conjugate addition to Michael acceptors such as methyl vinyl ketone to give β-arylated ketones in the presence of pentaaminosmium(II) <1997JOC130>. While the conventional Friedel–Crafts reaction requires high temperatures and Lewis acids this addition, which proceeds via formation of a η^2-arene complex with osmium, proceeds at $-40\,^{\circ}C$ in acetonitrile and triflic acid to give an osmium–anisole complex substituted with the electrophile at C-4. Decomplexation is achieved by heating.

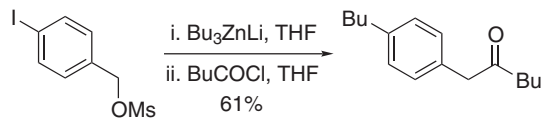
A variety of substituted aryl bromides undergo conjugate addition onto methyl vinyl ketone in good-to-high yield in the presence of a zero-valent nickel species generated *in situ* by the cathodic reduction of nickel(II) bromide in an undivided cell at $70\,^{\circ}C$ <2002EJOC105>. The conjugate addition of aryl chlorides is also possible upon raising the reaction temperature to $100\,^{\circ}C$.

3.04.2.3.2 From carboxylic acids and carboxylic acid derivatives

The acylation of benzyl organocopper reagents provides a useful method for the synthesis of α-aryl ketones. This reaction has now been extended to the use of functionalized benzylcopper reagents <2001T2371>. Benzyllithium **83** undergoes coupling with *t*-butanoyl chloride in the presence of 2 equiv. of copper(I) iodide in THF/HMPA at $-78\,^{\circ}C$ to give aryl ketone **84** in moderate yield (Equation (40)). Lithium trialkylzincates react with *p*-iodobenzyl methanesulfonate to give benzylzinc reagents that couple with acyl chlorides to give α-aryl ketones <1998T9317>. The benzylzinc reagent, formed by iodine–zinc exchange followed by 1,2-migration of the resulting arylzincate, couples with acyl chlorides at $-85\,^{\circ}C$ in THF to give the α-aryl ketone in moderate yield (Equation (41)).



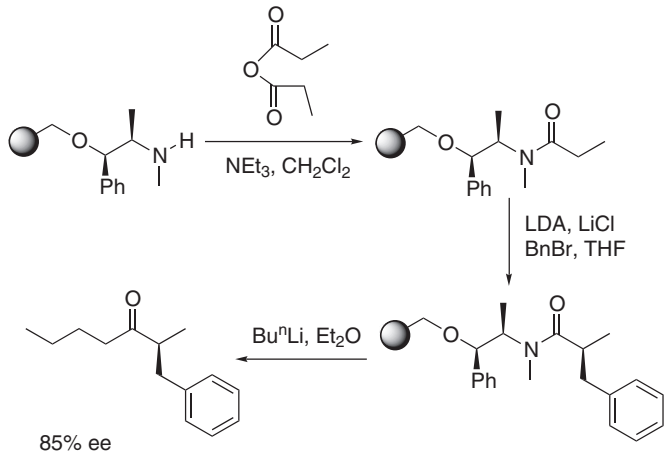
(40)



(41)

A variety of functionalized benzylic manganese reagents, prepared by oxidative addition of Rieke manganese to aryl halides, sulfones, and phosphonates, undergo coupling with acid chlorides to α-aryl ketones in high yield <2000JOC2322>.

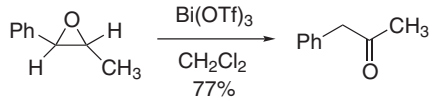
Enantioenriched α-benzyl ketones may be accessed by solid-phase asymmetric alkylation <2002OL4583>. Acylation of pseudoephedrine attached to Merrifield resin provides an immobilized amide that undergoes deprotonation and diastereoselective alkylation with benzyl bromide. Cleavage of the pseudoephedrine amide by treatment with an alkyllithium gives an α-benzylated ketone in high ee (Scheme 17).



Scheme 17

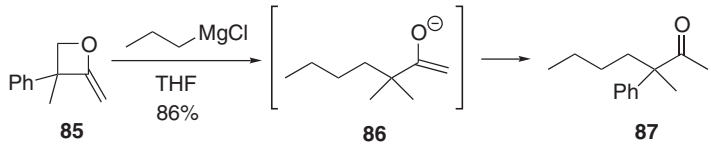
3.04.2.3.3 Other preparations

Aryl ketones may be prepared by ring opening of aryl-substituted epoxides and oxetanes. Aromatic epoxides undergo smooth rearrangment to α-aryl ketones in the presence of catalytic amounts of bismuth(III) triflate in dichloromethane <2001TL8129> (Equation (42)).



(42)

2-Methyleneoxetanes undergo ring opening at C-4 with stabilized organolithium reagents and Grignard reagents to give α-aryl ketones <2002T7101>. For example, oxetane **85** reacts with propylmagnesium chloride in THF under reflux to give enolate **86**, which is converted into aryl ketone **87** (Scheme 18).

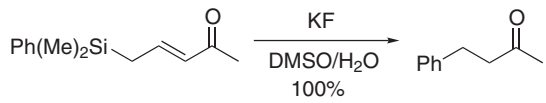


Scheme 18

Allylic alcohols undergo Heck coupling with aryl bromides and activated aryl chlorides in the presence of catalytic palladium–benzothiazole complex to give β-aryl ketones as the major product <2003EJOC1382>. The reaction is carried out in molten tetrabutylammonium bromide, and the robust catalyst is readily isolated from this ionic liquid at the end of the reaction. Terminal allylic alcohols are arylated with high regioselectivity while β-alkyl- and β-aryl-substituted substrates undergo coupling to give a regioisomeric mixture containing the β-aryl product as the major isomer.

The phenyl group of 4-phenyldimethylsilyl-3-buten-2-ones has been observed to migrate to the adjacent enone carbon to give 4-phenylbutan-2-ones in the presence of potassium fluoride in DMSO <2002JOC3911> (Equation (43)). The mechanism of this rearrangement is thought to

proceed via nucleophilic attack of fluoride at silicon followed by 1,2-aryl migration to generate an enolate. Further attack of fluoride at silicon followed by elimination of neutral silicon and quenching of the resulting benzylic anion gives the product.



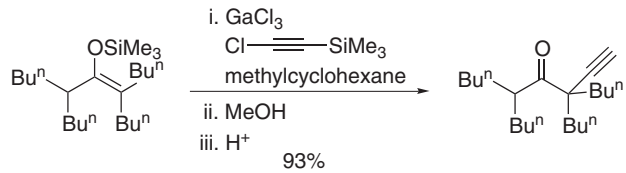
(43)

3.04.2.4 Alkynyl-substituted Dialkyl Ketones

3.04.2.4.1 From ketones

(i) Ethynylation of saturated ketones

The direct ethynylation of ketones has received little attention since the publication of COFGT (1995) <1995COFGT(3)111>. One notable new procedure for the synthesis of α-ethynyl ketones centers on the coupling of a silyl enol ether with a trimethylsilylethyne in the presence of gallium trichloride <2002OL2209> (Equation (44)). This process proceeds through carbometallation of an ethynylgallium with a gallium enolate formed *in situ* to give a variety of cyclic and acyclic ethynylated ketones in moderate-to-high yield.

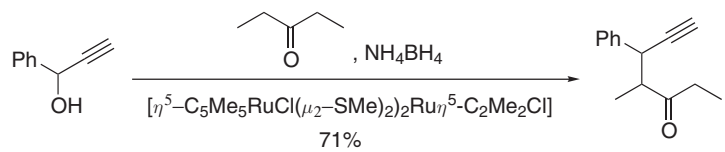


(44)

(ii) Propargylation of saturated ketones

A number of silyl enol ethers react as nucleophiles with carbocations generated from propargyl silyl ethers in the presence of Lewis acids such as trimethylsilyl triflate to give β-ethynyl ketones <2003OL51>. The outcome of this reaction depends on the substituents on both coupling components and often results in the formation of β-allenyl ketones.

Propargylic alcohols undergo propargylic substitution with a variety of nucleophiles in the presence of thiolate-bridged diruthenium complexes. This reaction may now also be performed in moderate-to-high yield with a variety of simple cyclic and acyclic ketones under mild and neutral conditions <2001JA3393> (Equation (45)).

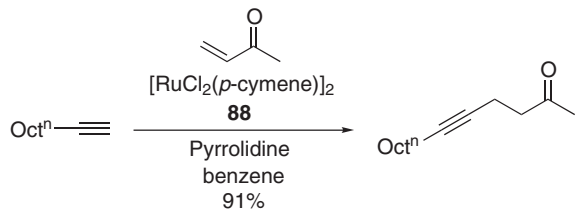


(45)

(iii) Conjugate addition of unsaturated nucleophiles to α,β-unsaturated ketones

While the conjugate addition of ethenyl and aryl groups is readily achieved by conversion into the corresponding organocopper reagent, the 1,4-addition of ethynylcopper compounds to enones under standard conditions does not proceed owing to the relative unreactivity of these organometallic reagents. Indeed, alkynes have seen much utility as nontransferable dummy ligands in the reactions of mixed cuprates. However, copper acetylides have been observed to add to a variety of cyclic enones in the presence of trimethylsilyl iodide and lithium iodide in THF to give the corresponding trimethylsilyl enol ether in good yield <1997JOC182>. It was also observed that copper acetylides prepared from copper(I) iodide gave higher yields of product than those prepared from copper(I) bromide or copper(I) cyanide.

Ruthenium acetylides, prepared from terminal alkynes and catalytic amounts of ruthenium complexes, also undergo 1,4-addition with α,β-unsaturated ketones. Initially, a nonhydride binuclear ruthenium catalyst was used in acetonitrile to effect this transformation in moderate yield and scope <1999T3937>. Recently, it has been discovered that 5 mol.% of catalyst **88** in the presence of 2 equiv. of pyrrolidine in benzene effects the 1,4-addition of a wide range of terminal alkynes to conjugated enones to give γ,δ-ethynyl ketones in high yield <2001OL2089> (Equation (46)). Formal Michael addition of propargyllindium reagents to enones is achieved by prior conversion of the enone substrate into the corresponding 3-*t*-butyldimethylsilyloxyalk-2-enylsulfonium salt using the methodology outlined in Section 3.04.2.1.1 <2003JA9682>. The addition of propargyl bromides to acyclic and cyclic 3-*t*-butyldimethylsilyloxyalk-2-enylsulfonium salts generated from enones proceeds in high yield to give δ,ε-alkynyl ketones.



(46)

3.04.2.4.2 *Fragmentation reactions*

No further advances have been made in this area since the publication of COFGT (1995).

3.04.3 HALO-SUBSTITUTED KETONES (α-, β-, AND MORE REMOTE HALOGENS)

3.04.3.1 Introduction

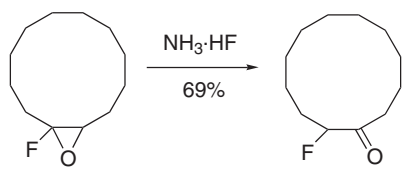
Haloketones are useful intermediates in organic chemistry and, while many of the methods outlined in the corresponding chapter in COFGT (1995) <1995COFGT(3)111> are still in routine use, a variety of new approaches utilizing more efficient and mild reaction conditions have been developed for the synthesis of such compounds. In particular, the unique biological activity of fluorinated compounds has stimulated the development of a number of new reagents and strategies for the synthesis of fluoroketones.

3.04.3.2 Fluoroaliphatic Ketones

3.04.3.2.1 *α-Fluoroaliphatic ketones*

(i) From epoxides

A variety of cyclic α-fluoroketones are accessed in moderate yield by treatment of 2-fluoroxiranes, obtained by peracid oxidation of fluoroalkenes, with triethylamine–hydrogen fluoride adduct at 125 °C <1996T2429> (Equation (47)).



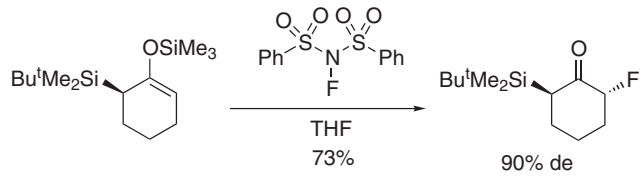
(47)

α-Thiosubstituted trifluoromethyl ketones are readily prepared in high yield by regioselective ring-opening of 1-trifluoromethylepoxy ethers with alkyl and aryl sodium thiolates in THF <1996S529>. The epoxide precursors are readily prepared by Wittig reaction of alkyl trifluoracetates and peracid oxidation of the resulting substituted alkenes.

(ii) From stable enol ether derivatives

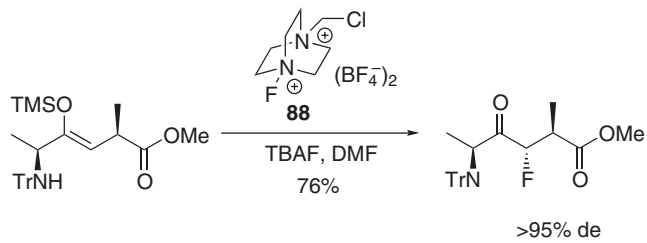
Tri-fluorinated enol tosylates are smoothly hydrolyzed to α-fluoromethyl ketones by using sodium hydroxide in DMSO/H_2O at 80 °C <2001SL1308>.

Cyclic silyl enol ethers of enantiopure α-silyl ketones undergo diastereoselective fluorination in high yield and ee using *N*-fluoro-benzenesulfonimide in THF at −78 °C <2001S2307> (Equation (48)). The enantiopure α-silyl ketone precursors are obtained by silylation of the corresponding SAMP-hydrazone and the silyl-protecting group is readily removed after fluorination by treatment with a fluoride source.



(48)

The (*Z*)-trimethylsilyl enol ethers of a variety of *N*-tritylated ketomethylene dipeptide isosteres undergo diastereoselective fluorination with Selectfluor **88** in DMF in the presence of TBAF (Equation (49)).

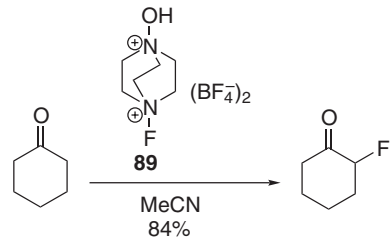


(49)

(iii) From ketones

While the methods available for the synthesis of α-fluoroketones from saturated, unsubstituted ketones is limited, a number of new methods have been developed for the direct synthesis of these targets from 1,3-diketones, β-keto esters, and aryl ketones.

A wide variety of ketones undergo regioselective α-fluorination in high yield using the electrophilic fluorinating agent 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane (Accufluor™ NFTH) **89** in methanol under reflux <1996TL3591, 2002S2609> (Equation (50)). This reagent is also effective for the fluorination of aryl alkyl ketones <2000CC1323>.



(50)

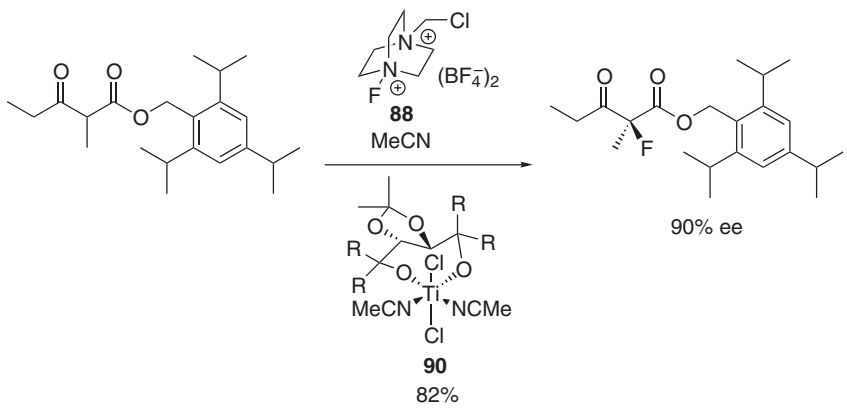
The diastereoselective fluorination of optically active α-silyl substituted silyl enol ethers outlined in the previous section (Equation (48)) proceeds in poor yield when applied to acyclic substrates. Better yields of α-fluorinated products are obtained by electrophilic fluorination of the lithium enolate of linear α-silyl ketones with *N*-fluorobenzene sulphonimide <2001S2307, 1997AC(E)2362>.

The majority of methods developed for the α-fluorination of ketones utilize 1,3-diketones and 1,3-keto esters as substrates yielding the corresponding 2-fluoro and 2,2-difluoro compounds as products.

It is possible to fluorinate certain 1,3-dicarbonyls using elemental fluorine diluted to 10% v/v with nitrogen <1995CC21>. This method results in high conversion of substrate but suffers from a lack of regioselectivity. Monofluorination of 1,3-diketones and β-keto esters is also achieved in high yield, regioselectively at the 2-position, using trifluoroamine oxide in the presence of

tributylammonium hydroxide <2003TL2799>. Use of 2 equiv. of fluorinating agent with substrates unsubstituted at the 2-position led to the isolation of difluorinated products in high yield.

β-Keto esters may also be fluorinated in an enantioselective manner. Fluorination of 2-substituted β-keto esters in the presence of the chiral titanium Lewis acid complex **90** using Selectfluor **88** leads to the isolation of monofluorinated products in high ee <2000AC(E)4359> (Equation (51)). Treatment of β-keto esters with catalytic amounts of axially chiral palladium(II) complexes results in the formation of chiral, square-planar palladium enolates that undergo fluorination with *N*-fluorobenzene sulfonimide to give α-fluorinated products in high yield and ee <2002JA14530>. Indanones, tetralones, and cyclic β-keto esters are fluorinated in high ee using *N*-fluoroammonium cinchona alkaloid tetrafluoroborates, formed by mixing Selectfluor and cinchona alkaloids, in acetonitrile <2001JA7001>.



(51)

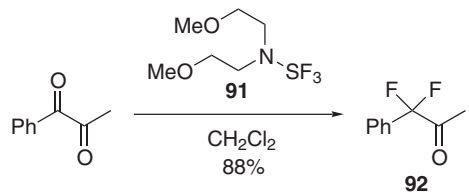
(iv) From acids or esters

A wide variety of methyl esters undergo nucleophilic trifluoromethylation to give α-trifluoromethyl ketones on treatment with Et_3GeNa and $C_6H_5SCF_3$ in HMPA <1997SL907>. Esters are also converted into trifluoromethyl ketones in a fluoride-induced trifluoromethyl-transfer procedure using trifluoromethyltrimethylsilane in the presence of catalytic quantities of TBAF in pentane <1998AC(E)820>. Ethyl 2,2-difluoro-2-trimethylsilylacetate effectively transfers a difluoroacetate group to acyl chlorides in the presence of potassium fluoride in DMF to give difluoro-substituted β-keto esters.

A novel procedure for the synthesis of trifluoromethyl ketones centers on the decarboxylation of α-trifluoromethyl-α-hydroxy acids <2002T8565>. The hydroxy acid precursors are readily accessed by Grignard reagent addition to ethyl trifluoropyruvate and saponification of the resulting hydroxyester. Decarboxylation is effected under mild conditions using cobalt(III) complexes in the presence of pivalaldehyde under an oxygen atmosphere to give the trifluoromethyl ketone in high yield.

(vi) Miscellaneous other preparations

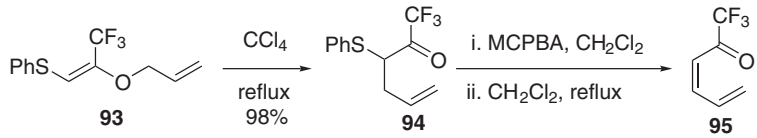
Deoxofluor **91** is a nucleophilic fluorinating agent that reacts with unsymmetrical α-diketones such as 1-phenyl-1,2-propanedione to give the difluoride **92** as the major product (Equation (52)) <2001JOC6263>. Deoxofluor also reacts with β-diketones to give vicinal difluoroenones.



(52)

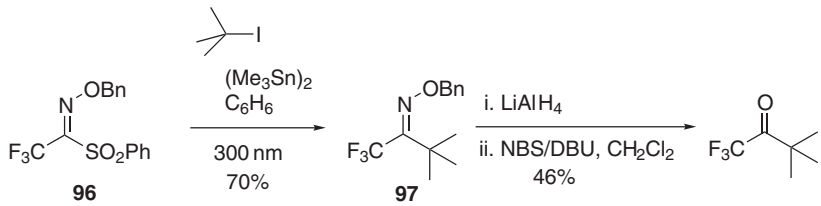
Buta-2,4-dienyltrifluoromethyl ketones are readily obtained by Claisen rearrangement of allyl-2-phenylsulfanyl-1-(trifluoromethyl)vinyl ethers <1996CC861>. For example, allyl vinyl ether **93**, prepared from 1-bromo-1-phenylsulfanyl-3,3,3-trifluoropropene and allyl alcohol, rearranges

upon heating to give unsaturated ketone **94**. Elimination of benzenesulphenic acid gives dienyl trifluoromethyl ketone **95** (Scheme 19).



Scheme 19

α-Difluoro-acylstannanes and silanes, readily prepared by Claisen rearrangement of difluoro-enolstannanes and -silanes, undergo benzylation and allylation under Stille coupling conditions or in the presence of TBAF, respectively, to give α-difluoro ketones <2001TL6377>. Alkyl iodides react with trifluoromethylsufonyloxime ether **96** in the presence of hexamethylditin upon irradiation at 300 nm in benzene to give oxime ethers **97**, which may be converted into trifluoromethyl ketones (Scheme 20) <2002TL7189>.



Scheme 20

3.04.3.2.2 β-Fluoroaliphatic ketones

β-Fluoroketones are often synthesized by the introduction of a trifluoromethyl group α- to a ketone. The traditional methods for introducing trifluoromethyl groups into ketones are often based on the use of fluorinated hydrocarbons such as halons and freons. Recent research has focused on developing new, more environmentally friendly fluorinating agents.

Ketene dithioacetals derived from ketones may be converted into α-trifluoromethyl ketones by stepwise addition of fluoride under oxidative fluoro de-sulfurative conditions <1998TL9651>. The ketene thioacetal is first treated with 1,3-dibromo-5,5-dimethylhydantoin and HF–pyridine complex in dichloromethane to give a difluorosulfide. The disulfide intermediate is then treated with MCPBA to give a sulfone that undergoes fragmentation in the presence of tetrabutylammonium fluoride to give the α-trifluoromethyl ketone. β,β-Difluoro-β-(methylthio)-ketones may be accessed by treating ketone-derived ketene dithioacetals with pyridine–HF and mercury(II) trifluoroacetate in dichloromethane <2000JFC35>.

The nucleophilic trifluoromethylating agent (trifluoromethyl)trimethylsilane is a popular reagent for the introduction of a trifluoromethyl group <1997CR757>. This fluorinating agent undergoes monoaddition with some 1,2-diones such as benzil, in the presence of caesium fluoride to give the corresponding 2-trifluoro-2-hydroxyketone <2001JOC1436>. Di-addition predominates with less sterically hindered 1,2-diones, however, giving the bis(trifluoromethyl)diol as the major product.

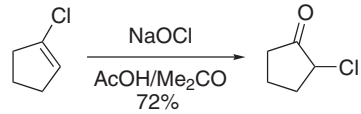
3.04.3.3 Chloroaliphatic Ketones

3.04.3.3.1 α-Chloroaliphatic ketones

(i) From alkenes or alkynes

Vinyl halides are traditionally converted into α-haloketones using *N*-halosuccinimides. In a mild and inexpensive alternative to this procedure, a vinyl chloride is treated with aqueous sodium

hypochlorite in acetone/acetic acid to give the corresponding α-chloroketone in high yield (Equation (53)) <2003JOC3323>.

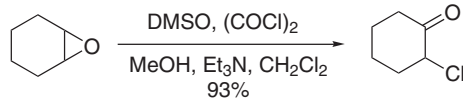


(53)

A potentially promising method for the synthesis of α-chloroketones in a regioselective manner centers on the reaction of nitroethenes with metal chlorides <1995JOC8320>. Under optimum reaction conditions, 1-nitrocyclohexene is converted into 2-chlorocyclohexanone in high yield using titanium(IV) chloride in dichloromethane. The mechanism of this process is thought to proceed via Nef reaction of an intermediate chloronitronate.

(ii) From epoxides

The oxidative ring cleavage of a range of epoxides to give α-chloroketones is effected under mild conditions using DMSO and oxalyl chloride in the presence of catalytic amounts of methanol in dichloromethane at −60 °C <1995T2467> (Equation (54)).



(54)

The reaction proceeds under typical Swern oxidation conditions via chloride anion ring opening of an epoxide coordinated to a sulfonium salt formed *in situ*. The intermediate chloroalkoxysulfonium salt provides the α-chloroketone on treatment with triethylamine. It is thought that the addition of methanol provides catalytic quantities of hydrochloric acid that assists the epoxide ring-opening. Aliphatic terminal epoxides provide α-chloroketones as the major product indicating that an S_N2 ring-opening is operative.

(iii) From stable enol ether derivatives

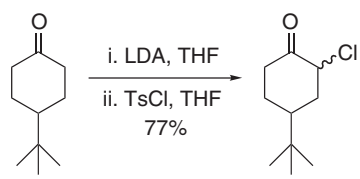
Silyl enol ethers are oxidized to α-chloroketones in moderate-to-high yield using *t*-butyl hydroperoxide as oxidant in combination with dichlorotitanium diisopropoxide, readily prepared from titanium tetraisopropoxide and titanium tetrachloride, in dichloromethane at −50 °C <1999JPR62>.

(iv) From ketones

While a number of methods exist for the direct chlorination of ketones to give α-chloroketones, recent research in this area has concentrated on developing more mild and efficient alternate procedures for this transformation.

The chlorination of a variety of ketones is readily achieved in good yield under heterogeneous conditions using sodium chlorite in the presence of manganese(III) acetylacetonate as catalyst and moist alumina in dichloromethane <1998SC131>.

Sulfonyl chlorides have been shown to act as sources of electrophilic chlorine, and this property has been exploited in a mild and inexpensive synthesis of α-chloroketones from ketones <1999TL2231>. Treatment of a variety of cyclic ketones with LDA in THF followed by the addition of *p*-toluenesulfonyl chloride at −78 °C leads to formation of the chlorinated ketone in good yield (Equation (55)).



(55)

A polymer-bound tosyl chloride is also an effective chlorinating agent in the above procedure. Cannulation of the lithium enolate into a THF-swelled commercially available polystyrene–tosyl chloride resin affords the chlorinated ketone, which is simply washed from the resin, in good yield.

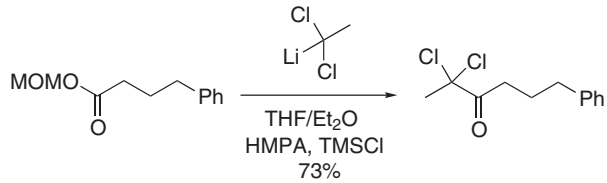
The direct chlorination of ketones may also be achieved under microwave-assisted solvent-free conditions <2004TL191>. Treatment of a variety of neat ketones with [(hydroxytosyloxy)iodo]-benzene and magnesium chloride and irradiation of the mixture with microwaves leads to isolation of the corresponding α-chloroketone in high yield.

A novel, operationally simple, method for the conversion of α-bromoketones into α-chloroketones involves the use of sulfur nitride complexes. A variety of α-bromoketones are converted into the corresponding α-chloroketone in high yield using tetrasulfide tetranitride:antimony perchloride complex in toluene <1997TL4227>.

(vi) From acids or esters

The homologation of esters with lithiated dihalomethanes and the acidolysis of α-diazoketones remain the standard methods used for the synthesis of α-chloromethyl ketones from carboxylic acid derivatives.

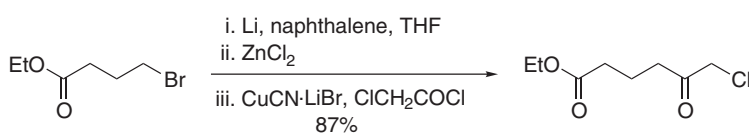
Methoxymethyl carboxylates can now also be used in the homologation reaction with dihaloalkanes. Treatment of a variety of linear methoxymethyl carbonyl-containing substrates with 1,1-dichloroethyllithium, generated from 1,1-dichloroethane using LDA or *n*-butyllithium, in the presence of trimethylsilyl chloride at $-100\,^{\circ}C$ affords the corresponding α,α-dichloroethyl ketones in good yields <2000CL1062> (Equation (56)).



(56)

α-Chloroketones of *N*-carbamate protected amino acids esters are converted into α-chloroketones using a related procedure. Treatment of a variety of methyl and ethyl esters of *N*-BOC-protected amino acids with the lithium anion of chloroiodomethane in THF at $-78\,^{\circ}C$ gives the chloroketone in high yield <1997TL3175>. This procedure is also highly amenable to scaleup. The toxic diiodochloromethane by-product may be removed by addition of sodium borohydride and the resulting precipitated chlorohydrin removed by filtration.

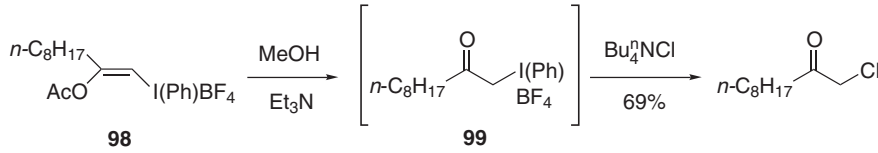
An alternative strategy for the synthesis of α-chloroketones involves the addition of an organometallic reagent to an α-chloroacyl chloride. This method has now been adapted to the preparation of substituted chloromethyl ketones <1995SC3923>. A variety of highly functionalized organo-zinc reagents may be accessed by oxidative addition of Reike zinc to organohalides. These reagents undergo copper(I) cyanide/lithium bromide complex-mediated coupling to chloroacetyl chloride in THF at $-35\,^{\circ}C$ to give chloroketones substituted with ethoxycarbonyl and nitrile groups in high yield (Equation (57)).



(57)

(vii) Miscellaneous Preparations

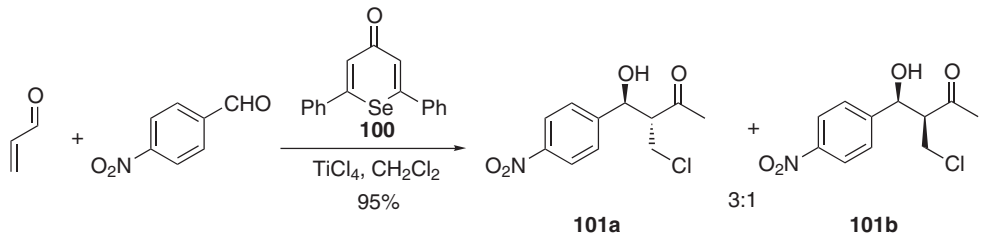
A novel procedure for the generation of α-chloroketones involves the nucleophilic substitution of α-γ^3-iodanyl ketones with halide anions <2002JOC4407>. Reaction of γ^3-iodane **98** with tetrabutylammonium chloride or sodium chloride in methanol leads to the formation of α-chloroketones via S_N2 attack of halide ion onto a α-γ^3-iodanyl ketone **99** generated *in situ* (Scheme 21). This process is applicable to the synthesis of a wide range of chloroketones and may also be used to synthesize fluoro-, bromo-, and iodoketones using the appropriate sodium or tetrabutylammonium halide salt.



Scheme 21

3.04.3.3.2 β-Chloroaliphatic ketones

β-Chloroaliphatic ketones are the major products in chalcogenide–titanium tetrachloride-mediated reactions of enones with aldehydes <2000T4725>. Aromatic aldehydes react with methyl vinyl ketone in the presence of selenopyranone **100** and titanium tetrachloride in dichloromethane to give chloromethylhydroxyketone **101** as a mixture of diasteroisomers in high yield (Equation (58)). The mechanism is postulated to proceed via conjugate addition of the chalcogenide followed by aldol reaction of the resulting enolate. Substitution of the chalcogen by chloride ion gives the products **101**, while elimination gives α-methylene-β-hydroxyketones, and these are isolated as the major product using preparative tlc as the purification technique.



(58)

3.04.3.4 Bromoaliphatic Ketones

3.04.3.4.1 α-Bromoaliphatic ketones

(i) From alkenes

Treatment of vinyl bromides with sodium hypobromite using the procedure outlined in Section 3.04.3.3.1.(i) gives α-bromoketones in high yield under mild reaction conditions <2003JOC3323>.

(ii) From epoxides

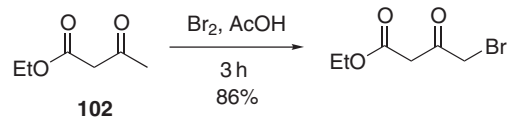
No further advances in this area have occurred since the publication of COFGT (1995).

(iii) From stable enol derivatives and enamines

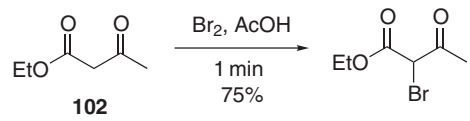
No further advances in this area have occurred since the publication of COFGT (1995).

(iv) From ketones

Unsymmetrical ketones are generally brominated at the more activated, internal carbon, and the terminally brominated product is obtained as a minor product. A new method has been developed, that proceeds via nonselective bromination followed by a selective debromination, to give access to either bromoketone product by performing the reaction under thermodynamic or kinetic control <2003OL411>. For example, β-keto ester **102** reacts with bromine in acetic acid for 3 h under thermodynamic control to give the terminal product in good yield (Equation (59)). In contrast, stirring the reaction mixture for 1 min under kinetic control gave the internal bromide as the major product (Equation (60)).



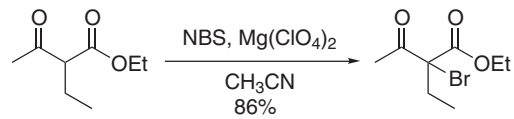
(59)



(60)

The α-bromination of ketones may also be achieved under solvent-free, microwave-induced conditions using dioxane-dibromide and silica gel <2003TL439> or using hydroxy(tosyloxy)-iodobenzene and magnesium bromide under solvent-free conditions <2004TL191>.

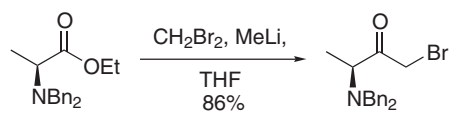
N-Bromosuccinimide is commonly used to brominate 1,3-dicarbonyl compounds at the α-position. This process has now been modified to give a mild and general method for the α-bromination of 1,3-dicarbonyls by the addition of catalytic amounts of Lewis acids <2002JOC7429>. Chelation of magnesium perchlorate to the carbonyl oxygens of the β-keto ester substrate activates the α-carbon allowing fast and mild bromination using NBS in ethyl acetate or acetonitrile at room temperature (Equation (61)).



(61)

(v) From acids or esters

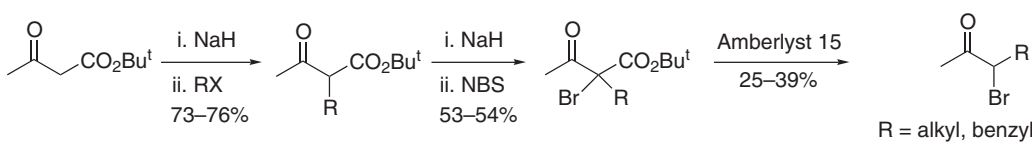
Esters may be converted into α-bromoketones on treatment with bromoalkyllithium reagents. In a recent example of this methodology, a range of hitherto unprepared α-aminobromoketones are accessed by treatment of the corresponding *N*,*N*-dibenzylated α-amino carboxylate with bromomethyllithium, prepared by reaction of dibromomethane with methyllithium at $-78\,^{\circ}C$ <1999JOC5048> (Equation (62)).



(62)

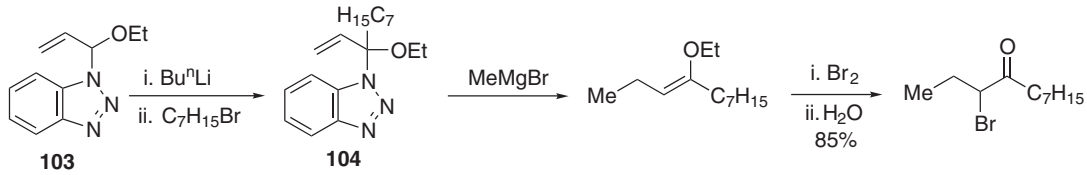
(vi) Miscellaneous preparations

The direct bromination of unsymmetrical ketones often results in the formation of mixtures of bromoketone products. A convenient preparation of unsymmetrical α-bromoketones that is regioselective and of potentially wide scope has been developed that centers on the bromination of *t*-butyl β-keto esters followed by acid-induced decomposition of the *t*-butyl ester group <1995SC1045>. Alkylation of *t*-butyl β-keto esters, obtained from Meldrum's acid, with a variety of saturated and unsaturated organohalides followed by bromination of the enolate using either NBS gives the bromo β-keto ester that decomposes to give the α-bromoketone on treatment with Amberlyst® 15 (Scheme 22).



Scheme 22

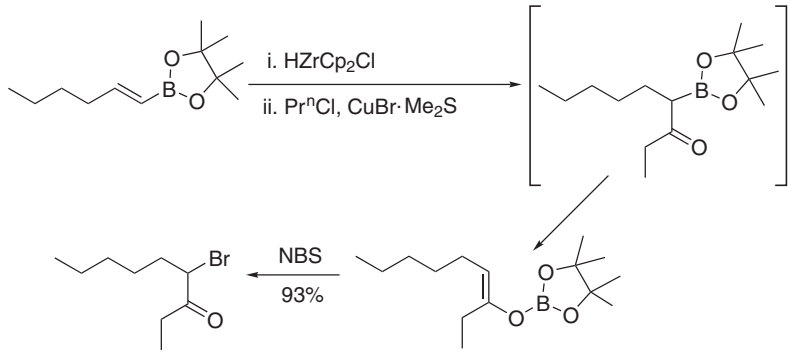
Another, highly novel approach to the synthesis of α-bromoketones of potentially wide scope centers on the generation of alkyl enol ethers regioselectively from benzotriazole derivates such as **103** <1995JOC7605>. Reaction of compound **104** with Grignard reagents leads to displacement of the benzotriazole group to give ethyl enol ethers that react with bromine *in situ* to give internally brominated ketones (Scheme 23).



103 **104**

Scheme 23

An interesting route to boron enolates provides a regioselective one-pot route to unsymmetrical α-bromoketones from readily available alkenyl boronates <1995TL5665>. Hydrozirconation of alkenyl boronates followed by treatment of the resulting *gem*-borazirconocene alkane with acid chlorides leads to the formation of α-bora-ketones. These intermediates rapidly rearrange to give boron enolates that undergo regioselective bromination using NBS to give α-bromoketones in high yield (Scheme 24).



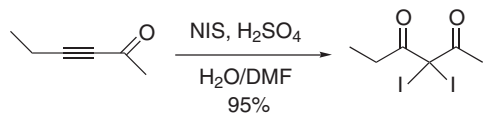
Scheme 24

3.04.3.5 Iodoaliphatic Ketones

3.04.3.5.1 α-Iodoaliphatic ketones

(i) From alkenes

Terminal and internal conjugated alkynones undergo reaction with NIS in DMF/H_2O and sulfuric acid to give 2,2-diiodo-1,3-diketone or 2,2-diiodo β-ketoesters in good yield <1998JOC4433> (Equation (63)). The reaction may also be performed in methanol allowing isolation of the product as the dimethyl acetal.



(63)

(ii) From epoxides

No further examples have been reported since COFGT (1995).

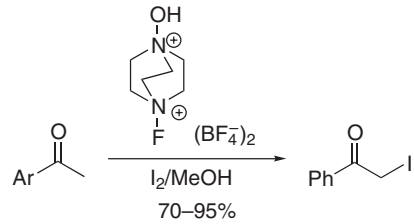
(iii) From stable enol derivatives and enamines

Enol acetates and 1,3-diones are iodinated to give the corresponding α-iodoketones under neutral conditions using *N*-iodosaccharine at room temperature <2003SC2917>.

(iv) From ketones

A variety of cyclic and acyclic ketones may be directly iodinated with iodine and ceric ammonium nitrate in high yield <1997BCJ421>. Unsymmetrical ketones may be regioselectively iodinated using this method when alcohols are utilized as the solvent and this selectivity is temperature dependent. For example, 2-hexanone is predominantly iodinated at the more substituted position at 25 °C but at 50 °C the terminally iodinated ketone is the major product. The preferential formation of a bulky cerium(IV)-alcohol complex at 50 °C, that coordinates to the enol oxygen is used to explain this temperature-dependent regioselectivity. Ketones may also be iodinated directly using [(hydroxytosyloxy)iodobenzene] and magnesium iodide in a solvent-free, microwave-induced process <2004TL191>.

Aryl alkyl ketones are iodinated in good yield using elemental iodine in the presence of Selectfluor in methanol at room temperature <2002CC488> (Equation (64)). While the mechanism of this process has not been fully established, it is proposed that an electrophilic iodine species is formed by oxidation of iodine by Selectfluor.

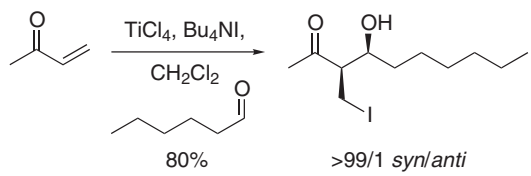


(64)

Ar = Ph, naphthyl, phenanryl, pyrenyl

3.04.3.5.2 β-Iodoaliphatic ketones

Aldehydes, vinyl ketones, and tetrabutylammonium iodide undergo a three-component coupling reaction in the presence of titanium tetrachloride to give *syn*-α-iodomethyl-β-hydroxyketones with high stereoselectivity in good yield <2001JOC7854> (Equation (65)). The reaction mechanism proceeds through conjugate attack of iodide onto the vinyl ketone to give a titanium enolate that undergoes a stereoselective aldol reaction with the aldehyde.



(65)

3.04.4 KETONES BEARING AN OXYGEN FUNCTION

3.04.4.1 OH-Functionalized Ketones

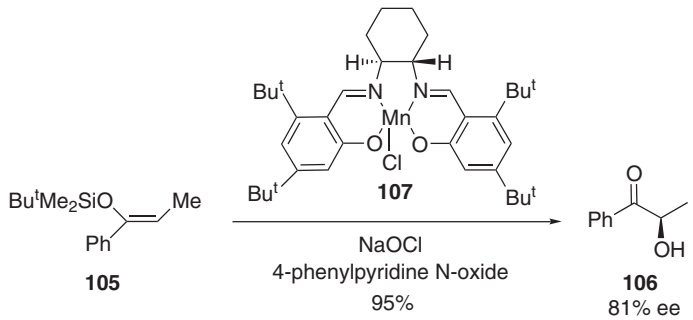
3.04.4.1.1 α-OH-Functionalized ketones

The α-hydroxyketone moiety is present in a variety of biologically active natural products and the hydroxyl group functions as an important stereocontrol element during transformations of the neighboring carbonyl group. Consequently, much recent research has been directed towards the development of synthetic routes towards these synthons.

In principle, one of the most convenient approaches to α-hydroxyketones is by the direct oxidation of ketone precursors. This is often achieved by oxidation of an enol tautomer or an enolate derivative. In the past, a range of enolates have been oxidized using a variety of oxidizing agents <1995COFGT(3)111>. Recently, titanium enolates, generated from the corresponding lithium enolate with titanium triisopropoxide or chlorotitanium diisopropoxide have been shown to undergo oxidation with *t*-butyl hydroperoxide at −78 °C in THF to give α-hydroxyketones <1995T3175>. The direct oxidation of ketones, via formation of the enol tautomer has also been developed to proceed under aerobic conditions. A variety of ketones undergo oxidation to the α-hydroxyketone using a bimetallic palladium(II) catalyst under 1 atm. pressure of oxygen in the presence of methanesulfonic acid to promote formation of the enol ether <2002JOM50>. β-Ketoesters are also oxidized to the corresponding α-hydroxy derivatives using molecular oxygen in the presence of cerium(III) chloride as catalyst <2003EJOC425>.

The oxidation of silyl enol ethers with MCPBA, known as the Rubottom oxidation, is an important method for the regioselective formation of α-hydroxyketones. Recent research in this area has been directed toward the search for alternative, more efficient oxidants to effect the transformation.

The oxidation of trimethylsilyl enol ethers is effected in a few minutes at room temperature using $HOF{\cdot}CH_3CN$ complex, an efficient oxygen transfer agent prepared by passage of nitrogen-diluted fluorine through aqueous acetonitrile <1999T3657>. Silyl enol ethers are oxidized to α-hydroxyketones in an economical manner using hydrogen peroxide as oxidant in the presence of catalytic quantities of commercially available methyltrioxorhenium <1998JOC4129>. A methyldiperoxorhenium complex, formed *in situ*, oxidizes a variety of cyclic and acyclic silyl enol ethers in high yield in the presence of acetic acid and pyridine. An asymmetric oxidation of silyl enol ethers has also been developed. A variety of silyl enol ethers are oxidized to optically active α-hydroxy ketones using chiral (salen)manganese(III) catalysts in the presence of various oxidants including sodium hypochlorite, hydrogen peroxide and MCPBA <1996TL6531>. The enantioselectivity of this process was found to be dependant on the oxidant used and the substitution pattern of the enol ether. For example, enol ether **105** gave hydroxyketone **106** on treatment with sodium hypochlorite in the presence of 4-phenylpyridine-*N*-oxide and catalyst **107** in dichloromethane (Equation (66)). Epoxides undergo oxidative ring-opening using DMSO as oxidant in the presence of Brønsted and Lewis acids. A recent variant on this procedure utilises an acidic clay in combination with DMSO to effect this transformation <1995SC3141>. A range of epoxides adsorbed onto KSF clay are rapidly oxidized using DMSO under microwave irradiation to give the α-hydroxyketone in good yield.

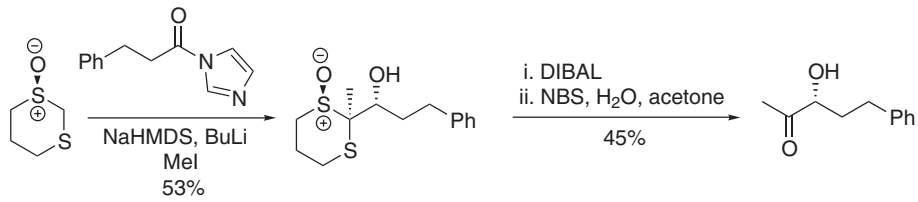


(66)

The generation and use of acyl anion equivalents is one of the most important strategies for the synthesis of α-hydroxyketones and of C—C bonds in general. Readers with an interest in the use of acyl anion equivalents and other umpolung reagents should also consult Section 3.04.1.14.

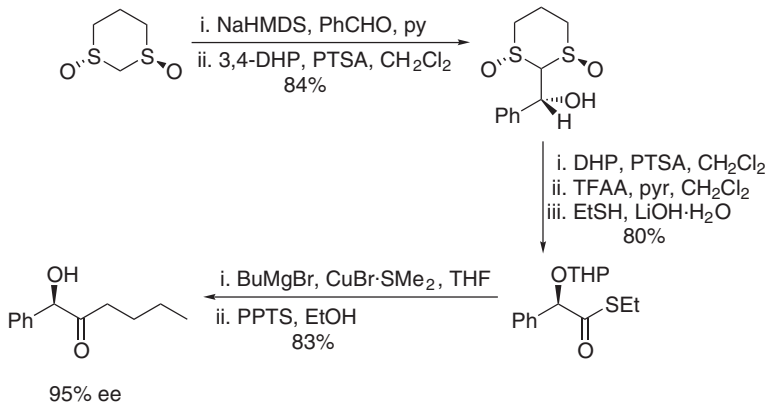
1,3-Dithianes continue to be the most popular acyl anion in use today. Much recent research has concentrated on developing optically pure dithiane sub-units that act as chiral acyl anion equivalents.

Optically active 1,3-dithiane 1-oxide, obtained from 1,3-dithiane using a modified Sharpless protocol, undergoes addition to acyl imidazoles in the presence of excess base and methyl iodide to give a 2-acyl-2-alkyl-1,3-dithiane 1-oxide in high ee <1996TL8929>. Diastereoselective DIBAL reduction followed by hydrolysis of the dithiane gives optically active α-hydroxyketone (Scheme 25). The stereoselectivity of the DIBAL reduction is reversed in the presence of zinc chloride giving access to the opposite enantiomer of the α-hydroxyketone.



Scheme 25

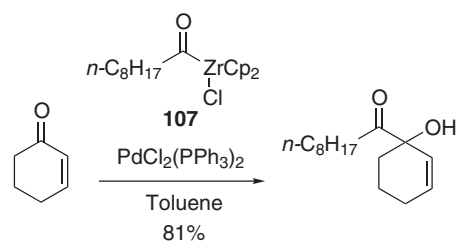
Trans-1,3-dithiane-1,3-dioxide is a related chiral acyl anion equivalent that has been applied to the synthesis of optically active α-hydroxyketones <1997T16213>. This dithiane, again, prepared using a modified Sharpless oxidation procedure, undergoes highly diastereoselective addition to aromatic aldehydes such as benzaldehyde. Pummerer reaction followed by sulfinylation gives a thioester that is converted into ketones on treatment with Grignard reagents in the presence of copper(I) catalysts (Scheme 26).



Scheme 26

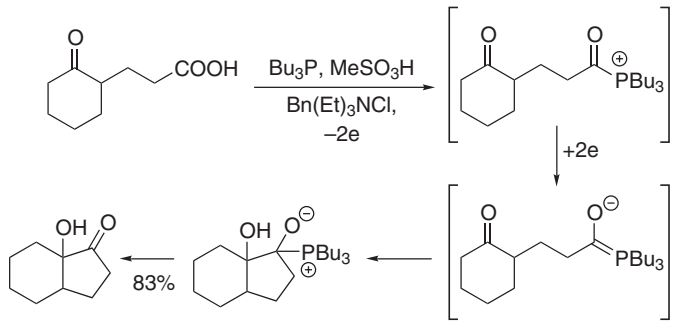
Imidoyllithium reagents are synthetic equivalents of acyl anions. However, in the past, the preparation of these compounds has been limited in scope. A range of imidoyllithium species may now be accessed from the corresponding chloroimine using lithium powder and a catalytic quantity of naphthalene <1997TL8903>. These acyl anion equivalents react with a variety of aldehydes and ketones in THF at $-78\,^{\circ}C$ to give α-hydroxyimines that may be hydrolyzed with aqueous hydrochloric acid to the corresponding α-hydroxyketone.

Acylzirconocene chlorides, prepared by hydrozirconation of alkynes with the Schwartz reagent followed by carbon monoxide insertion, are novel acyl metal reagents that undergo 1,2-addition onto a range of cyclic and acyclic enones in the presence of bisdiphenylphosphinepalladium(II) chloride to give α-hydroxyketone products in high yield <2002T7559>. Saturated ketones are unreactive substrates in this reaction and the reaction mechanism is thought to proceed by electron transfer from palladium(0), generated *in situ*, onto the enone followed by formation of an acylpalladium π-allyl complex. The regioselectivity of this process is highly dependent on the steric properties of the palladium complex. For example, while 2-cyclohexen-1-one undergoes 1,2-addition in high yield using acylzirconocene **107** in the presence of bis(triphenylphosphine)palladium(II) chloride (Equation (67)) the 1,4-adduct is the major product using palladium(II) acetate as catalyst.



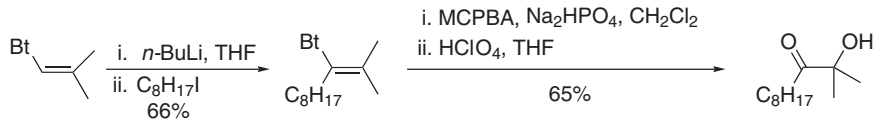
(67)

The use of acyl anions is limited to the intermolecular formation of C—C bonds owing to the difficulty in generating such nucleophiles in the presence of electrophiles. α-Oxy-ylides function as acyl anion equivalents and these may be generated electrolytically, in the presence of electrophiles, from acyl phosphonium ions <1995CC871>. Electroreduction of a mixture of keto acid and tributylphosphine in the presence of benzyltriethylammonium chloride and methanesulfonic acid generates a keto α-oxy ylide that undergoes cyclization to give an α-hydroxycycloalkanone (Scheme 27).



Scheme 27

The reaction of α-hydroxyacyl nucleophiles with electrophiles represents an alternative acyl anion-based strategy toward α-hydroxyketones. 1-(1-Alkenyl)benzotriazoles are readily converted into α-hydroxycarbonyl compounds by epoxidation followed by hydrolysis and, as they may be lithiated at the carbon α to the benzotriazole group, they may be thought of as α-hydroxyacyl anion equivalents <1996SC2657>. The α-lithio derivatives react with a variety of electrophiles including alkyl halides, aldehydes and ketones to give α-substituted 1-(1-alkenyl)benzotriazoles that are converted into α-hydroxyketones by epoxidation with MCPBA followed by hydrolysis with aqueous perchloric acid (Scheme 28).



Scheme 28

The mono-oxidation of a 1,2-diol is an attractive yet simple strategy for the synthesis of α-hydroxyketones. A number of procedures are known for the selective oxidation of secondary over primary alcohols and recent research has concentrated on developing methods for the mono-oxidation of *sec*,*sec*-diols. It has been found that DMDO is capable of mono-oxidizing symmetrical 1,2-*sec*,*sec*-diols to give α-hydroxyketones as the carbonyl group in the product alters the electronic environment of the neighbouring center making it less reactive towards the oxidant <1995TL3031>. This electronic effect is also exerted by a variety of carbon-based and heteroatom functionalities and the DMDO oxidation of a range of unsymmetrical *sec*,*sec*-1,2-diols is now predictable <1996T10969, 1998T14301>. In general, a carbinol directly linked to an electron-donating substituent is better oxidized than one linked to an electron-deficient substituent.

Reductase enzymes specifically oxidize alcohols of (S)-stereochemistry and thus have the potential for use in kinetic resolutions of diols giving optically active α-hydroxyketones as products. Both *syn*- and *anti*-1,2-diols may be kinetically resolved using *Bacillus stearothermophilus* diacetylreductase as enzymic oxidant <1998TA647>. A variety of (*S*,*S*) and (*R*,*R*)-*syn*-1,2-diols are oxidized using this enzyme to give (*S*)-α-hydroxyketones and unreacted (*R*,*R*)-diols. During oxidation of the *anti*-pair of diols, the (*S*)-hydroxy function adjacent to the smaller substituent is exclusively elaborated allowing formation of an (*R*)-α-hydroxyketone and resolution of the (*R*,*S*)-diol.

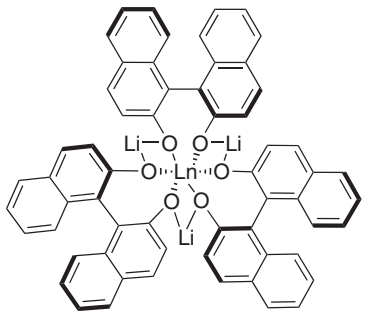
3.04.4.1.2 β-OH-Functionalized ketones

The most important method for the synthesis of β-hydroxyketones is through use of the aldol reaction—one of the most fundamental C—C bond-forming reactions available. This transformation is one of the most widely used reactions in synthesis today and, for the sake of brevity, only the most important new developments in this area will be discussed in this section. Readers seeking a more in-depth discussion of the aldol reaction are recommended to consult the recent comprehensive reviews published in this area <2000T917, 1997OR(51)1>.

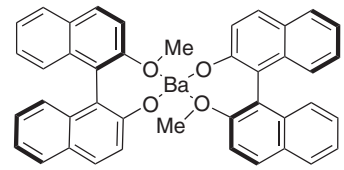
In common with many other important C—C bond-forming processes there is much contemporary interest in the development of asymmetric aldol reactions. In the past decade in particular, research has focused on the development of catalytic asymmetric aldol reactions <2002EJOC1595>. At the present time, the types of catalyst showing the most potential can be grouped into four main classes: (i) organometallic complexes, (ii) enzymatic catalysts, (iii) organocatalysts, and (iv) Lewis base catalysts.

(i) Organometallic complexes

Early research in the area of direct asymmetric catalysis of the aldol reaction centered on the development of chiral metal complexes incorporating both a Lewis acidic and a Brønsted basic site. Thus, both aldehyde and ketone are brought together in a chiral environment and optically active aldol products are obtained. The first-generation catalysts were based on lanthanum tris[(*R*)-binaphthoxide] complexes such as **107** <1997AC(E)1236>. Limitations associated with the use of this catalyst include relatively high catalyst loading and long reaction times. These limitations have been overcome by the development of the barium catalyst **108** that possesses a stronger Brønsted basic site <1998TL5561>. While catalyst **107** produces aldol products in good ee, the reaction between aldehyde and ketone in the presence of catalyst **108** proceeds more rapidly to give aldol products in high yield but modest ee.

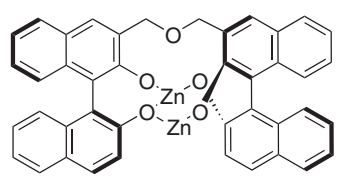


107

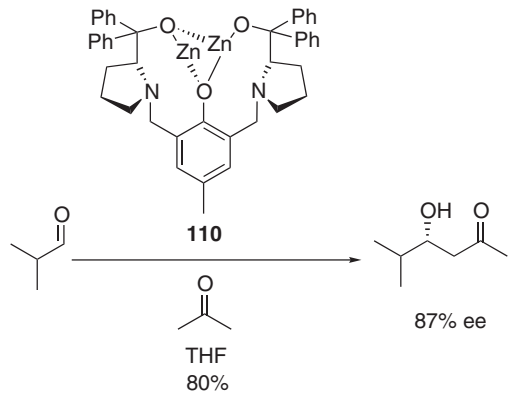


108

A number of asymmetric aldol catalysts based on zinc have also been developed. The zinc–zinc-linked BINOL complex **109** functions with α-hydroxyketones in THF at −30 °C as substrates to afford α,β-dihydroxyketones with *syn*-stereoselectivity and high yield and ee <2001OL1539>. Trost has also developed a novel series of zinc-containing chiral complexes such as **110** that catalyze the aldol reaction of a variety of aldehydes and ketones including α-hydroxy ketones (Equation (68)) <2000JAI2003, 2001OL2497>. The active catalyst is formed *in situ* by reaction of diethylzinc with the appropriate alcohol, formed from methylprolinate and *p*-cresol.



109



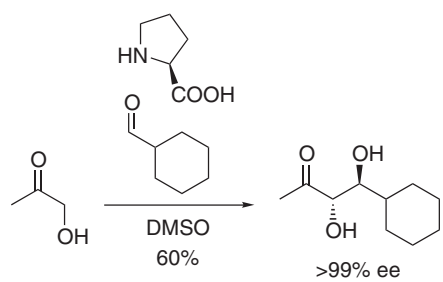
(68)

(ii) Enzymic catalysts

Aldolases are enzymes responsible for the *in vivo* formation of hexoses from 3-carbon precursors via aldol reactions. These enzymes are readily isolated from organisms and may be used in biocatalyzed aldol reactions to synthesize a wide range of natural and non-natural carbohydrates and this area has been extensively reviewed <1996CR443>. While these enzymes are capable of accepting a range of acceptor aldehydes, they are, however, specific for certain donors such as dihydroxyacetonephosphate (DHAP) or pyruvate. Thus, this approach to optically active α-hydroxyketones is limited. The reliance on expensive and labile DHAP has been recently circumvented by the *in situ* generation of arsenate esters from dihydroxyacetone <2001JOC4559>. The arsenate ester is generated using an arsenate buffer and undergoes aldol coupling to a variety of aldehydes in the presence of bacterial D-fructose-1,6-biphosphate aldolase.

(iii) Organo-catalysts

During the enzymatic catalysis of the aldol reaction, it is postulated that an intermediate chiral enamine is formed between the aldol donor and an amino acid residue at the enzyme active site. This observation has led to the discovery that simple amino acids, that may also form optically active enamines with aldol donors, can function as effective and highly economical chiral catalysts of the aldol reaction <2000JA2395>. Amino acids satisfy many of the criteria for a good catalyst and are cheap and readily available in both enantiomeric forms. L-proline has proved to be the most popular of these so-called organocatalysts <2002T2481> and has been shown to effectively catalyze the aldol reaction of a wide range of aldehydes and ketones, although a large excess of ketone is required and 30 mol.% proline is also needed. Aldol products with two stereogenic centers may also be formed using α-hydroxyketones in the presence of proline to give *anti*-ketodiols in high ee <2000JA7386> (Equation (69)).

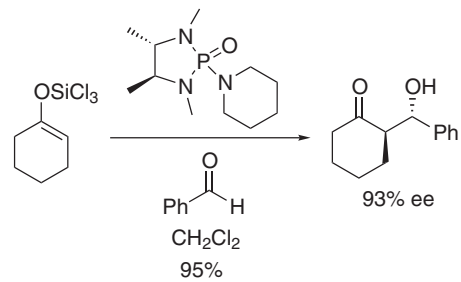


(69)

Other small molecules related to proline have also been found to be effective organocatalysts in the aldol reaction. Recently, it has been discovered that a range of β-hydroxyprolinamides derived from L-proline effectively catalyze the aldol reaction of aldehydes with neat acetone in high ee <2003JA5262>.

(iv) Lewis-base-catalyzed reactions

The Mukaiyama aldol reaction of enolsilanes with aldehydes is known to proceed in an enantioselective manner using chiral Lewis acids. The Denmark group have devised an alternative to this process that utilizes more reactive trichlorosilyl enolates in the presence of chiral phosphoramide Lewis bases <1996JA7404, 2000JA8837>. In contrast to the Mukaiyama reaction, these reactions are thought to proceed via a highly organized chair-like transition state incorporating hexacoordinate silicon bound to a phosphoramide ligand <1997JA2333>. Consequently, the Lewis-base-catalyzed procedure is a highly stereoselective, enolate geometry-dependent alternative to the Mukaiyama aldol reaction that proceeds with a wide variety of aldehydes and ketones (Equation (70)).

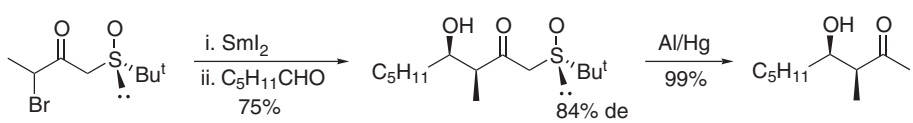


(70)

A number of alternatives to the classical aldol reaction have also been developed in recent years. Ir(I) cationic complexes catalyze the Mukaiyama reaction between enoxysilanes and acetals or aldehydes <2000TL1405>. Propargylic alcohols undergo 1,3-transposition in the presence of vanadium catalysts to give allenolates that may be intercepted by aldehydes to give aldol products <2001JA1230>. Tris(triphenylsilyl)vanadate catalyzes the addition of a variety of propargyl alcohols with benzaldehyde at 80 °C to give α-alkenyl-β-hydroxyketones in good yield. Homoallylic alcohols undergo rearrangement in the presence of Ru(II) catalysts to give ruthenium–enol complexes that may be captured by aldehydes in ionic liquids to give aldol products in high yield <2003OL657>. The ionic liquid/catalyst system is readily isolated and may be reused up to five times with no loss of reactivity.

Δ^2-isoxazolines, the products of nitrile oxide 1,3-dipolar cycloadditions, are readily converted into β-hydroxycarbonyls by N—O bond reduction followed by imine hydrolysis and thus function as latent aldol adducts. Nitrile oxide cycloadditions are readily performed in a stereospecific manner using stable, readily available starting materials. Thus, this cycloaddition/cycloadduct cleavage strategy is an attractive approach to synthesis of stereodefined aldol adducts. The use of nitrile oxide cycloadditions in the stereoselective synthesis of polyketides and other complex synthetic targets has been well demonstrated by the Carreira group <2001AC(E)2082, 2001JOC6410>. A variety of methods exist for the reductive cleavage of isoxazolines. The most recent convenient and chemoselective method utilizes samarium iodide as reductant in combination with boric acid to hydrolyze the resultant imine <2001OL1587>.

β-Hydroxyketones are also obtained by Reformatsky reaction of α-haloketones with aldehydes. Traditionally performed in the presence of zinc, a wide variety of other metals have been found to effect this reaction. Recently, titanium tetraiodide has been found to induce the Reformatsky reaction of a variety of α-iodoketones and aldehydes to give β-hydroxyketones in high yield <2001T9591>. The Reformatsky reaction of chiral α-bromo-α'-sulfinylketones with aldehydes proceeds in high diastereoselectivity to give *syn*-adducts in high yield in the presence of samarium iodide and the sulfoxide auxiliary is readily reductively cleaved to optically active β-hydroxyketones using aluminum amalgam <2003OL629> (Scheme 29).



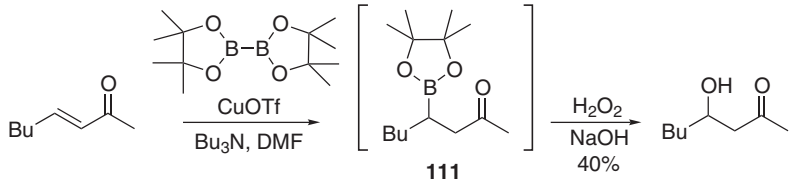
Scheme 29

α,β-Epoxyketones may be selectively reduced to β-hydroxyketones using a variety of reagents including samarium diiodide, lithium/ammonia, and tributyltin hydride/AIBN. Novel reagents for

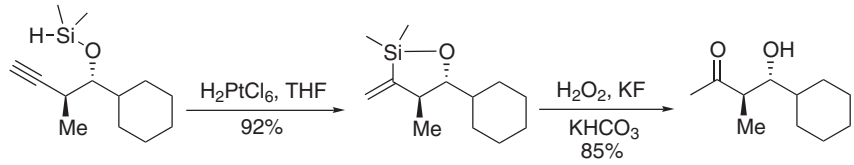
this transformation include sodium phenylseleno(triethyl)borate, prepared by reduction of diphenyldiselenide with sodium borohydride, <1997T12469> and bis(cyclopentadienyl)titanium chloride, prepared by *in situ* reduction of the corresponding dichloride <2001JOC1046>.

1,3-Diketones undergo bioreduction to optically active β-hydroxyketones using baker's yeast in an ionic liquid/water mixture <2001TL7517>.

The regioselective hydroboration/oxidation of α,β-unsaturated ketones provides a novel pathway to β-hydroxyketones <2000TL6821>. Bis(pinacolato)diboron adds to α,β-unsaturated ketones in the presence of catalytic amounts of copper(I) salts and tributylphosphine to give boration product **111**, which is oxidized under standard conditions to give the corresponding β-hydroxyketone (Scheme 30). A convenient route to β-hydroxyketones from homopropargylic alcohols has been developed recently. The intramolecular hydrosilylation of homopropargylic hydrodimethylsilylethers, using chloroplatinic acid, gives five-membered cyclic siloxanes that may be oxidatively cleaved to β-hydroxyketones using hydrogen peroxide in the presence of potassium fluoride and potassium hydrogen carbonate <2000OL2173> (Scheme 31). The homopropargylic alcohols are prepared by addition of allenylzinc reagents, prepared from propargyl mesylates in the presence of palladium(II) acetate and diethylzinc, to aldehydes.



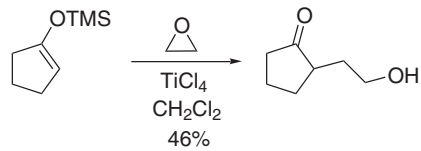
Scheme 30



Scheme 31

3.04.4.1.3 γ-Functionalized and more remotely functionalized ketones

Epoxides undergo ring-opening with silyl enol ethers to give the homoaldol product in moderate yield in the presence of titanium tetrachloride in dichloromethane at −78 °C (Equation (71)) <2001T583>. The reaction with monosubstituted epoxides is regioselective, occurring at the most-hindered position with propene oxide but at the least-hindered position with epi-chlorohydrin. A range of epoxides are ring-opened by enolates derived from cyclic ketones and lithium hexamethyldisilazide in the presence of boron trifluoride etherate to give γ-hydroxyketones in good yield <2003JOC3049>. The ring-opening is highly diastereoselective with the lithium enolates of enones such as 2-cyclohexenone to give the *syn*-adduct as the major product.



(71)

The terminal isopropyl group of 5-methylhexan-2-one is oxidized to the corresponding tertiary alcohol group to give the γ-hydroxyketone in 80% yield using electrochemical methodology <1997TL7067>. The reaction occurs in the presence of thallium(III) and hematoporphyrin in an undivided cell fitted with platinum anode and cathode with continuous bubbling of oxygen, and proceeds via formation of an oxidized hematoporphyrin-bound thallium(II) species at the cathode. A similar transformation is achieved in hydrogen fluoride–antimony pentafluoride in the presence of carbon tetrachloride <1996TL2967>. The reaction is also operative for linear,

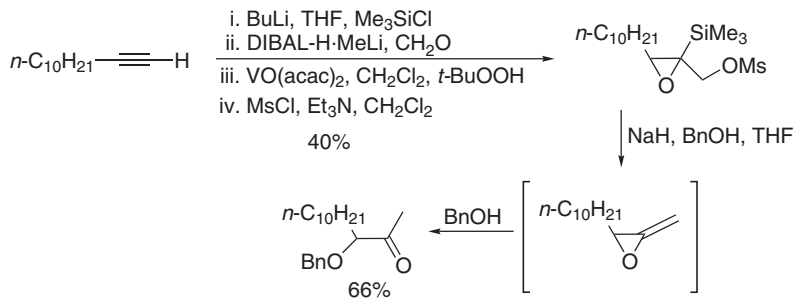
unsubstituted ketones such as heptan-2-one and octan-2-one giving access to γ- and δ-hydroxy ketones in good yield. The mechanism of this process proceeds via hydride abstraction by strong electrophiles formed *in situ* followed by trapping of the intermediate carbocation with water.

3.04.4.2 OR-Functionalized Ketones

A range of linear and cyclic benzoate esters are oxidized at positions in the hydrocarbon chain with methyl(trifluoromethyl)dioxirane in dichloromethane at $-20\,^{\circ}C$ to give ketoesters <1996JOC5564>. Oxidation occurs primarily at positions giving γ- and δ-ketoesters in good yield. Carbonyl compounds are readily functionalized at the α-position using iodosylbenzene in the presence of nucleophiles and this methodology has been used to prepare α-alkoxy-1,3-diones <2002SL1170>. The 1,3-dione may be functionalized with a range of alcohols using iodosylbenzene in the presence of boron trifluoride etherate in drichloromethane and 1.5 equiv. of alcohol substrate.

Alcohols undergo O—H insertion reactions with α-diazoketones to give α-alkoxyketones. These reactions are carried out in the presence of metal complex catalysts or Lewis and Brønsted acids. This transformation may now be carried out under more mild reaction conditions. Indium triflate is a water-tolerant mild Lewis acid that catalyzes the insertion reaction of diazoketones with a range of alcohols at room temperature <2002TL3133>. Lithium tetrafluoroborate catalyzes the reaction of a range of diazoketones with alcohols in acetonitrile under mild, neutral conditions to give access to a variety of α-alkoxyketones in high yield <2003TL5691>.

Epoxymesylates undergo reactions with a variety of sodium alkoxides to give alkoxyketones <1998T14265>. The epoxides, prepared from acetylenes in four steps, are converted into allene oxides on treatment with sodium alkoxides. These intermediates undergo ring opening *in situ* to give α-alkoxyketones (Scheme 32). The epoxidation may be performed under Sharpless conditions to give optically active epoxides that undergo ring opening without racemization to give α-alkoxyketones in good ee.

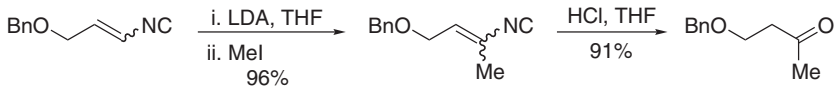


Scheme 32

Methoxyallene oxide, prepared *in situ* by peracid oxidation of methoxyallene, behaves as an equivalent of the titanium enolate of methoxyacetone in the presence of titanium tetraiodide and undergoes addition with acetals or aldehydes to give 2,3-dialkoxy or 2-hydroxy-3-methoxy ketones in good yield <2000OL4079>.

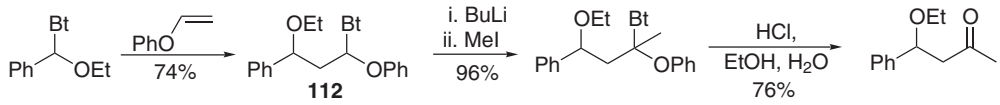
The Mukaiyama aldol reaction of silyl enol ethers with acetals is a well-known method for the preparation of β-alkoxyketones. This process usually requires the preparation of the silyl enol ether in a separate step. Recent work has been directed towards developing this process as a single-step reaction. The aldol reaction between ketones and acetals may now be effected in one pot by the addition of diisopropylethylamine and dibutylboron triflate to a mixture of ketone and acetal in dichloromethane at $-78\,^{\circ}C$ to give the β-alkoxyketone in high yield <2004OL127>. Diastereoisomeric mixtures of products are obtained with chiral acetals indicating that an S_N1 process, proceeding via formation of an oxonium ion from the acetal, is operative in this case.

An alternative strategy for the synthesis of β-alkoxyketones involves the generation and reaction of β-alkoxy-substituted acyl anion equivalents. 3-Benzyloxy-1-isocyanopropenes, prepared from benzyloxyacetals in five steps, are metallated with LDA to provide the 1-lithio derivatives that react with a variety of alkyl halides. Hydrolysis of the resulting unsaturated isocyanate provides the β-alkoxyketone <1996TL2437> (Scheme 33).



Scheme 33

β-Alkoxyketones are also accessible using benzotriazole-stabilised acyl anion synthons <1998JOC1473>. 1-(1-Alkoxy-1-arylmethyl)benzotriazoles react with phenyl vinyl ether to give intermediates such as **112** that are readily lithiated. Subsequent trapping with alkyl iodides followed by hydrolysis gives the β-alkoxyketone (Scheme 34).



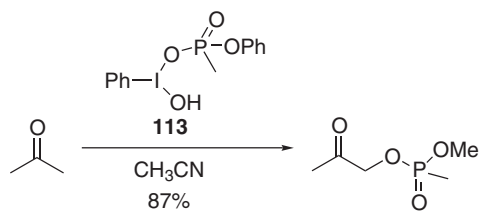
Scheme 34

3.04.4.3 OX-Functionalized Ketones

Linear aliphatic ketones are regioselectively converted into the corresponding α-sulfonyloxy derivative using copper(II) organosulfonates, prepared from the corresponding sulfanoyl chloride and copper(II) oxide in acetonitrile <1998TL3171>. The same transformation has also been achieved under solvent-free conditions under microwave irradiation <1999TL8877>.

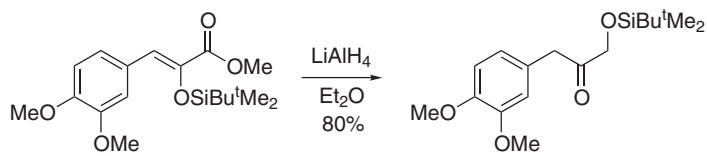
β-Ketosulfones may be synthesized from γ^3-iodanes in a manner similar to the preparation of α-haloketones as described in Section 3.04.3.3.1.(vii). Reaction of γ^3-iodanes with sodium benzensulphinate gives the β-ketosulfones in moderate yield via formation of an γ^3-iodanyl ketone <2002JOC4407>. In a similar manner, reaction of γ^3-iodanes with triethylamine and diphenylphosphinic acid gives α-ketodiphenylphosphinates and α-phosphoryloxyketones are obtained by reaction of γ^3-iodanes with the corresponding phosphate.

Phosphonate and phosphinate groups may be introduced to the α-position of ketones using novel hypervalent iodine oxyphosphorylating agents <1997TL2401>. Iodosobenzene reacts with phosphonic and phosphinic acids in acetonitrile to give reagents such as **113** that react with ketones and 1,3-dicarbonyls in acetonitrile under reflux to give the α-phosphonyloxylated product in moderate to good yield (Equation (72)).



(72)

α-Silyloxyketones may be generated from α-ketoesters in two steps by formation of the corresponding α-silyloxy-α,β-unsaturated ester followed by lithium aluminum hydride reduction <1999T6497>. The silylenolethers of α-ketoesters are formed under standard conditions. Reduction of the ester moiety in diethylether and silyl migration then results in formation of the α-silyloxyketone (Equation (73)). γ-Trimethylsilyloxy-β-ketoesters may be accessed by [2,3]-Wittig rearrangment of γ-allyloxy-β-ketoesters followed by quenching with trimethylsilyl chloride <2001TL5215>.



(73)

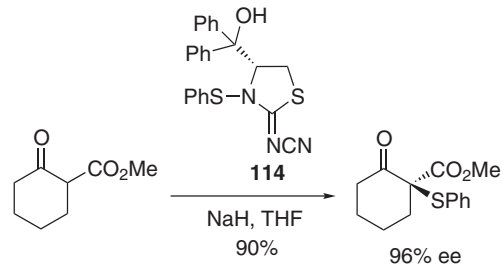
3.04.5 KETONES BEARING A SULFUR FUNCTION

3.04.5.1 SH- and SR-functionalized Ketones

3.04.5.1.1 α-SH and SR-functionalized ketones

α-Thioketones may be accessed by hydrolysis of the corresponding thioacetate derivative. The thioacetate moiety is usually introduced by nucleophilic displacement of halide with potassium thioacetate. This transformation is often performed under reflux and is generally not high yielding. A mild synthesis of thioesters from halides has been developed using DMF as solvent <1999TL603>. For example, α-bromoacetophenone is converted into the corresponding α-thioacetate in 96% yield under these conditions. The resulting thioacetate is hydrolyzed using sodium hydroxide in acetone or methanol at room temperature to give the corresponding thiol.

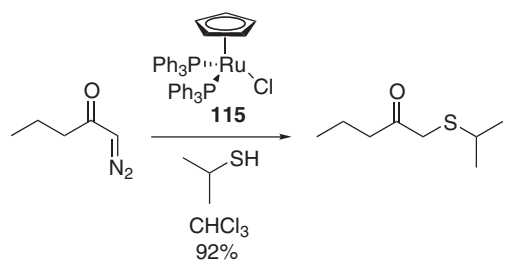
A common approach to the synthesis of α-sulfenyl ketones or α-ketosulfides is by sulfenylation of an enolate species using reagents such as disulfides or sulfenyl chloride. A mild synthesis of α-ketosulfides from the potassium enolate, using commercially available *N*-phenylthiocaprolactam as a novel sulfenylating reagent has been developed. Stirring a mixture of thiocaprolactam, ketone, and potassium *t*-butoxide in DMSO at room temperature gives access to a range of α-phenylthioketones cleanly and in high yield <1997TL2035>. 3-Phenylsulfenyl-2-(*N*-cyanoimino)thiazolidine is another novel, readily available sulfenylating agent that reacts with enolate derivates to give α-thiophenylketones <2000SL33>. This reagent is capable of sulfenylating lithium enolates, enamines and silyl enol ethers to give the α-phenylthioketone in good yield. Furthermore, a chiral derivative of this reagent **114** has been synthesized from L-cysteine that results in formation of the (*S*)-α-sulfenylketone (Equation (74)).



(74)

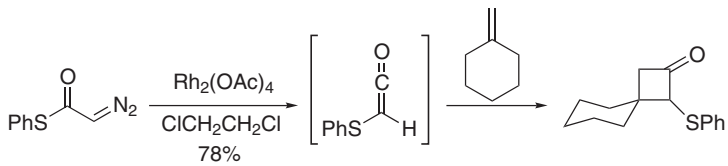
Asymmetric α-sulfenylation may also be achieved by reaction of metallated SAMP/RAMP hydrazones with disulfides <1998T10239>. Lithiation of the chiral hydrazone with LDA in THF at 0 °C followed by sulfenylation using diisopropyldisulfide or dimethyldisulfide at −100 °C gives the α-sulfenylated derivative in high yield and diastereoselectivity. Chemoselective oxidative cleavage of the hydrazone is effected without racemization to give α-sulfenylated ketones in high ee. β-Ketosulfoxides may be diastereoselectively sulfenylated using chiral phase-transfer catalysts under phase-transfer conditions <1999T12023>. In this process, *N*-benzylquininium chloride catalyzes the sulfenylation of β-ketosulfoxides in a two-phase solid–liquid system composed of anhydrous sodium carbonate in dichloromethane/benzene using methylmethanethiosulfonate as sulfenylating agent.

An alternative route to α-sulfenylketones is by insertion of α-diazoketones into the S—H bonds of thiols. This transformation may now be achieved under mild, chemoselective conditions in the presence of ruthenium(II) catalysts <1999JCS(P1)3079>. The half-sandwich complex **115** reacts with α-diazoketones to give a ruthenium(II) carbenoid that inserts into the S—H bond of propane-2-thiol in chloroform at 60 °C to give the α-sulfenylketone in high yield (Equation (75)).



(75)

α-Diazocarbonyl compounds are also used in a novel route to thio-substituted cyclobutanones. Treatment of α-diazothioesters with rhodium(II) acetate results in the formation of thioketenes via a thia-Wolff rearrangement. When this transformation is performed in the presence of ketenophiles such as ethenes a [2 + 2]-cycloaddition takes place to give α-thiocyclobutanones in moderate to high yield <2000JOC4375> (Equation (76)). The reaction may be performed with a range of alkenes and thioesters and gives access to the corresponding cyclobutenone when carried out in the presence of alkynes.



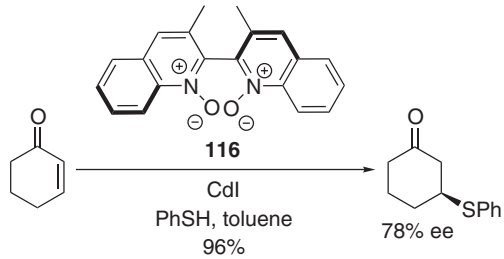
(76)

α-Keto-trithioorthoesters and α-keto-dithioacetals may be synthesized by reaction of acid chlorides, anhydrides, and amides with [tris(methylthio)methyl]lithium, obtained from tris(methylthio)methane and butyllithium, in THF at −95 °C <1995JOC6017, 1996JOC9572>. While variation of the reagent ratios and reaction conditions gives access to either product, it was found that [bis(methylthio)methyl]lithium is the reagent of choice for the conversion of *N*,*N*-dimethylamides into the α-ketodithioacetal.

3.04.5.1.2 β-Functionalized and more remotely substituted SH- and SR-functionalized ketones

The most important method for the synthesis of β-sulfenylketones is the conjugate addition of thiols to α,β-unsaturated ketones. The rate of this addition may be improved by the use of catalytic amounts of strong base or Lewis acid to activate the donor or acceptor, respectively. Research in this area has concentrated on developing more efficient and mild Lewis and Brønsted acid catalysts for this procedure and in developing asymmetric variants. Bistrifluoromethanesulfonimide is a Brønsted acid that catalyzes the rapid conjugate addition of benzenethiol and benzylmercaptan to α,β-unsaturated ketones in dichloromethane at room temperature <2003OL2141>. Bismuth(III) chloride is a novel Lewis acid that also catalyzes the hetero-Michael reaction of thiols to enones <1995SL984>. This compounds shows very strong catalytic activity in the conjugate addition process under mild conditions and low catalyst loadings.

Thiols add to cyclic enones in high yield and ee using chiral heterobimetallic complexes such as lanthanum tris(binaphthoxides) <1998JA4043>. The enantioselective conjugate addition of thiols is also achieved in high ee using linear α-substituted-α,β-unsaturated ketones in the presence of samarium tris(binaphthoxides). In this case, enantioselectivity arises by asymmetric protonation of the intermediate enolate by the protonated catalyst. Thiols also add to cyclic enones with moderate enantioselectivity in the presence of cadmium iodide and chiral *N*-oxide **116** (Equation (77)) <2000CC1851>.

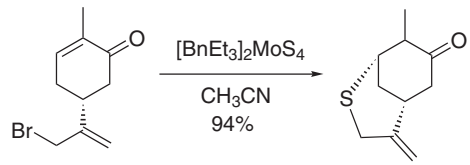


(77)

The malodourous nature of the starting thiols often makes these compounds unpleasant to handle. A solution to this problem has been developed utilizing aryl-substituted benzenethiols <2002TL8569>. 4-Trimethylsilylbenzenethiol is odorless and undergoes Michael addition with enones in the presence of TBAF or DBU to give the corresponding β-sulfenylated ketone in high yield. Protodesilylation is then achieved using trifluoroacetic acid.

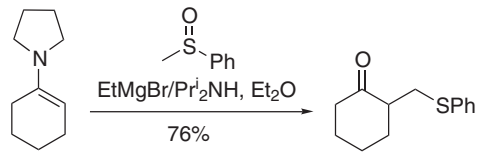
The hetero-Michael reaction is not limited to the use of thiols as donors. Benzyltriethylammonium tetrathiomolybdate effects cleavage of the disulfide bond in disulfides and symmetrical aryl- and alkyldisulfides undergo 1,4-addition onto enones in the presence of this compound in acetonitrile in high yield <2000AC(E)4316>. As benzyltriethylammonium tetrathiomolybdate converts alkyl and

aryl halides into disulfides it is possible to synthesize β-sulfenylated ketones in one pot from a mixture of tetrathiomolybdate, alkyl halide and enone. Furthermore, this tandem reaction may be performed in an intramolecular fashion to give spirocyclic and bicyclic skeletons (Equation (78)).



(78)

An alternative approach to the synthesis of β-sulfenylated ketones involves the reaction of an enol derivative or enamine with an α-sulfenylated carbocation equivalent. Treatment of simple alkyl sulfoxides with magnesium amides results in Pummerer rearrangement to give sulfur-stabilized carbocations, which react with enamines to give β-ketosulfides <1998T2691>. Treatment of 1-pyrrolidinocyclohex-1-ene with methylphenylsulfoxide in the presence of diisopropylamine/ethylmagnesium bromide gives the sulfenylalkyl product (Equation (79)). Use of methyl(methylthio)-methyl sulfoxide in this reaction gives access to the corresponding β-ketodithioacetal.



(79)

3.04.5.2 Higher-coordinated Sulfur-functionalized Ketones

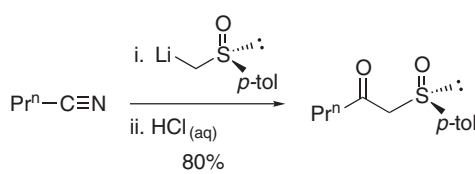
A common approach to the synthesis of ketosulfoxides is by oxidation of the corresponding sulfide. In general, many of the oxidizing reagents that can be used to oxidize alkenes can also be applied to the oxidation of sulfides. However, overoxidation to the corresponding sulfone often occurs. Oxodiperoxo-molybdenum complexes are novel oxidizing reagents that chemoselectivily convert sulfides into sulfoxides under mild conditions with no over-oxidation when coated on silica gel <2001T9669>. The corresponding sulphone is formed using these complexes in the absence of silica gel.

Optically pure sulfoxides are powerful chiral auxiliaries acting as stereocontrol elements for a variety of chemical transformations <1995CR1717>. Consequently, recent attention has focused on the development of stereoselective routes to sulfoxides. The synthesis and uses of chiral sulfoxides has been the subject of a recent review <2003CR3651>.

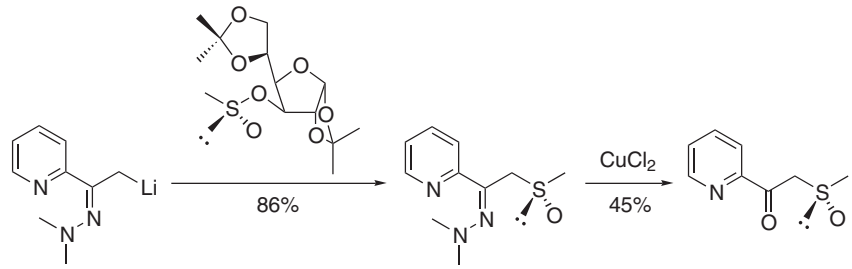
Optically active β-ketosulfoxides may be obtained by kinetic resolution of racemic β-ketosulfoxides. Oxidation of a racemic mixture of a variety of β-ketosulfoxides under modified Sharpless conditions using L-DET and furyl hydroperoxides leads to selective oxidation of the (*S*)-enantiomer leading to isolation of (*R*)-sulfoxide in moderate to high ee <1998TA2619>.

Enantiopure ketosulfoxides may also be accessed by enantioselective biological oxidation of sulfides. Chloroperoxidase, extracted from the marine fungus *Caldariomyces fumago*, oxidizes β-ketosulfides in the presence of hydrogen peroxide in citrate buffer to give predominantly the (*R*)-sulfoxide in high ee and yield <1999TA3219>.

Nitriles are transformed into optically active β-ketosulfoxides in high yield by reaction with the α-sulfinyl anion derived from chiral methyl-*p*-tolylsulfoxides <1999TL9301>. Addition of the lithium anion of (+)-(*R*)-methyl-*p*-tolyl sulfoxide to a variety of nitriles proceeds to give an intermediate imine that is hydrolyzed to the corresponding ketone on acidic work-up (Equation (80)). Optically active β-ketosulfoxides are also obtained by nucleophilic attack of lithiated hydrazones onto optically pure D-glucose-derived methanesulfinates <1997JOC287>. The (*R*)- or (*S*)-methanesulfinates are obtained by condensation of the methanesulfonylchloride with diacetone-D-glucose in the presence of base and undergo reaction with the α-lithioderivatives of *N*,*N*-dimethylhydrazone of heterocyclic methyl ketones with complete inversion of chirality at sulfur (Equation (81)).



(80)

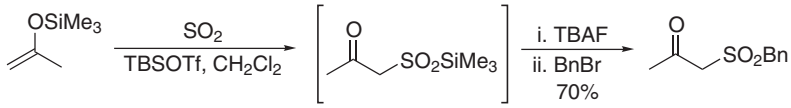


(81)

Most synthetic routes to β-ketosulfoxides are limited to the preparation of simple *S*-aryl and *S*-alkyl derivatives. A range of α-1-alkenylsulfenylated ketones have recently been prepared by coupling of trimethylsilyl enol ethers with 1-alkenylsulfinyl chlorides <1998JOC7825>. The sulfinylchlorides are readily accessed by chlorination of aryl-1-alkenylsulfoxides.

β-Ketosulfones may be prepared by Michael addition of sulfinic acids to enones. This approach is complicated by the relative instability of aliphatic sulfinic acids. A solution to this problem has been devised that centers on the *in situ* generation of aliphatic sulfinic acids by hydrosulfination of alkenes in the presence of palladium(II) or platinum(II) catalysts, diphosphine ligands and Michael acceptors <1997JOC422>.

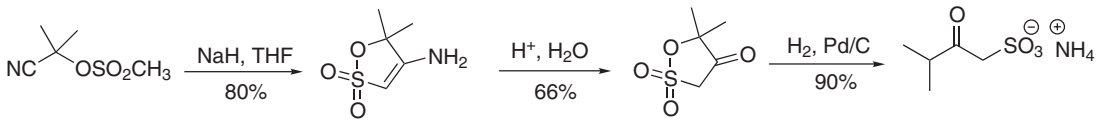
Silyl enol ethers undergo coupling with alkyl- and arylsulfonyl chlorides in the presence of ruthenium(II) phosphine complexes in benzene to give α-sulfonyl ketones in good yield via the *in situ* formation of sulfonyl radicals <1997JCS(P1)783>. Silyl enol ethers also undergo Lewis-acid-promoted ene reactions with sulfur dioxide in the presence of *t*-butyldimethylsilyl triflate to give silylsulfinates as intermediates to give β-ketosulfones <2002S225>. These intermediates are readily converted into a variety of functionalized sulfones on treatment with TBAF in the presence of alkyl halides (Scheme 35). A range of α-sulfonamido ketones are accessed by reaction of silyl enol ethers with *N*-alkyl-sulfonyl imines generated *in situ* from *N*-alkylsulfamoylchlorides in the presence of triethylamine in acetonitrile <1998T3589>.



Scheme 35

N-Acylbenzotriazoles, prepared by coupling of carboxylic acids and 1-(methylsulfonyl)benzotriazole, undergo reaction with α-lithiosulfones in THF at −78 °C to give β-ketosulfones in high yields <2003JOC1443>. This methodology provides a convenient route to a wide range of β-ketosulfones.

A novel approach to the synthesis of β-ketosulfonic acids involves the hydrogenation of β-keto-γ-sultones **118** <1997JOC7021>. The sultones are obtained by hydrolysis of oxathioles such as **117**, prepared by cyclization of cyanohydrin mesylates **116** (Scheme 36).



116 **117** **118**

Scheme 36

3.04.6 KETONES BEARING AN Se OR Te FUNCTION

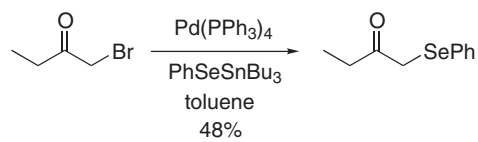
3.04.6.1 SeH-, TeH-, SeR-, or TeR-Functionalized Ketones

α-Selenylketones are intermediates of much utility in organic synthesis and the oxidation of β-ketoselenides followed by *syn*-elimination of the resulting selenoxide is one of the most important methods for the regioselective synthesis of enones. Consequently, a number of new methods for the synthesis of α-selenylketones have been developed.

α-Phenylselenylketones may be prepared on a large scale from ketones using phenylselenium trichloride <1997S101>. This reagent reacts with enolisable ketones in acetonitrile at room temperature to give intermediate phenyldichloro adducts that are reduced on addition of thiourea to give the α-phenylselenylketone. 2-Chloroselenobenzoyl chloride reacts directly with acetone under reflux for short periods of time giving 2-(acetylmethylseleno)benzoylchloride <2001TL4899>. This compound undergoes intramolecular acylation to give 2-acetylbenzo[*b*]-selenophen-3(2*H*)-one on further heating under reflux.

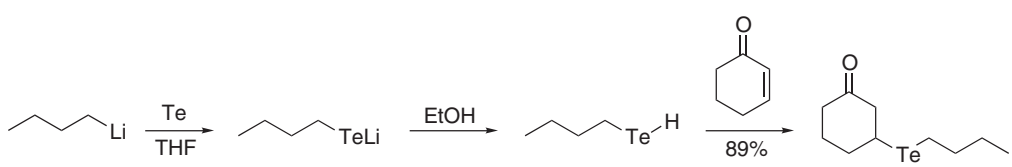
Silyl enol ethers react with a variety of selenium-containing electrophiles to give selenoketone products. In a recent example, trimethylsilyl enol ethers were converted into α-phenylseleno-γ-keto esters by reaction with α-chloro-α-phenylselenoesters <1996TL9173>. In the presence of zinc bromide, these selenenylating reagents form selenium-stablized carbocation species that react with silyl enol ethers in dichloromethane to give α-selenophenyl-γ-ketoesters in moderate to good yield. Silyl enol ethers also react with 3-(phenylseleno)allylic cations, generated by treatment of 3-(phenylseleno)propenal acetals with Lewis acids to give 5-(phenylseleno)pent-4-enones in good yield <2002JOC1078>. Functionalized α-phenylselenoketones may be accessed by the generation and reaction of β-phenylselanylenoxysilanes derived from α-phenylselenylketones. It has been found that use of triethylamine as base during the generation of such silyl enol ethers leads to the formation of enoxysilanes bearing a vinylic group as single regioisomers, while mixtures of regioisomers are obtained using potassium hydride or LDA <1995T9569>. These β-phenylselenylenoxysilanes undergo conversion into α,α'-bis(phenylseleno)ketones using a variety of electrophilic selenenylating agents <1995TL6453> and undergo crossed-aldol reactions with benzaldehyde in the presence of boron trifluoride etherate to give *syn*-β-hydroxy-α-selenophenylketones <1998TL4017>. The aldol reaction also proceeds using TBAF to give the products as mixtures of *syn* and *anti*-stereoisomers.

A common approach to the synthesis of α-selenylketones is by substitution of the corresponding α-haloketone. A range of α-haloketones are converted into samarium enolates in the presence of samarium(II) iodide or samarium(III) iodide in acetonitrile that undergo reaction with alkyl- and arylselenium bromides to give the α-selenylketones in good yield <1996SC1517>. While this procedure requires the use of rigorously dried solvent to avoid formation of the corresponding reduced ketone, the selenenylation of ketones may also be performed in aqueous media. Ketones undergo α-selenenylation using indium metal and diaryl- and dialkyldiselenides in THF/water to give the α-selenenylated ketone in good yield <1996SL1187> and α-bromoketones are also converted into α-selenoketones in acetonitrile/aqueous potassium phosphate using diphenyldiselenide and zinc dust <2001TL4597>. α-Haloketones may also be converted into selenylketones using transition-metal-catalyzed cross-coupling methodology. α-Bromo and α-chloroketones undergo coupling with phenyltributylstannylselenide, an air and moisture-stable selenenylating agent, in the presence of tetrakis(triphenylphosphine)palladium(0) in toluene at 60 °C to give α-selenoketones in moderate to good yield <2003JOC3599> (Equation (82)).



(82)

Organotellurides undergo transmetallation to give organolithium and organocopper derivatives and hence ketotellurides, have utility as functionalized intermediates in C—C bond-forming reactions. Vinyltellurides may be prepared by vinyl substitution using aryl- and alkyltellurolates, generated by reaction of organolithiums and elemental tellurium. Using this methodology, the enol phosphates of 1,3-diketones are converted into β-telluro-α,β-unsaturated ketones in THF at 0 °C <2001JOM43>. A range of electron-deficient alkenes including enones undergo hydrotelluration with alkyltellurols, formed by reaction of organolithiums with tellurium, followed by addition of ethanol to give β-telluroketones (Scheme 37) <2002TL1625>.



Scheme 37

3.04.6.2 Higher-coordinated Se- or Te-Functionalized Ketones

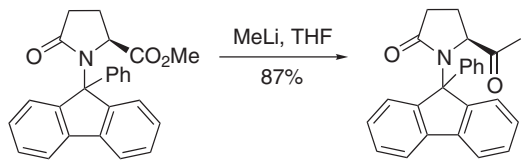
No further advances have occurred in this area since the publication of COFGT (1995).

3.04.7 KETONES BEARING A NITROGEN FUNCTION

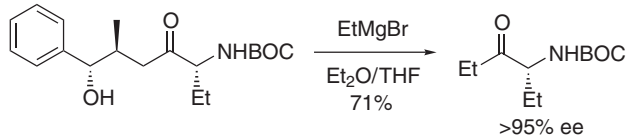
3.04.7.1 NH_2-, NHR-, and NR_2-Functionalized Ketones

3.04.7.1.1 α-NH_2-, NHR-, and NR_2-Functionalized ketones

Protected α-amino ketones are useful intermediates in the synthesis of natural products, bioactive compounds, and nitrogen heterocycles. The majority of recent studies in this area have concentrated on generating optically active α-aminoketones from amino acids. This is generally achieved by addition of organometallic reagents to *N*-protected amino acid esters or amides. *N*-Phenylfluorenyl-pyroglutamates, prepared from L-glutamic acid, undergo reaction with organolithium reagents such as methyllithium and phenyllithium to give the corresponding α-aminoketone in high yield with complete retention of enantiomeric purity <1997JOC4770>. For example, pyroglutamate **119** reacts with methyllithium in THF at −78 °C to give ketone **120** (Equation (83)). The success of this transformation depends on the stability of the tetrahedral alkoxide intermediate. In this case, it is the electron-withdrawing effects of the amide nitrogen coupled with the lithium-complexing ability of the fluorenyl system ensure that no tertiary alcohol is formed. *N*-Benzoyl-7-azabicyclo[2.2.1]-heptane-1-carboxylates also undergo reaction with organolithiums to give α-aminoketones <2002T10167>. In this case, it is thought that the tetrahedral intermediate is stabilized by H-bonding to the proximal benzoate carbonyl group. This transformation is also possible using acyclic amino acids. α-Amino-α′-chloroketones may be accessed by reaction of chloromethyllithium, formed by treatment of chloroiodomethane with methyllithium, with linear *N*,*N*-dibenzylated α-aminocarboxylates <1995JOC6696>. In a similar fashion, alkylated pseudoephedrine glycinamides react with organolithium and Grignard reagents to give *N*-BOC protected α-aminoketones in high ee (Equation (84)). In an alternative approach to the synthesis of α-amino ketones, amino acids are converted into activated esters by treatment with 2-chloro-4,6-dimethoxy[1,3,5]triazine and NMO at room temperature. The reaction mixture is filtered and Grignard reagent added along with 1 equiv. of copper(I) iodide at 0 °C to give the ketone in near quantitative yield <2001OL1519>.

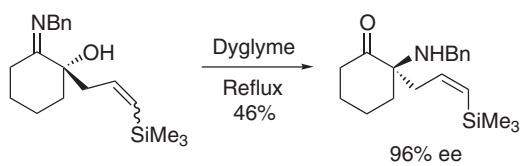


(83)



(84)

α-Disubstituted-α-aminoketones may be conveniently synthesized by thermal rearrangement of cyclic α-hydroxyimines in diglyme under reflux <1996T6647>. The imines are prepared from 1,2-diketones in four steps and undergo rearrangement in moderate to good yield with complete 1,2-chirality transfer in some cases (Equation (85)).

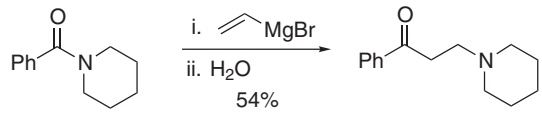


(85)

A novel approach to the synthesis of α-amino ketones involves addition of an acyl anion equivalent to an imine. Acylzirconocene chlorides act as acyl donors and react with imines in the presence of Lewis acids such as ytterbium(III) triflate and trimethylsilyl triflate to give imines <2003EJOC116>. It is possible to form the imines *in situ*. Thus, three-component couplings between acylzirconocene chlorides, aldehydes, and amines are possible giving α-aminoketones in good yield.

3.04.7.1.2 β-Functionalized and more remotely functionalized NH_2-, NHR-, and NR_2-functionalized ketones

β-Aminoketones may be prepared by Michael reaction of amines with enones. β,γ-Unsaturated ketones may also be used in this reaction in the presence of Lewis acids <2003SL2359>. Rearrangement to the α,β-unsaturated ketone occurs in the presence of aluminum trichloride in dichloromethane at room temperature followed by 1,4-addition of tosylamine to give the *N*-tosyl-β-aminoketone. Weakly nucleophilic carbamates can be induced to attack enones in a conjugate sense using a combination of iron trichloride and trimethylsilyl chloride in dichloromethane at room temperature to give Cbz- and ethoxycarbonyl-protected β-amino ketones in moderate to good yield <2003CC2570>. A convenient one-pot synthesis of β-amino ketones from amides has been developed utilizing vinylmagnesium bromide as nucleophile. Treatment of morpholine and piperidine amides with vinylmagnesium bromide in THF at room temperature results in sequential nucleophilic attack followed by aza-Michael reaction with the displaced amine after the quench to give the β-amino ketone in good yield <2000OL11> (Equation (86)). α-Aminoalkylcuprates are accessed by deprotonation of Boc-protected secondary amines with *sec*-butyllithium followed by transmetallation or by transmetallation of α-aminostannanes with *n*-butyllithium followed by reaction with copper(I) cyanide. These cuprates undergo conjugate addition to a range of cyclic and acyclic enones in THF in the presence of TMSCl to give Boc-protected γ-aminoketones <2000T2767>.



(86)

The classical approach to the synthesis of β-aminoketones is by use of the Mannich reaction, one of the most important reactions in organic synthesis. The traditional Mannich reaction proceeds under relatively harsh reaction conditions resulting in the formation of various side-products and is not easily applied to the synthesis of optically pure β-amino ketones. However, the Mannich process has much utility in the synthesis of functionalized amines for use in the pharmaceutical industry, and has also found wide application in the synthesis of alkaloidal natural products. In particular, the intramolecular variant of the Mannich reaction has proved to be a powerful method for the synthesis of complex azacyclic synthetic targets. Consequently, there has been much recent interest in the development of modified Mannich reactions of wider scope that proceed with high regio and stereoselectivity. A detailed discussion of all the modern variants of this procedure that have been developed since the early 1990s is beyond the scope of this chapter and hence only the salient features of the latest work in this area will be presented. Readers seeking an in-depth account of the recent modifications to this process and their applications in synthesis are directed to the recent review in this area <1998AC(E)1044>.

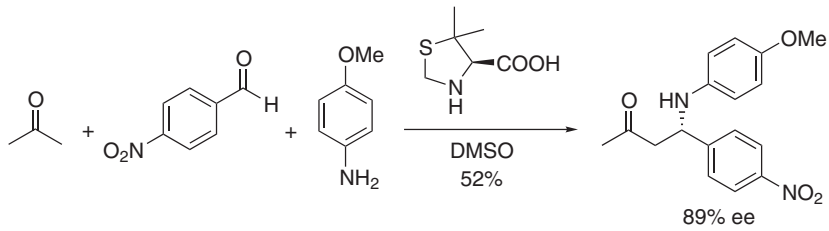
Much recent progress has been made in the development of asymmetric Mannich reactions. Optically active, β-amino ketones may be accessed by addition of chiral silyl enol ethers to iminium ions. Optically pure α-silylketones, obtained by silylation of metallated SAMP/RAMP hydrazones, are converted into the corresponding (*Z*)-silyl enol ethers using LDA and TMSCl and these undergo diastereoselective addition to iminium ions, generated from *N*,*N*-dibenzyl-*N*-methoxymethylamine in the presence of boron trifluoride etherate, to give α-silyl-β'-amino ketones <2002S2737>. Desilylation using ammonium fluoride and TBAF gives the corresponding β-amino ketone in high ee.

Asymmetric induction in the Mannich reaction can also be achieved using chiral catalysts. This has been achieved using organometallic catalysts and organic catalysts. The direct Mannich reaction of ketones may achieved in asymmetric fashion in the presence of aluminum

bis(binaphthoxide) complexes and lanthanum(III) triflate <1999T8857>. Ketones couple to aminomethyl ethers in toluene to give β-amino ketones in moderate ee using this catalyst. Far better enantioselectivities have been obtained using the zinc-linked BINOL complex **109**, that has also been utilized in catalytic asymmetric aldol reactions. α-Hydroxyketones react with imines in the presence of this catalyst in THF to give α-hydroxy-β-amino ketones in high yield and high *anti*-selectivity and 95–98% ee <2003JA4712>.

Silyl enol ethers may also be used as donors in catalytic asymmetric Mannich reactions with organometallic catalysts. Imines undergo addition with silyl enol ethers in high ee using zirconium bis(binaphthol)methane complexes in the presence of *N*-methylimidazole in toluene <1999TL2161>. Silyl enol ethers also add to imines using binuclear μ-hydroxy palladium(II) complexes to give optically active β-hydroxyketones. This reaction is thought to proceed by formation of a chiral palladium enolate to give the products in high ee <1999JA5450>.

The direct enantioselective addition of unmodified ketones to imines also proceeds via conversion of the nucleophilic donor into intermediate chiral enamines. This is achieved in the presence of optically pure secondary amines <2001TL199, 2003JOC9624>. Acetone undergoes addition to preformed aldimines in moderate to good ee in the presence of amine catalyst and DMSO and three-component couplings of acetone, aldehyde, and amine also proceed under these reaction conditions to furnish β-amino ketones in high ee (Equation (87)).

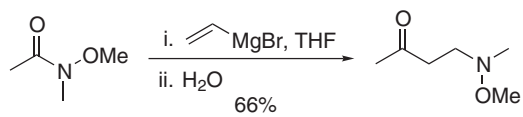


(87)

The classical Mannich reaction is restricted to the use of nonenolizable aldehydes and some recent efforts have been directed towards the synthesis of Mannich products from enolizable aldehydes. The use of concentrated ethereal lithium perchlorate as a reaction medium allows the three-component Mannich reaction to proceed under mild conditions with both enolizable and non-enolizable aldehydes <1998EJOC197>. Silyl enol ethers, enamines, and imines may be used as the nucleophilic donor and the reaction is found to proceed with high *anti*-diastereoselectivity. This transformation also proceeds in high ee using SAMP enamines as donors under these reaction conditions. Such Lewis-acid-catalyzed, three-component couplings require the use of anhydrous conditions. The use of indium trichloride as catalyst allows these couplings to take place in water using silyl enol ethers as donors and the Lewis acid catalyst may be isolated on completion of the reaction and reused <2000T3227>.

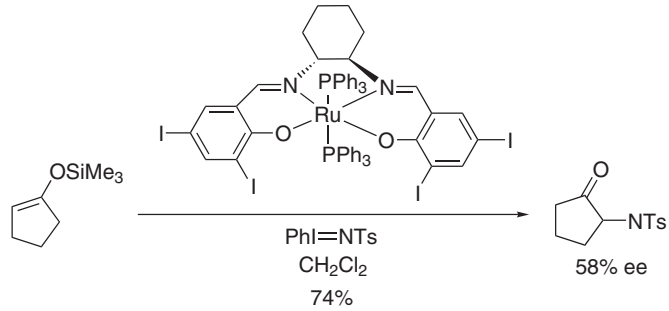
3.04.7.2 NHX- and NX_2-Functionalized Ketones

β-Methoxyamino ketones may be synthesized by addition of vinylmagnesium bromide to Weinreb amides. The reaction proceeds via nucleophilic substitution at the amide followed by Michael addition of the displaced amine fragment on quenching <2000OL11> (Equation (88)).



(88)

A variety of synthetic routes to *N*-tosyl-β-amino ketones exist. A range of silyl enol ethers undergo osmium tetroxide-catalyzed amino hydroxylation using chloramine-T as the nitrogen source and cinchona alkaloids as the chiral ligands in *t*-butanol to give *N*-tosyl-α-aminoketones in moderate yield but high ee <1998TA1001>. Silyl enol ethers also undergo asymmetric amidation in high ee using *N*-(tosylimino)phenyliodinane in the presence of chiral ruthenium(II) complexes in dichloromethane <2002CC124> (Equation (89)).



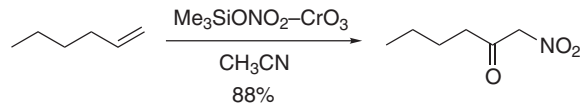
(89)

Optically active α-substituted-β-tosylaminoketones are prepared in high *anti*-selectivity and high ee by addition of (*Z*)-silylenolethers to *N*-tosylimines in the presence of (*R*)-Tol-BINAP-$CuClO_4$·$(MeCN)_2$ <1998JOC6090>.

The reduction of 2-acylaziridines provides a convenient route to β-aminoketones <1995JOC6660>. Samarium(II) reduces *N*-tosylaziridines, prepared by treatment of enones with *N*-(tosylimino)phenyliodinane, in THF/MeOH in a regioselective manner to provide a range of tosyl-protected β-aminoketones in high yield.

3.04.7.3 NY-Functionalized Ketones

The nitro group is a powerful activator of hydrogens on the adjacent carbon atom and thus this functionality has assumed some importance in C—C bond-forming processes. A number of functional group transformations can also be performed on the nitro group and these features, coupled with the versatility of the carbonyl group make α-nitroketones useful intermediates in synthesis. There are a number of methods for the synthesis of α-nitroketones. The most important involves treatment of an enol derivative with a nitrating agent. Silyl enol ethers undergo mild nitration with tetranitromethane in dichloromethane at room temperature <1996JOC627>. This reaction also proceeds at lower temperatures under photochemical conditions by irradiating the reaction mixture at $-40\,^{\circ}C$ with light of wavelength over 415 nm. This process is thought to proceed via one electron transfer from the silylenolether followed by homolytic coupling of a silyl enol ether cation radical with a nitro radical. Cyclic and acyclic alkenes are converted into α-nitroketones using trimethylsilyl nitrate, formed by reacting silver nitrate with trimethylsilyl chloride, and chromium trioxide <1995TL7149, 1999JOC4509>. A wide variety of unsubstituted alkenes undergo this conversion in acetonitrile at room temperature in moderate-to-good yield (Equation (90)).



(90)

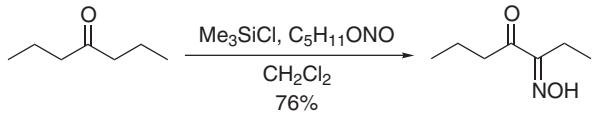
This process proceeds via nitration of the alkene by a nitronium cation in the presence of a chromate anion to give a nitro-substituted chromate ester that is converted into the α-nitroketone. This reaction also proceeds using trimethylsilylnitrate and DMSO as oxidant.

β-Nitroketones may be accessed by cross-coupling of *N*,*N*-bis(silyloxyenamines) with anions of aliphatic nitro compounds <1999S1767>. The initial product is a β-nitrooxime that is converted into the corresponding ketone using Jones reagent. β-Nitroketones may also be synthesized by reaction of silyl enol ethers with nitronate anions, formed from nitroalkanes and potassium hydroxide in methanol, in the presence of ceric ammonium nitrate <1995CL987>. The nitronate anion is oxidized by ceric ammonium nitrate to an α-nitroalkyl radical that adds to the silyl enol ether.

γ-Nitroketones are most conveniently prepared by Michael addition of nitronate anions onto enones. This may now be achieved using solid bases, formed by derivitization of amorphous silica and mesoporous silica with dimethylaminopropyl groups, as catalysts <1998SL625>. Addition of solid catalyst to a solution of enone in nitroethane gives a variety of γ-nitro ketones in good yield. The catalyst is reisolated by filtration and may be reused.

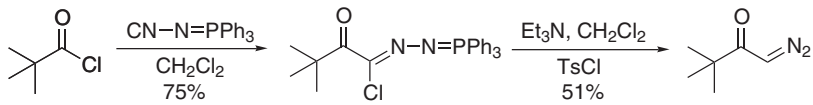
The development of new methods for the oximation of ketones has received little recent attention. The most recent approach to the synthesis of such compounds utilizes a mixture of trimethylsilyl chloride and isoamylnitrite in solution using dichloromethane or under solvent-free conditions at $-20\,^{\circ}C$ <2003TL2753>. This simple method converts a range of

ketones into 1,2-dione monooximes in good yield and proceeds via *in situ* formation of NOCl (Equation (91)).



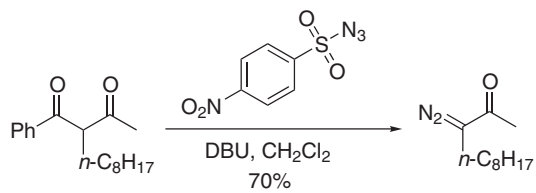
(91)

α-Diazoketones are intermediates in a range of chemical transformations including dipolar cycloadditions, cyclopropanations, and the homologation of carboxylic acid derivatives known as the Arndt–Eistert reaction. The most recent preparations of α-diazoketones utilize carboxylic acid derivatives as staring materials. Difficulties have been encountered in the synthesis of α-diazoketones from sterically hindered carboxylic acids. A solution to this problem has been devised that utilizes highly reactive acylmesylates under mild conditions <1999OL883>. Treatment of the acid with mesyl chloride and triethylamine at $-10\,^{\circ}C$ followed by addition of diazomethane gives the α-diazoketone in good yield. Carboxylic acids are also transformed into α-diazoketones by treatment with triphenylphosphine in the presence of NBS followed by reaction with diazomethane <2003TL4815>. In this approach, a variety of acids are first converted into acyloxyphosphonium salts that undergo conversion into the diazoketone on addition of an ethereal solution of diazomethane. 2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride) is an efficient promotor for the conversion of acids into amides, esters, and anhydrides and may also be used in combination with diazomethane, without rigorous exclusion of moisture, for the preparation of α-diazoketones <2000TL9943>. The drawbacks associated with the use of hazardous diazomethane have prompted the development of substitutes for this reagent. Commercially available trimethylsilyldiazomethane converts mixed anhydrides into α-diazoketones <2001TL7099>. The carboxylic acid is first converted into the anhydride by reaction with ethylchloroformate in THF. Subsequent addition of trimethylsilyldiazomethane in acetonitrile effects conversion into the diazoketone in good yield. *N*-isocyanotriphenyliminophosphorane is another readily prepared, stable substitute for diazomethane that may be deployed in the conversion of acid chlorides into α-diazoketones <2000SL526>. The initial product of this reaction is an α-ketohydrazidoyl chloride that is converted into the α-diazoketone on treatment with tosyl chloride and triethylamine (Scheme 38).



Scheme 38

α-Alkylated derivatives of benzoylacetone undergo debenzoylation/diazo transfer in high yield, and this procedure provides a convenient method for the synthesis of unsymmetrical α-diazoketones <1995JOC2283>. Benzoylacetone undergoes α-alkylation using potassium carbonate in the presence of tetra-*n*-butylammonium bromide. The products are then treated with DBU and *p*-nitrobenzenesulfonylazide in dichloromethane to give the α-diazoketone (Equation (92)).



(92)

α-Azidoketones may be synthesized directly from ketones using [hydroxy(*p*-nitrobenzenesulfonyloxy)iodo]benzene (HNIB) <2000SC4271>. Treatment of a ketone with HNIB gives an α-nosylketone that is converted into the azide using sodium azide in acetonitrile. Optically active α'-silylated-α-azido ketones may be obtained by treating α'-silylated-α-iodoketones, obtained by iodination of optically pure α-silylketones, with sodium azide. Subsequent racemization-free desilylation gives the α-azidoketone in high ee <1999SL719>. Triisopropylsilyl enol ethers undergo oxidative addition of azide anion in the presence of ceric ammonium nitrate to give

α-azidoketones in moderate to good yield <1995T11075>. A wide range of cyclic, acyclic, and functionalized α-azidoketones are accessed using this method, which may also be used to introduce an azide group to a tertiary center α to the carbonyl.

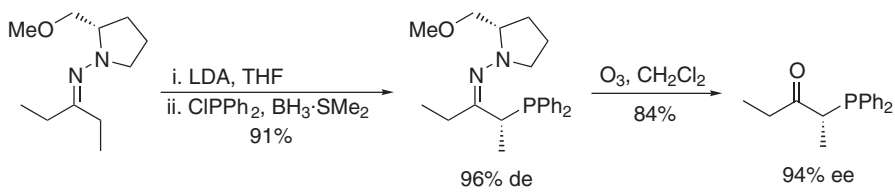
3.04.7.4 NZ-Functionalized Ketones

No further advances have occurred in this area since the publication of COFGT (1995).

3.04.8 KETONES BEARING A P, As, Sb, OR Bi FUNCTION

3.04.8.1 XR_2- and X^+R_3-Functionalized Ketones

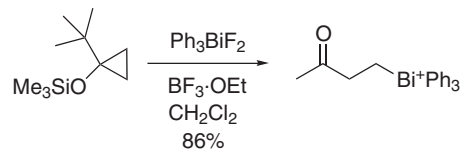
Phosphinylation of ketones may be achieved using chlorophosphines. Optically pure α-phosphinoketones may be accessed by phosphinylation of SAMP-hydrazones with chlorodiphenylphosphine <1996HCA118>. Treatment of SAMP-hydrazones with LDA in THF at 0 °C followed by treatment with the chlorophosphine and boron trifluoride etherate gives the (*S*,*R*)-α-phosphinylated SAMP-hydrazone in good yield and de. The chiral auxiliary is cleaved using ozonolysis to give access to the β-ketophosphine in high ee (Scheme 39).



Scheme 39

α-γ^3-Iodanyl ketones, accessed using the methdology discussed in Section 3.04.3.3.1.(vii), react with a wide variety of nucleophiles providing access to a range of α-substituted ketones <2002JOC4407>. Generation of these species in the presence of triphenylphosphine leads to the formation of β-keto phosphonium salts.

The corresponding ketobismuthonium salts have seen much less use in synthesis, primarily owing to the inaccessibility of these compounds. γ-Ketobismuthonium salts may now be efficiently accessed by reaction of silyloxycyclopropanes with triarylbismuth difluorides in the presence of Lewis acids such boron trifluoride diethyletherate and trimethylsilyltrifluoromethane sulfonate <1995JCS(P1)2543> (Equation (93)). These salts undergo reaction with halides and sulfur-based nucleophiles providing access to β-halo and sulfur-functionalized ketones and undergo elimination with potassium *tert*-butoxide to give α,β-unsaturated ketones.



(93)

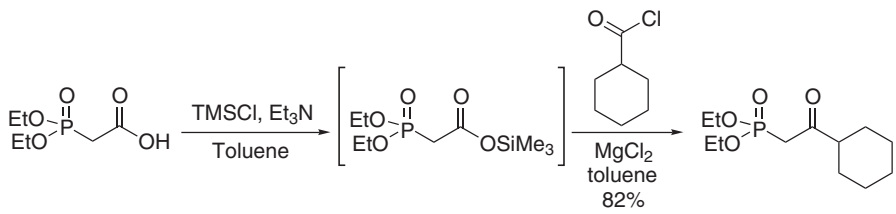
3.04.8.2 Higher-coordinated P-, As-, Sb-, or Bi-Functionalized Ketones

3.04.8.2.1 α-Higher-coordinated P-, As-, Sb-, or Bi-functionalized ketones

β-Keto phosphonates are useful compounds in organic synthesis as they are readily converted into enones via Horner–Wadsworth–Emmons reactions. The most common methods for the synthesis of these compounds are by Arbuzov reaction of phosphites with α-halo

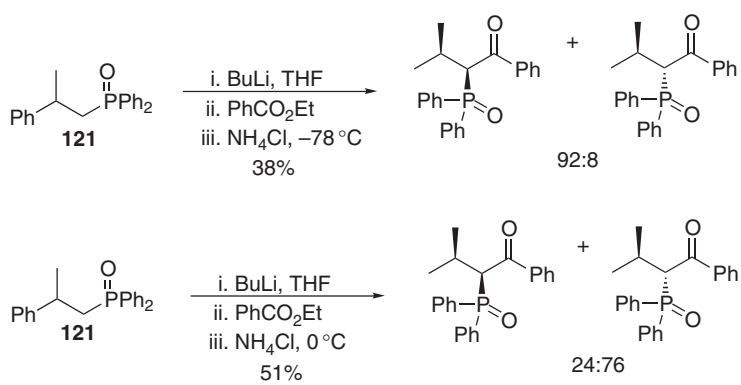
ketones and by acylation of phosphonate anions with carboxylic acid derivatives. Most recent research in this area has concentrated on further developing the latter route to β-ketophosphonates.

The reaction of the magnesium enolates of trialkylphosphonoacetates, formed using magnesium chloride and triethylamine, with acid chlorides and anhydrides gives the corresponding 2-acylphosphonoacetates that are readily decarboxylated to β-ketophosphonates in water under reflux <1996SC2561, 1996SC2487>. This route provides an operationally convenient access to a variety of β-ketophosphonates in good yield. β-Ketophosphonates are also accessed from phosphonoacetates by *in situ* conversion of the phosphonacetate into the corresponding triethylsilylphosphonoacetate using triethylamine and trimethylsilyl chloride <1997JCS(P1)1361>. Addition of an acid chloride and magnesium chloride as a chelating agent results in acylation followed by decarboxylation to give the β-ketoester (Scheme 40).



Scheme 40

Conditions have also been developed for the conversion of thioesters into β-ketophosphonates <1998SL828>. Treatment of *t*-butylthioesters with the lithium anion of dimethylethanephosphonate or dimethylmethanephosphonate, formed using *tert*-butyllithium in THF in the presence of DMPU, gives the β-ketophosphonate in good yield. This intermolecular acylation may be carried out in a highly stereoselective manner using either chiral phosphines or chiral esters <1996TL7465>. Reaction of the anion of phosphine oxide **121** followed by quenching at −78 °C with ethyl benzoate gives the *syn*-β-ketophosphine oxide as the major product, while quenching the reaction mixture at 0 °C gives a mixture of ketones more enriched in the *anti*-isomer (Scheme 41). The above reaction also proceeds with high diastereoselectivity when using chiral proline- and phenylalanine-derived esters.



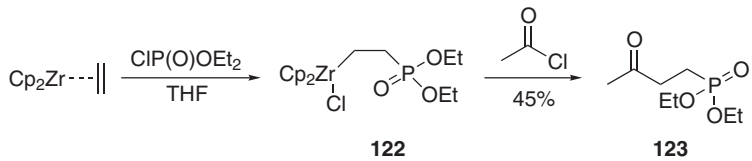
Scheme 41

A novel strategy for the synthesis of β-ketophosphonates centers on the rearrangement of lithiated 2-bromovinylphosphates <1998JOC2613>. Treatment of 2-bromovinylphosphates, accessed from α-bromoketones, with *n*-butyllithium effects halogen–metal exchange and induces a regiospecific vinyl phosphate/β-ketophosphonate rearrangement to occur.

3.04.8.2.2 β-Higher-coordinated and more remotely higher-coordinated P-, As-, Sb-, or Bi-functionalized ketones

γ-Ketophosphonates may be synthesized by conjugate addition of acyl anions onto vinylphosphonates. Acylcuprates are generated by reaction of dialkylcyanocuprates with carbon monoxide and react in a conjugate sense with diethylvinylphosphine to give the γ-ketophosphonate in good yield <1999OM1811>.

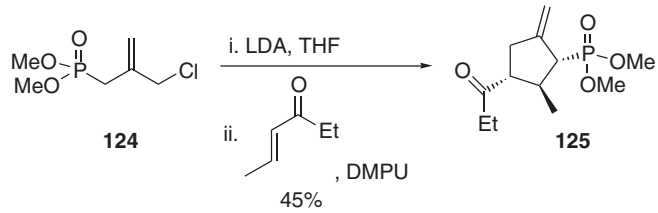
γ-Ketophosphonates are also accessed by reaction of β-anionic phosphonates with electrophilic acyl species. Zirconocene–ethene complex reacts with chlorodiethylphosphate to give zircono-ethylphosphonate **122** that undergoes coupling with acid chlorides to give γ-ketophosphonate **123** (Scheme 42).



Scheme 42

A variety of cyclic and acyclic β-ketophosphonates undergo chain extension to γ-ketophosphonates in the presence of diethylzinc and diiodomethane in dichloromethane at room temperature <2000JOC5615>. The process proceeds through the intermediacy of a cyclopropyl zinc alkoxide that undergoes ring opening to give the one-carbon homologated product.

δ-Ketophosphonates may be synthesized by conjugate addition of enolates to vinylphosphinates. This transformation proceeds in an enantioselective fashion using lithiated SAMP-hydrazones <1997T12961>. Oxidative cleavage of the 1,4-adducts provides 2,3-disubstituted 4-oxophosphonates in low de but high ee. The intermediate lithiophosphonate anions may be trapped with alkyl halides or sulfates to give access to 1,2-disubstituted 4-oxophosphonates. Cyclic γ-ketophosphonates are the products of Michael-induced ring-closure reactions of phosphorylated allylcarbanions with α,β-unsaturated ketones <2001EJOC1259>. Allylphosphonate **124**, deprotonated with LDA in THF, undergoes conjugate addition with enones in the presence of DMPU to give the *trans*,*trans*-adduct **125** stereoselectively and in moderate yield (Equation (94)).



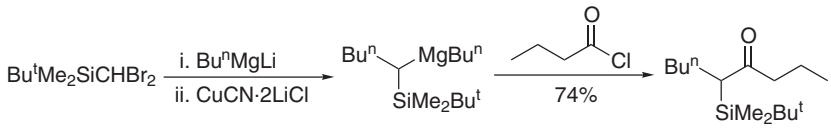
(94)

3.04.9 KETONES BEARING A METALLOID FUNCTION

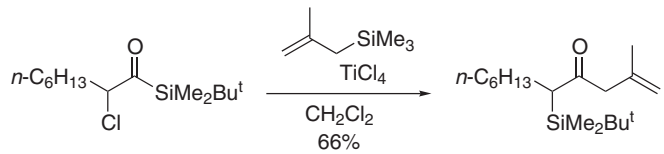
3.04.9.1 Silicon-functionalized Ketones

3.04.9.1.1 α-Silyl ketones

α-Alkylsilylmetal derivatives are important reagents in the Peterson olefination and are also useful compounds for the preparation of silylketones. The preparation of these reagents is usually achieved by addition of organometallic reagents to vinyl silanes or by deprotonation or halogen–lithium–halogen exchange <1995COFGT(3)111>. In a new approach, dibromomethylsilane is treated with a trialkylmagnesate in the presence of copper(I) salts to give α-silylalkylmagnesium reagents <2001AC(E)2085>. These compounds react with a range of acid chlorides to give α-silylketones in good yield (Scheme 43). α-Haloacylsilanes are readily prepared from α-haloepoxysilanes and may be converted into α-haloketones in the presence of titanium tetrachloride and nucleophiles <1996JOC4483>. Treatment of α-chloroacylsilanes with titanium tetrachloride leads to the formation of a silicon-stabilized carbocation. Nucleophilic attack of an allylsilane at the carbonyl group proceeds with migration of the silyl group to give the α-silylketone (Equation (95)).



Scheme 43



(95)

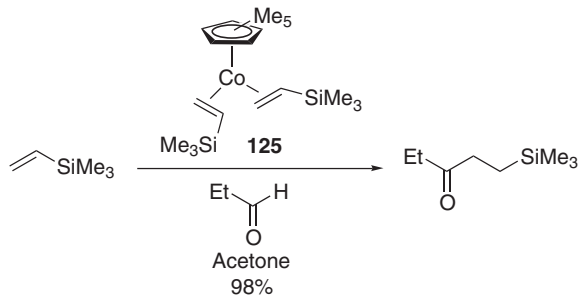
Organosilanes may be accessed by hydrosilylation of alkenes. Hydroxysilylation is now also possible using triethyl silane and catalytic amounts of *N*-hydroxyphthalimide (NHPI) and cobalt(II) acetate in the presence of oxygen <2003EJOC2286>. This radical process proceeds via formation of a triethylsilyl radical and when applied to the hydroxysilylation of α,β-unsaturated aldehydes and ketones gives α-triethylsilylketones by β-cleavage of intermediate hydroperoxides. Alkenylboranes may be converted into α-silyl ketones by reaction with trialkylsilyl anions <2000TL6541>. 1-Bromo-1-alkenylboronate esters are accessed by hydroboration of 1-bromo-1-alkynes. Subsequent treatment with trimethylsilylmethyllithium gives an ate complex. Migration of the trimethylsilylmethyl group onto carbon followed by oxidation using hydrogen peroxide and sodium acetate gives an α-trimethylsilylketone. Silyl-substituted enol ethers may be accesssed from vinylsilanes by an addition–elimination sequence <1997TL6763>. Alcohols and iodine may be added to vinylsilanes using bis(pyridine)iodonium(I) terafluoroborate in methanol. The resulting adducts undergo elimination of hydrogen iodide in the presence of DBU to give β-silyl enol ethers.

α,β-Epoxy-γ,δ-vinylsilanes may be alkylated at the α-position by metallation using *sec*-butyllithium in the presence of TMEDA followed by reaction with alkyl halides <2002SL553>. The products undergo palladium(0)-mediated ring-opening with 1,2-migration of the silyl group to give α'-silylated-β,γ-unsaturated ketones in high yield (Scheme 44).

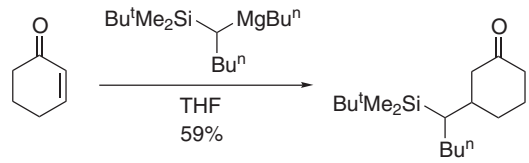
Scheme 44

3.04.9.1.2 β-Functionalized and more remotely silyl functionalized ketones

A new method for the synthesis of β-silylketones involves the transition-metal-catalyzed hydroacylation of vinylsilanes with aldehydes <1998JA6965>. Cobalt complex **125** catalyzes the conversion of vinyltrimethylsilane into a variety of β-silylketones in the presence of aldehydes under mild conditions (Equation (96)). γ-Silylketones may be accessed by conjugate addition of α-alkylmagnesium reagents, prepared according to the methodology discussed in Section 3.04.9.1.1 <2001AC(E)2085>. These reagents undergo conjugate addition to acyclic and cyclic enones to give γ-silylketones in moderate yield (Equation (97)).



(96)



(97)

3.04.9.2 Germanium-functionalized Ketones

No further advances have occurred in this area since the publication of COFGT (1995).

3.04.9.3 Boron-functionalized Ketones

No further advances have occurred in this area since the publication of COFGT (1995).

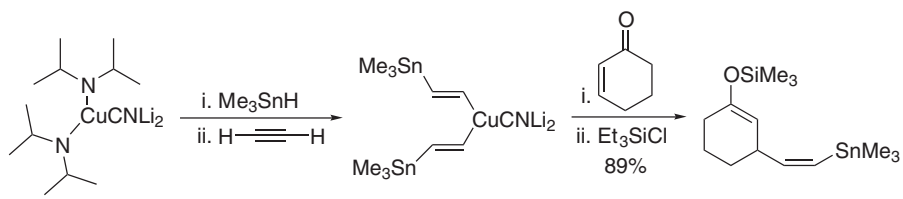
3.04.10 KETONES BEARING A METAL FUNCTION

3.04.10.1 Tin-functionalized Ketones

α-Diazoketones react with tributyltin hydride in a free-radical chain process to give α-stannyl-ketones <1996JCS(P1)769>. These reactions are initiated by di-*tert*-butylhyponitrite in benzene and also proceed using triphenyltin hydride and allyltributylstannane. Use of the latter stannane allows access to α-stannyl-γ,δ-unsaturated ketones that are readily destannylated on work-up with aqueous potassium fluoride.

β-Stannyl-α,β-unsaturated ketones may be accessed by hydrostannation of alkynyl ketones <2003JOC10087>. This transformation takes place under palladium catalysis using trineophyltin hydride and bis(triphenylphosphine)palladium(II) chloride in THF or under free-radical conditions in the presence of triethylboron in diethyl ether. The reaction proceeds in high yield and with high regio and stereoselectivity giving the (*E*)-isomer resulting from *syn*-addition.

β-Vinylstannyl- and alkylstannylketones may be prepared by reaction of stannylcuprates with enones. In a new and convenient route to bis(trimethylstannylvinyl)cuprates, higher-order bis(di-isopropylamido)cyanocuprates, prepared from LDA and copper(I) cyanide are reacted with trimethyltin hydride to give bis(trimethylstannyl)cyanocuprates <1995TL8749>. These reagents undergo addition to acetylene to give the stannylvinylcuprates which in turn undergo conjugate addition with cyclohexenone and derivatives in high yield in the presence of triethylsilylchloride (Scheme 45).



Scheme 45

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Biographical sketch

Vittorio Caprio was born in Welshpool, Powys, UK. He studied at Reading University, where he obtained a B.Sc. in 1994 and his Ph.D. in 1998 under the direction of Professor J. Mann. He then spent 2 years as a Postdoctoral Fellow in the laboratories of Margaret Brimble at The University of Auckland, New Zealand. Vittorio was appointed as a Lecturer in Organic and Medicinal Chemistry at the University of Auckland in 2001. His research interests center on the design of novel synthetic routes to bioactive alkaloids.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 135–214

3.05
Ketones: α,β-Unsaturated Ketones

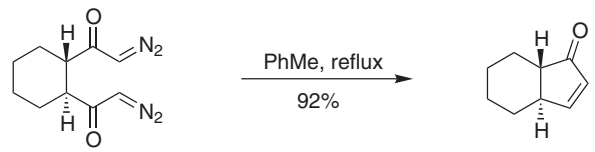
C. E. FOSTER and P. R. MACKIE
Avecia Ltd., Manchester, UK

3.05.1 KETONES BEARING AN α,β-ALKENIC BOND

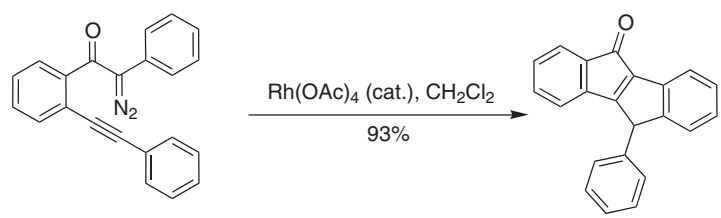
3.05.1.1 α,β-Unsaturated Ketones without Further Unsaturation

3.05.1.1.1 From diazoketones

α,ω-Diazoketones react intramolecularly to form large-ring α,β-unsaturated diketones, predominantly as (*E*)-isomers <1995COFGT(3)205>. Smaller rings (cyclopentenones and cyclohexenones) can also be prepared, though often in poor yield (Equation (1)) <1993CC556, 1995JOC2466>. Diazoketones also react intramolecularly with alkenes to give α,β-unsaturated ketones <1995COFGT(3)205>. Analogous reactions with alkynes lead to polycyclic indenone products (Equation (2)) <2000JOC3722, 1995JOC53>. In a related reaction of diazoesters, it was found that Cu(II)- and Rh(III)-modified clays facilitated the insertion of carbenes into the C—OH bond of acrylic acids to generate the α,β-unsaturated ketone <1999JCS(P1)3685>.



(1)



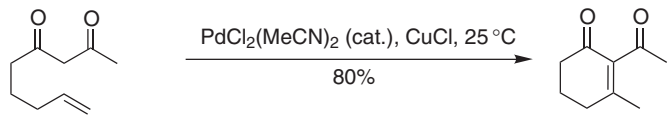
(2)

3.05.1.1.2 By elimination reactions

(i) By oxidative elimination of H_2 from a ketone

Acylated enolates and silyl enol ethers can be oxidized to α,β-unsaturated ketones, with the position of the resulting alkenic bond dictated by the regiochemistry of the enol derivative. Usually, the (*E*)-isomer is formed. Palladium salts are often chosen to remove the hydrogen, but quinones and chromium oxidants are also used <1995COFGT(3)205>. Palladium catalysis has been used to effect the intramolecular alkylation of alkenes. Hydrogen is lost at the same time to create an enone (Equation (3)) <2003JA648>. Iodoxybenzoic acid is employed as the oxidant in a high-yielding dehydrogenation of saturated ketones. The conditions and stoichiometry of the reaction can be used to control the number of double bonds introduced <2000JA7596>. Hypervalent iodine oxidants have also been used together with a pyridine *N*-oxide derivative to remove hydrogen from saturated ketones at room temperature and in good yield <2002AG(E)993>.

The use of HIO_3 has been reported to dehydrogenate ketones to give enones, whilst leaving alcohols unaffected <2002AG(E)1386>. Samarium diiodide has also been used to effect dehydrogenation <1995TL1145>.



(3)

(ii) By elimination of selenoxides

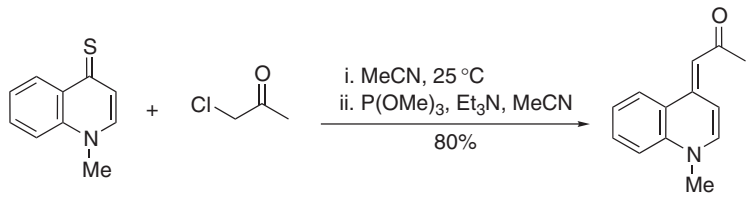
Selenium is introduced adjacent to the ketone function, often by reaction with phenyl selenyl chloride. Oxidation of selenium and *syn*-elimination is facile, usually producing the (*E*)-alkene. A variety of oxidants have been employed <1995COFGT(3)205>. Selenium has been used to attach molecules to polymer supports, with elimination being used to release the products <2000JCS(P1)3815>.

(iii) By elimination of HF, HBr, or HCl from an α-haloketone

A variety of methods can be used to prepare α-haloketones that undergoes elimination with base. Although the enolate usually reacts with an electrophilic halogenating agent, α-hydroxy ketones can also be used in a two-step dehydration sequence, whereby the alcohol is first converted into the halide before elimination <1995COFGT(3)205>. Hydrogen fluoride can be eliminated under mild conditions <1996S1363>. Vicinal dibromides can be debrominated using triethylamine with a telluroether catalyst <1996OPP117>, sodium thiophenoxide <1996JIC693>, or heating in HMPA at 160 °C <2001BCJ1089>.

(iv) By elimination of sulfoxides and sulfones

Sulfones and sulfoxides eliminate in a similar fashion to selenoxides, although harsher conditions are required <1995COFGT(3)205>. Sulfur can be removed from a sulfide to provide access to 4-alkylidine quinolines (Equation (4)) <1995S56>.

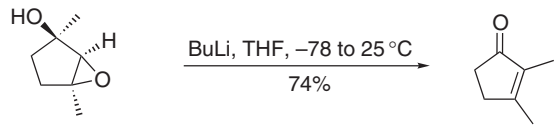


(4)

(v) By elimination of a hydroxy or alkoxy group

Enones can be prepared by dehydration of α-hydroxy ketones under acidic conditions <1995COFGT(3)205>.

Cyclic α-hydroxy epoxides are converted into α,β-unsaturated ketones on treatment with a strong base. It is believed that the reaction proceeds by a carbenoid pathway, with alkyl group migration (Equation (5)) <1995JA12700>. Thiourea dioxide also deoxygenates epoxides, transforming α-epoxy ketones to the corresponding enones in aqueous conditions <1997TL745>. α,β-Epoxy ketones can also be readily deoxygenated under mild conditions using molybdenum hexacarbonyl <2003TL2355>.



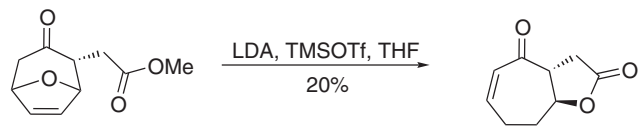
(5)

(vi) By elimination of a leaving group β- to a ketone

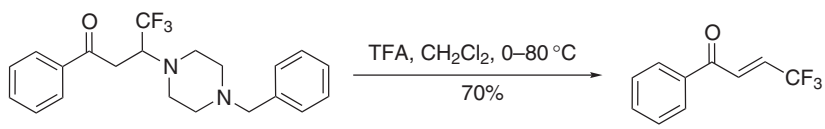
A number of functional groups can be eliminated from the β-position. These include hydroxy (the final stage of the aldol condensation), carboxylic acid, nitrite, cyano, and sulfone. The Mannich reaction between an enolizable ketone and an iminium species, followed by quaternization of nitrogen and elimination, leads to α,β-unsaturated ketones <1995COFGT(3)205>. The use of diarylborinic acid to dehydrate aldol adducts shows some diastereoselectivity, with *anti*-aldols dehydrating preferentially to *syn*-aldols <1997SL597>. Cerium chloride-mediated dehydration results in exclusive formation of (*E*)-isomers <2000OL1791>. Alkylation of a sulfide, β- to a ketone results in facile elimination <1998S89>. The treatment of α-chloro-β-hydroxy ketones with samarium diiodide or triiodide resulted in elimination to give the (*E*)-α,β-unsaturated ketone in good to excellent yield <2003TL1931>.

The Baylis–Hillman reaction provides a means to α-alkylate α,β-unsaturated ketones. The final step is the elimination of a β-ammonium ion. The use of a chiral tertiary amine in this reaction can result in good enantioselectivity being attained <2002AG(E)4507>. Recent work has examined the effect of salts on the rate of reaction <2003T5019>.

Cycloheptenones have been prepared via ring-opening bicyclic ethers (Equation (6)) <1996T11297>. A similar result occurred on ring-opening a *meso*-tropinone compound. The nitrogen was first quaternized and then a chiral lithium amide base was used to ring-open the 5-membered ring, resulting in the formation of the amino-cycloheptenone, with high enantiomeric excess (ee) <1997CJC754>. Quaternization is not necessary for elimination of amines, but heating with *p*-toluenesulfonic acid has been used effectively <1999TL4199>. β-Piperizinyl substituents were eliminated from a fluorinated ketone on treatment with trifluoroacetic acid (Equation (7)) <2001JOC4826>.

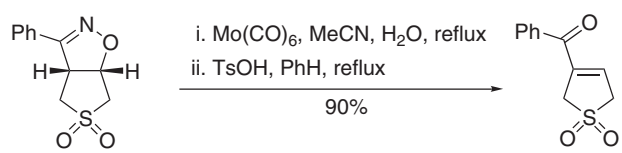


(6)



(7)

Cyclic *o*-alkyl oximes can be hydrolyzed to give β-hydroxy ketones, which subsequently lose water, forming the enone (Equation (8)) <1997SC2557>. If a phosponate ester is appropriately included in the substrate, then further reaction with aldehydes leads to dienones <2000JOC256>.



(8)

3.05.1.1.3 From vinyl compounds and carboxylic acid halides or their equivalents

(i) By reaction of a carboxylic acid derivative and a vinyl metallic reagent

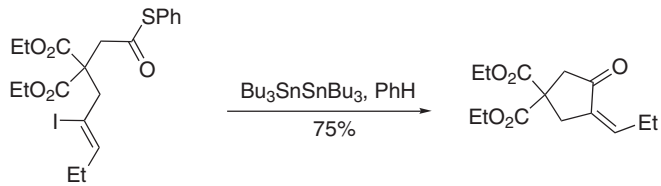
Vinyllithiums react with most carboxylic acid derivatives to give enones. Conditions are chosen to minimize formation of the tertiary alcohol. With other vinyl metallics, more reactive acid chlorides are typically employed <1995COFGT(3)205>. The reaction of vinylboronic acids with thiol esters is a high-yielding coupling to make α,β-unsaturated ketones <2000JA11260>. Vinylboronic acids can be acylated in a reaction catalyzed by a rhodium catalyst <2001CC2316>.

(ii) From vinyl silanes and acid chlorides

Vinyl silanes react with acid chlorides in the presence of Lewis acid catalysts. Effectively, the reaction replaces silicon with the acyl or aroyl group <1995COFGT(3)205>. No major developments of this reaction have been noted since the publication of COFGT (1995).

(iii) From alkenes and an acid chloride, anhydride, or acid derivative

Alkenes participate in Friedel–Crafts-type reactions to afford α,β-unsaturated ketones <1995COFGT(3)205>. This reaction has been achieved electrochemically <1995CL275>. Thio- and seleno-esters have been employed in intramolecular radical cyclizations, to form 2-alkylidine cyclopentanones (Equation (9)) with better yields attained with the selenium substrates <1996CC1335>. An alkene was, in effect, inserted into an amide C—N bond in an intramolecular photochemical reaction (Equation (10)) <1998TL7423>.



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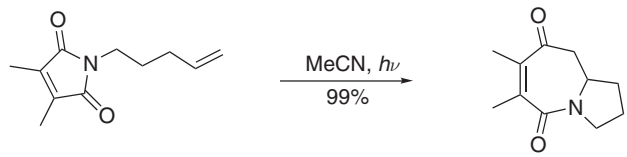
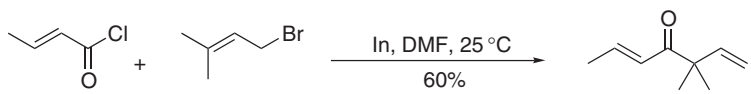


(10)

3.05.1.1.4 From α,β-unsaturated acid chlorides or their equivalents and carbon nucleophiles

(i) From acid derivatives and organometallic reagents

Organolithium and Grignard reagents react well with acrylic acid derivatives <1995COFGT(3)205>. Organogallium <1995TL1287>, manganese <1997TA1373>, cerium <1998TL4793>, aluminum and zinc <1997JOC4327> compounds have been used, all with good-to-excellent yields. An indium-mediated reaction with allylic substrates resulted in allyl migration (Equation (11)) <1997TL8745>. Carbenes derived from α-diazoesters react in high yield with α,β-unsaturated acids to provide ketones. A copper-modified clay is used as a catalyst for the reaction (Equation (12)) <1999JCS(P1)3685>.



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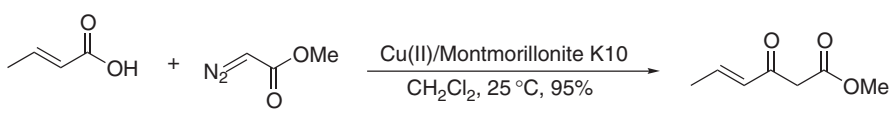
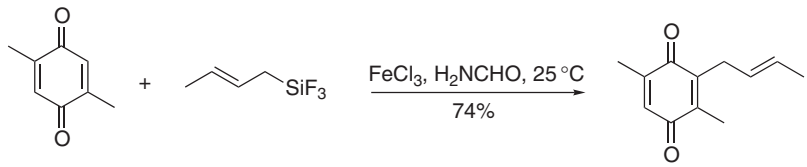


(12)

(ii) From α,β-unsaturated acid chlorides and an activated alkene

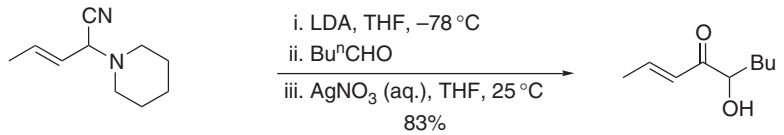
Electron-rich alkenes are acylated by α,β-unsaturated acid chlorides. Allyl silanes also react, with migration of the double bond and loss of silicon <1995COFGT(3)205>. Migration of the double bond does not occur in the allylation of quinones with allyltrifluorosilanes (Equation (13)) <1995TL2773>. Ortholithiated aryls react with unsaturated acid chlorides, in a palladium-catalyzed coupling <1995JOC2298>.



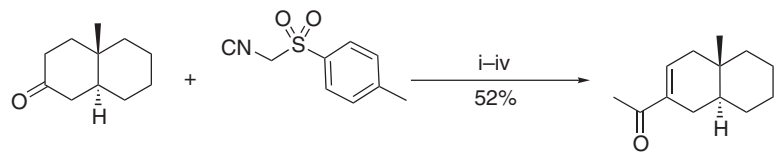
(13)

3.05.1.1.5 From alkylations of α,β-unsaturated aldehydes and their equivalents

"Umpoled" unsaturated aldehydes can be deprotonated and alkylated. Methods for reversing the polarity of the aldehyde include forming the trimethylsilyl cyanide adduct, dithiane, or using an allenyl ether <1995COFGT(3)205>. Metallated α-amino-β,γ-unsaturated nitriles react with aldehydes to produce α′-hydroxy enones, following hydrolysis catalyzed by silver nitrate (Equation (14)) <1999TL5301>. Tosylmethyl isocyanide (TosMIC) reacts with ketones, to give an umpoled aldehyde equivalent. Subsequent alkylation and hydrolysis to the carbonyl results in the formation of α,β-unsaturated ketones (Equation (15)) <1995JOC2188>. *N*-α-(Ethoxyallyl) benzotriazole serves as a synthon for the propenoyl anion, reacting with alkyl halides to provide enones (Equation (16)) <1995JOC7589>.

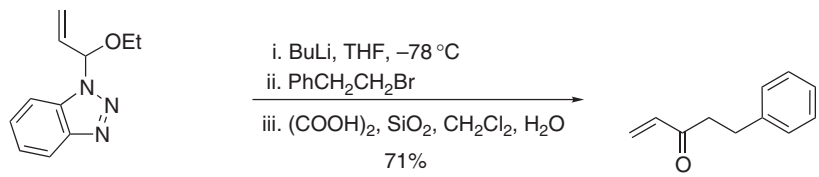


(14)



(15)

i. KOBut, THF; ii. $POCl_3$, NEt_3; iii. MeI, KOtBu, DME; iv. HCl



(16)

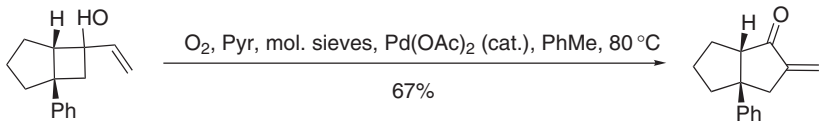
3.05.1.1.6 By oxidation reactions

A number of methods for effecting oxidations to α,β-unsaturated ketones in the solid phase have been collated in a review. The methods include oxidations of allylic alcohols and the allylic position of alkenes <2000JCS(P1)3815>.

(i) By oxidations of allylic alcohols

There are a number of reagents that effect the oxidation of secondary allylic alcohols to α,β-unsaturated ketones, manganese dioxide being the most commonly used <1995COFGT(3)205>. Sodium percarbonate has been used as an oxidant in a reaction catalyzed by a molybdenum complex <1996SL439>. Air has been used as the oxidant with palladium acetate <1998JOC3185> and also in the aerobic oxidation of allylic alcohols in the presence of TEMPO (tetramethyl-1-piperidinyloxyl) and CAN (ceric ammonium nitrate) <2003S2135>. The palladium-catalyzed aerobic oxidation of a tertiary allylic cyclobutanol resulted in a ring expansion and loss of hydrogen (Equation (17)) <1999JA2645, 2001JOC1455>. Hypervalent iodine oxidants have been used increasingly over the past decade, with the conditions employed affecting the course of the reaction. The stable free-radical TEMPO has also been used to mediate the reaction, apparently

preventing over-oxidation <1997JOC6974>. Chlorine dioxide gave quantitative oxidation of a bulky allylic alcohol to an enone <1996IZV1871>. Potassium permanganate supported on a zeolite catalyst has been used in respectable yield <1997TL5143>. Oppenauer-type oxidations proceed in high yields, using an aluminum complex together with a hydrogen acceptor, e.g., acetone <2002OL2669>. *Meso*-allylic diols can be desymmetrized by catalytic hydrogen transfer oxidation using a chiral ruthenium complex (Equation (18)) <1997AC300>.



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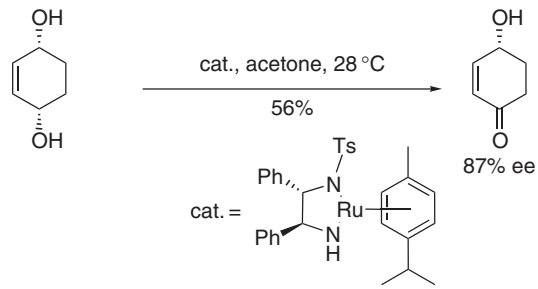


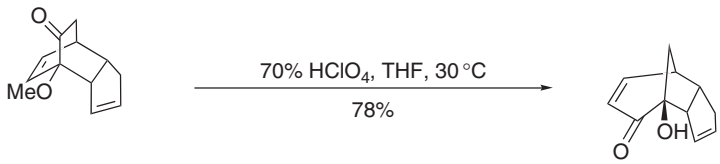
(18)

(ii) By oxidations of allylic methylene groups

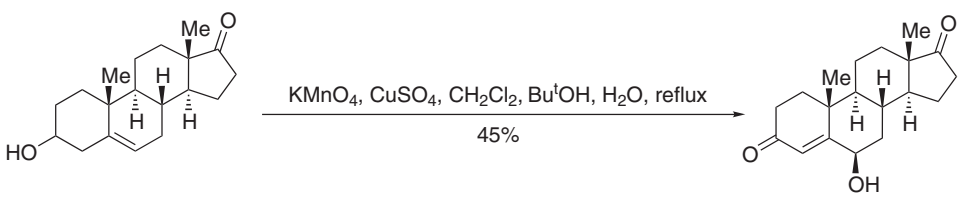
Allylic methylene groups can be oxidized to give α,β-unsaturated ketones. Reagents for this transformation include selenium dioxide, chromium trioxide, and organic peroxides <1995COFGT(3)205>. Palladium hydroxide, supported on carbon, was used to catalyze the peroxide allylic oxidation of alkenes under mild conditions <2003JA3232>.

(iii) Miscellaneous oxidation reactions

Partial ozonolysis of dienes can be used as a route to α,β-unsaturated ketones <1995COFGT(3)205>. A ring expansion to a cycloheptenone was observed on reaction of a bicyclo[2.2.2]octenone with perchloric acid (Equation (19)) <1996T3693>. Manganese salen complexes catalyze the asymmetric oxidation of dienylacetate to 4-hydroxy-cyclohexenone with NaOCl as the oxidant, with a 4-phenylpyridine-*N*-oxide co-catalyst <1996TL4389>. Homoallylic alcohols can be oxidized by permanganate to give δ-hydroxy-α,β-unsaturated ketones (Equation (20)) <1996JOC5665>. Dess–Martin periodinane has been used to remove allylic thioacetals, to regenerate ketones <2003OL575>. Silyl enol ethers have been oxidized by iodoxybenzoic acid and a pyridine *N*-oxide derivative to give enones <2002AG(E)996>. An alkene was brominated three times, including at the allylic position, with NBS and hydrolyzed with aqueous acetic acid to give an α,β-unsaturated ketone <2003T8975>.



(19)



(20)

3.05.1.1.7 Rearrangement reactions

(i) By Rupe rearrangements

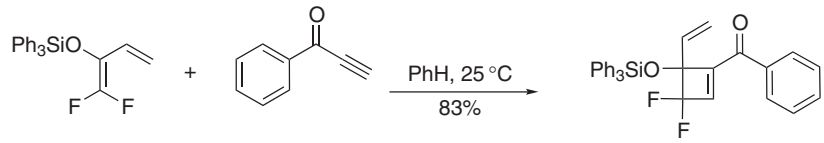
α-Alkynic alcohols undergo the Rupe rearrangement under acidic conditions to form α,β-unsaturated ketones <1995COFGT(3)205>. The rearrangement has been performed, in high yield, using zeolite catalysts <1996T8287>, and a platinum carbonyl complex catalyst, to promote alkyne hydrolysis and elimination <1997JOC669>. Strongly acidic cation exchange resins have been used as catalysts for the large-scale synthesis of α,β-unsaturated ketones via a Rupe rearrangement <2002MI216>. Propargylic alchohols have been isomerized to α,β-unsaturated ketones on solid supports <2000JCS(P1)3815>.

(ii) By rearrangement of propargylic alcohols

A similar reaction to the Rupe rearrangement results in the isomerization of 2-butyn-1,4-diols to α,β-unsaturated ketones, with one molecule of water being lost <1995COFGT(3)205>.

(iii) By [2+2]-cycloaddition reactions

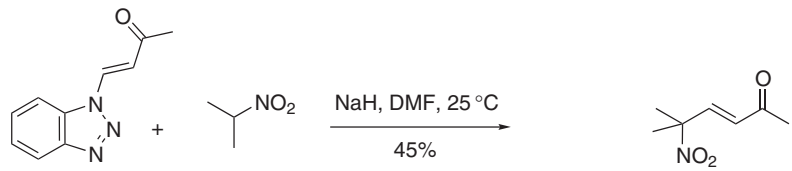
Allenes, alkenes, and occasionally alkynes undergo a [2+2]-addition reaction with ketenes. In the case of allenes and alkynes this addition leads directly to α,β-unsaturated ketones, whereas alkenes give cyclobutanones that undergo an elimination to an enone when a suitable leaving group is present on the ketene <1995COFGT(3)205>. Alkynyl ketones undergo a [2+2]-addition with difluoro silyl enol ethers, to give acylated cyclobutenes (Equation (21)) <1995JFC1>.



(21)

3.05.1.1.8 By displacement of a β-leaving group on an α,β-unsaturated ketone

Halogens, thiols, and other leaving groups can be replaced with alkyl groups in an addition–elimination reaction. Organocuprates are normally used as the source of carbanions <1995COFGT(3)205>. Benzotriazole can be used as the leaving group (Equation (22)) <1996SC3773>. Organostannanes react with iodoenones in a copper-mediated coupling <1996JA2748>. Amines were displaced from enaminones when Grignard <1998SC1743> or organocerium reagents were employed <1996MI913>. Tellurium-substituted enones react with zinc cuprates and eliminate in good yield <1995SL180>.



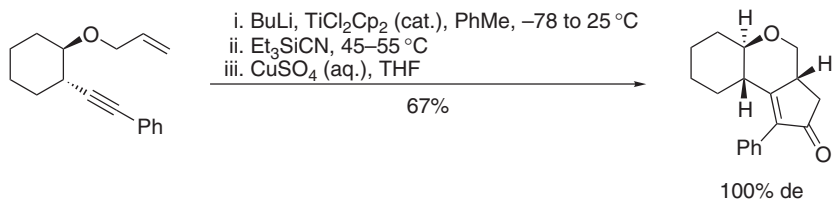
(22)

3.05.1.1.9 Oxy-Cope and Claisen rearrangements

The Cope and Claisen [3,3]-rearrangements, with suitable substrates, can provide α,β-unsaturated ketones. For the electrocyclic reaction to take place the substrate must be able to adopt a near-chair-like geometry with multiple bonds in a 1,5-relationship <1995COFGT(3)205>. A recent example of this rearrangement is illustrated in Section 3.05.1.4.1.(vi).

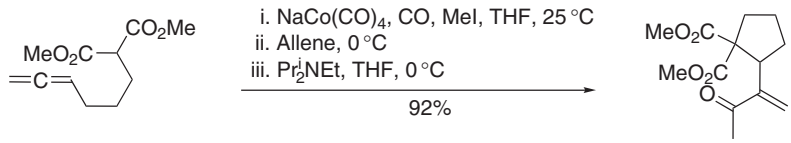
3.05.1.1.10 Carbonylation and related reactions

The Pauson–Khand reaction is commonly used to prepare cyclopentenones, and examples with assorted substitutents appear in the sections below <1995COFGT(3)205>. Supercritical carbon dioxide has been used as a solvent for both inter- and intramolecular variants of this reaction <1997JA10549>. *N*-Methyl morpholine-*N*-oxide has been found to promote the reaction with allenic substrates <1995TL4417>. Asymmetric Pauson–Khand reactions have been realized in aqueous conditions under atmospheric pressure. The choice of co-solvent had a significant impact on reaction times and yields, and it was found that the addition of an anionic surfactant both decreased the reaction time as well as increased the enantioselectivity <2003S2169>. A heterogeneous catalyst, comprising ruthenium/cobalt nanoparticles dispersed on charcoal, was used in a Pauson–Khand-type cyclization, together with pyridylmethyl formate in place of carbon monoxide <2003CC1898>. The reaction was used twice in a reaction that led to the formation of four fused cyclopentanes, sharing a common spiro center <2002JA6839>. A rhodium(I) catalyst promotes both a diastereoselective allylic alkylation and a Pauson–Khand-type reaction <2001JA4609>. The Pauson–Khand reaction has been applied in the solid phase <1999CRV1549, 2000JCS(P1)3815>. Cyclopentenones were prepared using triethylsilyl cyanide in the presence of a titanium catalyst (Equation (23)) <1996JOC2713>.



(23)

Carbon monoxide insertion reactions appear frequently in the recent literature and provide a means to acylate alkenes, usually, but not universally employing palladium catalysts. Chemical equivalents of carbon monoxide have been used, avoiding gas handling <1995COFGT(3)205>. Allenes insert into an acyltetracarbonylcobalt complex providing allyl complexes that undergo cyclization on treatment with base (Equation (24)) <1995TL509, 1995T12939>. An aroylcyanide, in effect, added across a terminal alkyne in a palladium-catalyzed, four-component coupling reaction (Equation (25)) <1996BCJ1629>. Benzyne derivatives undergo an atmospheric pressure carbonylation reaction to give 2-alkylidine-indanones <2001JA12686>.



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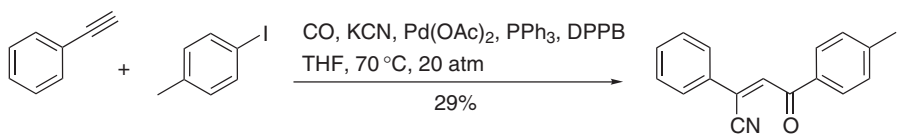
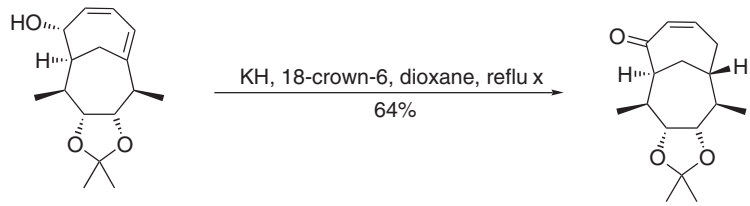


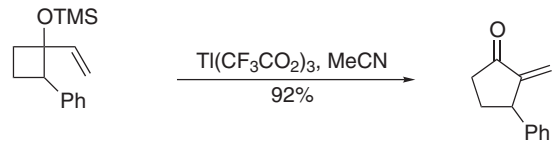
(25)

3.05.1.1.11 By isomerizations

Double bonds often migrate along a carbon chain to provide the most stable, conjugated system. This thermodynamic preference has been exploited in converting unsaturated ketones into α,β-unsaturated ketones. Acids, bases, transition metal catalysts, and elevated temperature have been used to effect the isomerization <1995COFGT(3)205>. Propargylic alcohols are isomerized to α,β-unsaturated ketones, using ammonium salts and an indium–ruthenium catalyst system <1995JA9586>. The strain in an anti-Bredt dienyl alcohol was relieved, to an extent, by isomerism to a contorted bicyclo[4.4.1]cycloundecenone ring system (Equation (26)) <1996JOC7992>. 1-Trimethylsilyloxy-1-alkenylcyclobutanes undergo a thallium(III)-catalyszd ring expansion to α-methylenecyclopentanones. The reaction works less well for larger ring systems (Equation (27)) <1996TL3865>.



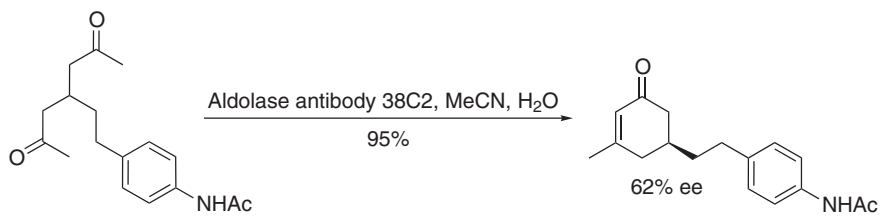
(26)



(27)

3.05.1.1.12 By aldol condensation reactions

Enolates, and their synthetic equivalents, react with aldehydes and ketones. The resulting β-hydroxy ketones are liable to dehydration, giving the most common method for the preparation of α,β-unsaturated ketones, the aldol condensation. The reaction is catalyzed by both acids and bases, and the two carbonyls involved can be made *in situ*, for example, by oxidation or deprotection, particularly for intramolecular aldol reactions. Preforming the enolate, e.g., by trapping as a silyl enol ether or using enamines, permits control over the regiochemistry of the addition step <1995COFGT(3)205>. Sequences involving hydroformylation followed by aldol reactions to form α,β-unsaturated ketones have been reviewed <1999CRV3329>. Samarium(III) iodide <1996SC3025> and indium trichloride have been used effectively as catalysts for aldol condensations <2003SC2995>. An enzyme-mediated aldol reaction demonstrated moderate enantiotopic group discrimination, to desymmetrize a *meso*-diketone (Equation (28)) <1999OL59>.

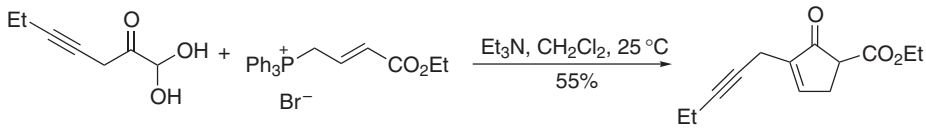


(28)

Solid-phase aldol and Knoevenagel reactions have been reviewed <1998JCS(P1)3293, 1999CRV1549, 2000JCS(P1)3815>. Other recent solid-phase aldol reactions have been reported. For example resin-bound aryl aldehydes react with ketones in a zinc-acetate-mediated condensation <2003TL2371> and microwave-assisted reactions have been investigated <2002MI154>.

3.05.1.1.13 By Wittig reactions

The Wittig reaction between an α-ketophosphorane and an aldehyde, leads to the formation of (*E*)-α,β-unsaturated ketones. In the Horner–Wadsworth–Emmons reaction, an α-ketophosphonate is used. These reactions are commonly employed in an intramolecular fashion to produce cyclic enones <1995COFGT(3)205>. A tellurium(IV) catalyst was found to promote Wittig-type reactions between aldehydes and α-bromoketones; in the presence of triphenyl phosphite, (*E*)-stereoselectivity was observed <2002JOC5320>. A three-component Horner–Wadsworth–Emmons-type reaction has been described, which also gives good (*E*)-selectivity. An alkyl phosphonate is reacted sequentially with an ester and then an aldehyde <1996TL9177>. Bisenones have been prepared via ozonolysis of a cycloalkene, followed by reaction with 2 equiv. of phosphorane <1995JOC5699>. Cyclopentenones can be prepared by a [3 + 2]-annulation of a phosphorane derived from a crotonyl ester and a glyoxal (Equation (29)) <1996TL5735>. Trifluoromethyl α,β-unsaturated ketones can be prepared with (*E*)-geometry, in a reaction that proceeds via a lithium enamide (Equation (30)) <1995JCS(P1)741>. Wittig-type reactions have been performed on polymer supports <1999CRV1549, 2000JCS(P1)3815>.



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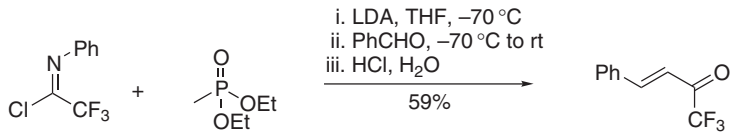


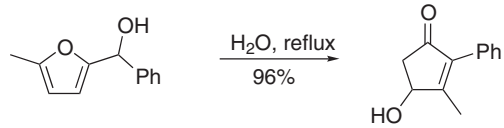
(30)

3.05.1.1.14 By Diels–Alder reactions

The Diels–Alder reaction provides a route to cyclohexenones, or acylated cyclohexenes, depending on whether the carbonyl (or equivalent) is contained in the diene or dienophile <1995COFGT(3)205>. α,β-Unsaturated ketones have been synthesized in solid-phase reactions <1998JCS(P1)3293, 1999CRV1549>.

3.05.1.1.15 By oxidations of furans

2,5-Disubstituted furans can be ring-opened oxidatively to provide enedicarbonyl compounds. A variety of oxidants including halogens, singlet oxygen, peracids, and chromium reagents have been utilized <1995COFGT(3)205>. A rhenium catalyst was used in a high-yielding ring-opening reaction <1998TL5651>. Boiling furyl alcohols in water isomerizes the molecule to a cyclopentenone in excellent yield (Equation (31)) <2000H185>. Hypervalent iodine oxidants have been used to convert furyl alcohols into oxygenated pyrans (Equation (32)) <1995TL3553>.



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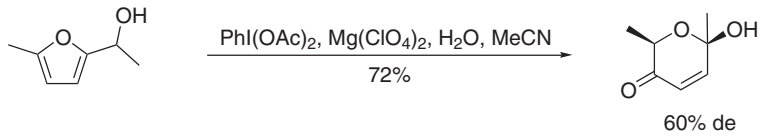
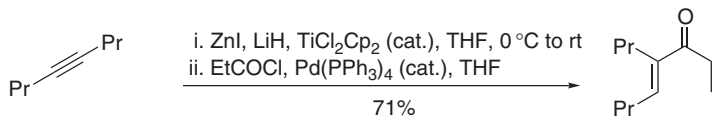


(32)

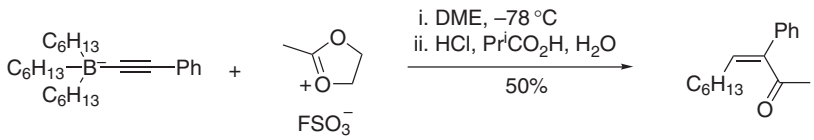
3.05.1.1.16 From alkynes

A number of preparations of α,β-unsaturated ketones are available from alkynes. α-Alkynyl ketones are susceptible to nucleophilic attack by organocuprates, leading to enones. Similar additions to esters, followed by Dieckmann condensation, give rise to cycloalkenones. α-Alkynic ketones can be partially reduced, with the choice of conditions allowing influence over the geometry of the resulting alkene <1995COFGT(3)205, 2001TL2015>. Boranes add across the alkyne bond, and, hence, subsequent migration of alkyl groups permits the synthesis of 3-substituted enones. Alkynyl ketones also participate in radical cyclizations, resulting in α,β-unsaturated ketones <1995COFGT(3)205>. Hydromagneziation of alkynyl silanes offers a route to (*Z*)-α,β-unsaturated ketones. The initial products are alkenyl Grignard reagents that undergo further reaction with alkyl iodides, giving substituted vinyl silanes, which can be acylated under Friedel–Crafts conditions to afford α,β-unsaturated ketones <2003SC1643>. Similarly, hydrozincation of alkynes proceeds in a *cis*-fashion to give organozinc reagents that can be acylated by acid chlorides (Equation (33)) <1995JOC290>. Aldehydes add across the triple bond of γ-alkynyl aldehydes, in an intramolecular hydroacylation reaction, to give cyclopentenones in good yield <2001JA11492>. The coupling of aldehydes with alkynes, facilitated by ytterbium triflate, results exclusively in the synthesis of *trans*-chalcones <2003SL552>.



(33)

Palladium-catalyzed coupling of arenes to alkynic ketones has been demonstrated for hindered arenes <2000JA7252>. A regiospecific and stereoselective route to (*Z*)-α,β-unsaturated ketones commences with the reaction of lithium alkynyltrialkylborates with dioxolanium fluorosulfonates, followed by acidic work-up. Highly substituted enones are accessible (Equation (34)) <1995T811>. A further route to highly substituted α,β-unsaturated ketones from alkynes comprises a hydroboration step followed by an aldol-type condensation. High yields can be obtained with the double bond originating from the alkyne, rather than elimination of water (Equation (35)) <1999JOC5822>. Cyclopentanones bearing tethered alkyne groups undergo radical reactions with ring expansion to give the hydroazulene skeleton (Equation (36)) <1995TL3015>. Several approaches to the synthesis of cyclopropenones have been described, including dichlorocarbene addition to an alkyne followed by hydrolysis of the resultant dichlorocyclopropene <2003JOC7833>.



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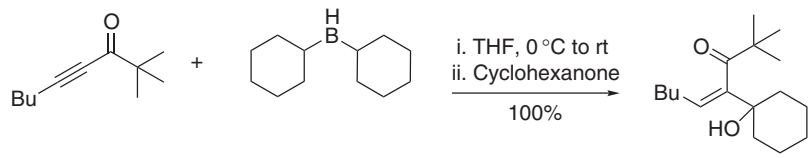

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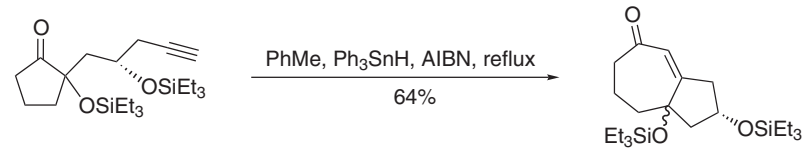
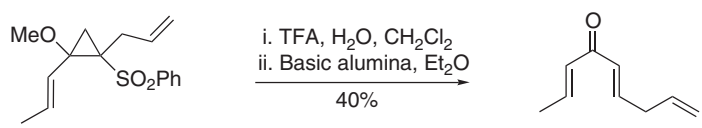


(36)

3.05.1.1.17 From cyclopropanes

Cyclopropanes have been used in several forms for the synthesis of α,β-unsaturated ketones, often in ring expansion reactions. The addition of a halogenated carbene to a silyl enol ether, followed by ring-opening of the cyclopropane with elimination, effectively allows the conversion of cyclic ketone into cyclic enone, with one extra carbon in the ring <1995COFGT(3)205>. Simmons–Smith-type cyclopropanations have also preceded ring-opening reactions to α,β-unsaturated ketones <1995T12955>. Ring-opening reactions of cyclopropanols occur predominantly with cleavage of the less-substituted C—C bond when palladium-catalysis is employed in an oxygen atmosphere <2000OL147>. Asymmetric dialkenic ketones are accessible from cyclopropane intermediates where a sulfone leaving group is present (Equation (37)) <1996TL9305>. Other ring expansions of cyclopropanes involve carbocation rearrangements, or the aldol condensation products of dicarbonyls formed in ring-opening reactions <1995COFGT(3)205>. Alkynyl cyclopropanols undergo a cobalt carbonyl complex-catalyzed rearrangement to 3-substituted cyclopentenones in good yield <1998JA3903>. Vinylcyclopropylacyl radicals cyclize to produce cyclohexenones (Equation (38)). Both reactions proceed via ketene intermediates <1997SL69>.



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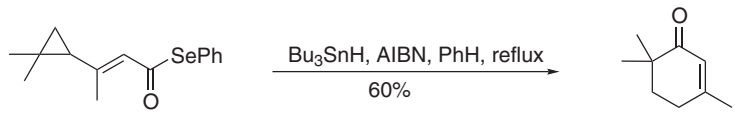
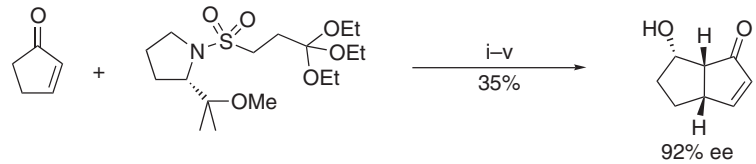


(38)

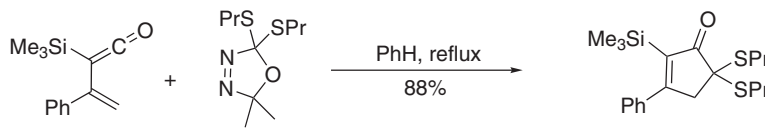
3.05.1.1.18 By cycloaddition reactions other than [4 + 2]-processes

[3 + 2]-Cycloaddition reactions have been used to prepare cyclopentenones <1995COFGT(3)205>. Deprotonated β-sulfonamidyl orthoesters react as 1,3-dipoles and undergo cycloaddition reactions. Elimination of the sulfonamide furnishes enones (Equation (39)) <1997AC627>. A [4 + 1]-cycloaddition between a thermally generated nucleophilic carbene and an alkenylketene produced functionalized cyclopentenones (Equation (40)) <2003OL263>.



(39)

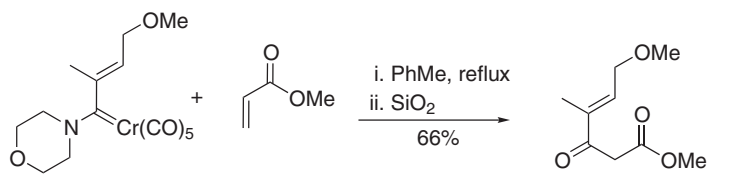
i. BuLi, HMPA, THF, –78 °C; ii. TMSCl, Et_3N, –78 to 20 °C; iii. TMSOTf, 78 °C; iv. Bu_2^iAlH, CH_2Cl_2, –50 °C; v. $PyrH^+TsO^-$, acetone, 0 °C



(40)

3.05.1.1.19 Miscellaneous reactions

Palladium catalysis facilitates addition to unactivated alkenes and provides another route to cycloalkenones, from silyl enol ethers with tethered alkene groups <1995COFGT(3)205>. The Suzuki reaction continues to be a well-used, high-yielding route to alkylated enones <2003T4377>. Palladium-catalyzed coupling reactions on the solid phase have been reviewed <1999CRV1549>. Fischer-type carbene complexes are prepared in a metathesis reaction with an enamine, and subsequently react with α,β-unsaturated esters, to give, after hydrolysis, α,β-unsaturated ketones (Equation (41)) <1995OM1429>. α,β-Unsaturated ketones react in olefin metathesis reactions with unsaturated esters, to effectively acylate β to the ketone (Equation (42)) <2001JA10417>.



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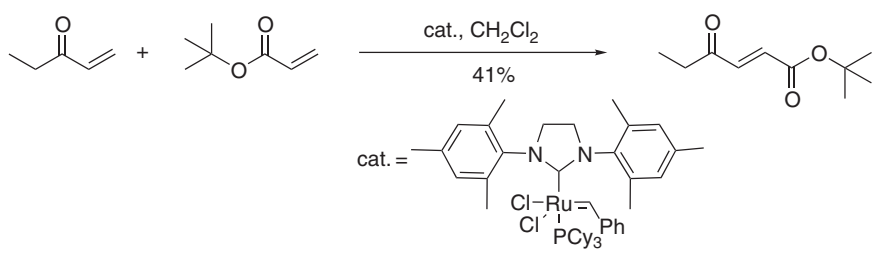
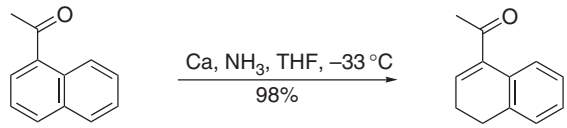


(42)

Acylated naphthalene compounds were reduced in a Birch-type reduction using calcium metal in liquid ammonia. The ketone function remained intact (Equation (43)) <1996JOC1493>. 1,6-Addition of lithium enolates to acylated naphthalene also resulted in reduction of the

naphthalene <1999SL81>. α-Propenyl-substituted cycloalkanones react in water with indium metal to create ring-expanded cycloalkenones. Subsequent reaction with DBU isomerizes the product with the alkene migrating into conjugation (Equation (44)) <1996JA4216>. Radical-mediated ring expansions have been used to prepare cyclooctenones from cyclohexanones <1999JA1217>, and cycloheptenones from cyclopentanones <2000T9241>. Azidoquinones undergo a ring-contraction reaction to afford cyclopentenediones (Equation (45)) <2002OL2337>. Allenic alcohols react with aldehydes in a vanadium-catalyzed reaction. The β-hydroxy ketone is formed with moderate diastereoselectivity (Equation (46)) <2001JA12736>.



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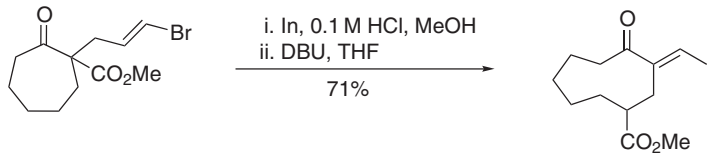

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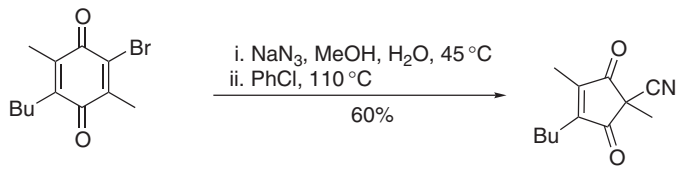

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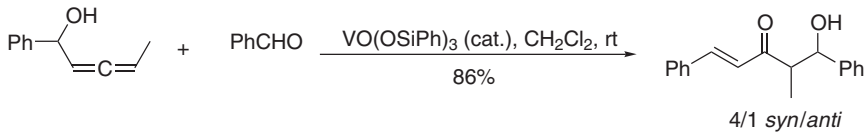


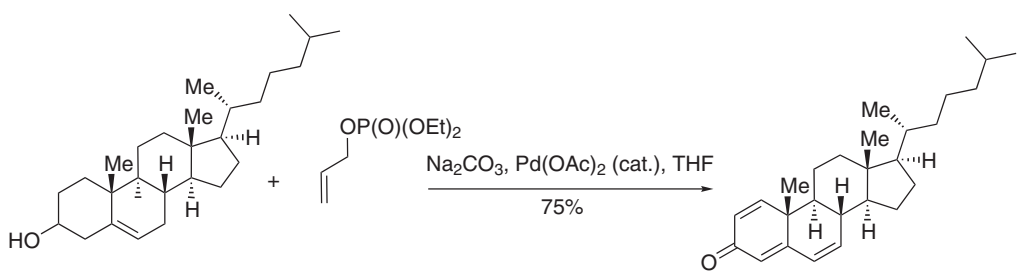
(46)

3.05.1.2 α,β-Unsaturated Ketones with Further Unsaturation

3.05.1.2.1 By elimination reactions

(i) By oxidative elimination of H_2

Hydrogen can be eliminated from α,β- or γ,δ-unsaturated ketones to produce conjugated dienones. A variety of reagents have been employed, including chloranil, DDQ, and chromium salts <1995COFGT(3)205>. A homoallylic alcohol was dehydrogenated using an unsaturated phosphonate ester (Equation (47)) <1998JOC5640>.



(47)

(ii) By elimination of halide

Elimination of hydrogen halide from α-halo-γ,δ- and γ-halo-α,β-unsaturated ketones is achieved under basic conditions <1995COFGT(3)205>. Diels–Alder reactions using 2-bromocycloalkenones with dienes, followed by elimination of hydrogen bromide, has been used to prepare dienones <1995TL1817>.

(iii) By elimination of hydroxy and alkoxy groups

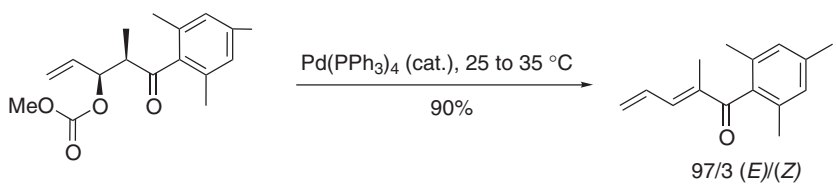
Dehydration of hydroxy-substituted ketones provides a route to unsaturated ketones with further unsaturation. The loss of water is accomplished under acidic conditions and may be preceded by esterification. Alkoxy groups can also be lost under acidic conditions <1995COFGT(3)205>. β-Hydroxy enol ethers eliminate alcohols to produce conjugated dienones <1999JOC5162>.

(iv) By elimination of sulfur and selenium groups

Thioether groups can be eliminated by first oxidizing to a sulfoxide <1995COFGT(3)205>. Sulfones eliminate almost quantitatively, using DBU as the base, from δ-sulfonyl-α,β-unsaturated ketones <1995JA3022>.

(v) Elimination of other groups

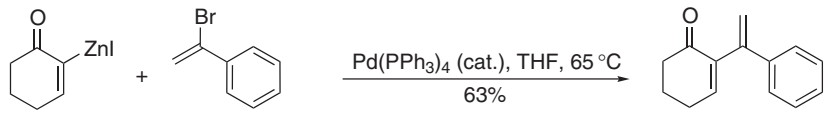
Ammonium ions can be eliminated from suitably substituted quaternized amines <1995COFGT(3)205>. Carboxylates also eliminate, albeit in poor yield, in the synthesis of cycloheptatrienones <1995AJC469>. Palladium-catalysis was used in the elimination of a carbonate ester to give a dienone, predominantly as the (*E*)-isomer (Equation (48)) <1998S83>.



(48)

3.05.1.2.2 By displacement reactions of a β-leaving group with a vinyl nucleophile

A variety of nucleophiles can be used in an addition–elimination sequence, effecting an overall substitution β to the ketone. The vinyl nucleophiles that undergo this reaction include Grignard, vinylboranes and vinyllithiums. Lithium acetylides react similarly <1995COFGT(3)205>. Palladium-catalyzed couplings have been used to effect the same overall substitution. For example, the reaction of a β-iodo-α,β-unsaturated ketone with alkynylstannanes <1994T2003>. Stille reactions have been accomplished in ionic liquids <2001OL233>. Similarly, vinylboranes react with halogenated α,β-unsaturated ketones, in the presence of palladium salts <1994JOM33, 1995TL1443>. Dienones can also be made by forming a vinylzinc reagent and reacting with a vinyl halide (Equation (49)) <1997JOM113>. Trifluoromethansulfonate leaving groups were displaced by alkynyl groups in similar coupling reactions <1997T9107, 1998JOM173>. Alkyl tellurides acted as a leaving group, in the reaction of β-telluro-α,β-unsaturated ketones with a copper/styrene complex. (*E*)-Geometry was preferred in the product <1995SL180>. Two molecules of a vinylstannane were coupled together, using copper(I) chloride in a synthesis of a dienedione (Equation (50)) <1998T10609>. A similar product, coupled through the 2,2′ position, was prepared by nickel-catalyzed coupling of the 2-iodo-α,β-unsaturated ketone (Equation (51)) <2001JOC2877>. Vinylstannanes react with 2-iodo-enones to give (*Z*)-2-alkenyl-α,β-unsaturated ketones <1993T4677>.



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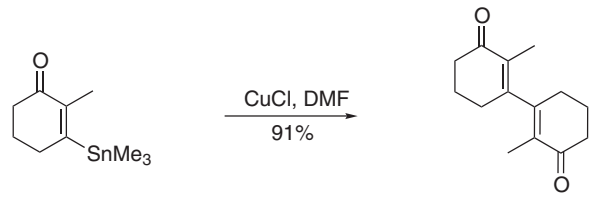

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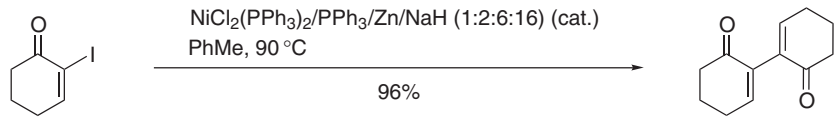
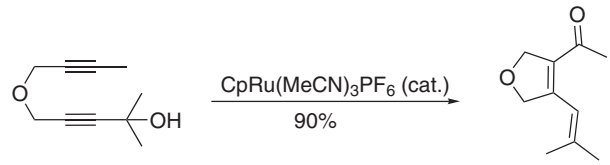


(51)

3.05.1.2.3 By isomerizations of double and triple bonds

A number of transition metal catalysts have been employed to isomerize alkynic ketones to α,β-unsaturated ketones. Allenic ketones also isomerize, and the double bonds of nonconjugated dieneones often migrate to the thermodynamically preferred conjugated isomers. The diene usually adopts an (*E*),(*E*)-geometry <1995COFGT(3)205>. Propargylic alcohols bearing another, tethered alkyne group undergo a cyclization reaction in the presence of a ruthenium catalyst, to produce α,β,γ,δ-unsaturated ketones in good yields (Equation (52)) <2002JA4178>.



(52)

3.05.1.2.4 From oxidations of further unsaturated allylic alcohols

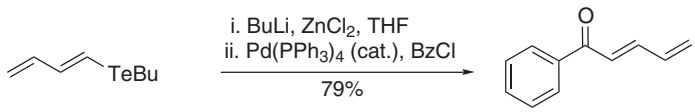
Allylic alcohols bearing further unsaturation may be oxidized by a number of reagents, as above, for allylic alcohols without further unsaturation. The reaction sometimes proceeds with an allylic rearrangement, if a tertiary allylic alcohol is used <1995COFGT(3)205>.

3.05.1.2.5 From reactions of further unsaturated α,β-unsaturated acids and their equivalents with carbon nucleophiles

α,β,γ,δ-Unsaturated carboxylic acid derivatives are susceptible to nucleophilic carbonyl attack by carbon nucleophiles <1995COFGT(3)205>. No significant developments of this reaction have been noted since the publication of COFGT (1995).

3.05.1.2.6 By Friedel–Crafts acylations of dienes

Further unsaturated α,β-unsaturated ketones can be prepared by the reaction of acid chlorides, or their equivalents, with conjugated dienes. Unsurprisingly, electron-rich dienes are commonly used <1995COFGT(3)205>. Vinyltelluroethers are acylated, effecting an overall substitution (Equation (53)) <1998TL1945>. The 1,4-addition of an alkene to an enone has been catalyzed by BF_3 (Equation (54)) <1997JOC2658>.



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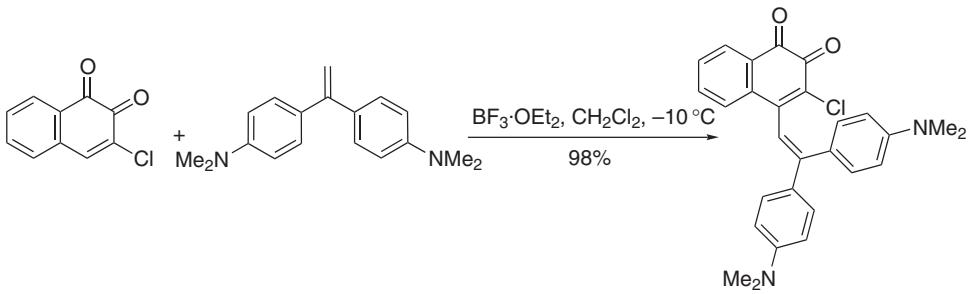
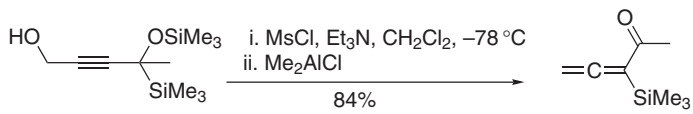


(54)

3.05.1.2.7 α-Allenic ketones

α-Allenic ketones are accessible via acylation of propargylic silanes or addition of Grignard reagents to protected β-alkynones <1995COFGT(3)205>. α-Trimethylsilyl-α-allenic ketones can be prepared in a two-stage sequence from a propargylic alcohol (Equation (55)) <1994TL2291>. Chlorine can also serve as the leaving group in place of the mesylate <1996SC803>. The acylation of enynes can produce α-allenic ketones (Equation (56)) <1995TL2459, 1996JOC6678> although β-halo-α,β-unsaturated ketones are often significant by-products. Elimination from enol phosphates provides another route to α-allenic ketones (Equation (57)) <1996JOC6096> as do Wittig reactions with ketene equivalents (Equation (58)) <1999SL1237>. Propargyl bromides react with acyl cyanides in an indium-mediated reaction (Equation (59)) <2001TL7287>.



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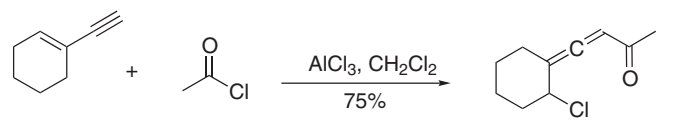

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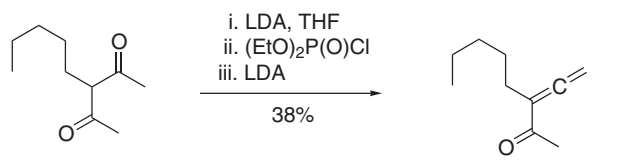

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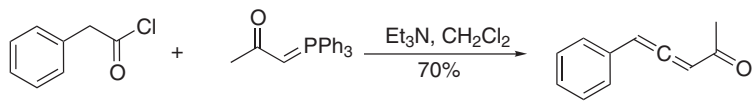

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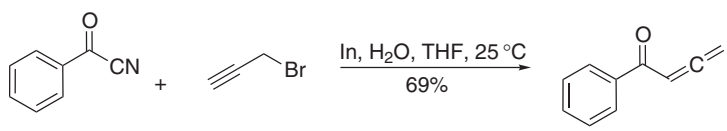


(59)

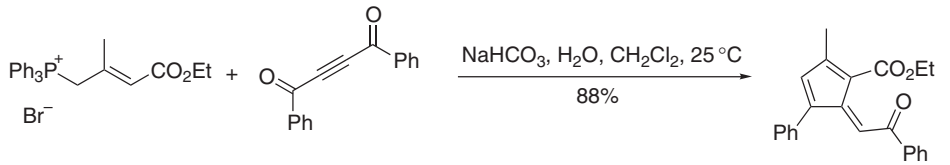
3.05.1.2.8 By aldol condensation reactions

The aldol reaction provides a general route to α,β-unsaturated ketones with further unsaturation. Usually, an unsaturated aldehyde reacts with a ketone under basic conditions. Robinson-type annelation reactions are commonly employed to provide access to dienones <1995COFGT(3)205,

1997T15711, 1998TL375, 1998T5623>. 2-Thio-substituted ynenones were prepared by condensation of an enol ether with the alkynyl aldehyde <1999JOC5162>. DBU was chosen as a base in the synthesis of a (*Z*),(*Z*),(*Z*)-trienone <1999SL1951>.

3.05.1.2.9 By Wittig reactions

The Wittig and related reactions are normally used routes to prepare α,β,γ,δ-unsaturated ketones <1995COFGT(3)205>. Potassium hexamethyldisilazide was used to good effect as a base in this reaction to produce (*Z*)-conjugated alkenes <1999TL6725>. Predominantly (*Z*)-geometry was observed in a Wittig reaction in the ionic solvent 1-butyl-3-methylimidazolium tetrafluoroborate. The solvent is both reusable and facilitates separation from triphenylphosphine oxide <2000CC2195>. [3 + 2]-Cycloaddition between a phosphonium salt and an alkynyl diketone was followed by a Wittig reaction. The sequence led to functionalized fulvenes (Equation (60)) <1996CL71, 1997JOC6529>. A Peterson olefination was employed to ensure the (*Z*)-geometry in the newly formed double bond of α′,β′-unsaturated enaminones (Equation (61)) <1997T2585>.



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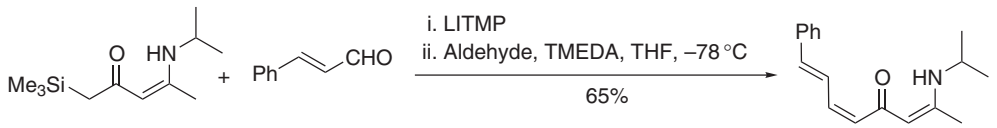


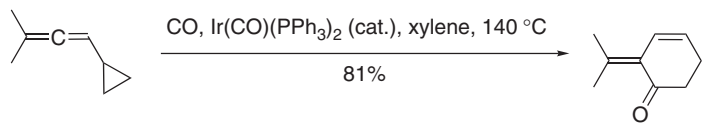
(61)

3.05.1.2.10 From pyrylium salts

Pyrylium salts can be ring-opened with a range of nucleophiles to provide access to substituted dienones. Electrocyclic ring opening of dihydropyrans can also serve as a route to α,β-unsaturated ketones with further unsaturation <1995COFGT(3)205>. No further developments of this reaction have been noted since publication of COFGT (1995).

3.05.1.2.11 From cyclopropanes

Ring-opening reactions and isomerizations of cyclopropane-containing molecules provide a number of routes to α,β-unsaturated ketones. Addition of an α-ketocarbene to a furan, followed by electrocyclic ring-opening of the resultant cyclopropane, provides an efficient route to doubly unsaturated 1,6-keto aldehydes <1995COFGT(3)205>. Dimethyallenylcyclopropane undergoes a carbonylation reaction, with an iridium catalyst (Equation (62)) <1998JOC4>. A cyclopropane-substituted chromium alkylidine complex reacted with a propargylic ester to produce a cyclopentenone with two exocyclic double bonds <2000T4985>.

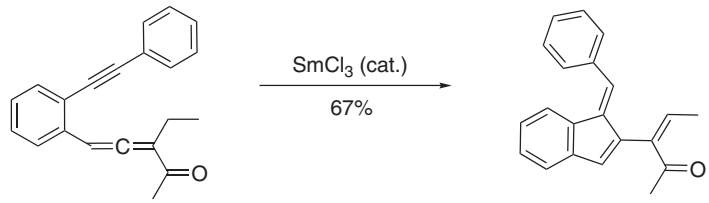


(62)

3.05.1.2.12 By Claisen rearrangements

The Claisen rearrangement normally produces γ,δ-unsaturated aldehydes or ketones from allyl, vinyl ethers. To produce α,β-unsaturated ketones with further unsaturation, either a propargylic ether is employed, or a group that is readily eliminated is incorporated into the unsaturated ether

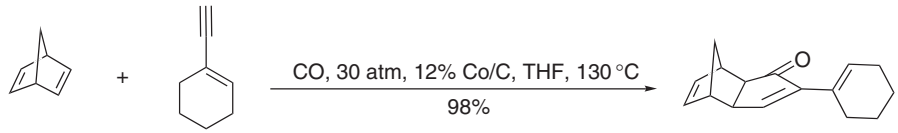
<1995COFGT(3)205, 1994JCS(P1)1749>. The isomerization of propargyl, vinyl ethers has been used to prepare a range of halogenated dienones <2003T4641>. Alkyne, allenes undergo an intramolecular ene rearrangement (Equation (63)) <1998T13751>.



(63)

3.05.1.2.13 Carbonylation reactions

Dienes can be acylated with carbon monoxide and an alkylating agent in the presence of an iron, cobalt, or nickel catalyst <1995COFGT(3)205>. Pauson–Khand reactions between enynes, carbon monoxide, and an alkene can give rise to cyclopentenones with further unsaturation. Cobalt on charcoal served as a recyclable heterogeneous catalyst for this reaction (Equation (64)) <2000AG(E)4158>. Enediynes reacted to form fused 5,7,5-tricyclic ring systems in the presence of a rhodium carbonyl catalyst (Equation (65)) <2000JA2385>.



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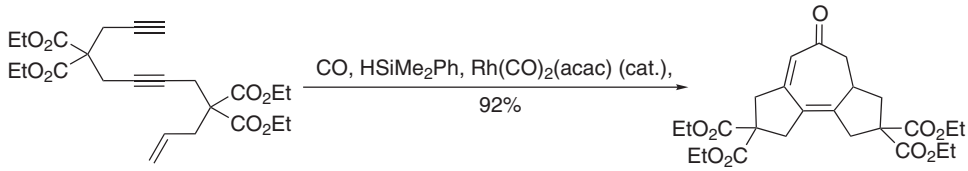
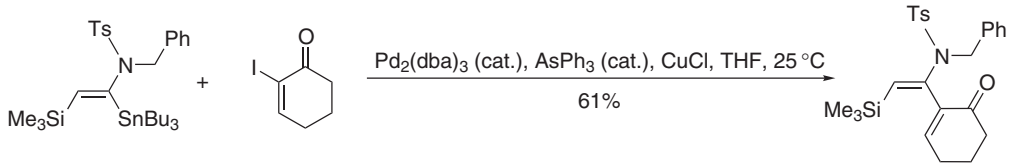


(65)

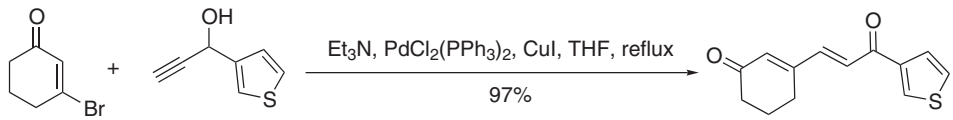
3.05.1.2.14 Miscellaneous methods

Palladium and other metals facilitate the coupling of vinyl halides with enseones to give dienones <1995COFGT(3)205>. Vinyl sulfonate esters (enol triflates) react analogously <1998SL1059>. This reaction has also been performed in supercritical carbon dioxide <1999SL345>. Stille coupling of an α-iodoenone with a vinyltin reagent led to functionalized enamides (Equation (66)) <2002MI1637>.



(66)

Terminal alkynes can be coupled to an enone to provide dienones, via an alkenylborane <1996SC2503>. Propargylic alcohols couple to haloenones to give *trans*-dienediones (Equation (67)) <2000AG(E)1253>. 1,6-Addition of an alkyllithium to aromatic ketones gave 2-acylcyclohexadienes (Equation (68)) <1995JA9091>. Alkynylcarbene complexes react with acetylacetone, followed by an enamine, to give cyclohexadiene products (Equation (69)) <1996JA10853>.



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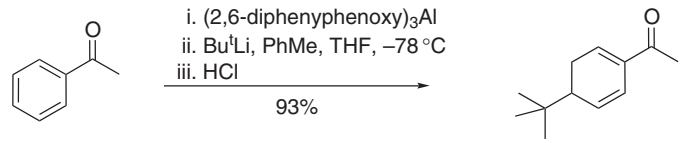

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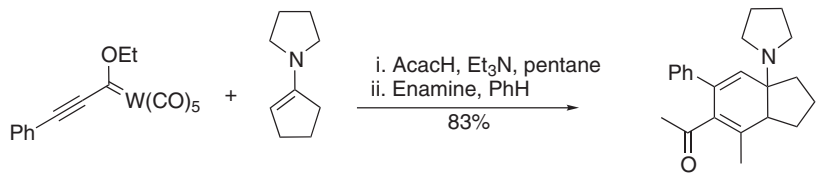
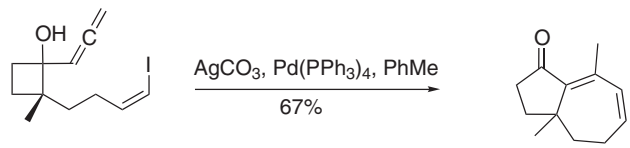


(69)

Ring opening of keto-substituted cyclobutenones provides access to α,β,γ,δ-unsaturated ketones <1995COFGT(3)205, 1998TL6343>. Allenyl cyclobutanols bearing a terminal vinyl iodide undergo a palladium-catalyzed cascade reaction to afford cyclopentanones fused to medium-ring dienes (Equation (70)) <1997JOC6450>. Alkynyl cyclobutanols also ring expand and couple with vinyl iodides to give 2-alkylidenecyclopentanones (Equation (71)) <2000OL3325>. α-Alkynyl cyclopentenones are accessible via an intramolecular rhodium-catalyzed acylation reaction of dialkynyl aldehydes (Equation (72)) <2001JA11492>. Free-radical intermolecular addition to a furan resulted in the formation of a dienone (Equation (73)) <1994SL721>.



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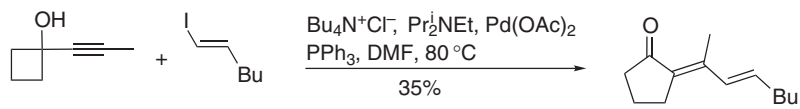

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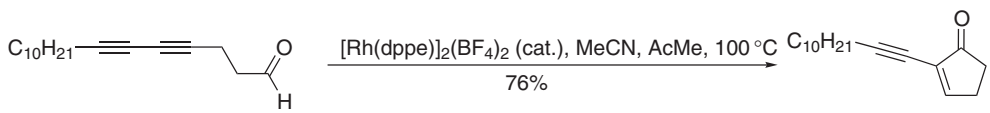
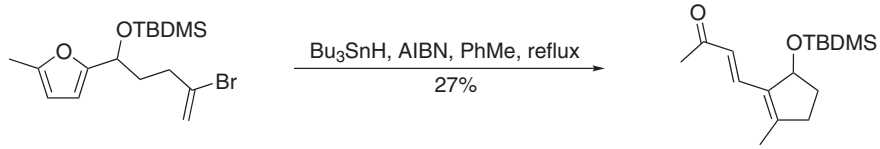


(72)



(73)

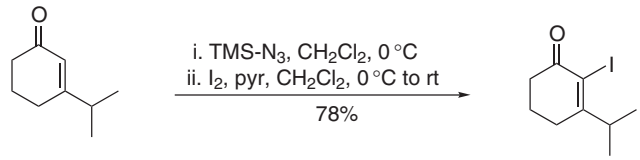
3.05.1.3 Halogenated α,β-Unsaturated Ketones

3.05.1.3.1 2-Halogenated α,β-unsaturated ketones

(i) By elimination reactions

Elimination of hydrogen halide from α,α- or α,β-dihaloketones furnishes 2-halo-α,β-unsaturated ketones in good yields <1995COFGT(3)205, 1996TL2377>. Harsher conditions are required in the case of elimination from α,α-dibromoketones. A variety of reagents such as interhalogen compounds can be used in addition–elimination sequences <1995COFGT(3)205>. The α,β-epoxyketone can be used in a sequence involving ring-opening by halide ion <1995COFGT(3)205> or TMS-halide

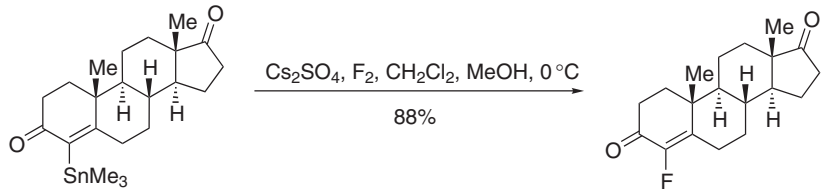
<1995SC2355>, followed by elimination to give the halogenated α,β-unsaturated ketone. Fluorine can be introduced at the 2-position by dehydrofluorinaton of a vicinal difluoroketone <1997T647>. α-Fluoro-α,β-unsaturated ketones can be prepared from trifluoromethyl ketones, in a multistep reaction. In the first stage, the ketone is converted into a silyl enol ether, and then reacted with an aldehyde. Finally, by once again forming a silyl enol ether and eliminating, the (*Z*)-fluoroenone is formed <2002TL6099>. Iodine may be introduced efficiently to α,β-unsaturated ketones, following initial reaction with TMS azide (Equation (74)) <1995TL6927, 1995TL9141, 1997SL968>. Vinyl silanes are also precursors to iodoenones <1999TL3839> and the reactions proceed with some control of stereochemistry.



(74)

(ii) Miscellaneous methods

α-Haloenones can be prepared via cyclopropanation of silyl enol ethers, using dihalocarbenes followed by ring-opening. Wittig-type reactions can be used to prepare α,β-unsaturated ketones <1995COFGT(3)205, 2003SC757>. A number of metallated alkenes on reaction with carboxylic acid derivatives provide α,β-unsaturated ketones. α-Hydroxy-α,β-unsaturated ketones can be converted into the α-halo compound <1995COFGT(3)205>. α-Fluoro-α,β-unsaturated ketones are accessible via the vinylstannane by reaction with caesium fluoroxysulfate (Equation (75)) <1995JCS(P1)2965>, or from vinylsilanes and aldehydes (Equation (76)) <2000TL971>. Palladium catalysis is used to couple (*E*) and (*Z*)-vinylstannanes with acid chlorides to give fluoroenones under mild conditions, preserving the alkene geometry (Equation (77)) <1999JOC3476>. α-Iodoenones can be prepared by addition of iodine to the α,β-unsaturated ketone, in the presence of a peroxydisulfate salt. The reaction appears to follow a radical pathway (Equation (78)) <1997CC1355>.



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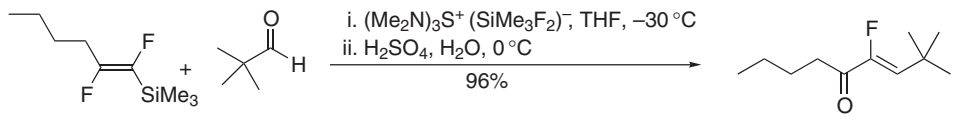

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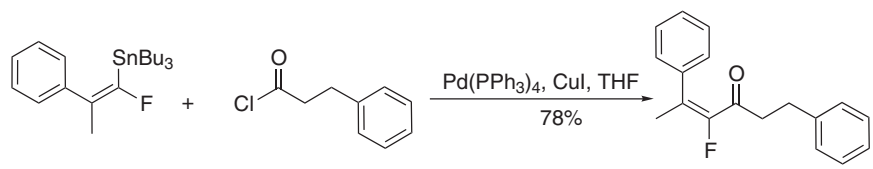

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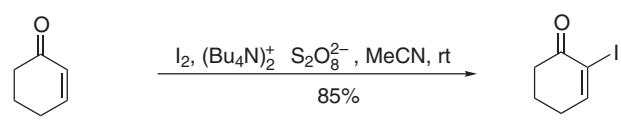
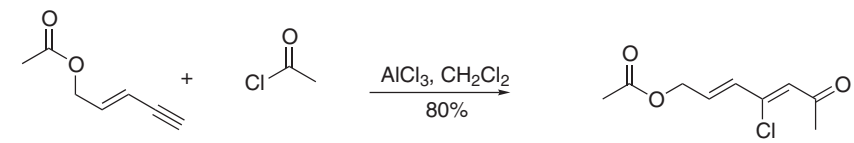


(78)

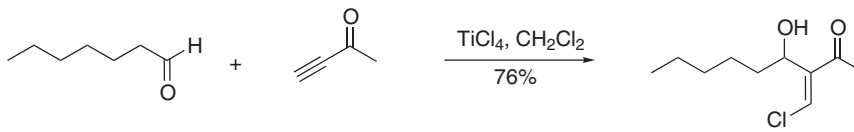
3.05.1.3.2 3-Halogenated α,β-unsaturated ketones

(i) From alkynes

The reaction of acid halides with alkynes is commonly employed to prepare β-halo-α,β-unsaturated ketones <1995COFGT(3)205>. Similarly dienones can be prepared (Equation (79)) <1995TL2459>. The reaction of aldehydes with alkynic ketones gives (*E*)-β-chloro enones when $TiCl_4$ is used as a Lewis acid and chlorine source (Equation (80)) <2000T2397>. Dimethyl sulfide acts as a catalyst for this reaction <2000AG(E)2358>. Similarly, 3-bromo-substituted α,β-unsaturated ketones have been prepared via a Baylis–Hillman-type reaction, using titanium tetrabromide addition to alkenyl ketones. The (*E*)-isomer is formed preferentially <2002SC1765>. The addition of HX to an alkenyl ketone also affords β-halo-substituted α,β-unsaturated ketones <1995COFGT(3)205>.



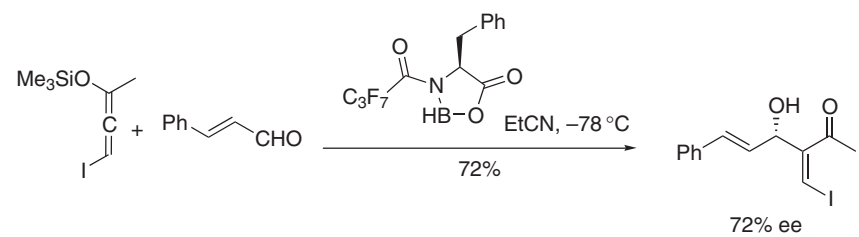
(79)



(80)

(ii) From allenes

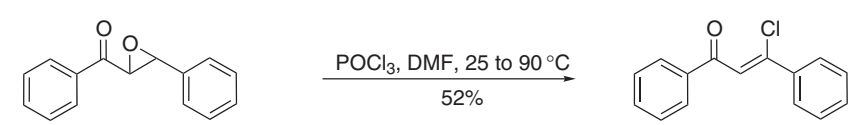
The addition of HCl to allenes can be used to prepare (*E*)-isomers of β-chloro-α,β-unsaturated ketones <1995COFGT(3)205>. An iodinated silyl allenol ether reacts with aldehydes to form adducts with good enantioselectively (69–98% ee) (Equation (81)) <2001OL823>.



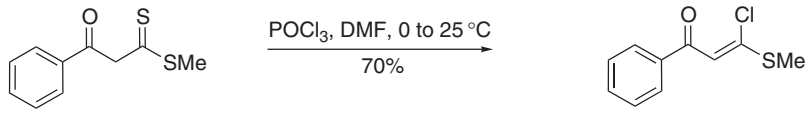
(81)

(iii) By halogenations of 1,3-dicarbonyl compounds

A wide range of reagents can be employed to prepare β-halo-α,β-unsaturated ketones from the corresponding 1,3-dicarbonyl compounds, often with good yields for symmetric diketones. The lack of selectivity in asymmetric diketones leads to mixtures <1995COFGT(3)205>. Treatment of α-epoxy chalcones with $POCl_3$/DMF gave a modest yield of the β-chloroenones (Equation (82)) <1995TL7287>. β-Ketodithioesters react with the same reagents to afford highly functionalized unsaturated ketones (Equation (83)) <1996SC847>. The treatment of 1,3-diketones with CBr_4 under reducing conditions, gave β-bromo-α,β-unsaturated ketones <1997JOC7061>. The use of CCl_4 resulted in lower yields and reduced selectivity for the (*E*)-isomer.



(82)



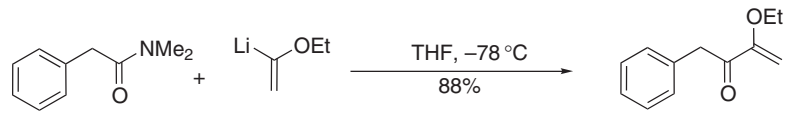
(83)

3.05.1.4 Oxygen-substituted α,β-Unsaturated Ketones

3.05.1.4.1 2-Oxygen-substituted α,β-unsaturated ketones

(i) From α-metallated enol ethers and acylating agents

The reaction of an acid chloride with a vinyltin reagent, in the presence of palladium, affords 2-alkoxy-α,β-unsaturated ketones. Similar products can be prepared from vinyllithiums and vinyl silanes <1995COFGT(3)205>. Improved yields were obtained using tetrahydropyran for lithiation of enol ethers prior to reaction with amides, in the synthesis of α-alkoxy-α,β-unsaturated ketones (Equation (84)) <1994TL7727>. Ultrasound ()))))) has been employed to achieve the acylation of a vinyllithium with the lithium salt of a carboxylic acid (Equation (85)) <1995JOC8>.



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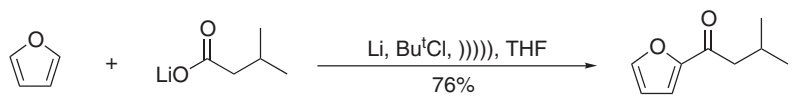
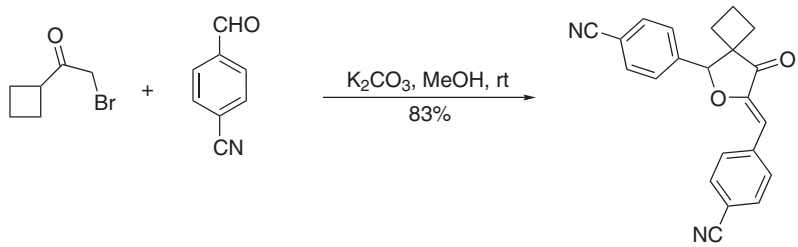


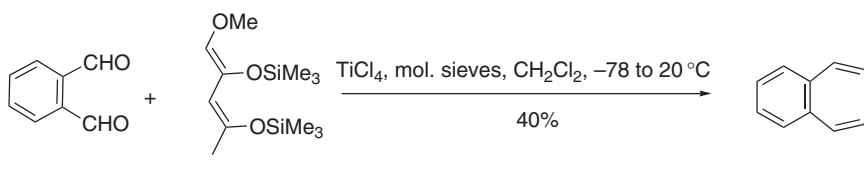
(85)

(ii) From α-alkoxyketones and a carbonyl compound

α-Alkoxyketones take part in condensation reactions with aldehydes and ketones to permit access to a range of α,β-unsaturated ketones, under both acidic and basic conditions <1995COFGT(3)205>. α-Alkoxy ketones react similarly with nitriles, using sodium ethoxide as a base in boiling ethanol <1995M945>. Two equivalents of an aryl aldehyde condense with an α-bromo ketone in a reaction believed to proceed via an epoxide (Equation (86)) <1994TL9367>. An α-alkoxy-tropolone was prepared from the double reaction of a silyl enol ether with phthaldehyde (Equation (87)) <2001SL526>.



(86)



(87)

(iii) From oxidative cyclizations of hydroxy-substituted vinyl ketones

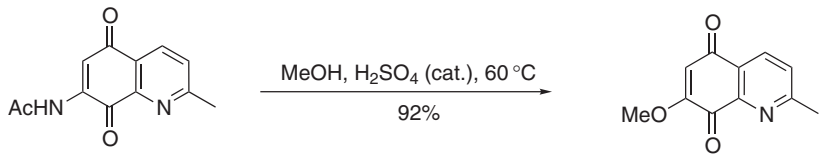
Aurones can be prepared from chalcones bearing a hydroxy function *ortho* to the carbonyl, the ring closure being catalyzed by a variety of soft metal salts <1995COFGT(3)205, 1995JOC6499>.

(iv) By elimination reactions from α-alkoxy-substituted ketones

Eliminations from suitably substituted ketones provide a route to α-alkoxy ketones <1995COFGT(3)205>. A range of phenols add to cyclohexenone oxide, followed by elimination of water, in a reaction performed using ultrasound <1995TL7363>.

(v) From α,β-unsaturated ketones

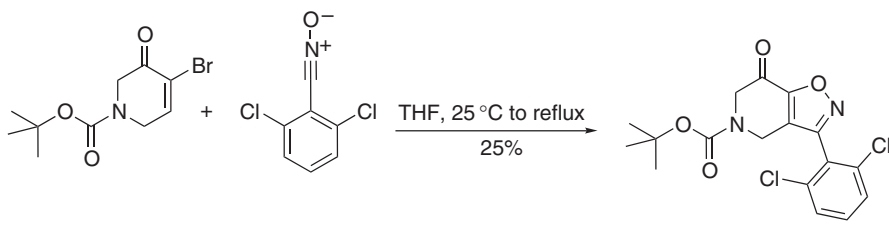
Hydrazones derived from α,β-unsaturated ketones can be β-brominated and α-alkoxylated. Elimination with base and regeneration of the ketone effects the overall conversion of enone into α-alkoxyenone <1995COFGT(3)205, 1994JOC6026>. Manganese triacetate serves as a mild oxidizing agent to regenerate the ketones <1997TL7267>. Amide groups have been replaced by alkoxy groups in quinoline-5,8-diones (Equation (88)) <1998JOC343>. Ruthenium-catalysis was employed to oxidize α,β-unsaturated ketones to α,β-dihydroxy-α,β-unsaturated ketones <1998TL7691>.



(88)

(vi) Miscellaneous methods

1,2-Addition of a Grignard reagent to an α-alkoxyacrylonitrile gives substituted ketones on acid work-up <1995COFGT(3)205>. α-Alkoxycyclopentenones have been prepared from an ester and an allylic ether bearing a benzotriazole substituent <1995JOC7605>. [3 + 2]-Cycloaddition reactions of nitrile *N*-oxides with vinyl bromides, followed by elimination, give rise to isoxazoles (Equation (89)) <1994TL3589>. Isoxazoles, fused to quinones, were prepared in a radical reaction <1999T11229>. Thermal ring expansion of a cyclobutenone bearing a dithiane substituent produced a cyclopentenedione (Equation (90)) <1995JOC735>. Similar cyclobutenones bearing allene groups underwent ring-expansion, followed by oxidation to permit access to highly oxidized quinones <1996JOC329>. Yet another ring expansion from a cyclobutenone led to a silylated 2-alkylidene-4-alkoxy-1,3-cyclopentenedione <1997JOC1292>. The presence of exocyclic diazoester functionality permits a further ring expansion to a diazapinedione (Equation (91)) <1999JOC707>. Fischer-carbene complexes undergo photochemical conversion into (*E*)-2-butene-1,4-diones (Equation (92)) <1995OM1461>. The Pauson–Khand reaction, using enol ethers as substrates, gives rise to α-alkoxy-cyclopentenones <1999OL1187>. An α-hydroxycyclopentenone was the product of reaction between an α-allenic amide and a vinyllithium reagent (Equation (93)). Here, the stereochemistry of the allene was transferred to the tetrahedral carbon <1999JA9895>. A related reaction, using an electron-rich chiral allene with an α,β-unsaturated amide, has also been described <2000OL2447>.



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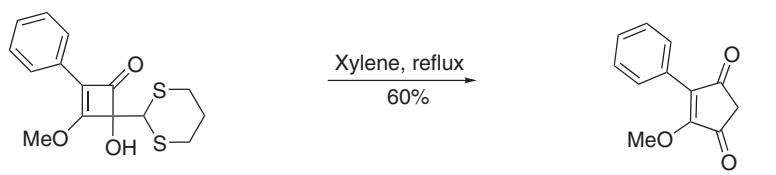

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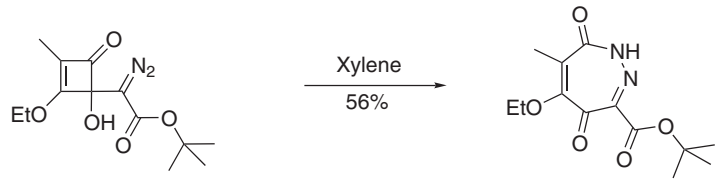

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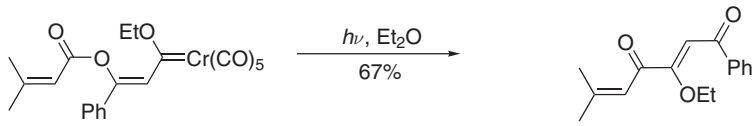
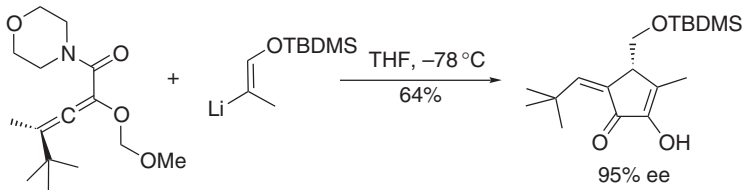
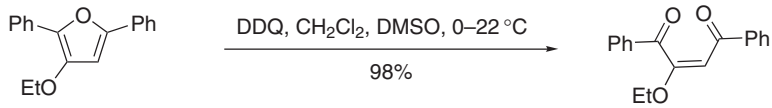


(92)



(93)

A number of oxidizing reagents have been used to effect the conversion of phenols and anisoles into quinones. A recent example is the use of 2,6-dichloropyridine-*N*-oxide, catalyzed by a ruthenium porphyrin complex <1995JA8879>. Furans can be oxidatively ring-opened to give *cis*-enediones (Equation (94)) <1996H1371>. Furfural condenses with ethyl diazoacetate, in the presence of a zeolite catalyst, to furnish the β-keto ester <1996SL369>. Diels–Alder reactions of *ortho*-quinones, generated *in situ* by electrochemical oxidation, afforded bicyclic adducts. The reaction was found to be accelerated by the presence of surfactants in aqueous solutions (Equation (95)) <1997CC1403>. An α,β-unsaturated ketone, with the alkene as part of a dihydropyran, was prepared via an isomerization of a tertiary allylic alcohol to a ketone (Equation (96)) <2000OL663>. The photooxidation of furans in air can be used to prepare hydroxy diones <2001T6003>.



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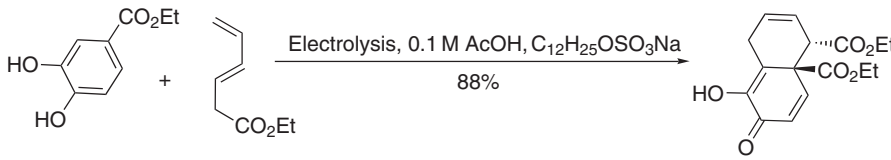

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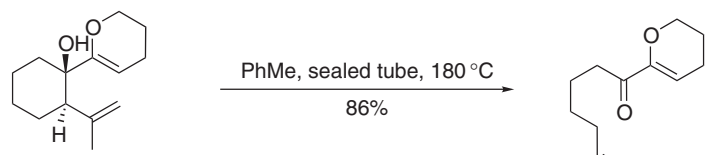


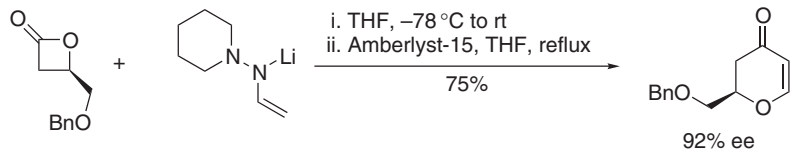
(96)

3.05.1.4.2 3-Oxygen-substituted α,β-unsaturated ketones

(i) By Diels–Alder reactions

Hetero-Diels–Alder reactions are commonly used to form dihydro-γ-pyrones, which proceed with the expected regio- and stereochemical outcomes <1995COFGT(3)205>. This reaction continues to be widely used, with a range of Lewis acid catalysts, and often with chiral auxiliaries <2001JA5366>. The use of both a chiral aldehyde and a chiral catalyst, resulted in very high

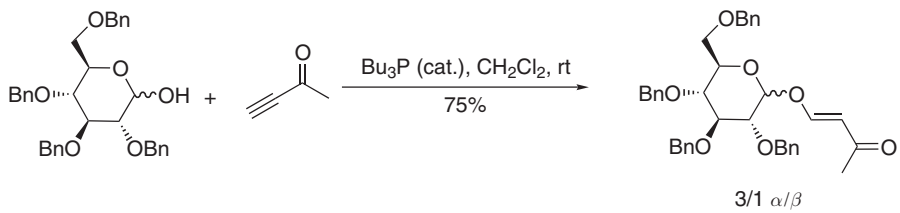
enantiomeric excesses being achieved <2002OL1795>. An alternative route to enantiomerically enriched dihydropyrones is the insertion of ethene into the acyl-C—O bond of chiral β-lactones (Equation (97)) <2002OL1823>.



(97)

(ii) From alkynes

The addition of an alcohol to an alkynyl ketone gives rise to 3-alkoxy-α,β-unsaturated ketones (Equation (98)) <1995COFGT(3)205, 1999TL1531>.



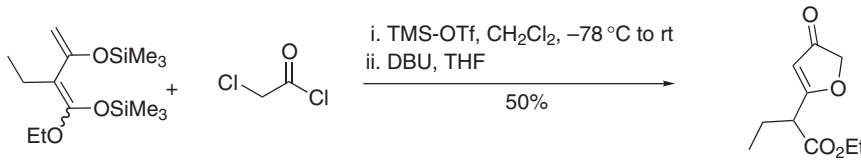
(98)

(iii) By Wittig reactions

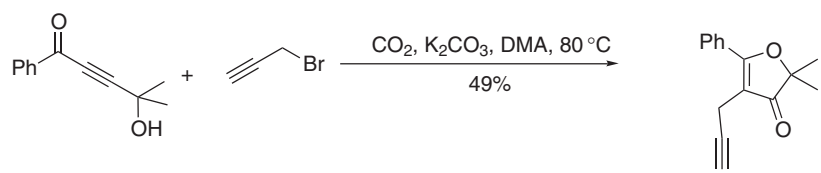
Oxygenated phosphoranes and β-keto-phosphonates can be used as substrates in Wittig-type reactions <1995COFGT(3)205>. No further developments of this reaction have been noted since the publication of COFGT (1995).

(iv) Preparation of 3(2H)-furanones

Functionalized 3(2*H*)-furanones can be made by reactions of 1,3-bis(trimethylsiloxy)buta-1,3-dienes with α-chlorocarboxylic acid chlorides (Equation (99)) <2000CC967>. 2,2,4,5-Tetrasubstituted furan-3(2*H*)-ones can be prepared from unsymmetrical alkynyl ketones in the presence of carbon dioxide (Equation (100)) <1996S1431>. Benzenesulfenyl chloride adds to conjugated silyl oxy-enones followed by cyclization, oxidation of sulfur, and elimination to give dihydrofuran-3(2*H*)-ones <1997JCS(P1)1267>. The reaction of triallyl orthoformate with ethyl diazoacetoacetate provides another route to functionalized furanones <1998TL8813>.



(99)



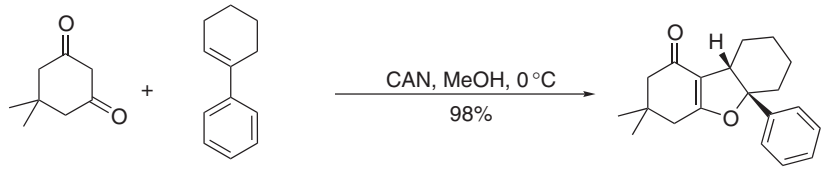
(100)

(v) By acylations of vinyl ethers

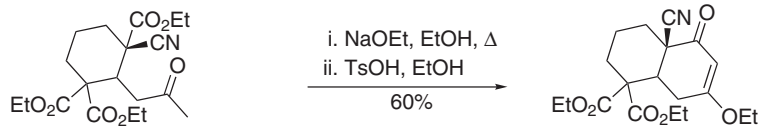
Enol ethers may be acylated (usually using Pd catalysis) to give 3-alkoxy-α,β-unsaturated ketones <1995COFGT(3)205>. No further developments of this reaction have been noted since the publication of COFGT (1995).

(vi) From 1,3-dicarbonyl compounds

β-Ketoesters react with 1,2- and 1,3-dielectrophiles to give furan-3-ones and dihydropyranones, respectively <1995COFGT(3)205>. 1,3-Diketones add oxidatively to alkenes in a reaction mediated by CAN, to give dihydrofurans (Equation (101)) <1995JCS(P1)187>. Manganese triacetate can also be used as the oxidant <2001H171>. Condensation reactions to prepare 1,3-diketones, followed by acid-catalyzed reaction with alcohols give rise to β-alkoxy-α,β-unsaturated ketones (Equation (102)) <1999JOC340>. The enol tautomer of a 1,3-diketone can be converted into an enol ether using 2-chloro-1,3-dimethylimidazolinium chloride (Equation (103)) <1999JOC6984>. Titanium tetrachloride acts as a Lewis acid and dehydrating agent in the preparation of β-keto enol ethers from 1,3 diketones <2001T217>. Stabilized carbon nucleophiles, including 1,3-diketones, undergo reactions with 2-chloroallyl acetates in the presence of a platinum catalyst to give furan derivatives bearing acyl substituents in the 3-position <1999JOC7523>. Medium and large cyclic vinyl sulfides react with 1,3-dicarbonyl compounds in the presence of silver carbonate on Celite (Fetizon's reagent) to form fused furan derivatives <2000OL1387>. Dihydrofurans are readily prepared by base-catalyzed cyclization of 2-alkenyl substituted 1,3-dicarbonyl compounds, following epoxidation by dimethyl dioxirane <2000TL10127>. Other routes to 3-acyldihydrofurans from 1,3-diketones have been described <1995JCS(P1)187, 1995JOC856, 1995HCA947, 1997TL2095, 2000S1091, 2001OL2717>. 3-Acyldihydropyrans are accessible from 2-allyl-1,3-diketones, in a palladium-catalyzed cyclization with vinyl halides <1998SL888>. A 1,4-dihydropyridine derivative was employed to reduce an enone followed by *o*-alkylation to form a cyclic ether (Equation (104)).



(101)



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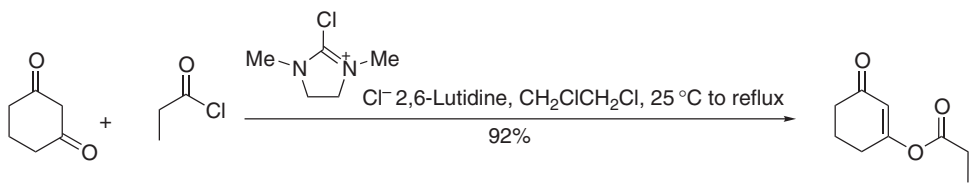

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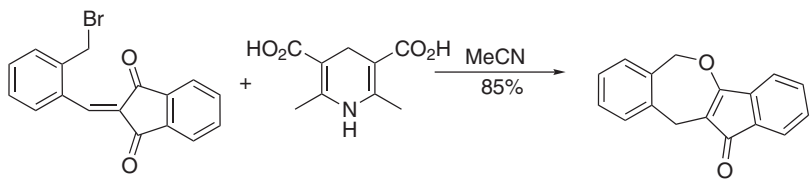
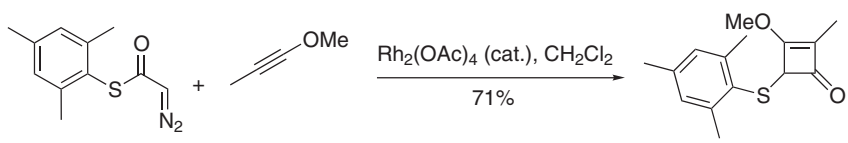


(104)

(vii) From [2+2]-cycloaddition reactions between alkoxyalkynes and ketenes

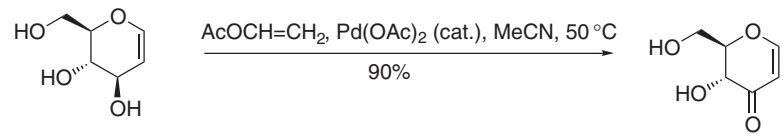
Treatment of α-diazo thioesters with rhodium acetate promotes a facile thia-Wolff rearrangement to prepare thio-substituted ketenes, which undergo cycloaddition reactions with alkoxyalkynes to afford 3-alkoxycyclobutenones (Equation (105)) <2000JOC4375>.



(105)

(viii) Miscellaneous methods

An addition–elimination sequence, with an oxygen nucleophile, can be used to displace a leaving group from a 3-substituted enone <1995COFGT(3)205>. The reaction of 3-fluorocyclopentenones with alcohols in the presence of trifluoromethanesulfonic acid results in overall substitution of fluorine by an alkoxy group <2001OL2345>. Uloses may be prepared by palladium-catalyzed oxidation of the corresponding allylic alcohols. Vinyl acetate is included in the reaction to accept the transferred hydrogen. In the absence of a sacrificial alkene, disproportionation is seen (Equation (106)) <1999T8331, 1999S1869>. Similar products are obtained on oxidation of protected glycols by hypervalent iodine reagents <1995JOC1228>. Dihydropyranones can be formed, by dehydrogenation of silyl enol ethers prepared from a hetero-Diels–Alder reaction, with CAN <1996JOC7600>. An alternative, stereospecific synthesis of 2,3-dihydro-4*H*-pyran-4-ones involves a mercury-catalyzed rearrangement of 1-alkynyl-2,3-epoxy alcohols <1998JOC3798>. Lewis acids catalyze the elimination of the diazo group in 3-diazochromanones to produce chromones <1998JCR(S)88>. Thioketones are converted into ketones in a solvent-free reaction using a clay-supported catalyst and microwave irradiation (Equation (107)) <1999SC1333>. The reaction between alkynes and cyclopropylcarbene chromium complexes resulted in stereocontrolled synthesis of five-membered rings fused to oxygen heterocycles <1999JOC1291, 2000T4985>. Other chromium alkylidine complexes react with substituted alkynes to give simple 3-alkoxycyclopentenones <1995SL812>. With ylides, similar cobalt–carbene complexes react to give 3-alkoxy-α,β-unsaturated ketones with reasonable stereospecificity (Equation (108)) <1996OM4612>. Benzil derivatives undergo a reaction with a bismuthonium salt to produce *O*-aroyl enolates as a mixture of isomers (Equation (109)). Under similar conditions ortho-quinones undergo a ring expansion to form hydroxytropinones (Equation (110)) <1999JCS(P1)1533, 1996CC2697>. A ring enlargement of γ-lactones, on reaction with propargylmagnesium bromide, resulted in formation of a cyclic enol ether (Equation (111)). The reaction proceeds via an α-allenic ketone <1996CC19>.



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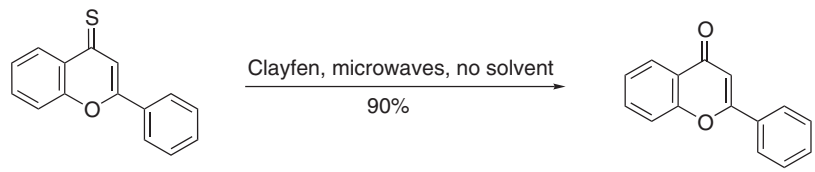

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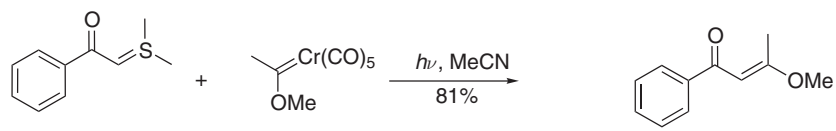

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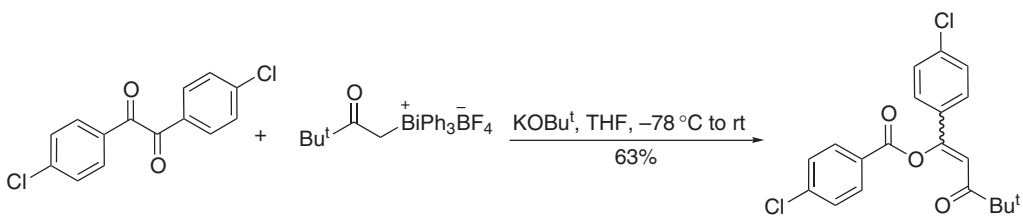

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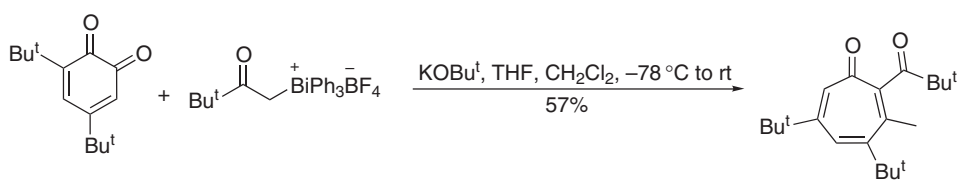

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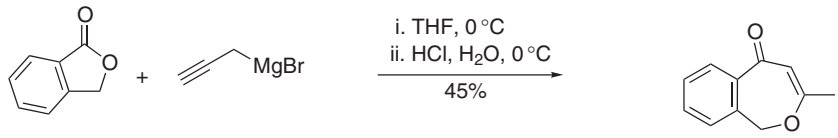


(111)

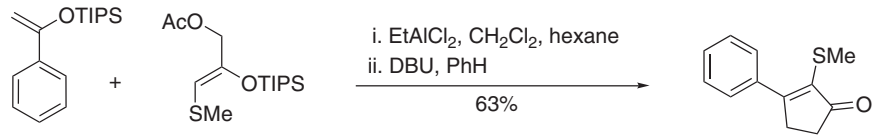
3.05.1.5 α,β-Alkenic Ketones with Sulfur-based Substituents

3.05.1.5.1 2-Thio α,β-unsaturated ketones

(i) By aldol condensation reactions

2-Thioketones condense with aldehydes in the most common preparation of 2-thio-α,β-unsaturated ketones. 2-Thioketones can be deprotonated with strong base, and then reacted with acid halides forming 2-thio-α,β-unsaturated ketones. β-Ketosulfones also undergo aldol-type condensations to afford vinyl sulfones <1995COFGT(3)205>.

2-Thioketones react with isothiocyanates in the presence of methyl iodide and sodium hydride to form 2,3-dithiosubstituted-α,β-unsaturated ketones <1995JPR29>. Cyclopentenones bearing 2-thioethers were prepared from a silyl enol ether in a [3 + 2]-annulation with an α-(methylthio)silyl enol ether (Equation (112)) <1998JA1724>. An acid-catalyzed dealkylation of an enol ether completed a synthesis of some perfluoroacyl alkenes (Equation (113)) <1999JOC5162>.



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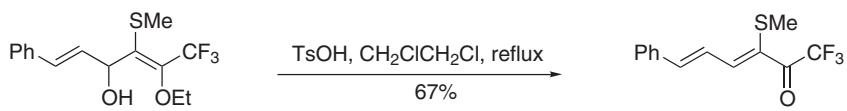


(113)

(ii) By Pummerer reactions

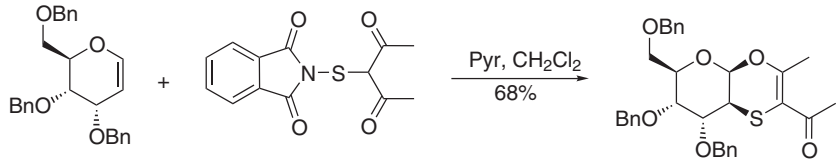
β-Ketosulfoxides undergo an elimination reaction, following *o*-acylation, to furnish 2-thio-α, β-unsaturated ketones <1995COFGT(3)205>.

(iii) Miscellaneous methods

Other methods <1995COFGT(3)205> for the preparation of 2-thio-substituted enones include dehydration of a 3-hydroxy-2-thio-substituted ketone, acylation of lithiated vinyl sulfides and Baylis–Hillman-type addition to a vinyl sulfone, with a tertiary amine and aldehyde, followed by oxidation of the resulting allylic alcohol.

Phthalimide sulfenyl chloride serves as a source of electrophilic sulfur, reacting with 1,3-dicarbonyl compounds and then further reacting with electron-rich alkenes in [4 + 2] reactions to give a variety of heterocyclic products (Equation (114)) <1995JOC6416, 1996AG805, 1998JOC6673, 1999JOC6490>. 2-Thioalkyl phenols can be oxidized to quinoidal systems using potassium hexacyanoferrate as an oxidant. Bromine substituents on quinoidal systems can be replaced by thiols, using copper catalysis, giving hindered thioethers, albeit in poor yield (Equation (115)) <1997JOC7464>. Singlet oxygen served as a dienophile in a reaction with a chiral sulfinylfuran (Equation (116)) <2000TA1183>. The Pauson–Khand reaction has been used to prepare complex fused cyclopentenones with 2-thioether substituents <2000S1009>. A rearrangement reaction of a propargylic xanthate with an acid chloride produced the substituted 1,3-dithiol-2-ones alongside other rearranged products (Equation (117)) <1995SL325>. A Fries rearrangement during the reaction of a

benzothiazinone with an acid chloride resulted in the formation of a new heterocycle (Equation (118)). The reaction proceeds via an *o*-acyl intermediate <1998JHC983>. 2-Aminothiophenols condense with acetyl acetone to give benzthiazines in a microwave-assisted reaction on alumina (Equation (119)) <2001SC711>.



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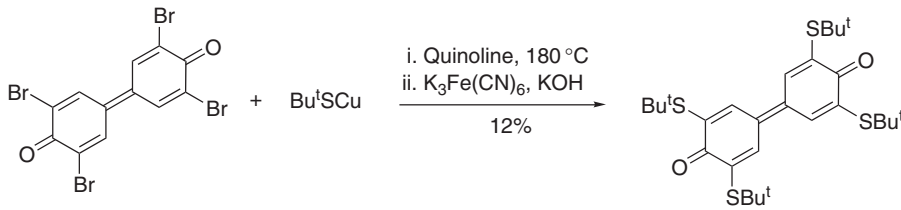

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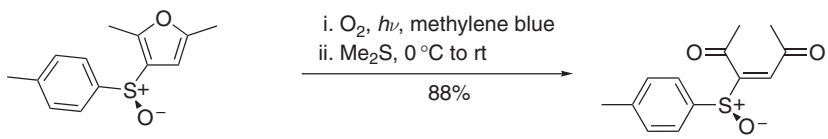

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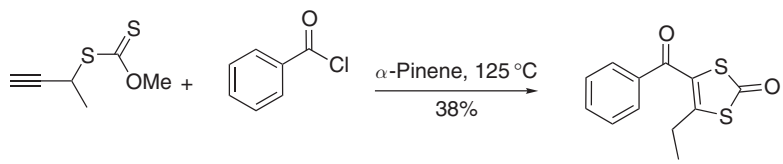

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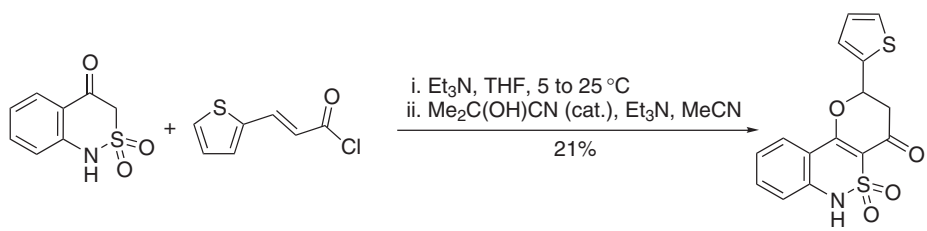
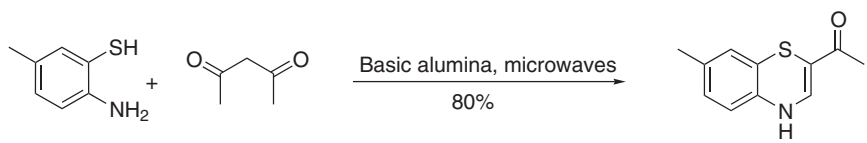


(118)

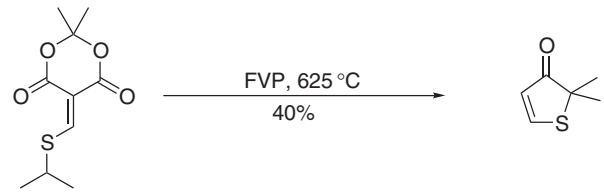


(119)

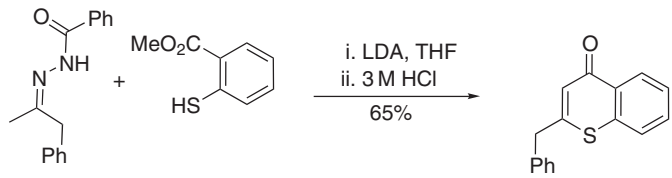
3.05.1.5.2 3-Thio α,β-unsaturated ketones

(i) By condensation reactions

Enolates, often prepared by the action of a hindered base on ketones, attack thiocarbonyl centers. Subsequent alkylation affords α,β-unsaturated ketones <1995COFGT(3)205, 1995SC2449>. Isothiocyanates can be used to give highly functionalized enones <1995JPR29>. Flash vacuum pyrolysis (FVP) of a Meldrum's acid derivative resulted in the formation of substituted thiophen-3(2*H*)-ones (Equation (120)) <1995JCS(P1)1209>. Thiochroman-4-ones are accessible via hydrazones (Equation (121)) <1998JHC45>.



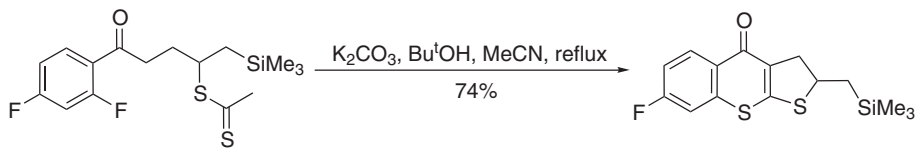
(120)



(121)

(ii) By β-leaving group displacement reactions

Sulfur nucleophiles efficiently replace the halogen in 3-halo-α,β-unsaturated ketones. Suitable nucleophiles include inorganic reagents, as well as thiols and thiophenols <1995COFGT(3)205>. Other leaving groups, e.g., benzotriazole <1996SC3773>, have been utilized, but halogens remain the most common. The reaction of a β-keto dithioester with phosphorus oxychloride permits access to β-chloro-β-alkylthio-α,β-unsaturated ketones <1996SC847>. Both fluorine substituents are easily replaced in a 3,3-difluoroenone using a thiophenolate nucleophile <1994T11637>. Fluorine was displaced in a nucleophilic aromatic substitution reaction to produce thiochromanones (Equation (122)) <1999TL2529>. Sulfur(IV) nucleophiles have been used to replace halogens, to give vinyl sulfones (Equation (123)) <1999S491>. Tetrathiomolybdate serves as a source of the S_2^{2-} nucleophile in a reaction that connects two α,β-unsaturated ketones via a disulfide bridge (Equation (124)) <2000IJC(B)734>.



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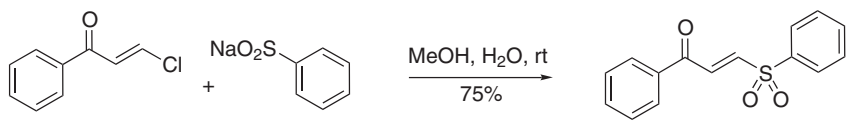

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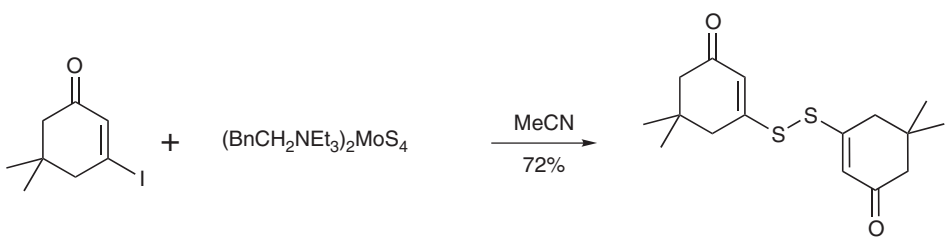
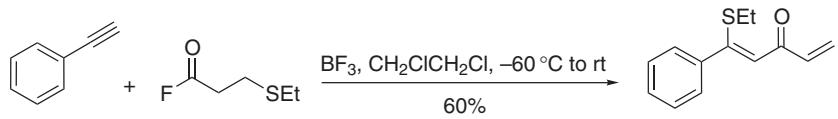


(124)

(iii) From alkynes

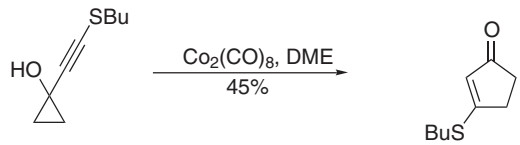
3-Thio-α,β-unsaturated ketones can be prepared by the addition of H–S across the triple bond of alkynic ketones <1995COFGT(3)205>. Radical addition of a thiol has been used to make 3-thiosubstituted indenones <1998T8207>. Electrochemical reduction of thiotosylates, in the presence of nickel complex catalysts, has also been employed to promote addition to alkynes

<1998TL8121>. β-Ethylthiopropionyl tetrafluoroborate, generated *in situ* from the corresponding acyl fluoride and gaseous boron trifluoride, reacts with alkynes to form 1-ethylthiopenta-1, 4-dien-3-ones (Equation (125)). The reaction proceeds through formation of a six-membered cyclic sulfonium salt, and is both regio- and stereospecific <1995SL1133>.



(125)

Chiral acetylenic sulfoxides have been used as substrates in cyclocarbonylation reactions to give rise to cyclopentenones bearing sulfoxide substituents <1995TA665>. 3-Thiosubstituted cyclopentenones have been prepared by rearrangement of alkynylcyclopropanols, in the presence of a cobalt–carbonyl complex (Equation (126)) <1998JA3903>. In a zirconium-mediated reaction, the elements of ethanal add across the triple bond of an alkynyl sulfone (Equation (127)) <1999CC1741>. Alkynamines react in a [2+2]-cycloaddition reaction with arylisothiocyanates to produce thietimines (Equation (128)) <2001SL361>. A [4+2]-cycloaddition reaction employing an ynone as the dienophile has been used to prepare 2*H*-thiopyran-2-thiones <1996BCJ2091>.



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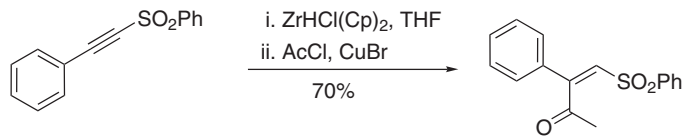

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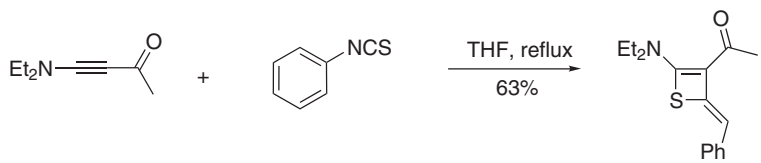


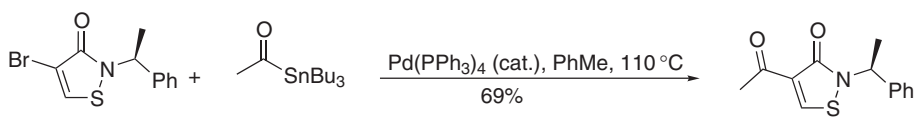
(128)

(iv) From 1,3-dicarbonyl compounds

3-Thio α,β-unsaturated ketones can be prepared from the corresponding 1,3-dicarbonyl compound (or its tautomer) by condensation with a thiol <1995COFGT(3)205>. β-Diketones react with CS_2 and methyl iodide to produce ketene dithioacetals <1999JCR(S)492>.

(v) By acylation reactions

Acylation of vinyl thioethers provides a route to 3-thiosubstituted α,β-unsaturated ketones <1995COFGT(3)205>. Palladium catalysis facilitates the replacement of bromine in the preparation of 1,2-isothiazoline-3-ones (Equation (129)) <1994TL6551>. Vinyl silanes react in the presence of a Lewis acid catalyst with acid chlorides to give enones <1997SL681>.

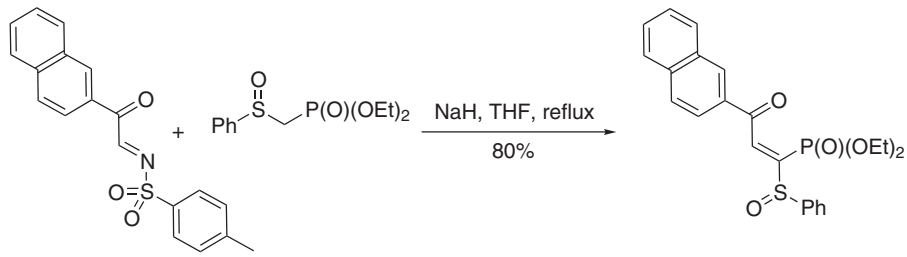


(129)

(vi) By Wittig reactions

Wittig-type reactions can be used to prepare sulfur-substituted enones. The reaction has been successfully employed where the sulfur is α- to phosphorus in the betaine, as well as with thioesters <1995COFGT(3)205, 1998JCS(P1)1389>.

(*E*)-α-Benzenesulfinylvinyl phosphonates can be prepared stereoselectively by a base-catalyzed reaction of a tosylimine (Equation (130)) <2000S99>.



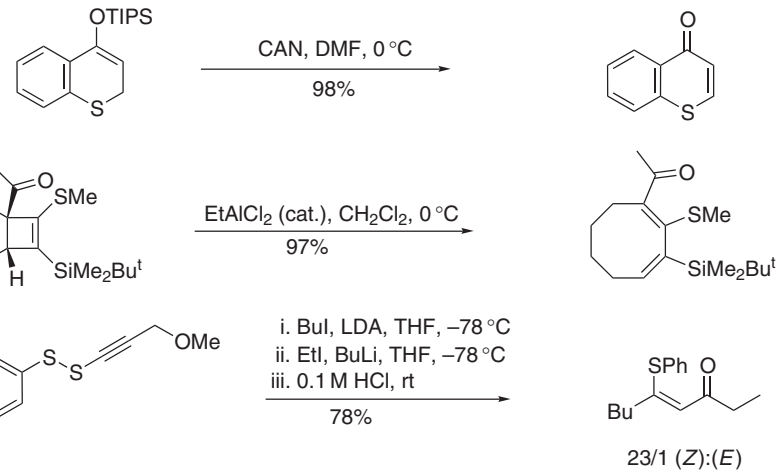
(130)

(vii) From 1,2 and 1,3-dithioles

A number of syntheses of α,β-unsaturated ketones have been described, starting from sulfur-containing heterocycles <1995COFGT(3)205>.

(viii) Miscellaneous methods

Other methods for the preparation of 3-thiosubstituted α,β-unsaturated ketones include Pummerer rearrangement and elimination of hydrogen halides from α-halo-β-sulfonyl ketones <1995COFGT(3)205>. The loss of hydrogen from silyl enol ethers can be achieved with CAN in DMF (Equation (131)) <1995TL3985>. Ring-opening reactions of cyclobutenes have been used to prepare 2,4-dienones, with a thioether in the 3-position. High yields of medium-ring dienes were obtained (Equation (132)) <1993CL621>. β-Alkyl-β-phenylthio-α,β-unsaturated ketones can be prepared by 2-alkylations of a functionalized alkyne (Equation (133)) <1995H13>. β-Sulfonyl-α,β-unsaturated ketones have been prepared by the radical addition of tosyl bromide to allenic alcohols <2002SC3263>.



(131)

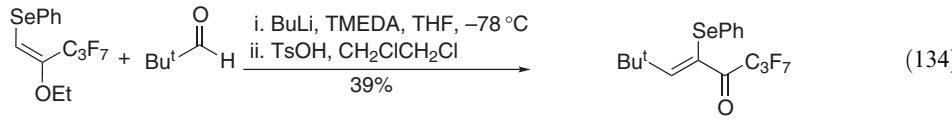
(132)

(133)

3.05.1.6 Selenium- and Tellurium-substituted α,β-Unsaturated Ketones

α-Selenium- and α-tellurium-substituted α,β-unsaturated ketones can be prepared by elimination reactions <1995COFGT(3)205>, usually following addition of a chalcogen nucleophile. β-Ethoxyvinyl selenides react with aldehydes and subsequently lose water to give α-seleno-α,β-unsaturated ketones (Equation (134)) <2000JOC4456>. (*Z*)-α-Alkyltelluroketones can be

prepared by hydrozirconation of alkynyl tellurides, followed by reaction with acyl chlorides in the presence of copper(I) iodide (Equation (135)) <1996TL7537>. α,β-Unsaturated ketones bearing selenium or tellurium in the β-position can be prepared by elimination reactions, following addition of a selenium or tellurium nucleophile to enones <1995COFGT(3)205>. The reaction of enol phosphates with butyltelluroate affords vinyl tellurides in reasonable yield (Equation (136)) <1999TL7717>. Selenium and tellurium derivatives of chalcones are accessible from telluroesters and terminal alkynes in a copper-catalyzed coupling (Equation (137)) <1998JOC4170, 1998TL1933>. Vinyl tellurides can be acylated with trifluoroacetic acid anhydride <1994CC2769>. α,β-Diseleno-α,β-unsaturated ketones can be prepared stereoselectively via hydrozirconation of the alkynyl diselenide, followed by transmetallation and acylation (Equation (138)) <2000S775>. Preparations of tellurium-substituted α,β-unsaturated ketones have been reviewed <2002MI929>.



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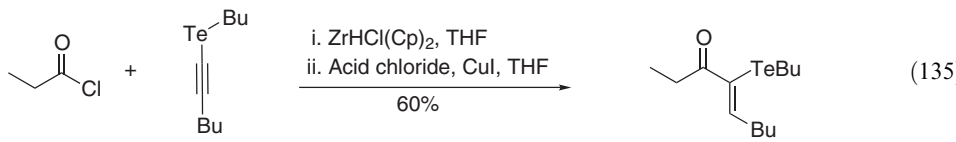

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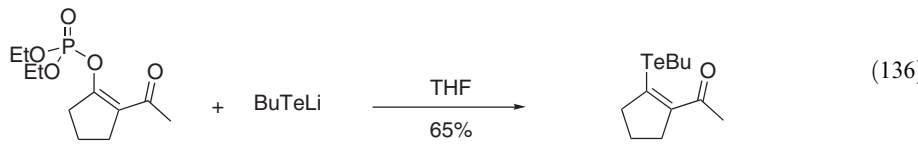

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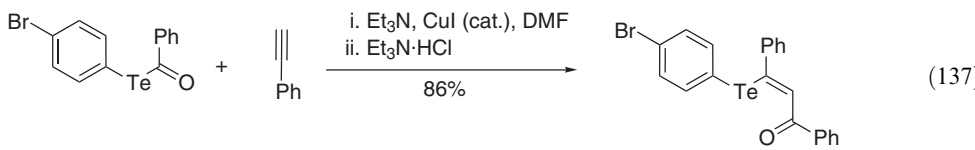

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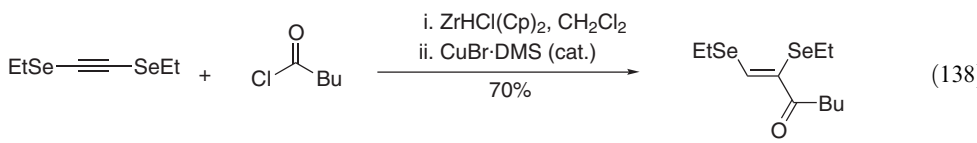


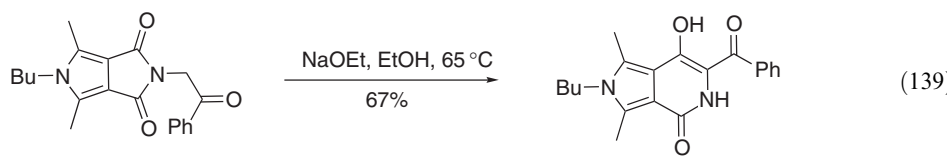
(138)

3.05.1.7 α,β-Alkenic Ketones with Nitrogen-based Substituents

3.05.1.7.1 2-Nitrogen-substituted α,β-unsaturated ketones

(i) From nitrogen substituted ketones and carbonyl compounds

Ketones bearing an α-nitrogen substituent condense with aldehydes to provide unsaturated ketones. The nitrogen may form part of an amide, sulfonamide, amine, pyridinium, nitro, or azide functional group <1995COFGT(3)205>. This reaction has been applied intramolecularly in a ring-opening, ring-closing sequence (Equation (139)) <1995PJC95>.



(139)

(ii) From α-halo ketones and an azide

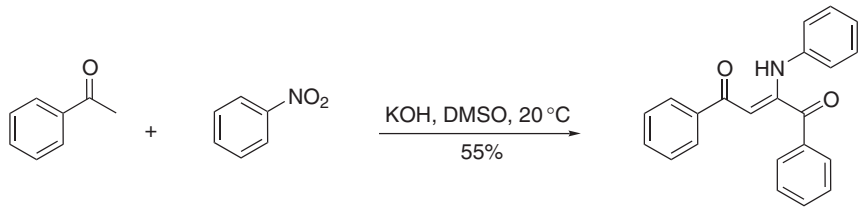
α-Azido-α,β-unsaturated ketones can be prepared, via an addition–elimination sequence, from α,β-unsaturated ketones. There are a number of ways of effecting this transformation, e.g., addition of bromine across the double bond, nucleophilic substitution by azide ion, then elimination. Alternatively, IN_3 adds across the double bond, before loss of hydrogen iodide <1995COFGT(3)205>.

(iii) From enamines and an acylating agent

Enamines normally react with acylating agents to give 3-nitrogen-substituted α,β-unsaturated ketones. However, α-metallated enamines do react to give 2-nitrogen substitution <1995COFGT(3)205>. Ruthenium-catalyzed carbonylation in the presence of alkenes has been achieved in good yield in a number of cases <1998JOC5129>.

(iv) Miscellaneous methods

There are a number of other ways for preparing 2-amino-vinyl ketones including the condensation of α-diketones with amines. Electrophilic cationic nitrogen species, e.g., nitrozating agents, attack 1,3-diketones, and the products can be reduced to 2-amino-3-hydroxy-α,β-unsaturated ketones. Diazonium salts couple to enolates to provide 2-azo-α,β-unsaturated ketones <1995COFGT(3)205>. Nitroarenes and acetophenone condense to give an aminovinyldiketone (Equation (140)) <1996MC72>. A silyl enol ether was converted into an unsaturated carbamate ester, via an α-azidoketone (Equation (141)) <1995T11075>. A highly substituted cyclopentenone was prepared from an allenyl ether and an alkenylnitrile, via a Nazarov-type cylization (Equation (142)) <2001TL2419>.



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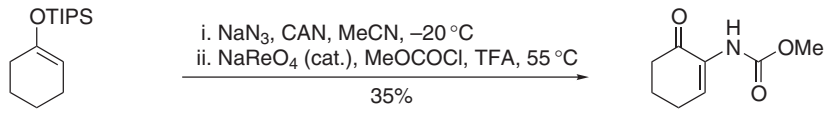

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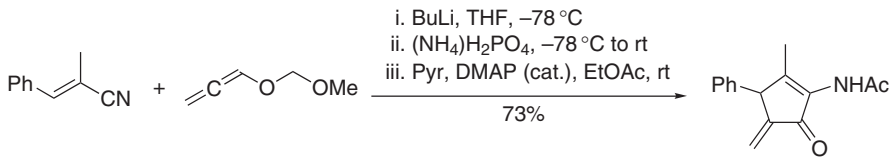


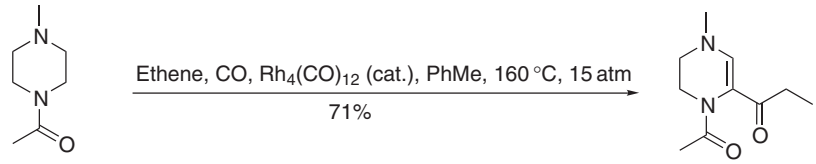
(142)

3.05.1.7.2 3-Nitrogen-substituted α,β-unsaturated ketones

(i) From enamines and an acid chloride

Enamines react with acid chlorides to produce β-nitrogen-substituted α,β-unsaturated ketones. A Lewis acid catalyst can be employed, depending on the reactivity of both species. In addition to acid chlorides, esters and anhydrides can be used, although this approach is most commonly used for cyclizations to form 5- or 6-membered rings <1995COFGT(3)205>. The use of DMAP as an acyl transfer catalyst for this reaction has been demonstrated <1997S117>. Substituted 4-pyridones can be prepared by intramolecular reaction of an enamine with an oxazolinone <1996TL8871>, diketene <1998H517>, or the reaction of an amidine with an unsaturated ester <1997BSF47>. Enamines

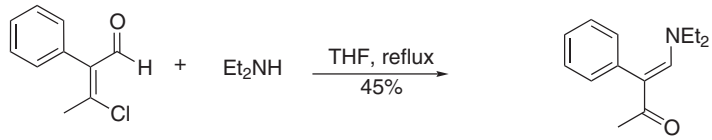
derived from the oxidation of amines can be acylated <1995COFGT(3)205, 1995MC197>. A piperazine was oxidized and acylated in a rhodium (or ruthenium) carbonyl-catalyzed reaction that was found to be substrate dependent (Equation (143)) <1997TL7565, 1997OM3615, 1998JOC5129>.



(143)

(ii) From β-dicarbonyl compounds or derivatives, and an amine

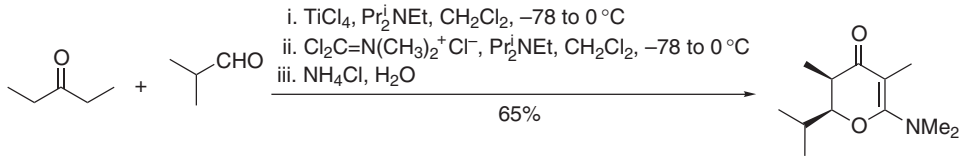
1,3-Dicarbonyl compounds undergo condensation reactions with amines to produce ketoimines, which exist predominantly as 3-nitrogen-substituted α,β-unsaturated ketones. The regiochemistry of the reaction can be controlled, as nitrogen attacks the more electrophilic carbonyl group. Internal hydrogen bonding may influence the ratio of isomers in the product. β-Alkoxy-α,β-unsaturated ketones can be used in place of the diketones, as can keteneacetals. Other leaving groups in the 3-position of an α,β-unsaturated ketone give rise to similar products, via an addition followed by elimination. For example, 3-haloenones, and 3-thio-substituted α,β-unsaturated ketones <1995COFGT(3)205>. The use of a silane catalyst resulted in a strong preference for (*E*)-geometry when a secondary amine was allowed to condense with a 1,3-diketone <1997SC4275>. 2 equiv. of methanethiol were lost from a ketene thioacetal, replaced by an amino amide <1996SC475>. A three-step sequence was required to replace bromine from a naphthoquinone. First, the alkene was hydrogenated, then the bromine replaced by an amine, before air oxidation restored the original oxidation state <1996JOC3031>. A 3-chloroenal condensed with a secondary amine to form an imine. Hydrolysis of the vinyl chloride produced afforded the 3-amino-α,β-unsaturated ketone (Equation (144)) <1996TL8751>.



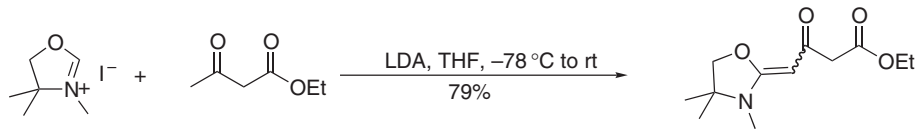
(144)

(iii) From ketones and formamide acetals

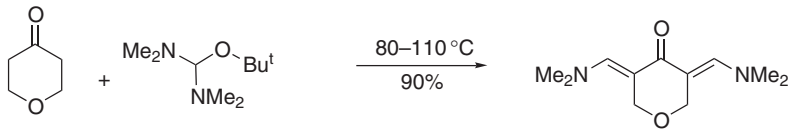
Formamide acetals undergo a condensation reaction with enolizable ketones, to produce a β-dialkylamino-α,β-unsaturated ketone. The (*E*)-isomer is usually produced <1995COFGT(3)205>. An alternative method for achieving a similar result is to employ phosphorus oxychloride to convert the formamide into a Vilsmeier reagent <1995CC1319, 1995T12869>. Vilsmeier reagents were used in a one-pot synthesis of 5,6-dihydro-4*H*-pyran-4-ones (Equation (145)) <1997T11211>. Oxazolinium cations can be ring-opened to give enaminones (Equation (146)) <1996IJC(B)881>. A further, analogous reaction employs the urea-derived alkoxy aminal, Bredereck's reagent (Equation (147)) <2001SL1129>.



(145)



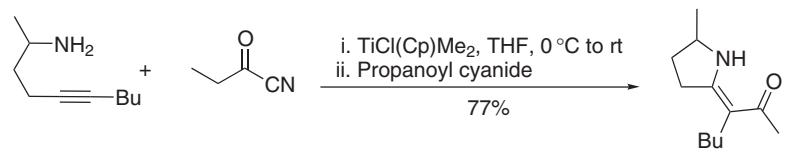
(146)



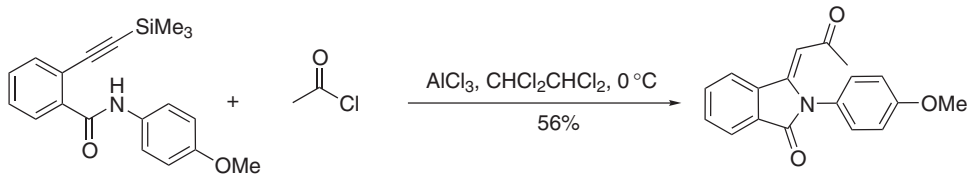
(147)

(iv) From amines and a ketoalkyne

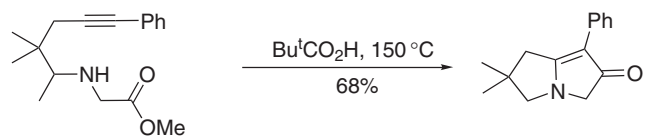
Amines react with alkynyl ketones to give enaminones, effectively adding across the triple bond. As above, the possibility of forming hydrogen bonds often leads to an increased proportion of *cis*-isomers <1995COFGT(3)205>. A titanium catalyst was used to effect a similar overall transformation from an alkyne amine with an acylating agent (Equation (148)) <1997OM1523>. Other acylation–cyclization sequences have been described (Equations (149) and (150)) <1997TL6937, 1999T12361, 1997SL1249>. Tertiary amines add to ynones resulting in a quaternary ammonium ion. Dealkylation of this ammonium ion resulted in the formation of a fused-ring system found in a class of alkaloids (Equation (151)) <1999MI1957>. Addition to the carbonyl of an alkynyl ketone, with rearrangement, has been recorded (Equation (152)) <2000T10075>.



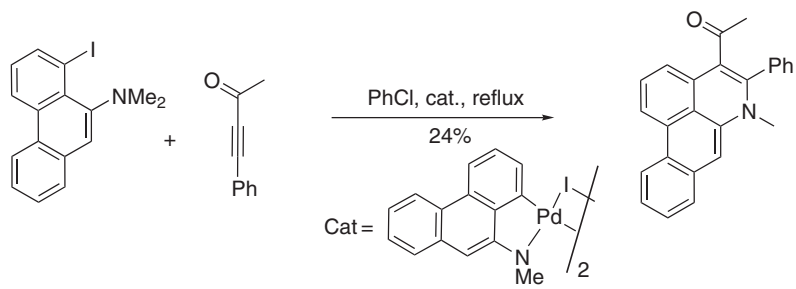
(148)



(149)



(150)



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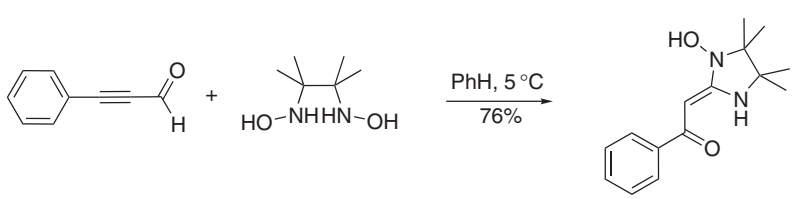
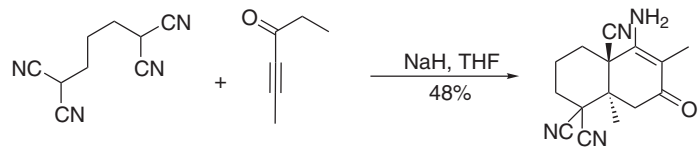


(152)

(v) Reactions of ketones with cyano compounds

Enolates add to cyano compounds resulting in the formation of an enaminone. In the presence of a suitable catalyst, addition to the cyano group of an aroyl cyanide is preferred over substitution <1995COFGT(3)205>. The use of an iridium catalyst resulted in an excellent yield <1998JA4244>. When an alkynyl ketone was reacted with a bismalononitrile, a bicyclic cyclohexenone was produced (Equation (153)) <1999OL1583>. Intramolecular addition of an aryllithium to a nitrile resulted in the synthesis of a 3-amino-2-indenone (Equation (154)) <1997TL8121>.



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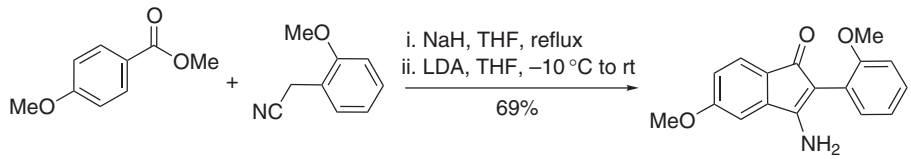


(154)

(vi) From carbonyl or thiocarbonyl compounds and Wittig-type reagents

Amides, imides, and thioamides are fairly poor substrates for Wittig-type reactions, with good yields obtained only in intramolecular cases <1995COFGT(3)205>. No further examples of this reaction have been noted since the publication of COFGT (1995).

(vii) From ketenes and an enamine

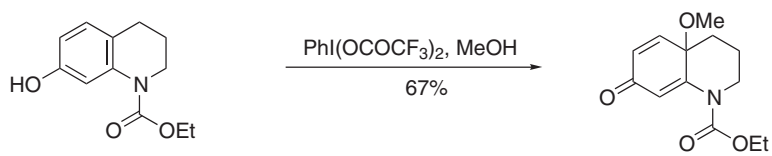
Ketenes and enamines take part in a [2 + 2]-cycloaddition, followed by ring-opening of the cyclobutanones <1995COFGT(3)205>. A similar reaction takes place between amino alkynones and isothiocyanates, although here the cyclobutene products are isolable <2001SL361>.

(viii) From oxime sulfonates and a silyl enol ether

Oxime sulfonates undergo a ring-expansion in the presence of Lewis acids to give intermediate iminium ions. These cations can be quenched by the addition of a silyl enol ether, giving an amino-substituted α,β-unsaturated ketone <1995COFGT(3)205>.

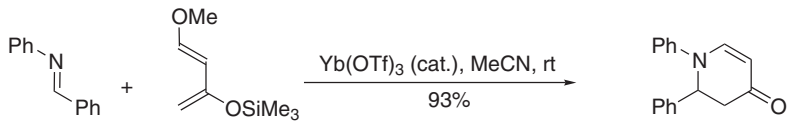
(ix) Miscellaneous methods

Other methods to enaminones include the reduction of isoxazoles or isoxazolines, and nitration of α,β-unsaturated ketones <1995COFGT(3)205>. Silyl enol ethers derived from 4-oxo-piperidines can be oxidized to the enone using CAN <1995TL3985>. The oxidation of a 3-aminophenol to a quinoidal system can be achieved via a hypervalent iodine oxidant (Equation (155)) <1999TL4183>. A range of acetanilides was oxidized directly to quinones with Dess–Martin periodinane <2001AG(E)207>. Quinones with nitrogen substituents can also be prepared from dimethoxybenzenes using cobalt trifluoride <1999SL1474>.

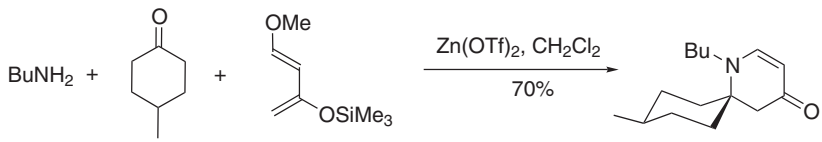


(155)

Hetero-Diels–Alder reactions have been reported a number of times, often between a Danishefsky-type diene and an imine, to give six-membered cyclic enaminones (Equations (156) and (157)) <1995S1195, 1997TL2829, 1998JOC4500, 1999TL5621, 1999TL7831, 2000SL1160, 2000OL3321>. A range of catalysts and conditions have been used, including chiral Lewis acids, giving ee values >80% <1998AG(E)979, 1999JOC4220>. Chiral imines have been used to direct the stereochemistry of the addition with high diastereoselectivity <1999TA4831>. Arylnitriles have also served as the dienophile <2001S828>. An unsaturated imine has been used in the place of a diene in a hetero-Diels–Alder reaction (Equation (158)) <2000JCS(P1)2827>.



(156)



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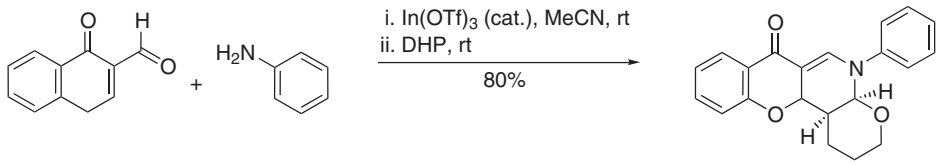
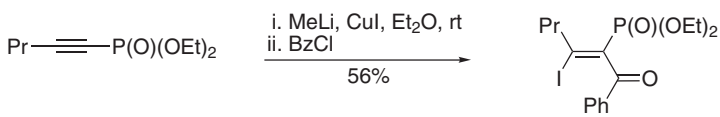


(158)

Chromium and tungsten alkylidine complexes have been employed to synthesize 3-amino-substituted-α,β-unsaturated ketones <1995SL812, 1995T11141>. Aminoalkynes have been used as substrates in Pauson–Khand reactions to prepare 3-nitrogen-substituted cyclopentenones <1998AG(E)489>. Similar reactions using a cyclopentadienyl cobalt–carbonyl complex resulted in a cycloaddition of cyclopentadiene to a cyclopentadienone <2000JOC7272>.

3.05.1.8 Phosphorus- and Arsenic-substituted α,β-Unsaturated Ketones

β-Keto-phosphonates condense with aldehydes to produce α-phosphorus-substituted enones. <1995COFGT(3)205>. β-Keto vinyl phosphonates can also be prepared from alkynylphosphonates by a cuprate addition followed by an acylation (Equation (159)) <1997JOM301>. A palladium-catalyzed coupling reaction has been used to prepare a β-diphenylphosphine-substituted α,β-unsaturated ketone. The unsymmetric phosphine is stabilized as the borane adduct (Equation (160)) <1999TL201>. α-Phosphono-α,β-unsaturated ketones have been prepared via a 1,3-migration of the phosphorus group in an iron–dienyl complex (Equation (161)) <2001JA12117>. Ozonolysis of β-keto esters bearing terminal alkenes afforded aldehydes that underwent an intramolecular cyclocondensation (Equation (162)) <1998TL3205>. Terminal cyclic enamines undergo a cycloaddition with alkynylphosphonates to give ring-expanded α,β-unsaturated cyclic ketones, bearing phosphonates in the α- position (Equation (163)) <1994TL3473>.



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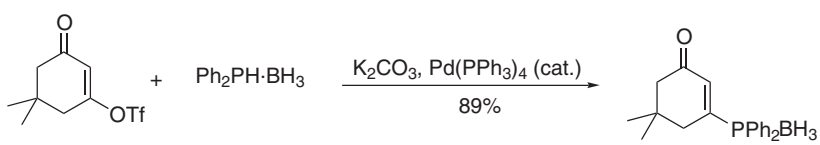
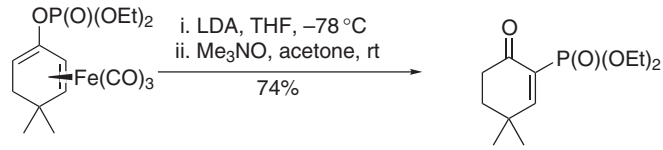
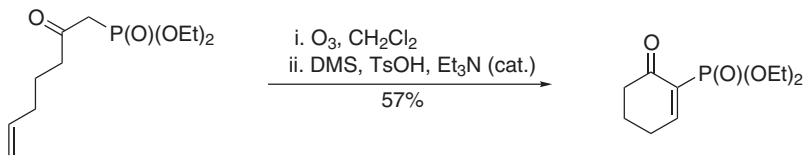


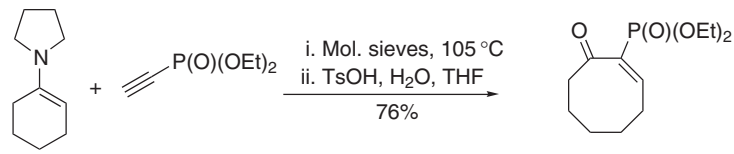
(160)



(161)



(162)



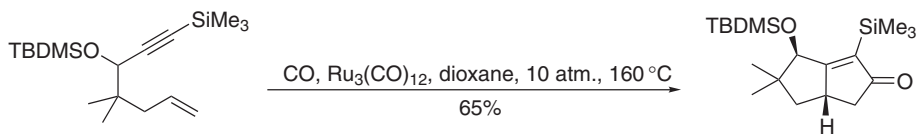
(163)

3.05.1.9 α,β-Alkenic Ketones with Silicon-based Substituents

3.05.1.9.1 2-Silyl α,β-unsaturated ketones

Acid chlorides add across silyl alkynes, in the presence of Lewis acid catalysts, to afford 2-silyl-3-chloro-α,β-unsaturated ketones. Metallovinylsilanes can be acylated to prepare 2-silicon-substituted enones in good yields. 2-Silylcyclohexenones are accessible via Diels–Alder reactions. Silicon-substituted alkynes undergo the Pauson–Khand reaction to give rise to 2-silylcyclopentenones <1995COFGT(3)205>.

The Pauson–Khand reaction is often used to prepare cyclopentenones, bearing silane groups. Although cobalt carbonyl complexes are usually employed, different transition metal-catalyzed reactions have also been used in this reaction. For example, ruthenium carbonyl catalysis (Equation (164)) <1997JOC3762> gave a marked increase in yield over the previous iron carbonyl method <1994OM1656>. Ruthenium carbonyl catalysis exhibits a tolerance of a variety of functional groups <1997JA6187, 1997JOC3762>. An iron carbonyl-mediated reaction has been employed to prepare cyclopentadienones from diynes <1993SL924>. The use of a rhodium carbonyl catalyst facilitates a silylative cyclocarbonylation with a diyne and silane (Equation (165)) <1995TL241, 1994JOC7594>. In those cases where the β,γ-unsaturated ketone was formed, rhodium chloride catalyzed a quantitative conversion into the α,β-unsaturated ketone. Allenynes are suitable substrates for a cyclocarbonylation reaction in the presence of molybdenum catalyst to give a product bearing an exocyclic double bond (Equation (166)) <1995TL2407, 1998JOC6535, 2000OL2869>. Titanium catalysts have been used, albeit leading to some saturated by-products <1995TL4261>. Chiral *t*-butyl sulfinyl-substituted enynes were used to provide bicyclic cyclopentenones in high enantiomeric excess (>96% ee), after cleavage of the chiral auxiliary <1999JA7411>. Reaction of a silyl alkyne with ethene was promoted with trimethylamine *N*-oxide <1995SL1083>. A solid-supported promoter, based on *N*-methylmorpholine-*N*-oxide, has also been developed, which can be regenerated and reused <1999CC2551, 2000SL1573>.



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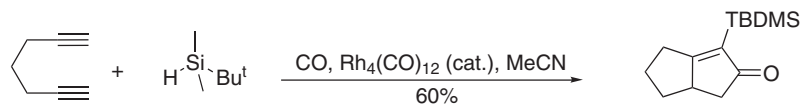

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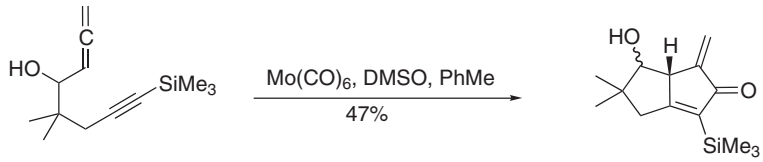
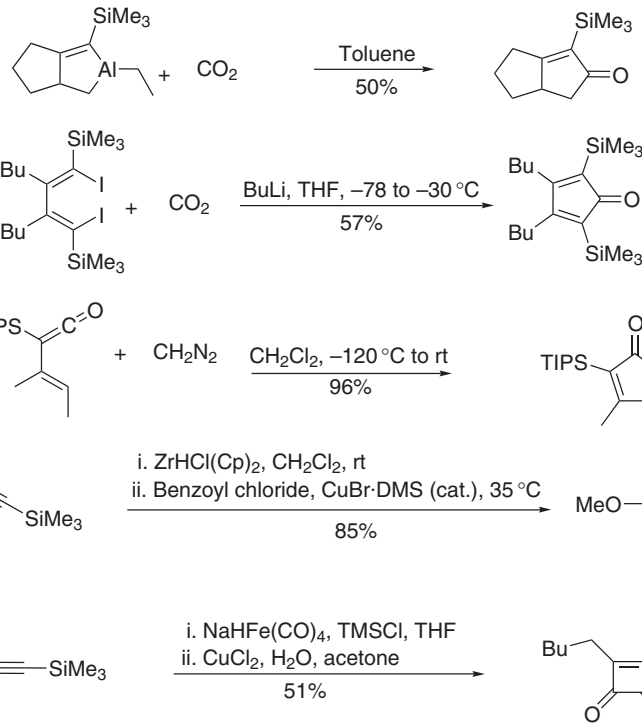


(166)

Cyclopentenones were also obtained if carbon monoxide and the alkene function were replaced by an α,β-unsaturated ester <1996JA8729, 1997JA10014>. Carbon dioxide acts as the electrophile on reaction with a vinylaluminum precursor (Equation (167)) <1998TL2503>. Carbon dioxide also reacts with dilithiated divinyl silanes to form the cyclopentadienone (Equation (168)) <2000JOC9157>. An alternative route to 2-silylcyclopentenones is the [4 + 1]-cyclization (Equation (169)) of a vinyl ketene with a carbene equivalent, such as an ylide or diazo compound <1998JA9690>. Alkynyl silanes can, in effect, be acylated by hydrozirconation, followed by transmetallation and reaction with an acid chloride (Equation (170)) <2000S775>. Aroylation of alkynyl silanes followed by cyclization was used to prepare indenones bearing silanes as a mixture of isomers <1996JOC6941>. The elements of glyoxal add across an alkynyl silane to generate a cyclobutenedione (Equation (171)) <1998JOC4930, 2000TL2719>.

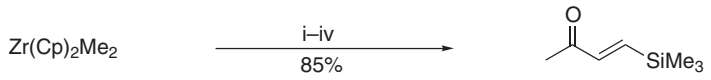


3.05.1.9.2 3-Silyl α,β-unsaturated ketones

β-Silylenones are accessible via a number of routes, including 1,4-addition to a silylynone, and 1,4-addition of a silyl cuprate to a β-chloroenone. β-Silylcycloenones can be prepared by rhodium-catalyzed oxidation of 3-(trimethylsilyl)cycloalkenes, in good yields, the oxidation being accompanied by migration of the double bond. β-Silylallylic alcohols can also be oxidized to the corresponding ketone <1995COFGT(3)205>.

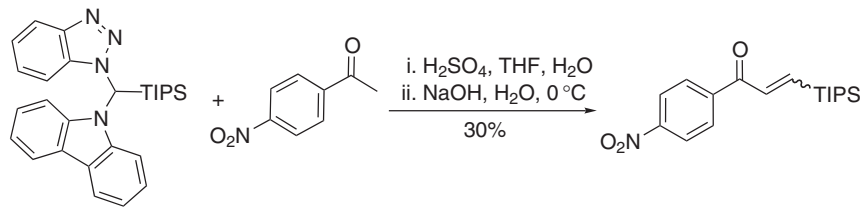
The equivalent of an aldehyde can be added across the triple bond of an alkynyl silane to generate β-silylenones using a zirconocene iminoacyl complex (Equation (172)) <1993JOC5595>. A dialkylzirconocene mediates the acylation of an alkynyl silane with benzonitrile <1998JOC6802>. Also serving as the equivalent of an aldehyde, α-benzotriazole-α-carbazole methyl silane condenses with methyl ketones (Equation (173)) <1994JOC5097>. Palladium catalyzes the formation of a cyclohexanone, bearing an exocyclic vinyl silane in an isomerization reaction, effectively an intramolecular Alder ene reaction (Equation (174)) <1996JA6625>.

Chromones bearing a vinyl silane have been prepared by nucleophilic substitution at silicon using vinyllithium reagents <1998TL1215>. Cobalt octacarbonyl in a stoichiometric amount mediates the isomerism of 1-(silylalkynyl)cyclopropanol to the cyclopentenone (Equation (175)) <1998JA3903>.



(172)

i. Bu^tNC, CH_2Cl_2; ii. $B(C_6F_5)_3$, CH_2Cl_2; iii. MeCCTMS, CH_2Cl_2; iv. MeOH, H_2O



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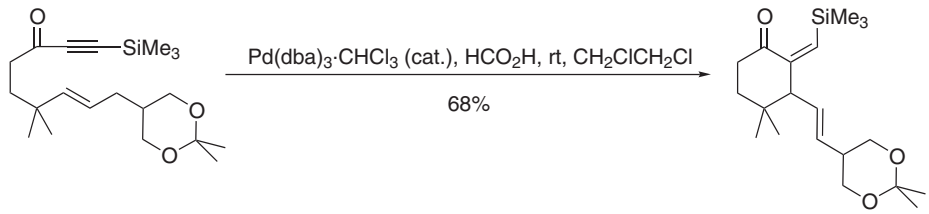

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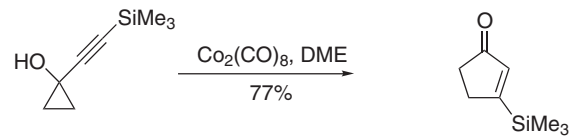
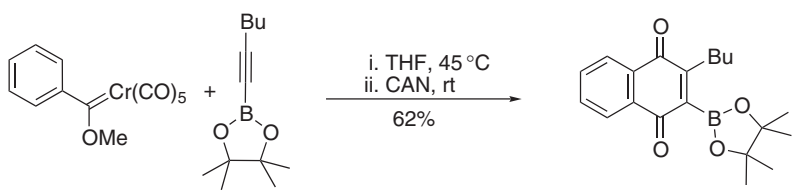


(175)

3.05.1.10 α,β-Alkenic Ketones with Metal Substituents

Some metal-substituted α,β-unsaturated ketones can be isolated and serve as useful synthetic intermediates. In particular, vinylboron and tin reagents are useful in palladium-catalyzed cross-coupling reactions. Boronate ester derivatives are accessible via a Fischer carbene benzannulation process (Equation (176)) <1999CC2107>. β-Keto vinylboronic esters are prepared via addition of an organozinc nucleophile to the corresponding aldehyde, followed by oxidation (Equation (177)) <1995TL4439>. Vinyl triflates are converted into β-boryl-α,β-unsaturated ketones in a palladium-catalyzed cross-coupling reaction <2002SL1880>. Tin can be introduced by cuprate addition to haloenones, followed by elimination <1995COFGT(3)205>. α-Trimethylstannyl-α,β-unsaturated ketones can be prepared by allylic photooxidation of vinylstannanes to give hydroperoxides, followed by dehydration (Equation (178)) <1994S557>, or via transmetallation from an organozinc iodide <1997T16711>. β-Stannylated enones have been prepared from propargylic alcohols, via palladium-catalyzed hydrostannylation, followed by mild oxidation <2002JOC6366>. Organozinc iodides have been used in palladium-catalyzed coupling reactions <1997JOM113>. Alkynyltungsten complexes undergo Pauson–Khand reactions to give isolable tungsten complexes of cyclopentenones <1999JA4066>. Manganese complexes of α,β-unsaturated ketones can be prepared by the reaction of methylmanganese carbonyl complexes with diynes <1998TL4843>.



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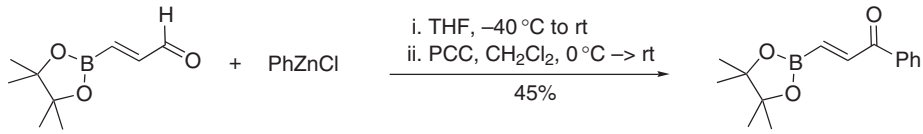

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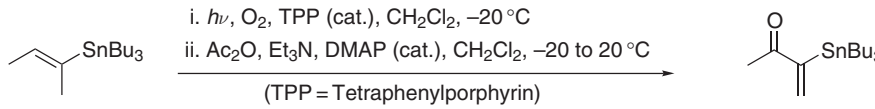
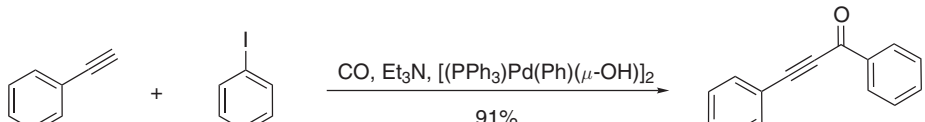


(178)

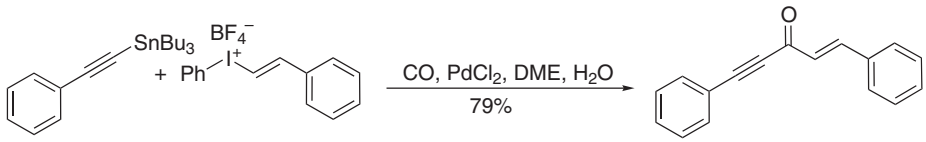
3.05.2 KETONES BEARING AN α,β-TRIPLE BOND

3.05.2.1 By Acylations of Alkynes

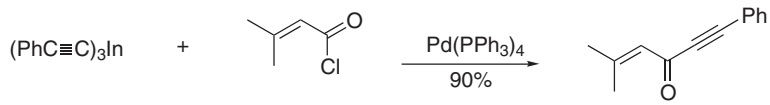
The acylation of acetylide anion or equivalent is commonly used to prepare ynones. Many metal acetylides have been employed, often using transition metal catalysis, with excellent yields. A wide variety of acylating agents, including acid chlorides, amides, and acid anhydrides have been used <1995COFGT(3)205>. Palladium salts catalyze the reaction of carbon monoxide with an alkyne and aryl iodide (Equation (179)) <1994S1149> or hypervalent iodonium aryls. Silyl alkynes <1997T3027> and tin alkynes react similarly, without the base. Vinyliodonium salts can be used (Equation (180)) <1998S823> as can antimony(V) aryls <2000JOM38>. The use of triorganoindium compounds allows the transfer of all three alkyne groups in high yield (Equation (181)) <2001JA4155>.



(179)



(180)



(181)

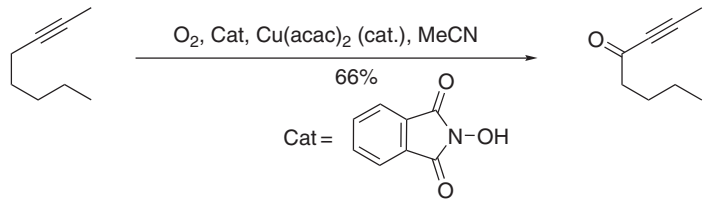
3.05.2.2 Elimination Reactions

The elimination of hydrogen halide from an α- or β-haloenone, or eliminating 2 equiv. of hydrogen halide from an α,β-dihaloketone furnishes alkynic ketones. The sequence of halogenation of an α,β-unsaturated ketone followed by didehydrohalogenation offers a means to effect dehydrogenation to form the ynone <1995COFGT(3)205>. No further developments of this reaction have been noted since the publication of COFGT (1995).

3.05.2.3 By Oxidation of Alkynic Alcohols and Propargylic Methylene Groups

A wide variety of reagents exist for the oxidation of propargylic alcohols to α-alkynic ketones <1995COFGT(3)205>. Commonly, MnO_2 or CrO_3-derived oxidants are used. Molecular sieves were found to catalyze the oxidation of acetylenic alcohols with *t*-butylhydroperoxide <1996TL7849>. The use of diselenodibenzoate as a catalyst gave very efficient oxidation with an *N*-chlorosulfonamide reagent <1996BCJ3601>.

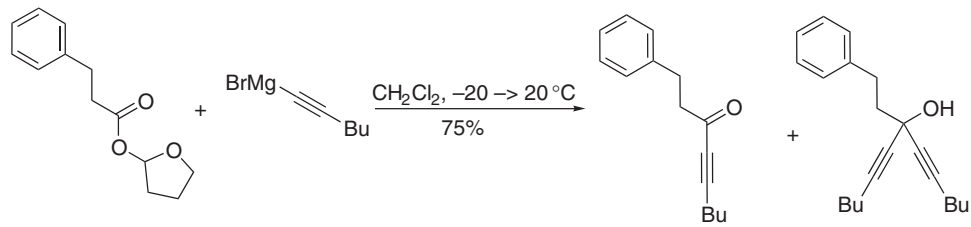
The methylene group adjacent to an alkyne can also be oxidized to a ketone. Chromium trioxide/pyridine or a peroxide are commonly employed <1995COFGT(3)205>. Aerobic oxidation has been used to effect this transformation (Equation (182)) <1998CC2037>. Similar regioselectivity, to produce the ketone rather than the aldehyde, was seen when *t*-butylhydroperoxide was used <2001JOC4087>.



(182)

3.05.2.4 By Reaction of a Carbon Nucleophile with Alkynic Acid Halides and Derivatives

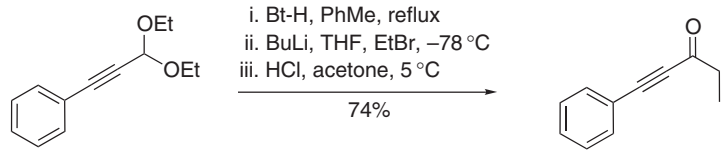
Carbon nucleophiles react as expected with appropriate acid halides and derivatives to give alkynic ketones <1995COFGT(3)205>. A recent example is the reaction of 1 equiv. of an alkynyl Grignard reagent with an ester (Equation (183)). The ketone and tertiary alcohol were produced in a 5:1 ratio <1996JOC6071>.



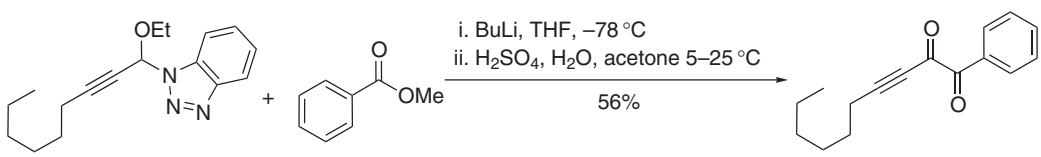
(183)

3.05.2.5 Miscellaneous Methods

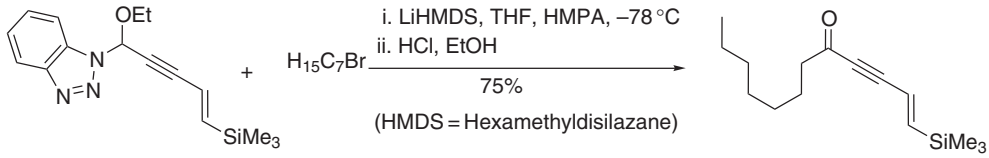
Alkynic aldehydes can be used in an umpolung sequence by forming a propargylic dithiane followed by deprotonation and then alkylation <1995COFGT(3)205>. Recently benzotriazole chemistry has been used to effect similar transformations in good yield (Equation (184)) <1995JOC7612>. This method has been applied to other functionalized ketones, for example, α-diketones (Equation (185)) <1997JOC4125> and enynones (Equation (186)) <1997JOC8201>. An efficient route to a fluorinated alkynic ketone has been described (Equation (187)) <1999JOC2873>. Effectively, carbon monoxide can be inserted adjacent to a triple bond, in a carbene reaction (Equation (188)). The formation of the cyclopropenone competes with the insertion reaction <1995S969>.



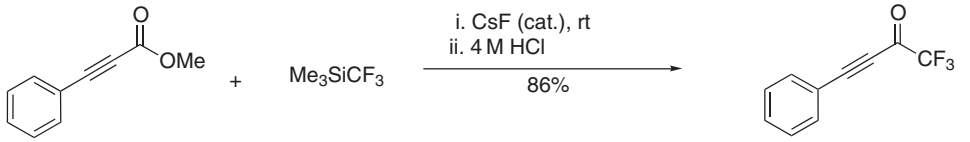
(184)



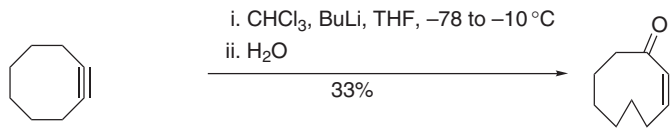
(185)



(186)



(187)



(188)

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Biographical sketch

Clive E. Foster was born in Derby in 1971 and studied from 1990 to 1996 at Durham University, England. He obtained his Ph.D. under the supervision of Professor David Parker. Following a year as a Royal Society ESEP Research Fellow with Professor Manfred T. Reetz at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany, he took up his current position at Avecia. He currently works in the Ink Jet Printing Materials Research Group and has interests in conjugated molecules for applications as colorants and as advanced materials.

Philip R. Mackie was born in Aberdeen, studied at the University of Glasgow where he obtained a B.Sc. in 1995 and a Ph.D. in supramolecular chemistry in 1998 under the direction of Drs Andrew Benniston and Robert Peacock. From 1998 until 2000 he worked as a Research Fellow at Trinity College, University of Dublin, under the direction of Dr. Paul Kruger and Professor John Kelly as part of an EU project focusing on coordination complexes with novel magnetic and photophysical properties. In 2001, he moved to the Electrophotography and Displays business of Avecia Ltd., based in Manchester, where he is currently employed as a Research Chemist within the Organic Semiconductors team.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 215–266

3.06 Ketones Bearing an α,β-Aryl or -Hetaryl Substituent

F. ALDABBAGH
National University of Ireland, Galway, Republic of Ireland

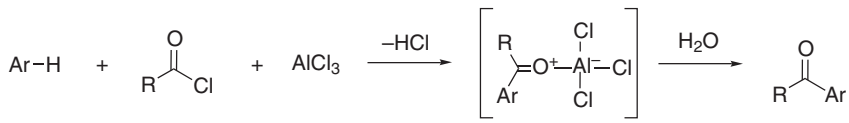
3.06.1 GENERAL METHODS

This chapter reviews the preparations of aromatic ketones published since the review by Walter <1995COFGT(3)277>. Particular attention is made to new methods; however, syntheses of aromatic ketones involving the synthesis of aryl or heterocyclic rings are not included. The oxidation of secondary benzylic alcohols remains the most common method of preparing aromatic ketones, although large advances have been made in direct syntheses including the Friedel–Crafts acylation, the reaction of acyl derivatives with organometallics, carbonylation reactions, and transition metal-mediated hydroacylations that directly convert aldehydes into ketones. In order to avoid overlap with Chapters 3.04 and 3.05, only methods specifically dealing with aromatic ketone synthesis are covered; however, some overlap regarding general methods of preparation are unavoidable.

3.06.1.1 Friedel–Crafts Acylations

The Friedel–Crafts acylation reaction is one of the oldest and most important methods of preparing aromatic ketones. The reaction traditionally proceeds by the treatment of the aromatic substrate with acylchloride, carboxylic anhydride, or carboxylic acid in the presence of a stoichiometric amount of Lewis acid, such as $AlCl_3$, $TiCl_4$, $SnCl_4$, or BF_3 <B-1973MI001, 1991COS(2)733, 1991COS(2)753>. However, stoichiometric amounts of graphite <1997CC1567> and polymer-supported $AlCl_3$ <1999JCR(S)568> have recently been shown to promote acylations using acid chlorides and bromides. The reaction stops after only one acylation, as the aryl ketone product is deactivated with respect to the aromatic substrate. The reaction also displays high regioselectivity toward substitution at the *para*-position when *ortho–para* directing substituents are present.

The acylation proceeds by the interaction of the aromatic substrate (ArH), acyl halide (e.g., acid chloride), and Lewis acid (e.g., $AlCl_3$) liberating hydrogen halide (e.g., HCl) to produce a complex **1** of the aromatic ketone and Lewis acid from which the ketone is liberated by hydrolysis, as shown in Scheme 1. If the inert complex **1** with the aryl ketone is partially dissociated, the reaction can become catalytic. This may be achieved with high temperatures, but this usually leads to side reactions <1972S533>. Industrially, $AlCl_3$ is the most important Lewis acid; however, it is also not stable to the aqueous work-up, and so cannot be reused. Moreover, stoichiometric amounts of traditional Lewis acids are always required, as all are moisture sensitive and are easily decomposed or deactivated in the presence of small amounts of water. In fact, the search for an economical and efficient catalyst that can be applied to a wide range of aromatics is ongoing. Section 3.06.1.1.1 reviews catalytic systems using the most common acylating agents: acid halides and anhydrides. The other sections deal with less popular acylating agents.



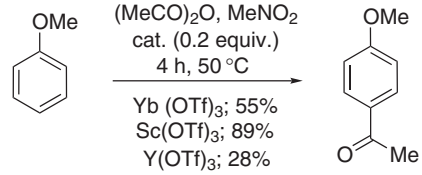
1

Scheme 1

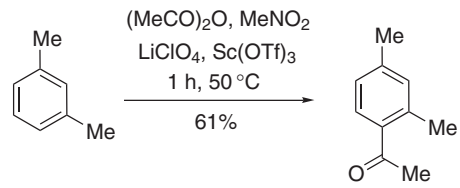
3.06.1.1.1 *Catalytic reactions with acid halides and acid anhydrides*

Since the 1990s, several transition (in particular rare-earth metal triflates, <2002CRV2227>) and lanthanide elements have been reported as efficient catalysts for the Friedel–Crafts acylations <B-2000MI001>. The most important feature of these Lewis acids is their stability to the aqueous work-up, which allows the use of only catalytic quantities. For example, scandium <1994SL545> and copper triflate <2001T241> can be used in catalytic quantities for the reaction of substituted benzenes with acid chlorides and anhydrides (also see Section 3.06.2.3.1 for Lewis acids in Fries rearrangements). Equation (1) demonstrates that scandium triflate is a more efficient catalyst than previously reported metal triflate catalysts. Lanthanide triflates $\{Ln(OTf)_3\}$ and bis(trifluoromethylsulfonyl) amides $\{Ln(NTf_2)_3\}$ <1996SL171> are only weak Lewis acids, and can only be used with aromatics activated by electron-donating groups (e.g., anisole) with

acylations of benzene and toluene not possible. An alterative system was reported using lithium perchlorate ($LiClO_4$), which forms cationic species with lanthanide, scandium, and hafnium triflates {$Ln(OTf)_3$} <1995TL409, 1996CC183>. For example, the $LiClO_4$ (4 equiv.)–$Sc(OTf)_3$ (0.2 equiv.) system proved to be a reusable catalytic system for the selective acylation of toluene and xylenes, as represented by the acylation of *m*-xylene using acetic anhydride (Equation (2)). For the reactions in Equations (1) and (2) only a single acetylated product was given and no other isomers were detected by GLC.

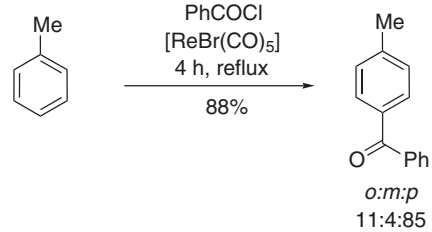


(1)



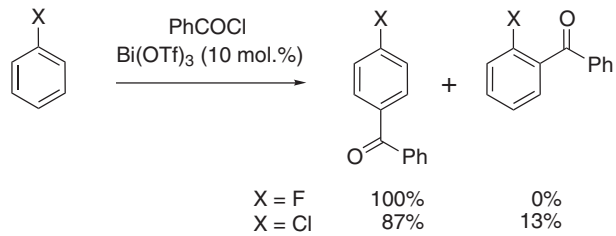
(2)

Kusama and Narasaka <1995BCJ2379> reported that aroylation of toluene and *m*-xylene was also possible in the presence of a catalytic quantity of bromopentacarbonylrhenium(I) ([$ReBr(CO)_5$]) with the predominate formation of the *para*-substituted products, as shown in Equation (3).



(3)

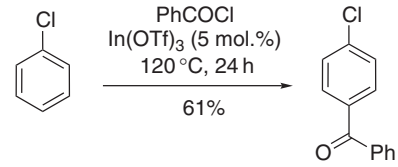
Bismuth(III) derivatives such as the oxides, oxychlorides, and carboxylates show good catalytic activity for the acylation of aromatic ethers. This is explained by the preferential complexation of the active Bi-species with the acid chloride rather than the aromatic ketone product <2002SL181>. However, for efficient acylation of nonactivated or slightly deactivated aromatics, such as benzene, toluene, fluorobenzene, and chlorobenzene, bismuth(III) triflate {$Bi(OTf)_3$} had to be used <1997TL8871>. Equation (4) shows that the benzoylation of fluorobenzene (reaction at reflux) and chlorobenzene (at 120 °C) led to the isolation the *para*-substituted products in good yields and selectivity. Gallium nonafluorobutanesulfonate {$Ga(ONf)_3$} was also shown to be an efficient catalyst for aroylation with acid chlorides and anhydrides of some nonactivated aromatics using various reaction conditions <2000SL403>. However, with these catalysts and aromatics, only aroylation and not alkanoylation reactions were reported.



(4)

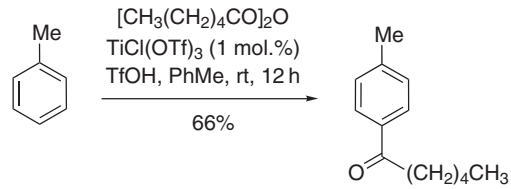
Indium(III) complexes are becoming increasingly widespread in organic chemistry, because of their use as robust Lewis acid catalysts. $In(OTf)_3$ was reported to be an effective catalyst (1 mol.%) for the room-temperature regioselective *para*-acylation of anisole with acetic anhydride in the presence of full molar equivalents of $LiClO_4$ in nitromethane <2001TL773>. At much higher

temperatures, the benzoylation of benzene in 79% yield and chlorobenzene (Equation (5)) could also be carried out without the addition of $LiClO_4$ (the formation of other benzoylated isomers was not reported) <2002TL4789>.



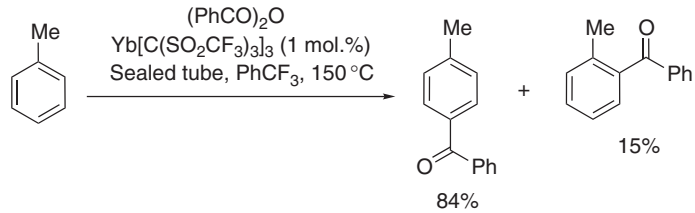
(5)

Catalytic acylations of nonactivated aromatics have also been achieved by using a combination of trifluoromethanesulfonic acid (TfOH) with a transition metal triflate. Various aroylations of benzene, chlorobenzene, and fluorobenzene were achieved using 10 mol.% of $Hf(OTf)_4$ and TfOH with acid chlorides <1998TL4697>. Further, the use of $TiCl(OTf)_3$ (1 mol.%) and TfOH (10 mol.%) allowed the introduction of various alkanoyl as well as benzoyl substituents into a variety of aromatics including toluene, as shown in Equation (6) <1996CL739>. It is assumed that the catalytic cycle involves $TiCl(OTf)_3$ activating the carboxylic anhydride by generating a catalytic amount of Tf-carboxylic anhydride along with titanium carboxylate. The active mixed anhydride immediately reacts with the aromatic substrate to give the desired aromatic ketone, and titanium carboxylate regenerates the catalyst by TfOH.



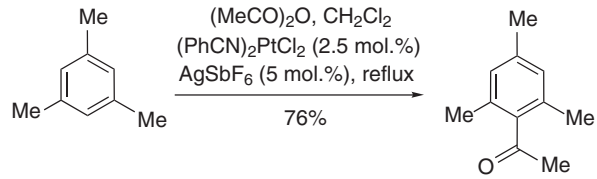
(6)

Barrett and co-workers <2002SL1635> used ytterbium(III) methide complexes with low catalyst loadings of 0.1 mol.% for acylation of anisole and 1 mol.% for other aromatic substrates (Equation (7)). Earlier, the same group had used ytterbium(III) methide complex to achieve fluorous biphasic catalysis with successful recycling of the catalyst achieved by extraction of the spent reaction mixture with perfluoromethyl decalin <2000SL847>.



(7)

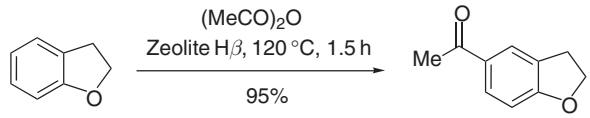
Cationic late transition metals {$(PhCN)_2PtCl_2$ and $AgSbF_6$} were proven to be efficient catalysts for acylation of moderately to strongly activated arenes, as shown in Equation (8) <2001OL417>. The latter authors reasoned that inhibition by the formation of the inert complex **1** between the aryl ketone and the catalyst can be avoided by using late transition metals with "soft" centers, which are a mismatch for the "hard" ketone carbonyl oxygen atom.



(8)

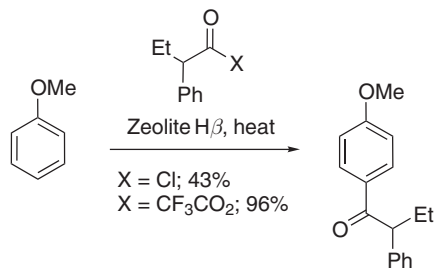
Solid-supported and heterogeneous catalysts are discussed in Section 3.06.1.1.2. Zeolite-catalyzed acylations using acid halides and anhydrides of aromatic ethers have received a considerable amount of attention, and have been commercialized <1998USP(5)817,878>. Smith and co-workers <2003OBC1560> recently reported that the large-pore zeolite Hβ is an efficient catalyst for the acylation of arylethers, as shown in Equation (9). The advantages of this system

are that the zeolite can be easily recovered, regenerated, and reused to give almost the same yield as that given with the fresh zeolite. However, zeolites seem limited to reactions involving only highly activated aromatic substrates.



(9)

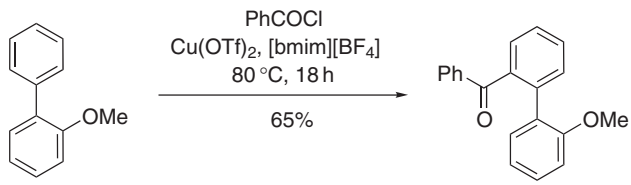
Stable and nonhygroscopic heteropolyacid, aluminum dodecatungstophosphate ($AlPW_{12}O_{40}$), was recently reported to be an effective catalyst (3 mol.%) for the Friedel–Crafts acylations of activated aromatics with carboxylic acids in the presence of trifluoroacetic anhydride (TFAA, 1.4 mmol) (see Equations (78) and (79), Section 3.06.3) <2003TL5343>. Similarly, zeolite catalysts using 2-phenylbutanoyl trifluoroacetate formed *in situ* from the reaction of 2-phenylbutanoic acid and TFAA were shown to be an efficient acylating agent for anisole, as shown in Equation (10) <2003OBC2321>. The order of reactivity of acylating agents was reported to be as follows: mixed anhydride with TFAA > simple anhydride > acid chloride > carboxylic acid <2003OBC2321>.



(10)

In an earlier paper by Smyth and Corby, the reaction of acyl trifluoroacetates with phosphoric acid in the presence of TFAA was reported to lead to the ready formation of acylbis(trifluoroacetyl)phosphates, which were used for the ambient temperature acylation of anisole <1998JOC8946>.

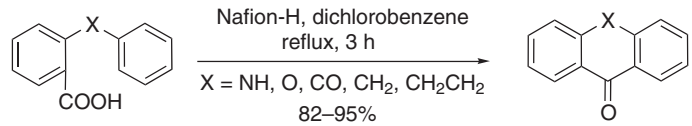
Wilkes and co-workers were the first to report acylations in the ionic liquid, 1-methyl-3-ethylimidazolium chloride (EmimCl) with added $AlCl_3$ <1986JOC480>. The active catalyst was identified as $Al_2Cl_7^-$. It was later shown that for the same system, anisole, chlorobenzene, toluene, or naphthalene can be acylated with ethanoyl chloride in yields and regioselectivity that were equal to the literature best <1998CC2097>. This acidic ionic liquid was also used in the efficient acylation of ferrocene <1996CC2753> and indoles (Equation (88), Section 3.06.4.3). An alternative ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4], was found to be an efficient medium for aroylations and ethanoylations using acid chlorides and anhydrides with $Cu(OTf)_2$ proving to be the most efficient catalyst, as represented by Equation (11) <2002GC129>. Benzoylation of 2-methoxybiphenyl gave exclusively the substitution product 2-(2-methoxyphenyl)benzophenone in [bmim][BF_4], and not the expected benzoylation of the position *para* to the methoxy group. The advantage of these systems is that the catalyst/ionic liquid can be recycled.



(11)

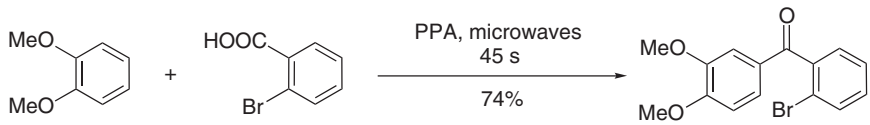
3.06.1.1.2 Reactions with carboxylic acids

Carboxylic acids are not as popular as acid chlorides and anhydrides as acylating agents. However, there are still numerous examples of their use. Intramolecular Friedel–Crafts acylations with carboxylic acids are usually promoted by strong Brønsted (see Equation (74), Section 3.06.2.4) and Lewis acids <1991COS(2)753>. A recently introduced Brønsted acid catalyst is Nafion-H (perfluorinated sulfonic acid resin) <1999SL1067>. By using the latter procedure various biarylketones were prepared as shown in Equation (12). Other Brønsted acid solid-supported catalysts reported to promote carboxylic acid acylations include the Envirocat Epic® <1999SC(29)2587>.



(12)

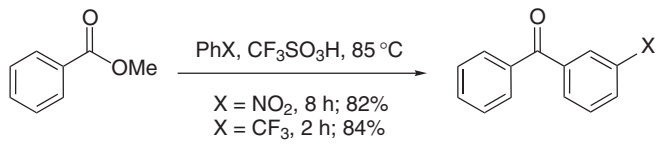
Polyphosphoric acid (PPA) is often used in place of the much more strongly acidic reagents, $AlCl_3$ or concentrated sulfuric acid <B-1973MI001, 1999CCC533>. However, the viscosity of PPA itself and of reactions involving the reagent mean that magnetic stirring is usually not feasible. Elevated temperatures and mechanical agitation are usually required, conditions that are not particularly amenable to modern-day parallel synthesis. In order to overcome these problems, Learmonth <2002SC(32)2757> has reported the Friedel–Crafts acylation of some anisole derivatives using microwaves, as represented by the example in Equation (13).



(13)

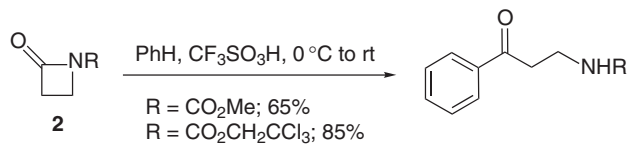
3.06.1.1.3 Reactions with miscellaneous acylating agents

Olah and co-workers <B-1973MI001> introduced ionic acyl ion equivalents $MeCO^+SbF_6^-$ and $PhCO^+SbF_6^-$, which are capable of acylating nonactivated aromatics in highly acidic media <1995JA3037>. Methyl benzoate can be protolytically activated by trifluoromethanesulfonic acid, and reacted with various aromatics to give benzophenone derivatives in good yields <2000T7199>. Equation (14) shows that even highly deactivated aromatics such as nitrobenzene and trifluoromethylbenzene can be efficiently converted into the respective *m*-substituted benzophenones.

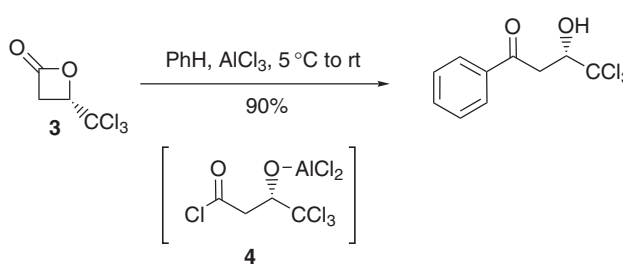


(14)

Trifluoromethanesulfonic acid was used by Anderson and Tepe <2002OL459> to promote the ring opening of azetidinones with acylation of aromatic substrates. This very mild Friedel–Crafts acylation is illustrated in Equation (15) for the acylation of benzene with various *N*-acylated 2-azetidinones **2**. Earlier, Fujisawa and co-workers had shown that β-trichloromethyl-β-propiolactone **3** was an efficient chiral acylating agent of a variety of aromatics, as represented by the example in Equation (16) <1997TL1593>. Complete stereochemical integrity in the acylated products was achieved, with acid chloride **4** reported as the reactive acylation intermediate. Both ring-opening acylation procedures were extended to the acylation of nonactivated and activated benzenes, as well as naphthalene and pyrrole derivatives.



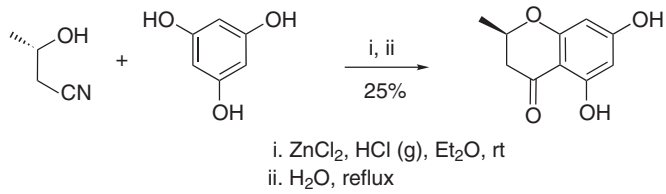
(15)



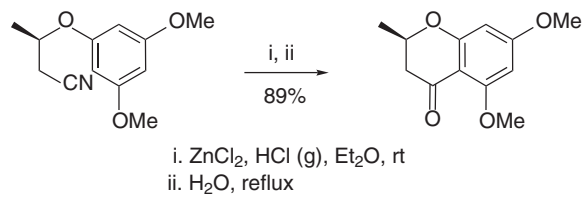
(16)

3.06.1.1.4 The Houben–Hoesch synthesis

This method of aromatic acylation is closely related to the Gatterman aromatic aldehyde synthesis (Chapter 3.03). It consists of the condensation of nitriles with phenols in the presence of HCl and zinc chloride ($ZnCl_2$) <1991COS(2)733, 1995COFGT(3)277>. The reaction probably proceeds via the addition of HCl to the nitrile to give a reactive imidoyl chloride <B-1973MI001>. The reaction usually requires highly activated substrates with electron-releasing substituents (e.g., phenols, phenolic ethers, and aromatic amines). A one-pot intermolecular Houben–Hoesch reaction is shown in Scheme 2; however, the intramolecular reaction was much more efficient giving higher yields of the required chroman-4-one, as shown in Scheme 3 <1994TL6347>.



Scheme 2



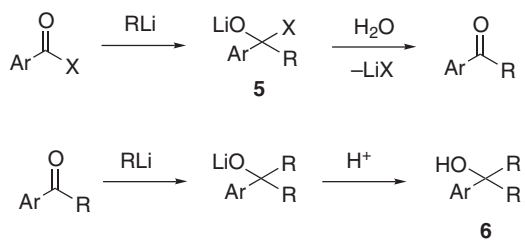
Scheme 3

3.06.1.2 Electrophilic Acylation of Organometallic Species

The electrophilic acylation of organometallic species by carboxylic acid derivatives is among the most widely used methods of aromatic ketone synthesis. Notable reviews have been carried out by Walter <1995COFGT(3)277>, O'Neill <1991COS(1)397>, Lawrence <1998JCS(P1)1739>, and Dieter <1999T4177>.

3.06.1.2.1 Acylation of organolithium reagents

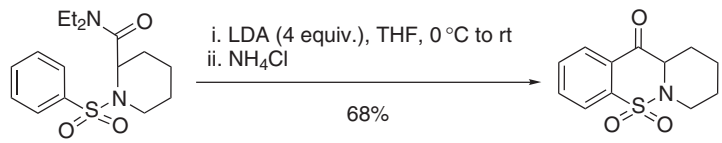
Direct acylations of organolithium species by simple carboxylic acid derivatives are generally not widely applicable due to the decomposition of the so-formed tetrahedral lithium species (e.g., **5**) before work-up leading to further reaction between the organolithium and the required ketone to give the tertiary alcohol **6**, as outlined in Scheme 4. Over-addition is thus favored because the ketone is more reactive than the weakly electrophilic substrate.



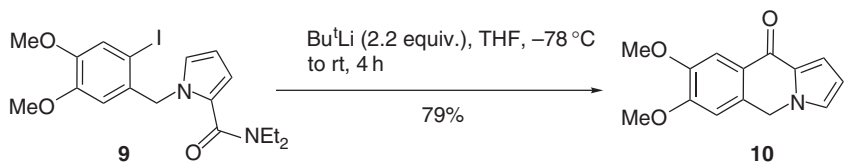
Scheme 4

Stabilization of lithium intermediates can greatly facilitate ketone formation, and the reader should consult the reviews by O'Neill <1991COS(1)397>, Walter <1995COFGT(3)277>, or Clayden <B-2002MI001> for a survey of recent methods used. Preventing the enolization of the lithium carboxylate by the addition of $CeCl_3$ has also been reported to greatly increase the yield of ketones in the reaction of organolithiums and lithium carboxylates <1994TL203>.

Weinreb <1981TL3815, 2000JPR(342)340> discovered that *N*-methoxy-*N*-methylamides were the best acylating agents for organolithiums. An impressive intermolecular example of this reaction is given in Equation (82), Section 3.06.4.1, and several other recent examples exist <2000JMC3878>, including the preparation of α-chloroarylketones by the intermolecular coupling of aryllithiums or aryl Grignard reagents with *N*-methoxy-*N*-methylamide-substituted chloroacetic acid derivatives {$ClCH_2CONMe(OMe)$} <1996SL225>. Among the many examples of intramolecular carbanion cyclizations onto Weinreb amides, the preparation of benzocyclobutenones in quantitative yields was reported via the generation of aryllithiated anions using *t*-butyllithium at −78 °C <1997CJC817>. Similarly, the treatment of *N*-sulfonylaminoamide **7** with excess LDA led to carbanion cyclization with the *N*,*N*-diethylcarbamoyl group acting as an effective leaving group to produce the benzothiazinone **8** in good yield (Equation (17)) <1997SL1079>. More recently, when the aromatic ring was suitably activated by methoxy substituents, *N*-(*o*-iodo-benzyl)pyrrole **9** was effectively cyclized via the formation of the intermediate aryllithium to give the isoquinoline nucleus **10** shown in Equation (18) <2000TL5211>. Intramolecular LDA/TMEDA or LITMP-mediated cyclizations of remote aryllithiums onto *N*,*N*-diethylcarbamoyl groups have also been used to give acridones and dibenzoazepinones in high yields <1998SL419, 2001TL385>.

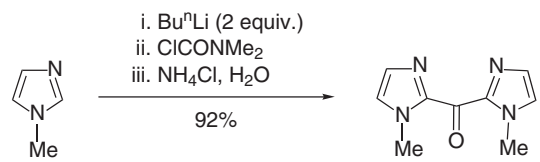


7 **8** (17)



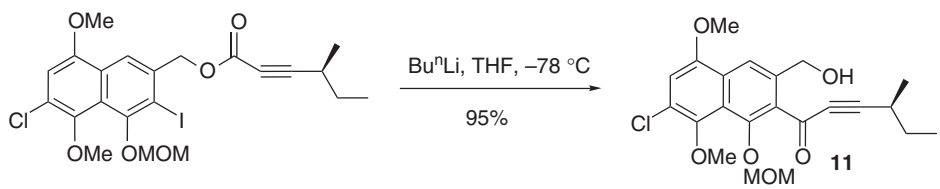
9 **10** (18)

The preparation of various biaryl symmetrical ketones by the addition of aryllithiums to *N*,*N*-dimethylcarbamyl chloride, as represented by the preparation of bis(2-imidazolyl)ketone in Equation (19), was described by Breau and co-workers <2000S1253>.



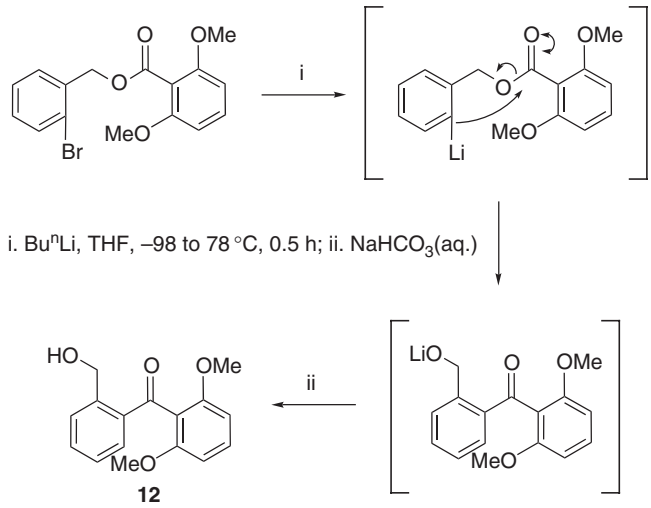
(19)

Equation (20) shows the use of organolithiums in facilitating the intramolecular acyl transfers, as in the formation of 2-acylnaphthalene **11** in almost quantitative yield. Compound **11** was formed as an equilibrium mixture with its hemiacetal form <1999CC1005>.



11 (20)

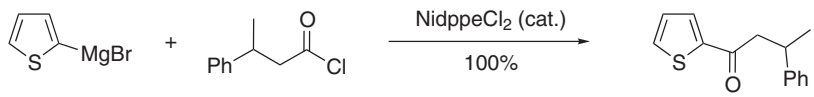
Nicolaou and co-workers reported a useful acylation procedure for the synthesis of sterically congested benzophenones, which involved generation of an aryllithium intermediate followed by the nucleophilic substitution onto an ester to give a thermodynamically favored alkoxide, as outlined in Scheme 5 <1995CEJ454>. The strategy gave benzophenone **12** in 87% overall yield.



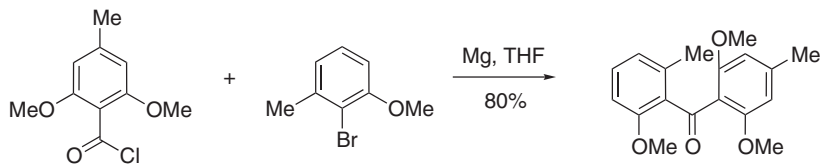
Scheme 5

3.06.1.2.2 Acylations of Grignard reagents

Organolithium and organomagnesium (Grignard) reagents exhibit similar reactivity toward carboxylic acid derivatives. Again special conditions are required in order to avoid the simultaneous presence of the organomagnesium compound and ketone. Usually, the Grignard reagent is added to an excess of the acid chloride at the lowest possible temperature with THF proven to be a best reaction solvent <1979TL4303>. There are now several metal additives (catalysts) known to prevent the addition of the Grignard reagent to the required ketone <B-1995MI001>. For example, a catalytic amount of NidppeCl$_2$ can be used in THF at 0 °C in the formation of a variety of aromatic ketones (Equation (21)) <1995TL9185>, but sometimes a catalyst is not required, as shown in Equation (22) for the coupling of the Grignard reagent with a sterically congested acid chloride <1995JCS(P1)2355>.

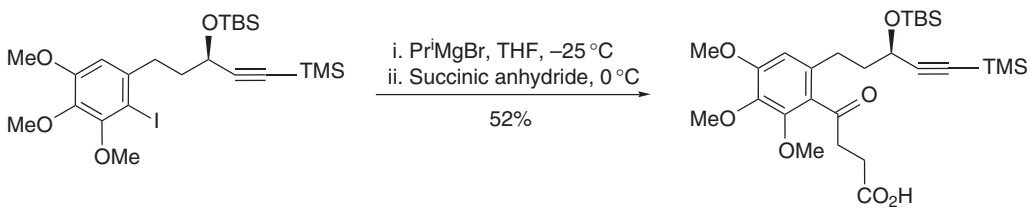


(21)



(22)

Grignard reagents have been shown to react with anhydrides to give ketones; iodide **13** could be converted to the corresponding Grignard compound by the treatment with *i*-PrMgBr, subsequent addition onto succinic anhydride in THF directly afforded the desired 4-keto-carboxylic acid **14** in reasonable yield (Equation (23)) <2002AG(E)1524>.

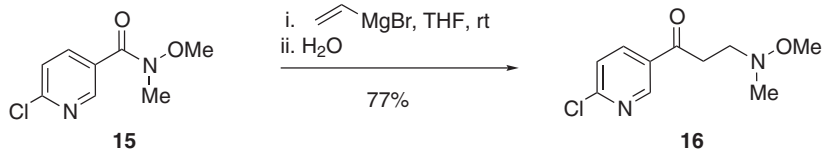


13 **14**

(23)

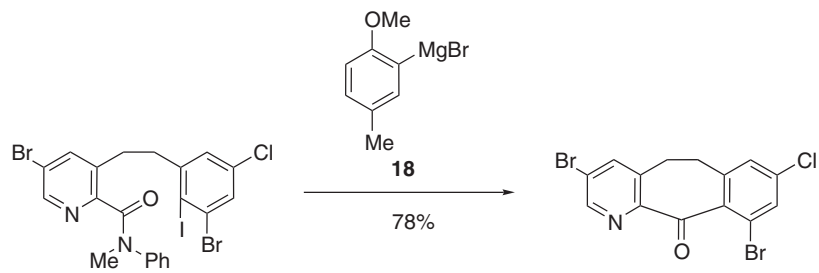
However, as with organolithium reagents, amides are often superior acylating agents for Grignard reagents. Gomtsyan reported the synthesis of β-aminoketones **16** from Weinreb amides **15** <1981TL3815> could be achieved by the sequential nucleophilic substitution at the carbonyl

group by vinylmagnesium bromide to give a vinylketone *in situ*, which underwent a Michael addition by the magnesium amide (Equation (24)) <2000OL11>.



15 16 (24)

A new anisole-based Grignard reagent **18** was reported by Wu and co-workers, which allowed regioselective intramolecular anionic acylations of sterically congested substrates to occur in good yields, as represented by the example in Equation (25). Alkyl- and aryllithium reagents were found to be unsuitable, as there was no chemoselectivity in halogen–lithium exchanges. Simple Grignard reagents such as *i*-PrMgBr and PhMgBr gave intractable mixtures due to addition to the amide group of **17**, and so the bulkier Grignard reagent **18** proved to be the most effective.

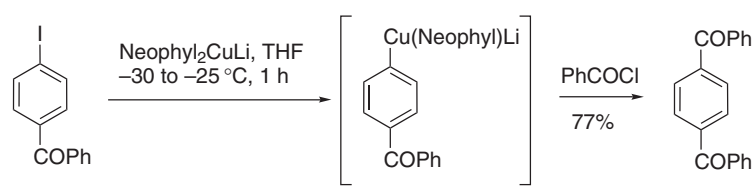


17 (25)

There are also recent examples of aromatic ketones formed via the addition of Grignard reagents to thioesters, as shown by Equation (86) (Section 3.06.4.2), and an unexpected addition to carboxylic acids shown in Equation (75) (Section 3.06.2.4).

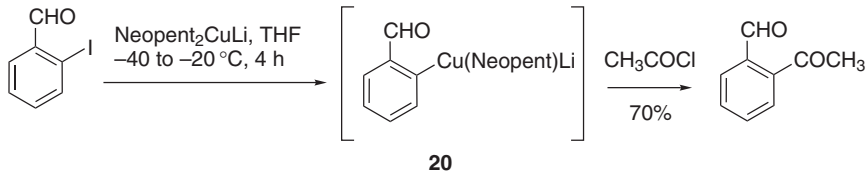
3.06.1.2.3 Acylations of organocopper reagents

The reaction between acid halides and lithium dialkylcopper reagents (R_2CuLi) to give high yields of ketones is well established <1969JIC167, 1972JA5106, 1988TL4513>. The reaction occurs under mild conditions, and is generally tolerant of the presence of iodo, keto, ester, nitro, or cyano groups in the acid chloride. Recently, Piazza and Knochel reported an impressive synthesis of functionalized aromatic ketones using the sterically hindered reagents, $(PhMe_2CCH_2)_2CuLi$ ($Neophyl_2CuLi$) and lithium dineopentylcuprate ($Neopent_2CuLi$), which were shown to undergo highly selective I/Cu exchanges in the presence of other reactive functional groups such as ketones (Scheme 6), aldehydes (Scheme 7), and esters <2002AG(E)3263>. The resultant mixed organocuprates (**19** and **20**) were quenched with acid chloride electrophiles to give the respective aromatic ketones in good yields.



19

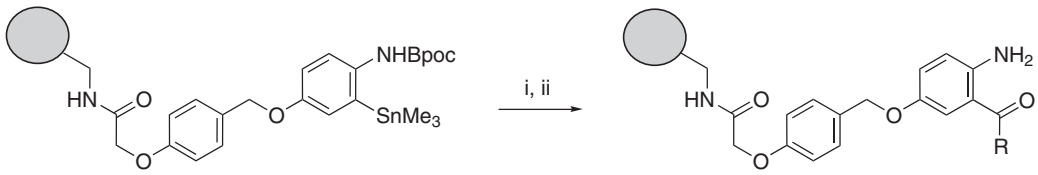
Scheme 6



Scheme 7

3.06.1.2.4 Acylations of organotin reagents

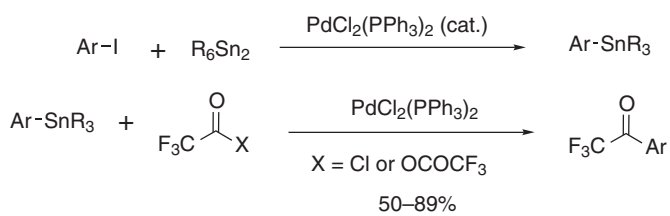
The palladium-catalyzed coupling of acid chlorides with organotin compounds has become an established general route to aromatic ketones. The reaction was first reported by Migita <1977CL1423> and by Stille <1978JA3636, 1983JOC4634>. The reaction now bears the name of Stille <B-1998MI001>, who first showed that the reaction has the following advantages: (i) high to quantitative yields of ketones can be obtained; (ii) the reaction is very mild, and can tolerate many other functional groups in the acid chloride and tin reagent; and (iii) there is no need for an inert atmosphere, since both the tin reagent and catalyst are air stable. Bearing in mind these advantages, Stille coupling is ideal for solid-supported organic synthesis. Ellman, one of the pioneers of combinatorial synthesis of small molecules, along with Plunkett, reported Stille couplings of the solid support-bound stannane **21** with aromatic and aliphatic acid chlorides mediated by the "ligandless" catalyst $Pd_2dba_3{\cdot}CHCl_3$ (Scheme 8) <1995JA3306, 1995JOC6006>. While the ligandless catalyst provided a rapid reaction at room temperature, coupling with $Pd(PPh_3)_4$ required elevated temperatures and some cleavage of the Bpoc {2-(4-biphenylyl)isopropyloxycarbonyl} group was observed. The Bpoc-protecting group was removed by brief treatment with 3% TFA to give the support bound 2-aminoarylketone **22**. The 2-aminoarylketones **22** were then incorporated directly into a 1,4-benzodiazepine library. The 1,4-benzodiazepines were formed in impressive overall yields of 52–82% from the initial substrate loading.



i. $Pd_2dba_3{\cdot}CHCl_3$, Pr^i_2EtN, K_2CO_3, THF, RCOCl
ii. 97:3, CH_2Cl_2/TFA

Scheme 8

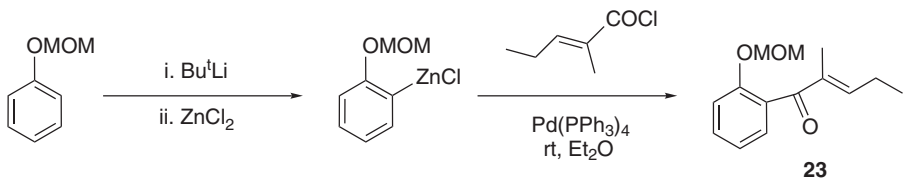
Guiles reported the Pd(0)-mediated cross-coupling of aryltrialkyltins derived from aryl halides with trifluoroacetic chloride and anhydride to give aryl trifluoromethyl ketones, as represented by Scheme 9 <1995SL165>.



Scheme 9

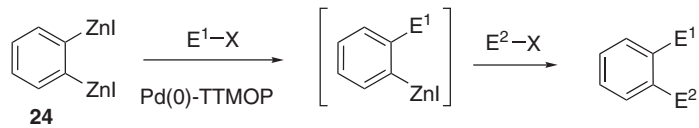
3.06.1.2.5 Acylation of organozinc reagents

Organozinc reagents have found extensive use in aromatic ketone synthesis owing to their versatility and inherent tolerance of sensitive functional groups. Organozinc reagents are typically obtained via an *o*-metallation followed by a transmetallation (Scheme 10) <1995JOC2298>. Scheme 10 shows an example of a palladium-catalyzed cross-coupling with an acid chloride, which allowed the synthesis of the α,β-unsaturated aromatic ketone **23** in 75% overall yield.



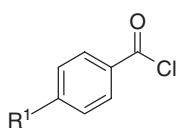
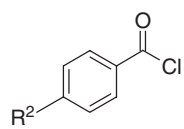
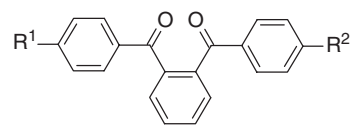
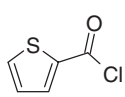
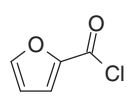
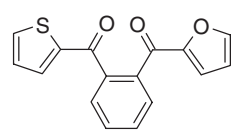
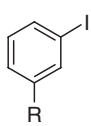
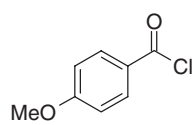
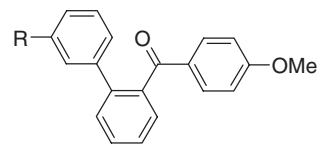
Scheme 10

Alternatively, Takagi and co-workers showed that the zinc may be inserted directly into the C—I bonds by using ultrasound irradiation conditions. *o*-Phenylenedizinc(II) iodide **24** was prepared from *o*-iodobenzene using zinc powder and ultrasound. Compound **24** proved to be a unique reagent supplying 1,2-phenylene dianions for Pd(0)-catalyzed cross-coupling with acid chlorides to form symmetrical ketones in high yields <1994CL2055>. This was extended by the same group to the synthesis of unsymmetrical ketones shown in Scheme 11. Pd(0)-tris(2,4,6-trimethoxyphenyl)phosphine {Pd(0)-TTMOP}-catalyzed consecutive cross-coupling of *o*-phenylenedizinc(II) **24** with two different acyl or aryl halide electrophiles allowed the formation of a wide variety of unsymmetrical 1,2-diacyl and 1-acyl-2-aryl benzenes <2000TL4629>. Table 1 shows a few of the ketones produced using this prolific reaction.



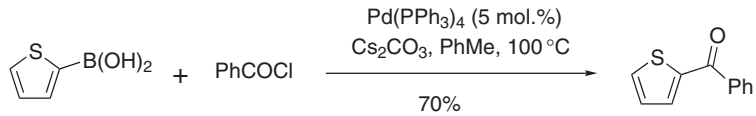
Scheme 11

Table 1 Consecutive cross-coupling of *o*-phenylenedizinc **24** with acid and aryl halides

E^1—X	E^2—X	Product	Yield (%)
			
		R^1, R^2 = CN, H	73
		R^1, R^2 = OMe, H	90
			77
			
		R = CF_3	82
		R = Cl	69

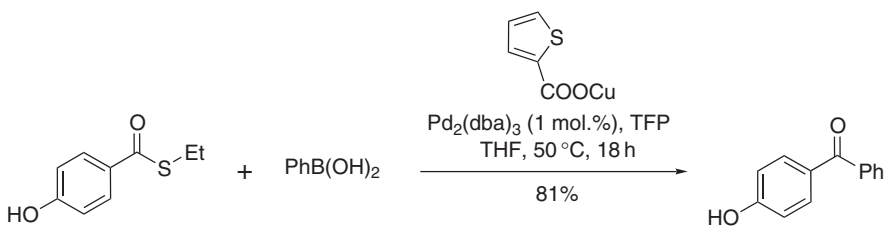
3.06.1.2.6 Acylation of organoboron reagents

Since Uemura and co-workers <1993JOM(443)253> reported the synthesis of unsymmetrical aromatic ketones using a palladium(0)-catalyzed coupling of acid chlorides with $NaBPh_4$, organoboranes have become one of the most popular nucleophilic reagents in ketone synthesis (also see carbonylative cross-couplings, Section 3.06.13). An aqueous $Pd(OAc)_2$-catalyzed $NaBAr_4$ coupling with acid chlorides has been reported <1999TL3057> and, under anhydrous conditions upon the addition of 5 equiv. of caesium carbonate, the successful $Pd(PPh_3)_4$-catalyzed coupling of acid chlorides with readily available arylboronic acids was achieved (Equation (26)) <1999TL3109>. Acid chlorides can also react with trialkylboranes in the presence of $Pd(PPh_3)_4$ to yield various alkyl and aryl ketones in good yields <2000TL999>.



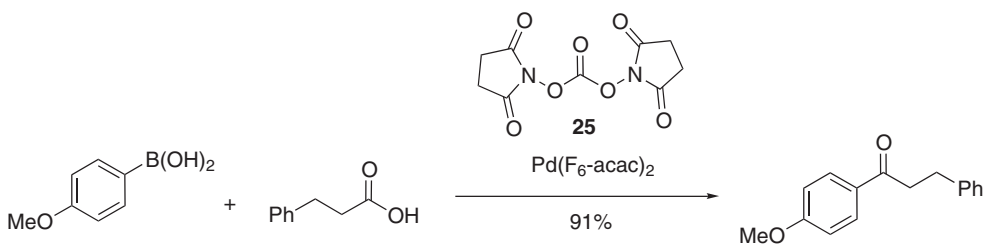
(26)

A versatile base-free synthesis of aryl ketones by a palladium-catalyzed {$Pd_2(dba)_3 \cdot CHCl_3$/tris(2-furyl)phosphine (TFP)} copper-mediated {Cu(I) thiophene-2-carboxylate} coupling of thioesters with boronic acids has been reported, and an example is given in Equation (27) <2000JA11260>.

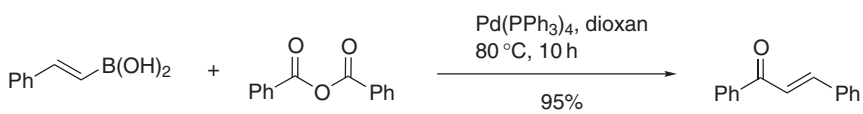


(27)

Gooßen and Ghosh reported the first direct couplings of arylboronic acids with carboxylic acids, which were activated *in situ* for the oxidative addition to the palladium(0) catalyst by either pivalic anhydride <2001AG(E)3458> or di(*N*-succinimidyl)carbonate **25** (Equation (28)) <2001CC2084>. More recently, *in situ* activation of carboxylic acids toward oxidative addition to $Pd(PPh_3)_4$ catalysts was achieved by using dimethyldicarbonate <2002BCJ1333, 2002SL1237>. These activators facilitated easy aqueous work-ups, as most of the by-products are water soluble: *N*-hydroxysuccimide (by-product of **25**), methanol and CO_2 (by-products of dimethyldicarbonate), and boric acids. Alternatively, the anhydride was coupled directly with the organoboronic acid <2002BCJ137>, as shown by the example given in Equation (29).



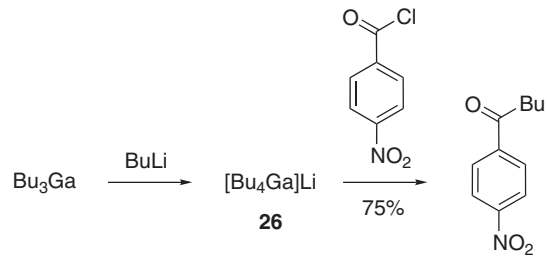
(28)



(29)

3.06.1.2.7 Acylations of miscellaneous organometallic reagents

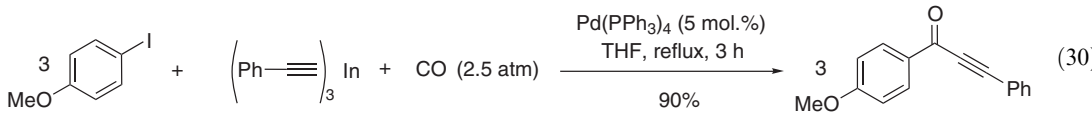
Huang and co-workers prepared tetraorganogallium ate complexes **26** *in situ* by the addition of an organolithium to a triorganogallium, which reacted smoothly with acid chlorides, as shown by the example in Scheme 12 <1995TL1287>.



Scheme 12

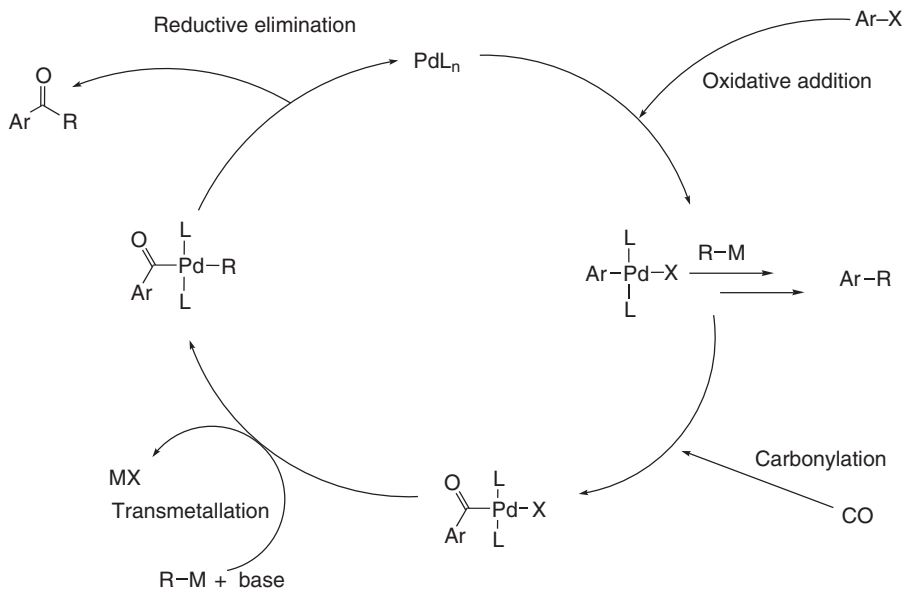
3.06.1.3 Aryl Ketones by Carbonylative Cross-coupling Reactions

The transition metal-catalyzed three-component cross-coupling reaction between aryl electrophile, aryl metal reagent, and carbon monoxide (CO) has become a straightforward method for preparing unsymmetrical aromatic ketones <B-1998MI002, 2002CUOC(6)1097>. Magnesium, aluminum, boron, silicon <1995SL823>, tin <2001TL265>, and zinc <1995JOC1365, 1997JCS(P1)865> have been used as the aryl metal reagent. More recently, highly efficient Pd(0)-catalyzed triorganoindium carbonylative couplings have been carried out, as shown by the example in Equation (30) <2003S780>.



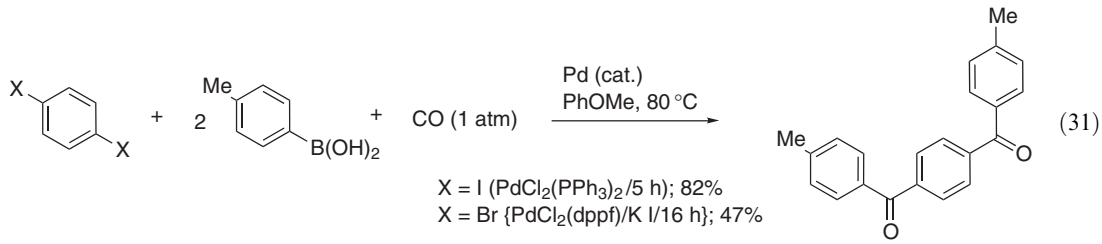
(30)

However, since the 1990s, palladium-catalyzed cross-couplings using arylboronic acids as the aryl metal have become the most popular system. Arylboronic acids have the advantage of being readily available, nontoxic, thermally stable, inert to water and oxygen, and highly tolerant of the presence of sensitive functional groups. Scheme 13 shows the general catalytic cycle for the palladium-catalyzed cross-coupling carbonylation <1995CRV2457>. The mechanism is analogous to a direct coupling except for the carbon monoxide insertion that takes place after the oxidative addition of the arylhalide (Ar—X) to a Pd(0) to form Ar—Pd(II)—X, and prior to the transmetallation with R—M (e.g., arylboronic acid).



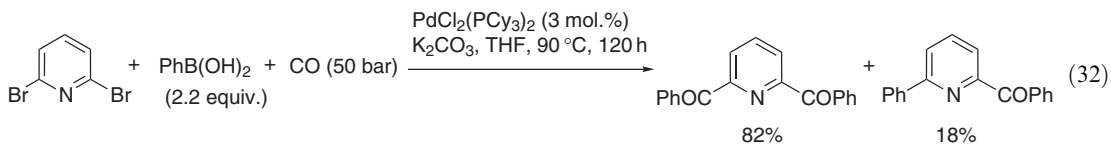
Scheme 13

Miyaura and co-workers <1998JOC4726> showed that the reaction of arylboronic acids with aryl electrophiles (ArI, ArBr, and ArOTf) under an atmospheric pressure of carbon monoxide could be used to generate a wide variety of unsymmetrical biarylketones, when carried out in ansole at 80 °C in the presence of a palladium catalyst and a base. Equation (31) shows the extension of the methodology to the preparation of diketones via a sequential double carbonylation.



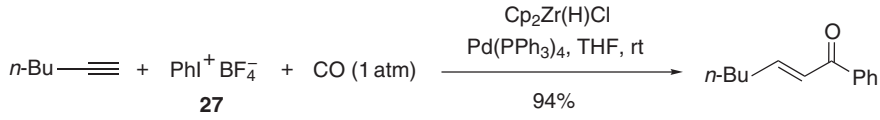
(31)

The catalyst, $PdCl_2(PPh_3)_2$ (3 mol.%), with 3 equiv. of potassium carbonate was effective for aryl iodides; however, the use of $PdCl_2$(dppf) (3 mol.%) along with 3 equiv. of KI (and 3 equiv. of K_2CO_3) was a prerequisite for the selective carbonylation of aryl bromides. This is because aryl bromides react much more slowly in the oxidative step than aryl iodides leading to faster rates of transmetallation than carbonylation, thus yielding considerable amounts of the direct coupled biaryl products (e.g., Ar—R). The ligand dppf (1,1′-bis(diphenylphosphino)ferrocene) is known to accelerate the rate of CO insertion compared to transmetallation, thus allowing a more selective ketone synthesis from aryl bromide substrates. Imidazolium ligands have also been shown to be effective catalysts for the carbonylative couplings of aryldiazonium ions with arylboronic acids in the presence of palladium acetate catalyst <2002TL9137>. Alternatively, the use of greater pressures of carbon monoxide can suppress the formation of the side product, Ar—R. Recently, 2,6-dibromopyridine was shown to give optimal yields of 2,6-dibenzoylpyridine using 50 bar pressure of CO, as shown in Equation (32) (GLC gave quantitative yields of products in the ratio shown) <2003T2793>.

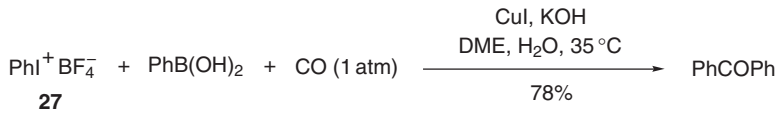


(32)

Kang and co-workers have carried out cross-coupling carbonylation reactions by replacing the aryl halide electrophile with hypervalent aryliodonium salts (e.g., **27**) to achieve efficient room temperature preparations of aromatic ketones <1998SC(28)1481, 1998S823>. Pd-catalyzed coupling reactions with various alkenoyl- and alkanoylzirconocene chlorides to form aryl-substituted alkyl and vinyl ketones were reported (Equation (33)) <2002JCS(P1)459>. In addition to palladium, copper(I) iodide was used as an efficient catalyst for the carbonylative coupling of iodonium salts **27** with organoboronic acids and organostannanes <1996JOC9082>. Good yields of ketones were obtained under mild conditions, as represented by the preparation of benzophenone shown in Equation (34). [^{11}C]-Substituted benzophenones were also prepared using this procedure by the incorporation of ^{11}CO in very high radiochemical yield <2000JCS(P1)1033>.

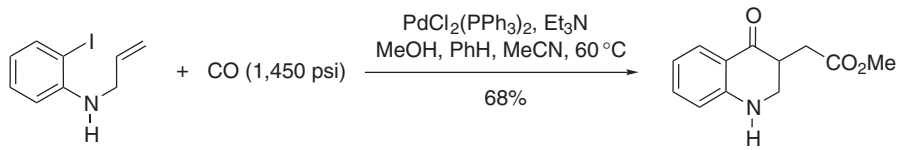


(33)

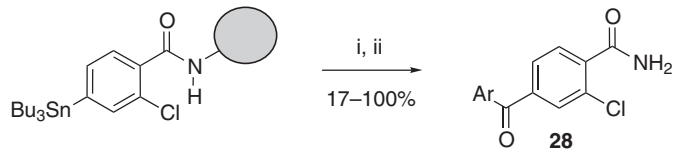


(34)

When significant pressures of CO were applied (1,450 psi), the Pd(0)-catalyzed cross-coupling methodology was extended to cyclization reactions, as shown in Equation (35) <2001JOC2175>. Lesser pressures of CO (40–60 psi) were required to perform the three-component solid-phase Stille couplings shown in Scheme 14 <2001TL175>. Yields were given upon cleavage from the Rink resin with TFA, with the biaryl ketones **28** obtained in >95% purity.



(35)

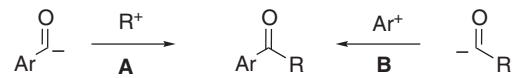


i. ArX, $Pd(PPh_3)_4$, CO (40 psi), DMSO, 80 °C,
X = I, 18 h; X = Br, 3 days
ii. 1:1 TFA/CH_2Cl_2, 0.5 h

Scheme 14

3.06.1.4 Acyl Anion Equivalents in Aromatic Ketone Synthesis

Acyl anion equivalents are "umpoled synthons," which on alkylation **A** or arylation **B** can provide aryl alkyl ketones either spontaneously or after a simple hydrolytic step (Scheme 15) <1995COFGT(3)277>.

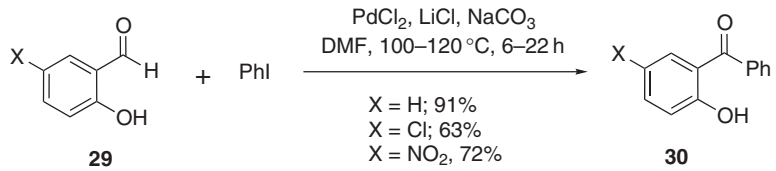


Scheme 15

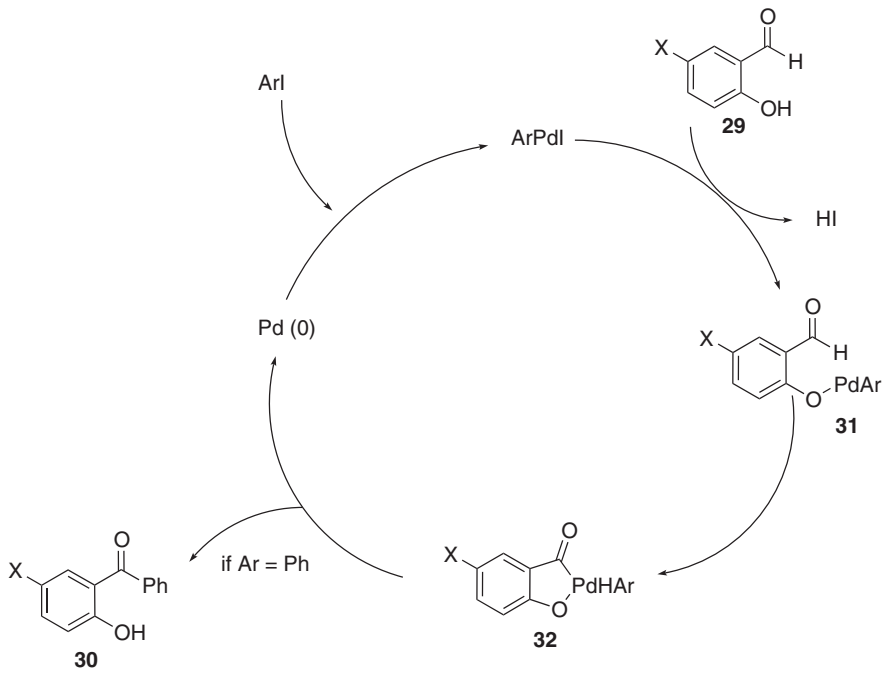
Walter <1995COFGT(3)277> described 2-alkyl-1,3-dithianes, protected cyanohydrins and acyl radicals as examples of acyl anion equivalents. In this review the two alternative approaches to aromatic ketones are introduced, which enable the direct conversion of aldehydes into ketones. These are hydroacylation, which allows the direct coupling of organic halides with aldehydes via the activation of the aldehyde hydrogen by a transition metal catalyst (Section 3.06.1.4.1), and homologation of aldehydes into benzylic ketones (Section 3.06.2.2). Recent developments in the use of acyl radicals as acyl anion equivalents are discussed in Section 3.06.1.4.2.

3.06.1.4.1 Hydroacylation—the transition metal-mediated conversion of aryl aldehydes into aryl ketones

Traditionally, aldehydes are converted into ketones by a two-step process involving the reaction of a Grignard reagent with the aldehyde followed by oxidation to the ketone. Thus, direct routes for converting aldehydes into ketones are highly desirable. Miura and co-workers <1996CL823> reported the direct smooth catalytic arylation of hydroxybenzaldehydes with aryl iodides using a catalytic system of $PdCl_2$/LiCl in the presence of Na_2CO_3 giving a variety of 2-aroylphenols. The cross-coupling between iodobenzene and salicyl aldehydes **29** is shown in Equation (36). Scheme 16 shows a general catalytic cycle for the reaction, involving oxidative addition of the iodobenzene to the Pd(0) species generated *in situ* followed by the reaction with **29** forming an aryl(aryloxy)palladium intermediate **31**. Then, a second oxidative addition of the aldehyde C—H bond to the metal affords Pd(IV) species **32** and the subsequent twofold reductive elimination is proposed to give the product 2-aroylphenol **30**.

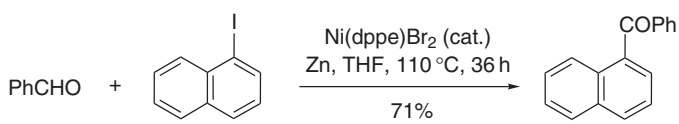


(36)



Scheme 16

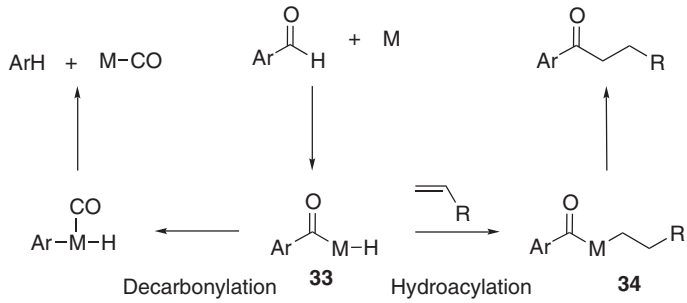
Cheng and co-workers reported the coupling of aryl iodides with aryl aldehydes in the presence of Ni(dppe)Br_2 and Zn to give the corresponding biaryl ketones in fair-to-good yields (Equation (37)) <2002JOC1682>. As with previous nickel-catalyzed coupling reactions, only bidentate-phosphine nickel complexes proved effective. The use of aryl iodides was essential as aryl bromides gave the corresponding alcohols, and THF was found to be the best solvent. The role of zinc metal was to reduce Ni(II) to Ni(0) to initiate the catalytic process and facilitate the reductive elimination to regenerate Ni(0). Zn(II) also acts as a Lewis acid during the catalytic cycle.



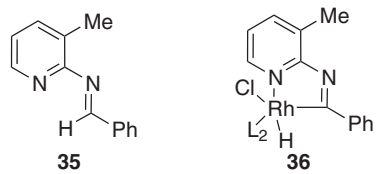
(37)

Scheme 17 shows a different hydroacylation involving an aldehyde and terminal alkene. The key step of the mechanism is the cleavage of the aldehyde C—H bond by a transition metal complex to generate a reactive metal hydride **33**. There are two distinctive pathways that **33** can take: an unwanted decarbonylation to give a hydrocarbon and metal carbonyl, or the required hydrometallation of the alkene substrate to give an acylmetal alkyl complex **34**, and final reductive elimination to give the ketone.

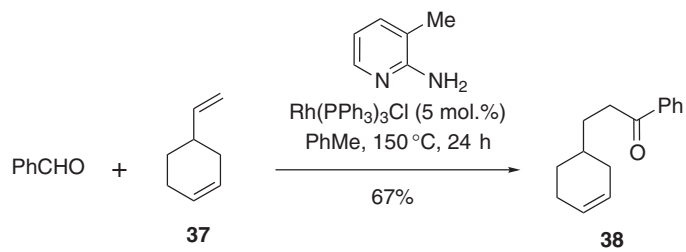
One way of suppressing the decarbonylation is by stabilizing **33** through chelation or cyclometallation. For example, using *N*-(3-methyl-2-pyridyl)-*N*-(1-phenylmethylidene)amine **35**, in which the carbonyl group of the aldehyde is masked by an imino group providing a 1,5-relationship between the coordination site and the C—H bond. This structure promotes acylation by placing the metal in the correct position to cleave the C—H bond via coordination yielding a stable acylmetal hydride complex (e.g., **36**) <1999SL1>. Hydrolysis of the subsequently formed ketimine provides the product, ketone.



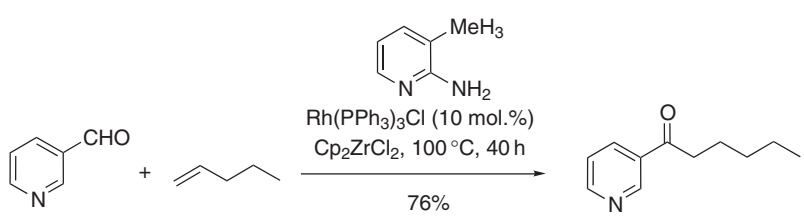
Scheme 17



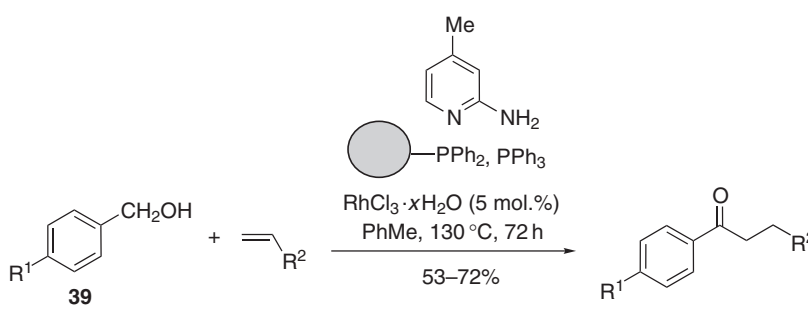
Using these principles, Jun and co-workers <1997JOC1200> reported the synthesis of various ketones by one-step intermolecular hydroacylation of aldehydes by using the co-catalyst system of rhodium(I) complex (Wilkinson's catalyst) and 2-amino-3-picoline, as illustrated by the reaction of the chiral alkene, 4-vinylcyclohexene **37** with benzaldehyde to afford the corresponding ketone **38** with retention of the asymmetric center in the 3-cyclohexenyl group (Equation (38)). The research group of Jun has published prolifically on this reaction including the hydroacylation of various heteroaromatic aldehydes with 1-pentene, as illustrated by the reaction of pyridine-3-carbaldehyde given in Equation (39) <1997TL6673>. Further, highly active Rh(I) catalyst systems for intermolecular hydroacylations have been reported <2000AG(E)3070>, including the direct synthesis of aromatic ketones from benzyl alcohols **39** and 1-alkenes, as shown in Equation (40) <1998AG(E)145, 1999TL8897>. The first step must involve an oxidation of the benzylalcohol **39** by hydrogen transfer to the alkene, so forming the aromatic aldehyde *in situ*.



(38)

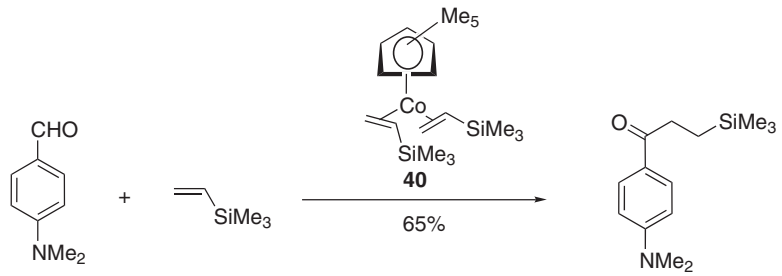


(39)



(40)

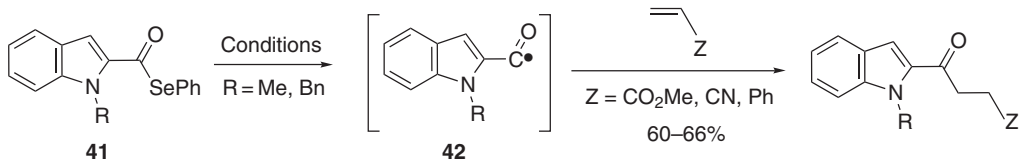
Brookhart and co-workers <1997JA3165, 1998JA6965> have described a very mild room temperature hydroacylation reaction of vinyl silanes by aromatic aldehydes using the cobalt(I) complex **40** as a catalyst, as shown in Equation (41).



(41)

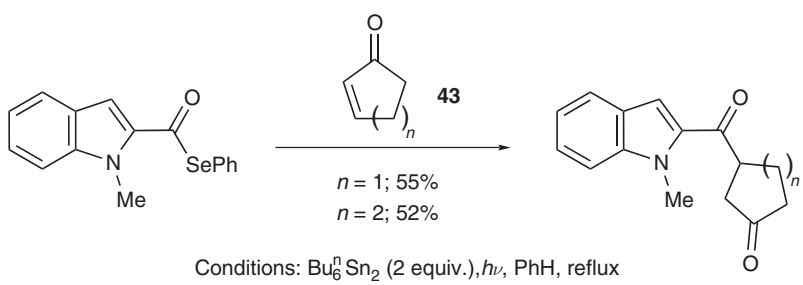
3.06.1.4.2 Acyl radicals

In contrast to acyloxyl radicals ($RCO_2^{\bullet}$), which irreversibly eliminate carbon dioxide to give the respective alkyl radical ($R^{\bullet}$), acyl radicals only undergo decarbonylation reversibly, since alkyl radicals add to carbon monoxide, but not to carbon dioxide <1999CRV1991, B-2000MI002>. Moreover, aryl acyl radicals are less prone to decarbonylation than alkyl acyl radicals; therefore, with the added benefits of regio- and chemoselectivity that can be achieved under optimized free-radical conditions, acyl radicals are a useful means of generating aromatic ketones. Acyl radicals can be classified as acyl anion equivalents because they are nucleophilic, and so can readily undergo additions onto electron-deficient alkenes. This was recently demonstrated by Bennasar and co-workers <2001OL1697, 2001JOC7547> with the generation of nucleophilic 2-indolylacyl radicals **42** from phenylselenoesters **41**, which underwent efficient additions onto methyl acrylate, acrylonitrile, and styrene, as shown in Equation (42). To minimize the reduction of the intermediate acyl radical **42** by *n*-Bu_3SnH, photolysis of *n*-Bu_6Sn_2 was used in the case of the addition onto the α,β-unsaturated cyclic ketones **43** represented in Equation (43). Radicals **42** were also used to form biaryl ketones via intermolecular homolytic aromatic substitutions onto substituted pyridines <2001OL1697>.



(42)

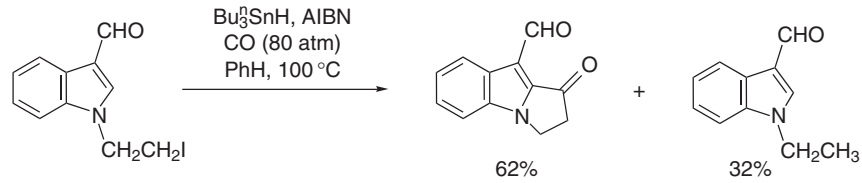
Conditions: Bu^n_3SnH (1.2 equiv.), AIBN (2 equiv.), slow addition, PhH, reflux



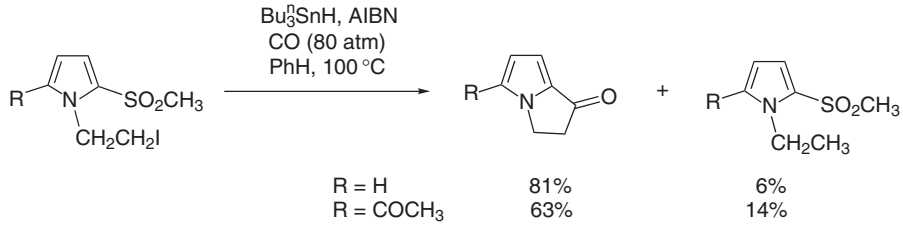
(43)

Conditions: $Bu^n_6Sn_2$ (2 equiv.), $h\nu$, PhH, reflux

Alternatively, acyl radicals can be generated by the trapping of alkyl or aryl radicals by CO. Recently, alkyl acyl radicals generated via carbonylation were shown to undergo intramolecular cyclizations onto the activated 2-position of indole <1999TL7153> and pyrrole <2000TL3035> to form good yields of bicyclic aromatic ketones, as shown by Equations (44) and (45), respectively. An improvement to the latter procedure was reported, which eliminated the requirement for high pressures of CO. This involved the generation of acyl radicals from acyl selenide radical precursors with subsequent cyclization onto the activated pyrrole-α-positions <2001TL7887>.



(44)



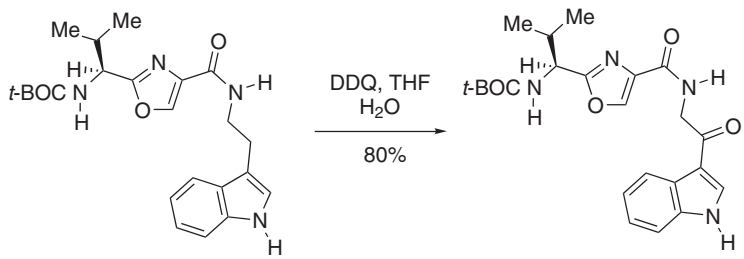
(45)

3.06.1.5 Oxidation

Walter <1995COFGT(3)277> briefly reviewed many of the reagents commonly employed for the oxidation of methylene carbon atoms, secondary alcohols, and alkenes to aromatic ketones. Volume 7 of *1991 Comprehensive Organic Synthesis* is dedicated to oxidation reactions <1991COS(7)>. A brief survey of more recent oxidation reactions has also been carried out by Lawrence <1998JCS(P1)1739>. Since the 1990s, a multitude of new oxidizing systems has been introduced which follow the proviso of being selective, nontoxic, and operate under mild (neutral) conditions. The following sections give examples of oxidants, which have grown in popularity since 1995, and briefly review some newly introduced reagents.

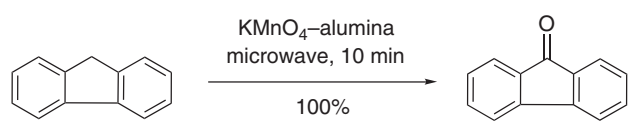
3.06.1.5.1 Oxidations of benzylic methylene groups

Benzylic methylene groups are activated toward oxidation, and can be converted into aromatic ketones using a multitude of reagents. DDQ is often used, as represented by the example in Equation (46) <2000TL831>.



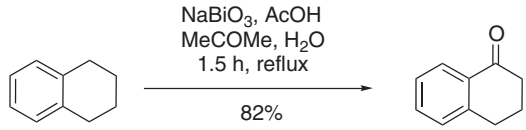
(46)

Solid-supported reagents have grown in popularity in recent years <2001T4637>; for example, the solvent-free oxidation of benzylic methylenes with $KMnO_4$ supported on montmorillonite K10 was recently reported <2002TL5165>. $KMnO_4$ impregnated on alumina can also be used to selectively oxidize benzylic methylenes to aromatic ketones, but the reaction is very slow when performed at room temperature. The reaction can be significantly accelerated by using dry microwave irradiation conditions. Equation (47) shows the conversion of fluorene into fluoren-9-one, which was complete in 10 min, and under the same conditions diphenylmethane was oxidized into benzophenone in 30 min <1997JCR(S)342>.

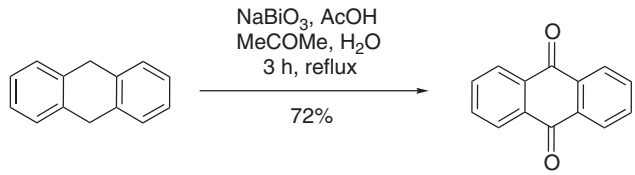


(47)

Further new methods include the use of sodium bismuthate ($NaBiO_3$) in a refluxing aqueous solution of acetic acid, and acetone was reported to oxidize benzylic methylenes in polycyclic systems, as shown in Equations (48) and (49) <1998TL7247>. Nicolaou and co-workers <2002JA2245> have shown that excess IBX (2-iodoxybenzoic acid) used at elevated temperatures has a similar reactivity, successfully oxidizing various benzylic methylenes to aryl aldehydes and ketones (Chapter 3.03).

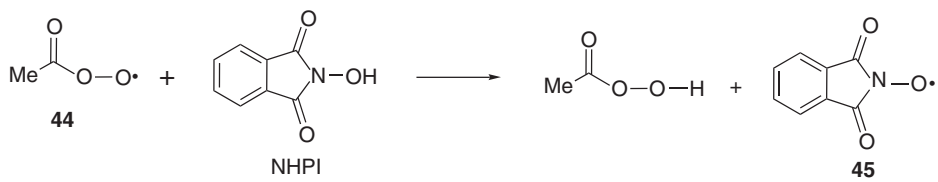


(48)

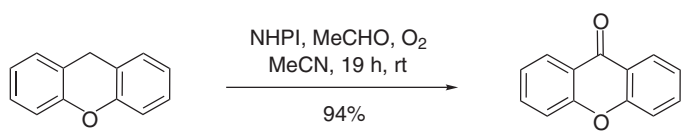


(49)

Room temperature oxidations with molecular oxygen have been reported, including the recent use of a complex Co(II)/Ni(II)/Cr(III)/*N*-hydroxyphthalimide (NHPI)–PhCHO system <2003EJO578>. Earlier, Einhorn and co-workers had reported efficient O_2-oxidations in the absence of transition metal catalysts in which acetaldehyde is the co-oxidant forming peracid radical **44** *in situ*, which in turn oxidizes NHPI as shown in Equation (50) <1997CC447>. Phthalimide *N*-oxyl **45** is a fairly stable but highly reactive free radical, which is known to be the key intermediate in NHPI oxidations. An example of this oxidation is shown in Equation (51). This system could also oxidize some activated secondary benzylic alcohols to aromatic ketones. MCPBA in the presence of $NaHCO_3$ was reported to oxidize benzylic methylenes to ketones, but only in the presence of oxygen. The latter suspected radical reaction was limited though, as it failed for 3-ethylpyridine and aromatics substituted by electron-withdrawing groups (e.g., 2-ethyl-1-nitrobenzene) <1999TL8915>.



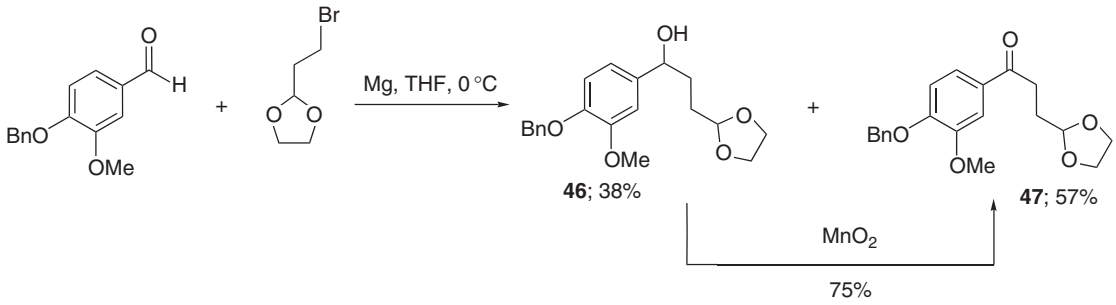
(50)



(51)

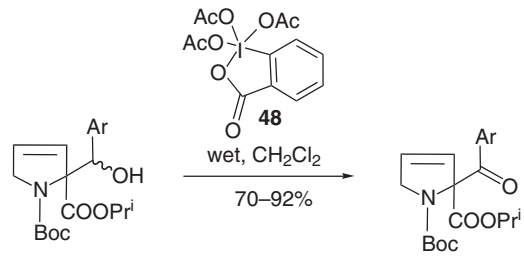
3.06.1.5.2 Oxidations of secondary benzylic alcohols

Rather than direct acylation, aromatic ketones may be obtained via a Grignard reaction on an aromatic aldehyde followed by oxidation of the resultant secondary alcohol. For example, the reaction shown in Scheme 18 gave the expected alcohol **46**, and unexpectedly the aryl ketone **47** <2000TL2207>. The formation of **47** was attributed to the air oxidation of alcohol **46**, and exemplifies the ease with which secondary benzylic alcohols may be oxidized into ketones. There are a multitude of oxidizing agents for alcohols, and because of the activated nature of the benzylic position, most can easily oxidize secondary benzylic alcohols to ketones. The focus of the following section is on new selective and mild oxidizing reagents, but oxidants that have grown in popularity since 1995 are also discussed. Many of the oxidations used to prepare aromatic aldehydes can also be used for aromatic ketones (see Chapter 3.03). But as shown in Scheme 18 traditional oxidants are still widely used including the reliable oxidant-activated manganese dioxide, which directly oxidized **46** to **47** in 75% yield. Chemical manganese dioxide produced for dry battery manufacture can also be used to efficiently facilitate benzylic alcohol oxidations <1998SL35>.



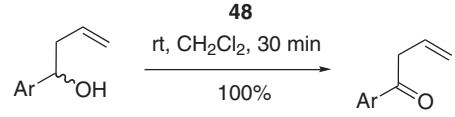
Scheme 18

The Dess–Martin periodinane **48** has become one of the most widely used oxidizing agents, and is known to be activated by water <1994JOC7549>, as shown in Equation (52) for the conversion of hindered secondary benzylic alcohols into ketones <2000TL989>.



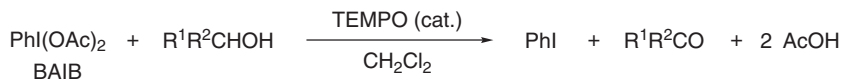
(52)

The Dess–Martin reagent **48** is one of the mildest oxidation techniques, as exemplified by Equation (53). The neutral conditions prevent isomerization to the more stable α,β-unsaturated ketone, which was observed when the acidic conditions of the traditional Jones reagent or PCC were employed <2002T7381>.



(53)

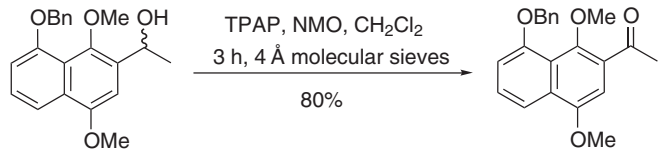
Oxidizing systems using stable nitroxyl free radical (or nitroxide, $R_2NO^{\cdot}$) catalysts have received plenty of recent interest as mild oxidants of alcohols <1996S1153>. Recently introduced systems include the use of catalytic amounts of the commercially available nitroxide, TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxyl) in the presence of [bis(acetoxy)iodo]benzene (BAIB) for the conversion of primary and secondary alcohols into carbonyls (Equation (54)) <1997JOC6974>. Catalytic TEMPO in the presence of poly[4-(diacetoxyiodo)styrene] in acetone was reported as an environmentally friendly system <2003S21>.



(54)

Other nonmetallic reagents include positive halogen reagents such as sodium or calcium hypochlorite, NBS, bis(quinuclidine)bromine(I) reagents, and the more recently introduced bis(*sym*-collidine)bromine(I) hexafluorophosphate <2000TL8881>. These nonmetallic reagents are often promoted as alternatives to activated-DMSO reagents (such as Moffatt or Swern), which produce malodorous dimethyl sulfide as a by-product.

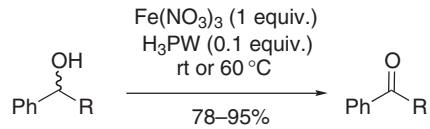
TPAP (tetrapropylammonium perruthenate, $(CH_3CH_2CH_2)_4NRuO_4$) is a mild, nonvolatile oxidant for alcohols, which is rendered catalytic if used in combination with the co-oxidant NMO <1994S639>. TPAP/NMO has become a popular oxidizing system; Equation (55) shows a recent example of its use <2000TL1107>.



(55)

Late transition metals have been reported as effective catalysts for radical oxidations of benzylic alcohols into ketones. These include $Pd(OAc)_2$, which, in the presence of pyridine bases in toluene at 80 °C under an oxygen atmosphere, catalyzed the oxidation of benzylic alcohols into aromatic aldehydes and ketones <1998TL6011>. Dirhodium(II) tetraacetate ($Rh_2(OAc)_4$) was used as a catalyst for the oxidations of benzylic alcohols using stoichiometric amounts of *t*-butylhydroperoxide in CH_2Cl_2 <2002TL139>.

Much attention has recently been given to the development of oxidizing systems that do not use toxic and environmentally damaging volatile organic solvents (VOSs). These include performing oxidations in solventless systems under microwave irradiation conditions. Clay-supported iron(III) nitrate (clayfen) <1997TL2043>, silica-supported manganese dioxide <1997TL7823>, and alumina-supported wet chromium(VI) nitrate <1998TL1481> have all been shown by Varma and co-workers <2002T1235> to be particularly effective for the oxidation of various benzylic alcohols to aldehydes and ketones under microwave irradiation conditions. Similarly, solventless microwave irradiation conditions were used, when iron(III) nitrate was activated by adsorption onto zeolite, providing a novel oxidizing system called zeofen <1999CC833>. More recently, iron(III) nitrate in the presence of a catalytic amount of tungstophosphoric acid (H_3PW) was introduced as a new oxidizing system <2003S408>. Equation (56) shows the selective mild oxidation of benzylic alcohols to ketones, which were complete in 10–60 min without the use of solvent or microwaves. Another recent method involved heating secondary benzylic alcohols in molten tetra-*n*-butylammonium bromide with catalytic amounts of palladium chloride in an oxygen-free atmosphere to produce the corresponding ketones in yields of 67–91%. The ammonium salt apparently stabilizes the palladium catalyst during the dehydrogenation, and the catalyst–ammonium salt system could be recycled, but gradually loses its reactivity <2002TL6641>.

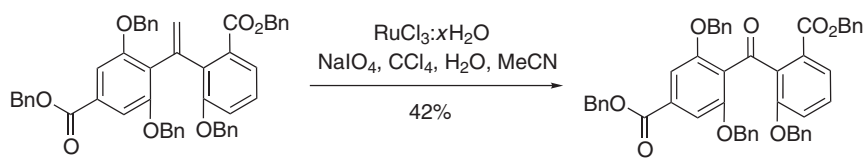


(56)

Traditional reagents such as manganese dioxide <2002TL6149> and PCC adsorbed onto neutral alumina <2003T3493> have also been shown to be expedient solventless oxidants. Finally, potassium ferrate (K_2FeO_4) in *n*-pentane in the presence of clay supports has been shown to efficiently oxidize benzylic alcohols to aldehydes and ketones <1996JOC6360>.

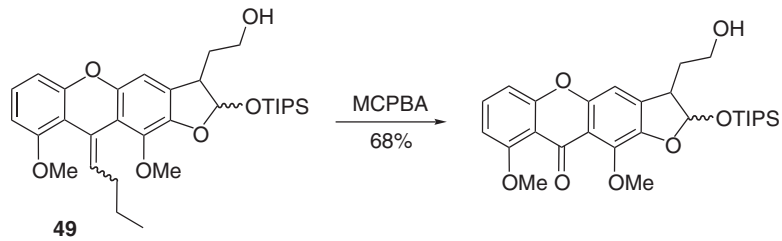
3.06.1.5.3 Oxidative cleavage of double bonds

Recent examples of the use of oxidative cleavage of double bonds to yield aryl ketones include the use of ruthenium tetraoxide by Skrydstrup and co-workers <2002T2231> to give the desired benzophenone moiety in the synthesis of the protein kinase C inhibitor, balanol, as shown in Equation (57).



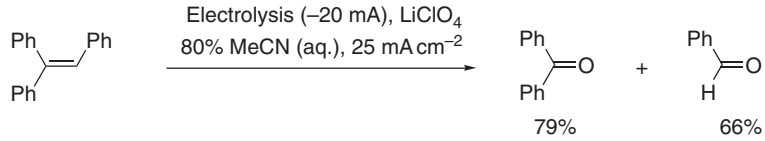
(57)

Casillas and Townsend <1999JOC4050> proposed the butenyl group in **49** as a protecting group for aromatic ketones, which allowed further chemical modifications on the xanthone nucleus prior to efficient one-step oxidative cleavage as shown in Equation (58).



49 (58)

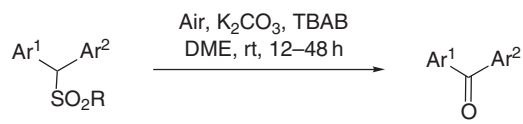
Electrochemical cleavage of styryl olefins has been reported to give aromatic ketones, as demonstrated in Equation (59) <1997SL1385>.



(59)

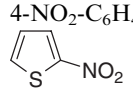
3.06.1.5.4 Oxidation of nitro-α-sulfonylphenylmethanes

Wojciechowski <1997SC(27)135> showed that nitro-α-sulfonylphenylmethane derivatives can undergo oxidation in the presence of solid K_2CO_3 and TBAB in DME to give good yields of nitrobenzophenones, as shown in Equation (60) and Table 2. A further example is given in Equation (77) (Section 3.06.2.4).



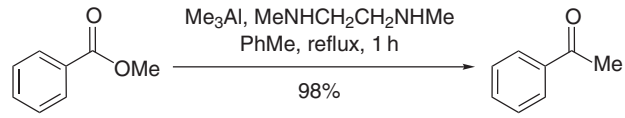
(60)

Table 2 Synthesis of nitrobenzophenones from nitro-α-sulfonyldiphenylmethane derivatives according to equation (60)

Ar^1	Ar^2	R	*Yield (%) of nitrobenzophenones*
Ph	4-NO_2-C_6H_4	$(CH_2CH_2)_2NO$	54
4-MeO-C_6H_4	4-NO_2-C_6H_4	Ph	86
Ph		Ph	67
	4-NO_2-C_6H_4	Tol	80

3.06.1.6 Reduction of Aryl Esters to Aryl Ketones

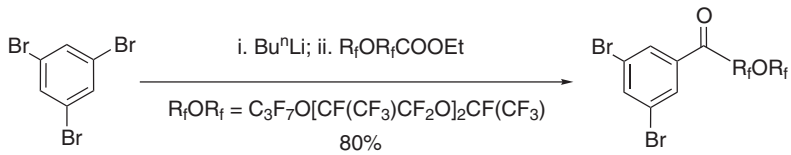
The direct conversion of carboxylic esters into ketones is usually difficult to achieve owing to the fact that the ketone is more reactive toward nucleophiles than the starting ester, and in most cases overreacted products, such as tertiary alcohols, are obtained. The most common reducing agent for the conversion of esters into aldehydes is DIBAL-H, diisobutylaluminum hydride, and *i*-Bu_2AlH. Organoaluminum complexes generated from trialkylaluminum and diamine were reported by Ahn and co-workers <1998JOC7590> to facilitate the direct conversion of esters into ketones, without the formation of over-addition products. Equation (61) shows the conversion of methyl benzoate into acetophenone. Replacing Me_3Al by Et_3Al could equally give the corresponding ethyl ketones.



(61)

3.06.2 PHENYL KETONES AND SUBSTITUTED ANALOGS

A survey of the reactivity of monoalkyl, dialkyl, polyalkyl, halophenyl, alkoxyaryl and phenylthiol ketones was carried out by Walter, and will not be repeated in this review <1995COFGT(3)277>. Friedel–Crafts acylations of slightly activated and de-activated phenyl derivatives have been reported (see Section 3.06.1.1); however, electrophilic acylations of their organometallic derivatives are often more amenable. For example, the reaction between organolithium intermediates and perfluoroesters was reported to give high yields of aromatic ketones, as represented by the example in Equation (62) <1995JFC(75)117>.

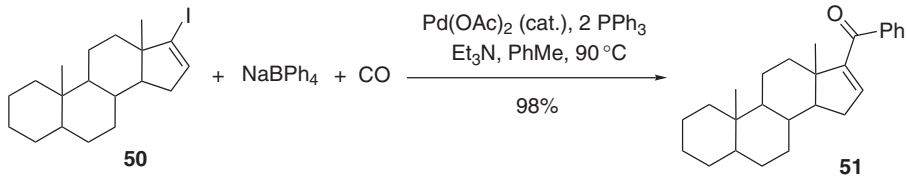


(62)

In addition, anisole and its activated derivatives readily undergo Friedel–Crafts-type reactions with strong *para*-selectivity, with many recent examples provided in Section 3.06.1.1.1. Furthermore, alkoxy aromatic substituents are compatible with most general methods covered in this review. Phenylthiolketones are similarly activated toward Friedel–Crafts acylations, but *ortho*- and *para*-directing effects are less than those of oxygen analogs. Sulfur can also compete with benzylic alcohols in certain oxidation reactions, and can poison catalysts in palladium-mediated reactions.

3.06.2.1 Phenyl Ketones

There are now many electrophilic acylating agents capable of the acylation of benzene under mild conditions. However, the electrophilic acylation of readily available phenylorganometallic reagents is often the methods of choice. Complex and simple phenyl ketones <2001TL265> can be prepared by the many techniques described in the previous sections including the palladium-catalyzed three-component cross-coupling reaction between an alkyl halide (e.g., **50**), $NaBPh_4$, and carbon monoxide (CO), as shown in Equation (63) for the synthesis of the steroidal phenyl ketone derivative **51** <2000T3415>.

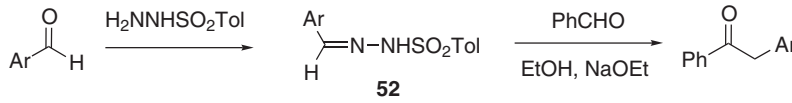


50 **51**

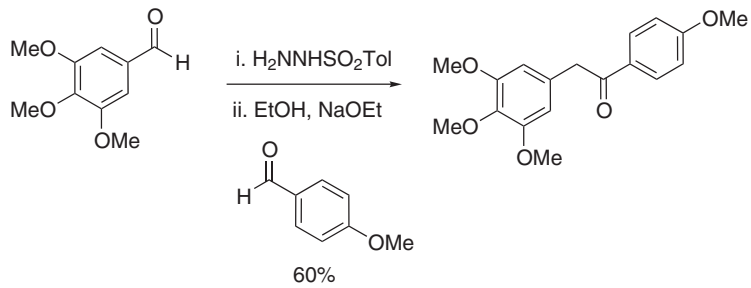
(63)

3.06.2.2 Benzylic Ketones

Section 3.06.1.4.1 gave examples of the direct conversion of aldehydes into aromatic ketones. The one-step conversion of aldehydes into benzyl ketones can be achieved by homologation of the aldehyde via a diazo-intermediate. Scheme 19 shows the homologation of aromatic aldehydes to benzylic ketones; the aryl aldehyde is first converted to the corresponding tosylhydrazone **52** and then reacted with a second aromatic aldehyde (e.g., benzaldehyde) under basic conditions in hot ethanol to give the benzylic ketone <2000JOC6458>. This methodology is an improvement on previous homologations of aldehydes into benzylic ketones as no isolation of toxic and/or explosive aryldiazomethanes is required, and it is applicable to the preparation of wide range of both aliphatic and aromatic benzylic ketones (e.g., Equation (64)).

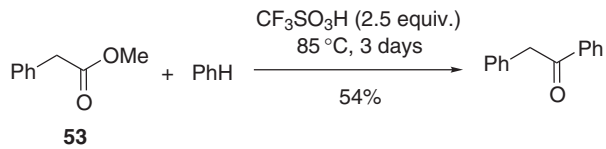


Scheme 19



(64)

An alternative example of the preparation of benzylic ketones is provided by the activation by trifluoromethanesulfonic acid of methyl phenylacetate **53** toward a Friedel–Crafts reaction with benzene, as shown in Equation (65) (see Section 3.06.1.1.3) <2000T7199>.



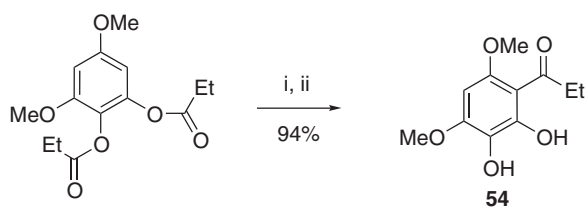
(65)

3.06.2.3 Phenolic Ketones

The most widely used preparation of phenolic ketones is the Fries rearrangement. The following section is a short review of relevant Fries rearrangements reported since 1995.

3.06.2.3.1 The Fries rearrangement

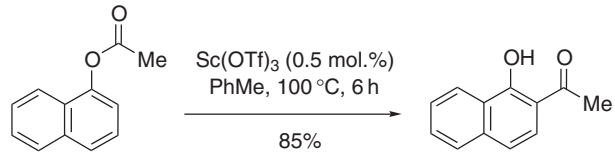
The Fries rearrangement is a Lewis acid-catalyzed rearrangement of phenolic esters to *ortho*- and *para*-substituted ketones <1991COS(2)733>. Scheme 20 shows an example of a recent Fries rearrangement mediated by $AlCl_3$, which was followed by hydrolysis to give the required ethyl aryl ketone **54** in 94% overall yield <2000TL5501>.



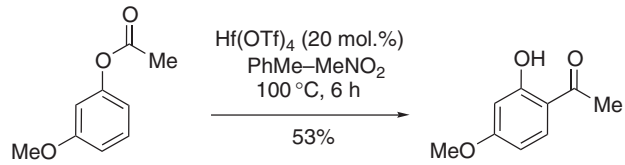
Scheme 20

However, certain Fries rearrangements occur only sluggishly in the presence of $AlCl_3$, and often the drastic conditions employed induce severe side reactions <1992S738>. In the 1990s, significant advances were made with the introduction of alternative Lewis acid catalysts, which allow the reaction to occur under mild conditions with often complete *ortho*-regioselectivity <B-2000MI001>. Titanium tetrachloride <1992S738>, scandium triflate <1995CC1527>, hafnium triflate <1996TL2053>, and zirconium tetrachloride <1996TL7659> have all been reported to catalyze the Fries rearrangement of

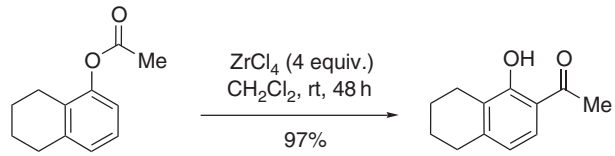
phenol and naphthol esters to give 2-hydroxyphenyl and 2-hydroxynaphthyl ketones in good-to-excellent yields. Representative examples are shown in Equations (66)–(68).



(66)

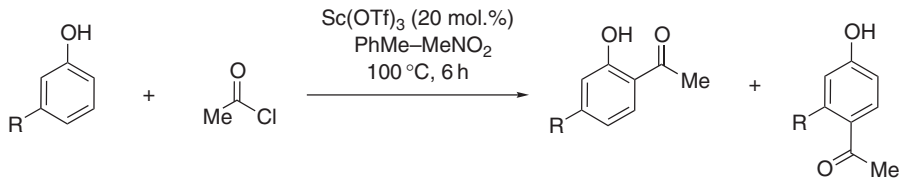


(67)



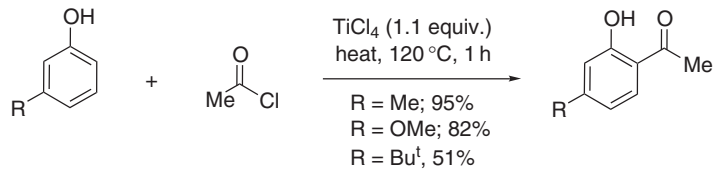
(68)

Kobayashi and co-workers were the first to show that the efficiency of the transformation could be increased by the formation of the 2-hydroxyaryl ketones directly from the free phenol or naphthol without the prior isolation of the ester. An example is given in Equation (69); the authors assumed a two-step reaction mechanism involving the formation of the ester followed by Fries rearrangement. Both $Sc(OTf)_3$ <1995SL1153> and $Hf(OTf)_4$ <1996TL2053> were used to effectively catalyze this transformation with no trace of the latter Lewis acids trapped by the functional groups involved, as is the case with conventional Lewis acids (see Section 3.06.1.1).



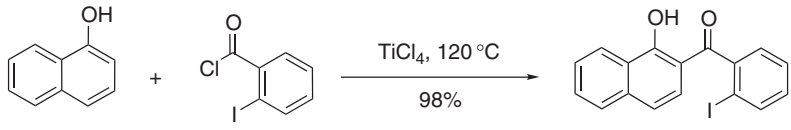
(69)

Similarly, titanium(IV) chloride was most recently shown to mediate the regioselective *ortho*-acylation of phenols and naphthols allowing the preparation of a range of 2-hydroxyphenyl and 2-hydroxynaphthyl ketones in moderate-to-high yield <2003S267>, as shown in Equation (70). The procedure showed complete selectivity even when the *para* position was unsubstituted with acylation always occurring at the sterically least shielded *ortho* position.



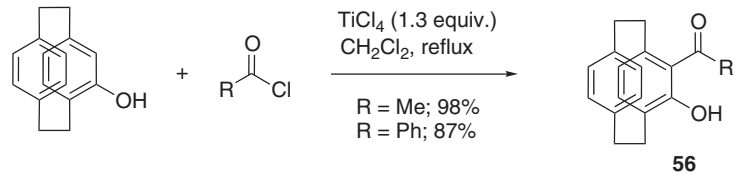
(70)

$TiCl_4$ is a much milder Lewis acid than $AlCl_3$ and is now in general use for the synthesis of 2-hydroxyarylketones, as shown in the examples given in Equations (71) <2000TL5317> and (72) <2000EJO3295> for the respective synthesis of 2-hydroxynaphthylketone **55** and *ortho*-acylhydroxy[2,2]paracyclophane **56**.



(71)

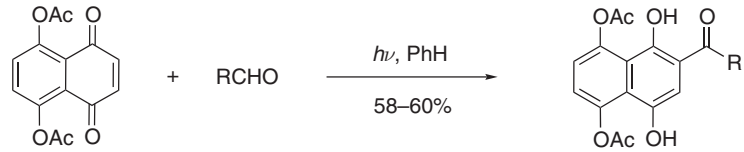
55



56 (72)

3.06.2.3.2 *Miscellaneous methods of phenolic ketone synthesis*

The photoreaction between a quinone and an aldehyde is known as the "photo-Friedel–Crafts acylation." The reaction probably proceeds by H-abstraction from the aldehyde by the electronically excited quinone to produce an acyl radical, which adds to a second ground-state quinone in a free-radical chain reaction, although alternative mechanisms exist. A recent example is shown in Equation (73), where the irradiation of the 1,4-naphthoquinone in the presence of various aldehydes resulted in the acylated hydroquinones **57** in good yields <2001S1275>.

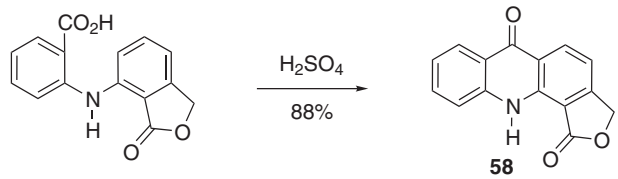


57 (73)

Section 3.06.1.4.1 described the Pd(0)-catalyzed cross-coupling reaction of salicylaldehydes and aryl iodides proceeded smoothly to give a variety of *o*-hydroxybiaryl ketones; examples are given in Equation (36).

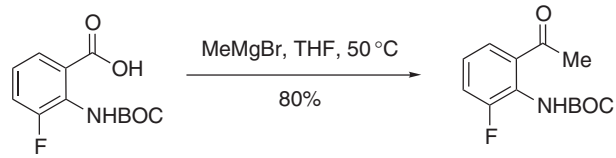
3.06.2.4 *N*-Substituted Phenyl Ketones

Aryl amides tend to form complexes with Lewis acids making Friedel–Crafts acylations difficult. However, concentrated sulfuric acid may be used with carboxylic acid acylating agents to perform efficient Friedel–Crafts-type cyclizations, as shown in Equation (74) for the preparation of acridone **58** <2001JOC612>.



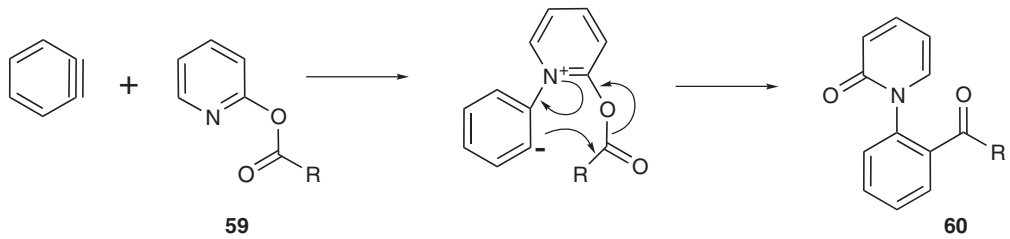
58 (74)

Amazingly, direct Grignard reagent addition onto benzoic acid to give aromatic ketones has also been reported. In latter reaction, *o*-aminoarylketones were formed in good yields, when the amino moiety of the anthranilic acid was protected with BOC (Equation (75)), trifluoroacetyl, or pivaloyl protecting groups <2001TL2097>.



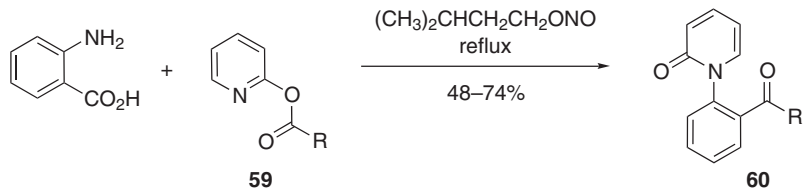
(75)

Cheng and co-workers prepared a series of 1-(2-acylphenyl)-2-pyridones **60** via an unusual 1,4-addition of 2-pyridyl carboxylates **59** to the 1,2-position of benzynes, as demonstrated by the mechanism in Scheme 21, and represented by Equation (76) <2001JOC3646>. Although the authors stressed that a concerted pathway via a six-membered cyclic transition state was also possible.



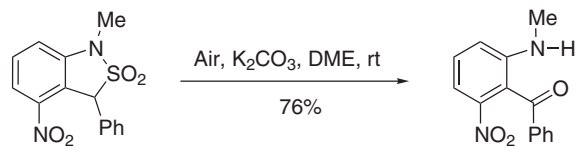
59 **60**

Scheme 21



59 **60** (76)

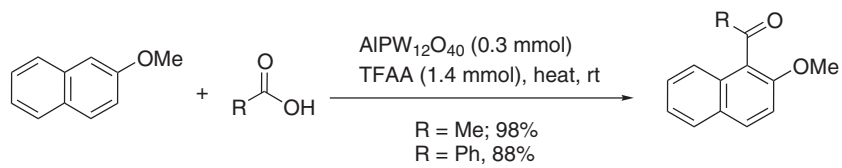
Equation (77) shows an example of the efficient conversion of 3-phenylbenzosultams to the respective benzophenone derivatives using an autoxidation reaction <1997SC(27)135>.



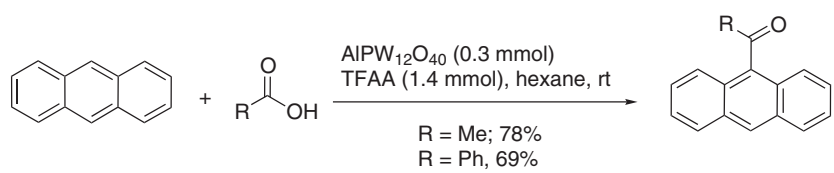
(77)

3.06.3 POLYCYCLIC ARYL KETONES

Naphthalene and activated naphthalenes such as methoxynaphthalenes can be readily alkanoylated and aroylated by typical Friedel–Crafts conditions with acid chlorides in the presence of a Lewis acid with the regioselectivity dependent upon the reaction temperature and identity of the Lewis acid <1994JCS(P1)1703>. 1-Methoxynaphthalene was reported to give the 4-benzoylated isomer in 93% yield using benzoyl bromide and graphite as the acylating agent and catalyst, respectively <1997CC1567>. Friedel–Crafts acylation of 2-methoxynaphthalene and anthracene has been reported to selectively give the 1- and 9-respective ketone isomers in good yields using carboxylic acids and aluminum dodecatungstophosphate ($AlPW_{12}O_{40}$) as the respective acylating agent and catalyst (Equations (78) and (79)) (also see Section 3.06.1.1.2) <2003TL5343>. Since 1995, there have been no further reports of acylations of higher polycyclic aromatics, although they will undergo Friedel–Crafts acylations quite easily <1995COFGT(3)277>.



(78)

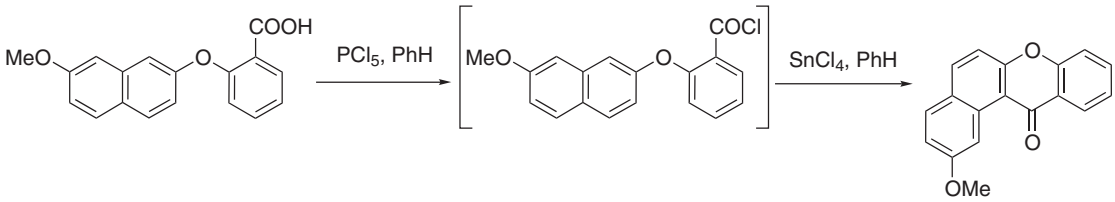


(79)

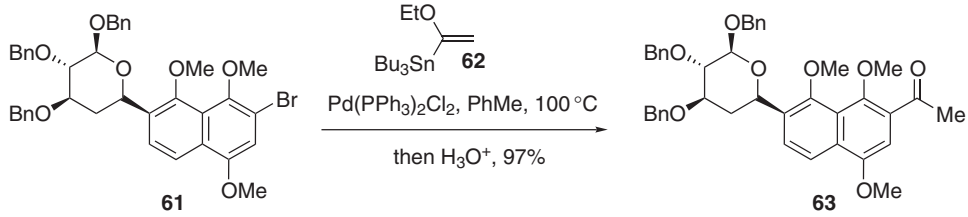
There are many examples of intramolecular Friedel–Crafts acylations including the $SnCl_4$-catalyzed acylation shown in Scheme 22 <2002OL1067>.

Alternatively, transition metal-mediated protocols may be used as represented by Equation (80). Bromomethoxynaphthalene **61** was efficiently acylated using a palladium-catalyzed coupling with α-ethoxyvinyltributyl tin **62** to afford the 3-ethanoylnaphthalene **63** <2000TL2991>. It was

noted that the introduction of an acyl group via lithiation of the bromide **61** was unsuccessful due to the highly basic nature of the naphthyl anion; however, the lithiation–acylation protocol can be used with some naphthalene derivatives as shown in Equation (20) (Section 3.06.1.2.1).



Scheme 22



(80)

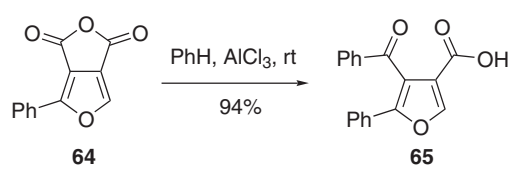
Periasamy and co-workers reported that polycyclic hydrocarbon aromatic aldehydes and ketones can be prepared by the treatment of the polyaromatic hydrocarbon with sodium metal, and quenching the highly conjugated radical anion with an appropriate carboxylic ester. For example, sodium naphthalenide gave *n*-propyl-1-naphthyl ketone (74%) and methyl-1-naphthyl ketone (60%) on reaction with methyl butanoate and ethyl acetate, respectively <1999SC(29)677>.

3.06.4 HETARYL KETONES

The reader should note that a different approach to the review of heteroaryl ketone preparations has been taken compared to that carried out by Walter <1995COFGT(3)277>, which reflects the major areas of research activity since the 1990s.

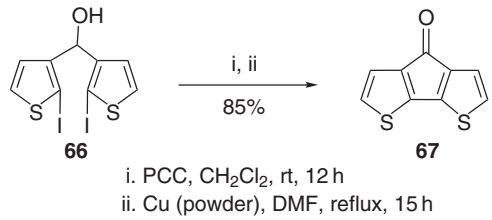
3.06.4.1 Furanyl Ketones and Ketothiophenes

Furan and thiophene readily undergo Friedel–Crafts acylations, although mild conditions are required for furan, which is sensitive to strong acidic media and easily polymerizes. Moreover, furanyl and thiophenyl ketones have be prepared using most of the previously discussed general methods <1995COFGT(3)277>. A curious Friedel–Crafts acylation was reported by Ye and co-workers <2001H265> in which unsymmetrical-substituted cyclic anhydride **64** was reported to give a single product **65** (Equation (81)). This surprising regioselectivity was general for acylation with toluene and chlorobenzene, which also gave only the 3-benzoyl-substituted product.



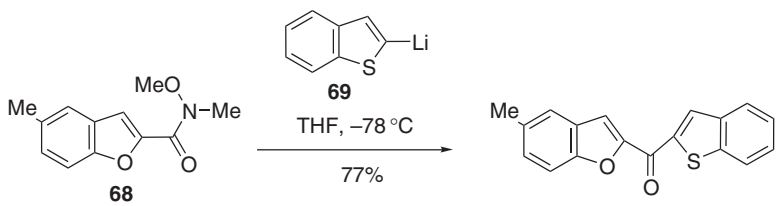
(81)

A new efficient three-step synthesis of 4*H*-cyclopenta[2,1-*b*:3,4-*b*′]dithiophen-4-one **67** was recently described involving the initial one-pot synthesis of bis-(2-iodo-3-thienyl)methanol **66** followed by PCC-oxidation and Ullmann coupling as shown in Scheme 23 <2002S1053>. Ullmann couplings have been used to couple thiophene rings at the 2-position in earlier preparations of **67** <2000S1253>.



Scheme 23

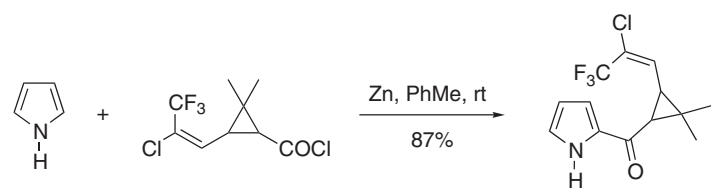
There have been no further developments in the preparation of benzofuranyl- and benzothiophenyl ketones. Benzofuranyl ketones are usually prepared by ring synthesis methods, and are prone to acidic polymerization. Benzothiophenyl ketones undergo electrophilic acylation at the 3-position, although selectivity varies with the type of Friedel–Crafts catalyst used. Both benzofuranyl and benzothiophenyl ketones have been prepared via the organometallic methods previously discussed, and are not specifically covered in this review <1995COFGT(3)277>. More recently, the preparation of Weinreb's amide derivative **68** allowed selective acylation of 2-lithiobenzo[*b*]thiophene **69** in 77% yield, as shown in Equation (82) <1997H1363>.



(82)

3.06.4.2 Pyrrolic Ketones

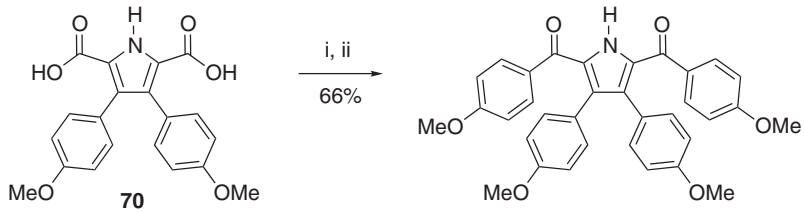
The preparation of 2-ketopyrroles by a direct Friedel–Crafts *C*-acylation on pyrrole is difficult, because of acid-catalyzed polymerization of the highly nucleophilic pyrrole nucleus. Recently, new milder Friedel–Crafts conditions have been introduced to overcome this limitation (see Section 3.06.1.1.3) <2002OL459>. Alternatively, 2-acylpyrroles can be formed by Vilsmeier–Haack methods using a combination of an *N*,*N*-dimethylacetamide and $POCl_3$ <1954JCS3842, 1971JOC2897>, and 2-ketopyrroles can be formed by many indirect methods. Yadav and co-workers <2002TL8133> reported the regioselective acylation of pyrrole at the 2-position using various acid chlorides in the presence of zinc powder in toluene at ambient temperature, as represented by the example in Equation (83).



(83)

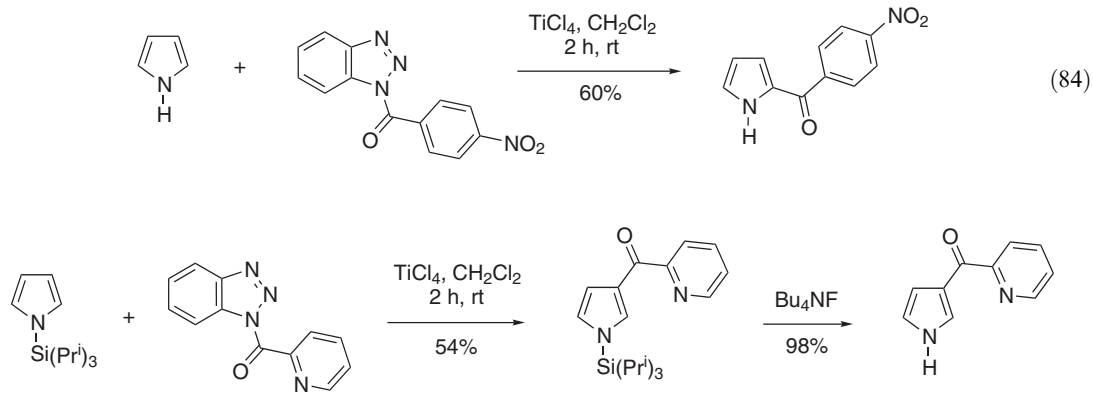
Alternatively, the acid chloride derivative of pyrrole acids can be used as the acylating agent as shown in Scheme 24. As part of the total synthesis of marine pyrrole alkaloid, polycitone B; Steglich and co-workers <2002OL3287> performed a double Friedel–Crafts acylation on anisole with the acid chloride derivative of 2,5-pyrrole dicarboxylic acid **70**.

Most recently, Katritzky and co-workers reported a very mild and regioselective acylation of pyrrole and *N*-methylpyrrole using *N*-acylbenzotriazoles in the presence of $TiCl_4$ <2003JOC5720>. Various 2-acylpyrroles were prepared in good-to-excellent yields, as represented by the example in Equation (84). The methodology was also used to regioselectively prepare 3-acylindoles (Section 3.06.4.3), and 3-acylpyrroles in good yields, as represented by the example in Scheme 25. The bulky triisopropylsilyl (TIPS) protecting group was necessary to direct the acylation onto the pyrrole-3-position. Classically, 3-acylpyrroles are obtained via a Friedel–Crafts acylation on pyrrole-*N*-substituted by electron-withdrawing groups (e.g., SO_2Ph) with the latter protecting groups removed using strongly alkaline conditions <1983JOC3214, 1993JOC7899>.



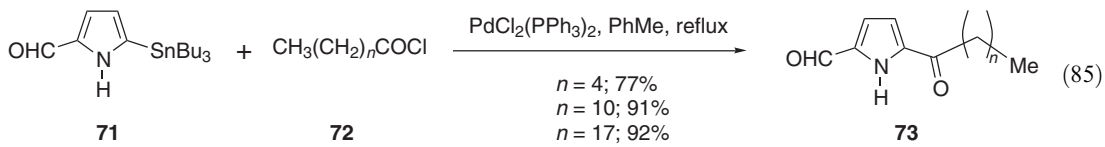
i. $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C, 2 h
ii. PhOMe, $AlCl_3$, CH_2Cl_2, rt, 12 h

Scheme 24



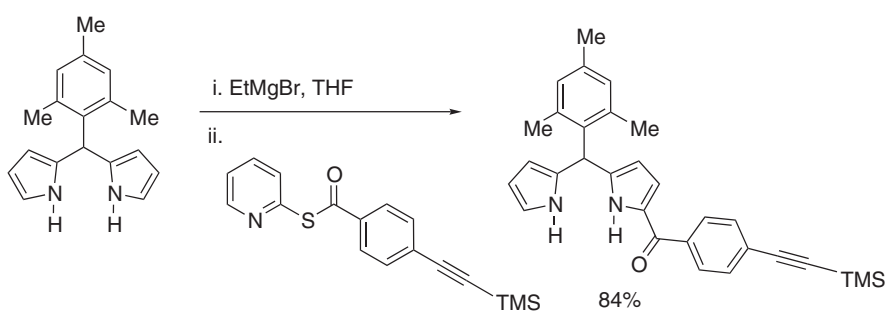
Scheme 25

Nabbs and Abell reported an efficient Pd(II)-catalyzed Stille-coupling between 5-(tri-*n*-butylstannyl)pyrrole-2-carboxaldehyde **71** and various fatty acid chlorides **72** to give exclusively the 5-acylketones **73**, as shown in Equation (85) <1999BMCL505>.



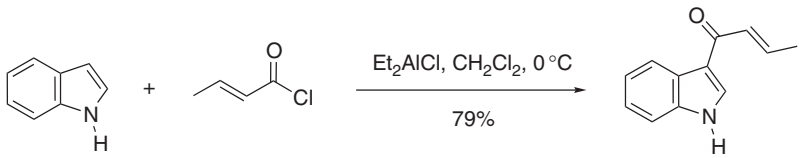
71 **72** **73**

Equation (86) shows an example of the monoacylation of 5-aryldipyrromethane reported by Lindsey and co-workers <2000JOC1084, 2000JOC7323>, which involved sequential treatment with EtMgBr (2.0 equiv.) followed by pyridyl thioester (2.5 equiv.). A subsequent acylation at the 9-position was possible by treatment with a large excess of EtMgBr (5 equiv.) followed by the acid chloride.



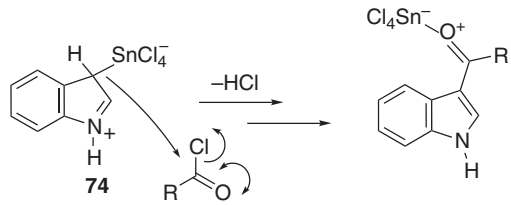
3.06.4.3 Ketoindoles

The 3-position on indole is the preferred site for electrophilic aromatic substitution, and acylation occurs readily under general Friedel–Craft conditions <1997H347>. Intramolecular Friedel–Crafts reactions of *N*-acyl-3-(indol-3-yl) propanoic acid chloride onto the indole-5-position in the presence of $AlCl_3$ catalyst has been reported <1994S506>. However, when acid chlorides are used for the acylation of *NH*-unsubstituted indoles, liberation of HCl is unavoidable. Indole will also self-polymerize or form di-indolylmethanes under acidic conditions, and relatively neutral conditions are required to obtain 3-acylindoles in good yields. In order to overcome this problem the reaction was recently performed in the presence of the weaker Lewis acid, dialkyl aluminum chloride (Equation (87)) <2000OL1485>. Alternatively, the zinc salt may be formed of the *NH*-unsubstituted indole, which may be acylated under normal Friedel–Crafts conditions with $AlCl_3$ as the Lewis acid <1997SC(27)2125>.



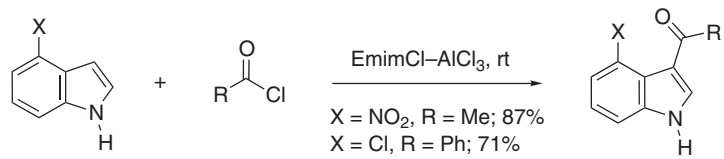
(87)

However, Ottoni and co-workers <2001OL1005> recently found that by changing the addition order of reagents, the polymerization of indole, *N*-acyl, and 1,3-diacylindole side-product formation can be completely avoided. The Lewis acid had to be added first to the indole in CH_2Cl_2 to form intermediate **74** with subsequent addition of the acid chloride to the suspension followed by nitromethane as a cosolvent, which gave the required 3-acyl indoles cleanly in good yields (Scheme 26). Addition of $MeNO_2$ was necessary as it increased the solubility of the solid indole–Lewis acid complexes **74**, so shortening the reaction time and raising the yields of the 3-acylindoles significantly.



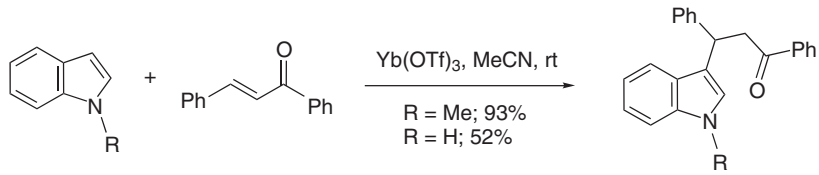
Scheme 26

Friedel–Crafts acylations of indoles containing electron-withdrawing substituents were reported in the strongly acidic ionic liquid, 1-ethyl-3-methylimidazolium chloride (EmimCl) with added $AlCl_3$, as shown by the examples given in Equation (88) <2002TL5793>.



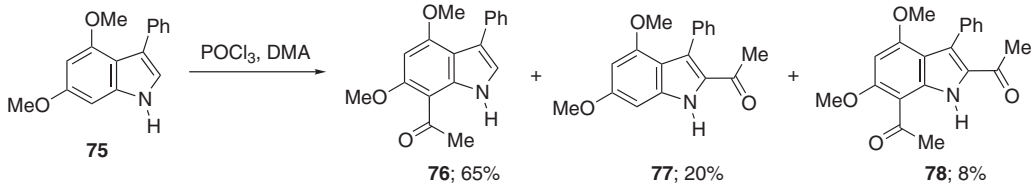
(88)

N-Acylbenzotriazoles were also found to be regioselective acylating agents for the indole-3-position of *NH*-unsubstituted indoles in the presence of $TiCl_4$ at room temperature (see Section 3.06.4.2) with self-polymerization and other indole side-reactions avoided <2003JOC5720>. Conjugate additions via the nucleophilic indole-3-position onto α,β-unsaturated double bonds have been reported using various protic and Lewis acids. Lewis acids such as ytterbium triflate, $Yb(OTf)_3$ <1996SL1047> and indium trichloride, $InCl_3$ <2001S2165> were shown to promote particularly effective Michael additions. Examples of the $Yb(OTf)_3$-catalyzed reaction are shown in Equation (89).



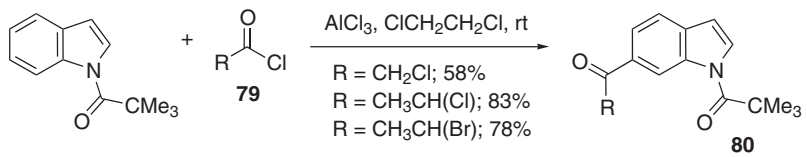
(89)

However, if the 3-position is substituted, and the fused benzene ring especially activated, then acylation of the benzene ring becomes more favorable. Equation (90) shows a Vilsmeier–Haack reaction on the highly activated indole **75** resulted in 7-ethanoylindole **76** as the major product with the less favored 2-substituted indoles **77** and **78** formed as minor products <2002JOC2464>.



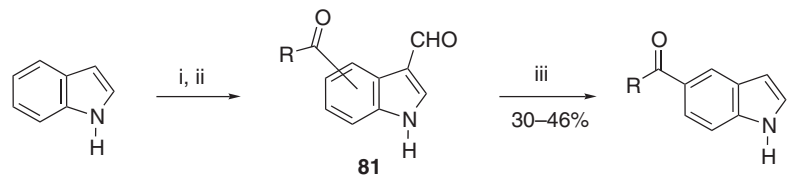
(90)

The direct introduction of substituents at the 6- and 2-positions remains a problem, and the majority of synthetic routes introduce these substituents early as part of the preparation of the indole skeleton by a Fischer-type process. The placement of electron-withdrawing groups at the 1- and 3-positions usually helps to promote acylations at the 6-position. It is well established that 1-acyl-2,3-dialkylindoles are acetylated at the 6-position under Friedel–Crafts conditions <1936JCS40>. More recently, 2,3-unsubstituted 1-acylindoles were shown to react regioselectively with α-halogenacylchlorides **79** in the presence of aluminum chloride to produce 1-acyl-6-halogenacylindoles **80** in good yields, as shown in Equation (91) <1994TL2699>. This methodology was later extended to the use of carboxylic anhydrides as acylating agents with basic hydrolysis facilitating the removal of the *N*-acyl group <2001TL1467>.



(91)

Demopoulos and Nicolaou reported the three-step preparation of 5-acyl- and aroylindoles from indole in 30–46% overall yield, as shown in Scheme 27 <1998S1519>. Friedel–Crafts acylation of the Vilsmeier–Haack intermediate of indole gave exclusive acylation at the benzene ring with predominant formation of the 5-isomer. For preparative purposes, it was not necessary to separate these isomers **81**, and deformylation with Pd—C in mesitylene allowed the easy isolation of the 5-isomer.

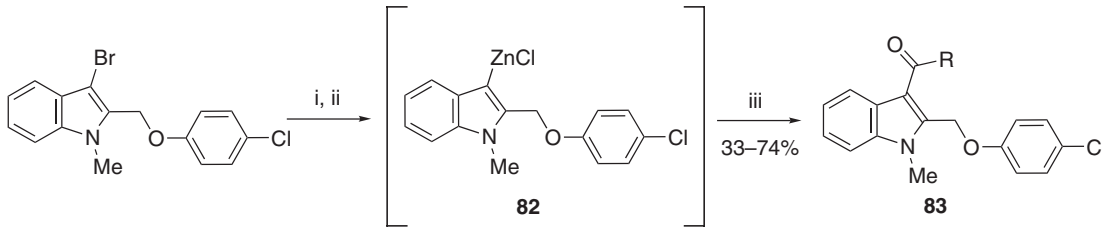


R = Me, Et, Pr^i, Ph, *p*-MeOC$_6$H$_4$

i. $(COCl)_2$, DMF, $ClCH_2CH_2Cl$, 0 °C to rt
ii. $AlCl_3$, RCOCl, $ClCH_2CH_2Cl$, 0 °C to rt
iii. Pd-C, mesitylene, reflux, 2–7 h

Scheme 27

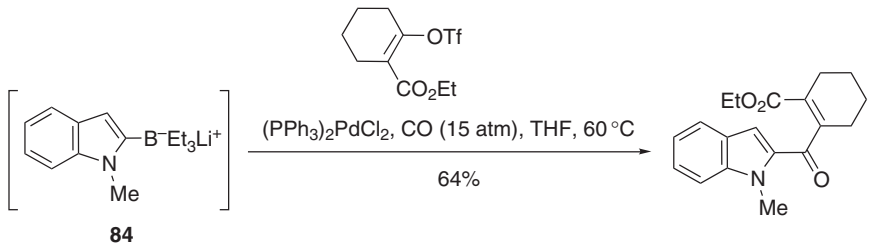
Acylindoles can also be obtained via palladium-catalyzed coupling reactions, as shown in Scheme 28 for the preparation of 3-acylindoles **83** from the coupling of 1,2-disubstituted-3-indolylzinc chloride **82** with an appropriate acid chloride <1997TL4749>.



i. Bu^tLi; ii. $ZnCl_2$, THF; iii. RCOCl, $(PPh_3)_2PdCl_2$, THF

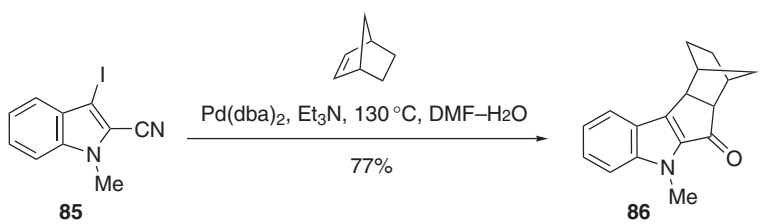
Scheme 28

2-Indolyl ketones can be regioselectively prepared using a palladium-catalyzed carbonylative cross-coupling reaction, as has been applied to the preparation of most classes of aromatic ketones (see Section 3.06.1.3); the borate complex **84** generated *in situ* from 2-lithio-1-methylindole and triethylborane was cross-coupled with CO and aryl iodides, alkenyl iodides, or cycloalkenyl triflates to provide a simple route to a variety of 2-indolyl ketones (Equation (92)) <1994JOC2634>.



(92)

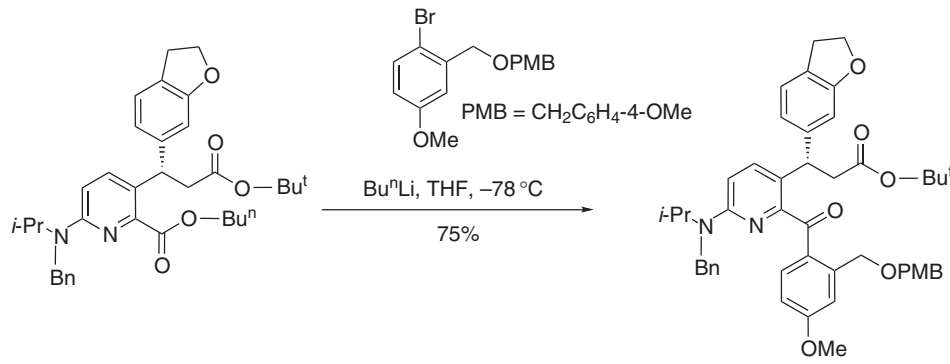
Larock and co-workers <2002JOC9276> devised an efficient palladium-catalyzed annulation of aromatic 1,2-iodonitriles (e.g., **85**) with bicyclic sterically hindered alkenes to give polycyclic aromatic ketones. The methodology is exemplified by the formation of the norbornene adduct **86** of the *N*-methylindole **85** in 77% yield (Equation (93)). The mechanism of such reactions involves oxidative addition of **85** to the Pd(0) catalyst with the resultant Pd(II) species undergoing insertion by the norbornene. Subsequent addition across the nitrile triple bond produces an iminopalladium intermediate, which is hydrolyzed to the ketone <2002TL2133>. Compound **86** is structurally related to the key intermediate in the synthesis of the natural product, yuehchukene and its analogs.



(93)

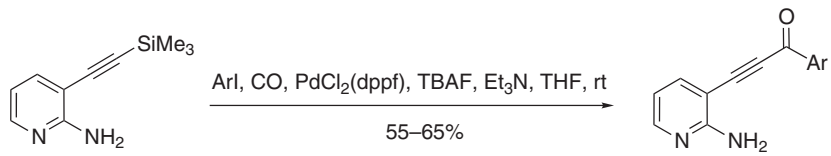
3.06.4.4 Pyridyl Ketones

Although pyridine cannot undergo electrophilic aromatic substitutions using Friedel–Crafts conditions, there are many pyridine carboxylic acid derivatives that will undergo effective Friedel–Crafts acylations <1995COFGT(3)277>. Pyridine–Weinreb amide derivatives are good acylating agents for nucleophilic organolithium and Grignard reagents (see Sections 3.06.1.2.1 and 3.06.1.2.2). An impressive chemoselective addition of aryllithium to a 2-pyridine *n*-butyl ester was reported by Kato and co-workers, as shown in Equation (94) <2002T3409>.



(94)

3-Organotin derivatives have been reported to undergo palladium-catalyzed coupling reactions with acid chlorides <1992TL3003>. Halogenated pyridine derivatives can undergo transition metal-mediated carbonylative cross-coupling reactions to form biaryl ketones (see Equation (32), Section 3.06.1.3). Equation (95) shows the synthesis of 3-(2-amino-5-methylpyridin-3-yl)-1-arylprop-2-yn-1-ones **88** via a facile palladium-catalyzed carbonylative cross-coupling using the nucleophilic trimethyl silane derivative **87** and aryl iodide in a carbon monoxide atmosphere <2002S1912>.

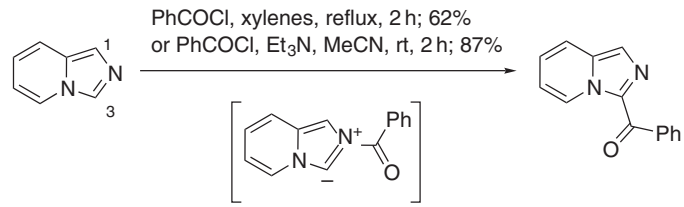


87 **88**

(95)

3.06.4.5 Ketones Derived from Miscellaneous Heterocycles

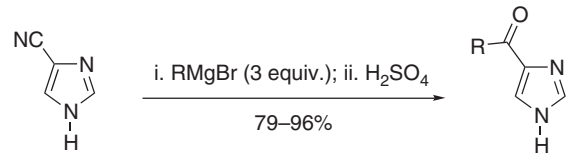
Direct *C*-acylations under Friedel–Crafts conditions are generally not applicable to diazoles, thiazoles, and oxazoles, because of the reduced nucleophilicity of the aromatic ring and the complexation of the acylating agent or Lewis acid to the heteroatom, although there are some exceptions <1995COFGT(3)277>. Hlasta and Silbernagel <1998H1015> reported that the regioselective acylation of imidazo[1,5-*a*]pyridine with benzoyl chloride under thermal and basic conditions provided exclusively the 3-substituted ketone, as shown in Equation (96). This result is in contrast to the Friedel–Crafts acylation, which occurs exclusively at the more nucleophilic 1-position. An analogous ylide **89** to that observed in the acylation of imidazoles was proposed as an intermediate.



89

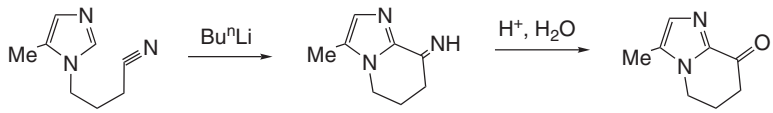
(96)

Kawakami and co-workers recently reported an efficient one-pot synthesis of 4(5)-acyl-1*H*-imidazoles from 4(5)-cyanoimidazole via the addition of a Grignard reagents followed by acidic work-up (Equation (97)) <2003S677>. Various 4(5)-ketoimidazoles were prepared without the need for chromatography or any protection or deprotection of the imidazole.



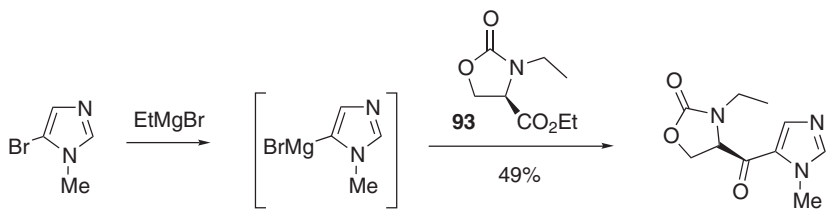
(97)

An anionic 6-*exo-dig* cyclization/addition of the 2-lithiated imidazole onto a nearby nitrile followed by aqueous hydrolysis of the resultant imine **90** resulted in the preparation of the natural product, sibyllimycine **91**, as shown in Equation (98) <1996AG(E)545>.



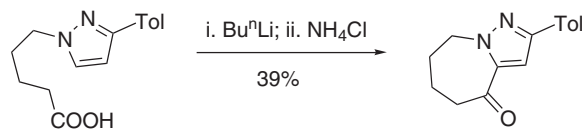
90 **91** (92%) (98)

The preparation of the pilocarpine analog **94** was achieved on gram scale and in high-enantiomeric purity via the reaction of the imidazole-5-substituted Grignard reagent **92** with oxazolidinone ester **93**, as shown in Equation (99) <2002JOC5913>.

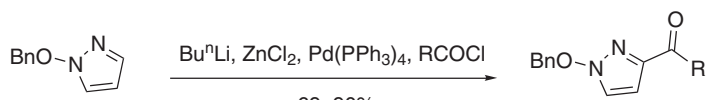


92 **93** **94** (99)

Ketone derivatives of pyrazoles have been reported by a direct lithiation of the pyrazole-5-position followed by a Parham-type cyclization, and an *ortho*-lithiation/transmetalation followed by a Pd(0)-catalyzed cross-coupling with an acid chloride as shown in Equations (100) and (101), respectively <1997SL1013, 1998S1604>. Alternatively, pyrazole-2-phenyl ketone was prepared in 72% yield by lithiation of the pyrazole-2-position followed by anionic addition onto benzonitrile and acidic work-up <1999SL765>.

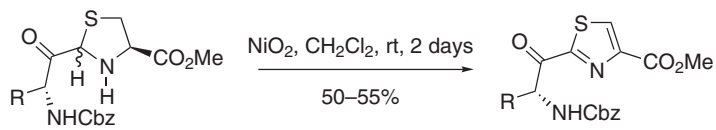


(100)



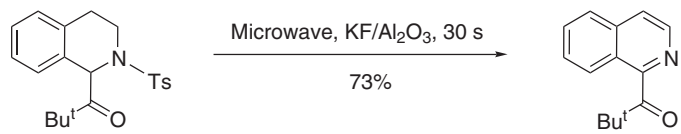
(101)

Nickel peroxide (NiO_2) is a known oxidizing agent, which allows the conversion of thiazolidines to thiazoles <1978JOC1624>. McKervey and co-workers <2000TL1279> used NiO_2 to convert thiazolidines into thiazoles **95** in good yields without racemization of the carbobenzoxy protected amide substituent (Equation (102)). This was an improvement from the manganese dioxide-mediated oxidation, which gave the racemized thiazoles.



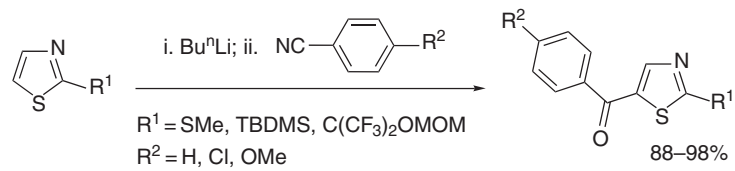
95 (102)

A much more rapid rearomatization reaction was recently reported involving microwave-assisted solventless oxidative desulfonation and subsequent dehydrogenation to give aromatized 2-isoquinoline ketones; an example is given in Equation (103) <2002SL907>.



(103)

A new procedure for the preparation of 2-substituted-5-(ketoaryl)thiazoles was recently reported by Marcantonio and co-workers <2002TL8845> involving the formation of the thiazole anion and subsequent addition onto aryl nitriles to give the desired ketones after aqueous hydrolysis, as shown in Equation (104).



(104)

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Biographical sketch

Fawaz Aldabbagh was born in Baghdad, Iraq in 1971. He studied B.Sc. in 1994 and did his Ph.D. in 1997 at Brunel and Loughborough Universities, UK under the direction of Professor W. R. Bowman. He spent 2 years working as a Postdoctoral Research Fellow with Professors I. D. Jenkins and W. K. Busfield at Griffith University, Brisbane, Australia, before taking his current position as a Lecturer in Organic Chemistry at National University of Ireland, Galway in April 2000. Fawaz has diverse research interests including controlled/living nitroxide-mediated free-radical polymerizations, the synthesis of biologically active heterocyclic systems using free-radical chemistry, as well as research interests in other areas of organic and polymer chemistry. Fawaz is also the author of Chapters 3.03 and 5.01.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 267–308

3.07
Aldehyde and Ketone Functions Further Substituted on Oxygen

D. A. SELDEN and D. M. HODGSON
University of Oxford, Oxford, UK

3.07.1 CARBONYL YLIDES

3.07.1.1 Introduction

Carbonyl ylides are 1,3-dipolar reactive intermediates. The parent 2-oxatrimethylene structure and other similar nonstabilized carbonyl ylides have been accessible only recently in a synthetically useful form (see Section 3.07.1.5); the bulk of the synthetic advances in the formation and use of carbonyl ylides have employed carbonyl ylides possessing electron-withdrawing groups at one carbon center of the 1,3-dipole and mildly electron-donating groups at the other.

Since COFGT (1995), the majority of the work in this area has concerned the formation of carbonyl ylides from carbene precursors, mainly via metal-catalyzed diazo-decomposition. This method initially generates a metallocarbene, and leads to the possibility of then forming a catalyst-associated carbonyl ylide; this has led to the examination of the use of chiral ligands in

catalysts to allow enantiodiscrimination in the ylide formation and subsequent reactions. A new avenue of asymmetric synthesis has arisen as a consequence of this development, and is covered under the Sections 3.07.1.3.1.(ii) and 3.07.1.3.2.(ii).

3.07.1.2 Carbonyl Ylides from Oxiranes

The generation of carbonyl ylides from oxiranes may be achieved by thermal ring opening (allowed process is conrotatory), photochemical ring-opening (allowed process is disrotatory), and electron-transfer catalysis. The first two are covered here.

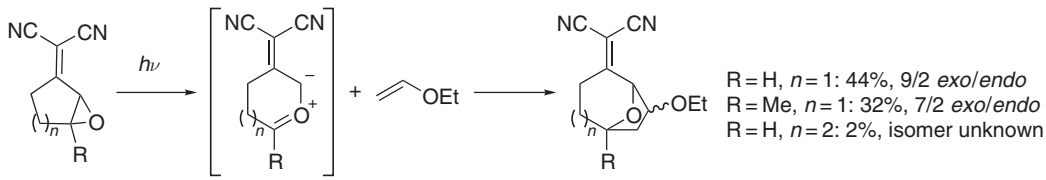
The main developments since the previous edition are in the areas of thermal and photochemical ring-opening, with the ylides mainly undergoing inter- or intramolecular cycloadditions across C=C or C=S bonds, with regioselectivity in accord with FMO analysis and/or computational studies.

3.07.1.2.1 Intramolecular cycloadditions: oxirane to oxygen heterocycle

No further advances have occurred in this area since the publication of chapter 3.07.1.2 in <1995COFGT(3)313>.

3.07.1.2.2 Intermolecular cycloadditions: oxirane to oxygen heterocycle

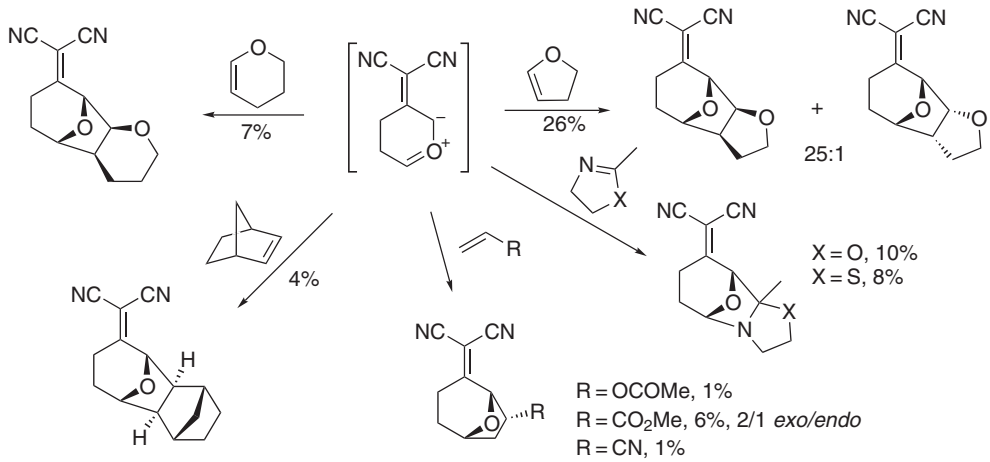
Kotera and co-workers <1998JCS(P1)313> have described the photochemical ring-opening of α,β-unsaturated-γ,δ-epoxy nitriles. Attempted cycloaddition reactions of the resulting carbonyl ylides with ethyl vinyl ether are reported to give none of the expected products when mononitriles are used; with dinitriles, the expected cycloadducts are obtained in yields decreasing with increasing size of the carbonyl ylide ring (Equation (1)). The difference in reactivity between mono- and dinitriles is ascribed to the calculated difference in size of the $HOMO_{dipolarophile}$–$LUMO_{dipole}$ gap. Lower yields with larger cyclic carbonyl ylides are suggested to be due to the larger distance between the carbon termini of the ylide, leading to less effective overlap with the orbitals of the dipolarophile. All the cycloadduct regioselectivities are in accord with the calculated orbital coefficients. Unfavorable steric interactions and secondary orbital interactions in the *endo*-transition states may explain the stereoselectivity in favor of the *exo*-products. A related acyclic ylide gave rise to four product stereoisomers, but still exhibited the expected regioselectivity.



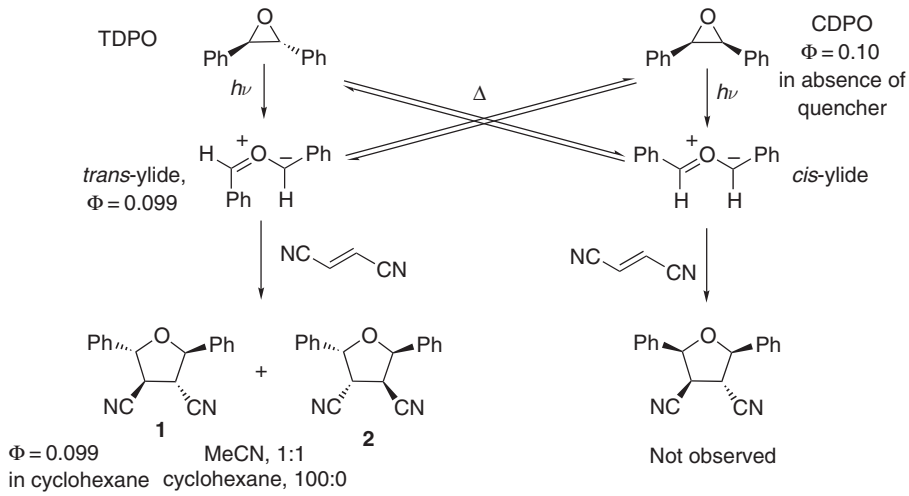
(1)

Extension to other dipolarophiles such as dihydrofuran, dihydropyran, norbornene, 2-methyl-2-oxazoline, and 2-methyl-2-thiazoline gave high regio- and *exo*-selectivity, though poor yields (Scheme 1) <1999H2147>. Use of vinyl acetate gives a very low yield, ascribed to the large $HOMO_{dipolarophile}$–$LUMO_{dipole}$ gap, and methyl acrylate and acrylonitrile give the opposite regioselectivity to that expected. Replacement of the nitrile groups of the substrate with esters was attempted; the mononitrile–monoester substrate gave a very low yield (2%) of cycloadduct with ethyl vinyl ether, and the diester substrate gave no cycloadduct.

Lipson and co-workers have investigated the photochemistry of *trans*-2,3-diphenyloxirane (TDPO) <1997JOC2409>. The ylide formed from TDPO may close to *cis*-2,3-diphenyloxirane (CDPO) in the absence of a dipolarophile by a symmetry-allowed electrocyclization, or may be captured by a dipolarophile to form a cycloadduct (Scheme 2). It was concluded that under these conditions no thermal fragmentation or rearrangement of the ylide occurs, but that symmetry-forbidden closure of the *trans*-ylide to TDPO or isomerization to the *cis*-ylide followed by allowed closure to TDPO were possible. In the presence of fumaronitrile, photochemical decomposition of TDPO in cyclohexane gave the all-*trans*-isomer of the cycloadduct **1**, whereas in



Scheme 1

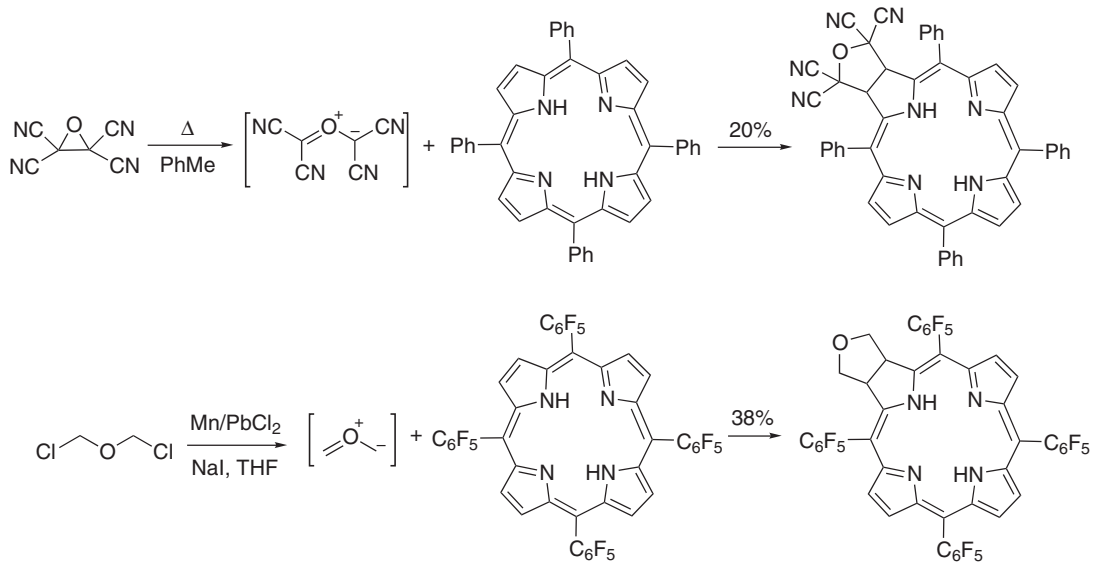


Scheme 2

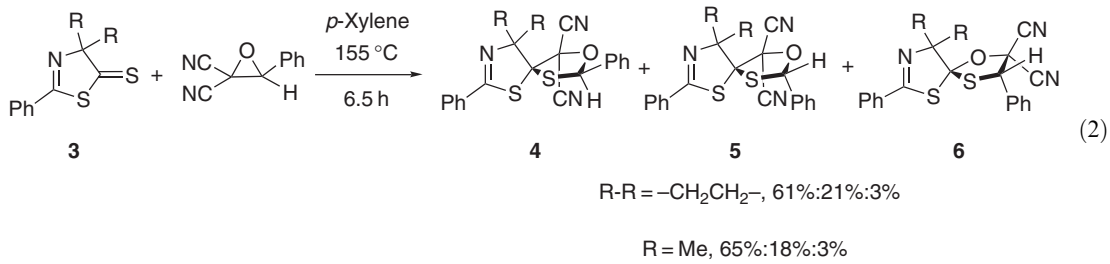
acetonitrile a 1:1 mixture of the two expected adducts, all-*trans*-**1** and *cis-trans-cis*-**2**, were formed; the suggested explanation is that the ionic character of the ylide causes the alteration in product distribution with solvent.

Fleming and Dolphin <2002TL7281> have studied the thermal formation of the ylide from tetracyanooxirane and its subsequent cycloaddition to an electron-rich porphyrin (Scheme 3). Owing to the stabilization of the ylide by the four cyano groups, no cycloadduct was obtained with an electron-poor porphyrin. The "parent" carbonyl ylide (2-oxa-trimethylene), generated by elimination (*vide infra*, Section 3.07.1.5), gives cycloadduct only with the electron-deficient porphyrin.

Meier and co-workers <1997HCA1190> have described the thermal opening of epoxides and the cycloaddition of the resulting ylides with C═S functionality. Adamantyl thioketone and cyclobutane dithione gave low yields of cycloadducts, which were ascribed to the thermal instability of the thioketones. The use of dithioketones gave no double addition products, even when the monoadduct was heated in the presence of additional oxirane. Use of thiazole thione **3** as a dipolarophile led to both *cis*-**5** and *trans*-**4** adducts (1:3 ratio), along with a small quantity of the nucleophilic addition product **6** (Equation (2)). The cycloaddition regiochemistry is rationalized by considering the greatest contribution to the resonance structures of the ylide to be that with the negative charge located α- to the cyano groups, and the cycloaddition to be under kinetic control, resulting in the formation of the more sterically crowded isomer. This result is in agreement with computational studies.



Scheme 3



(2)

R-R = –CH_2CH_2–, 61%:21%:3%

R = Me, 65%:18%:3%

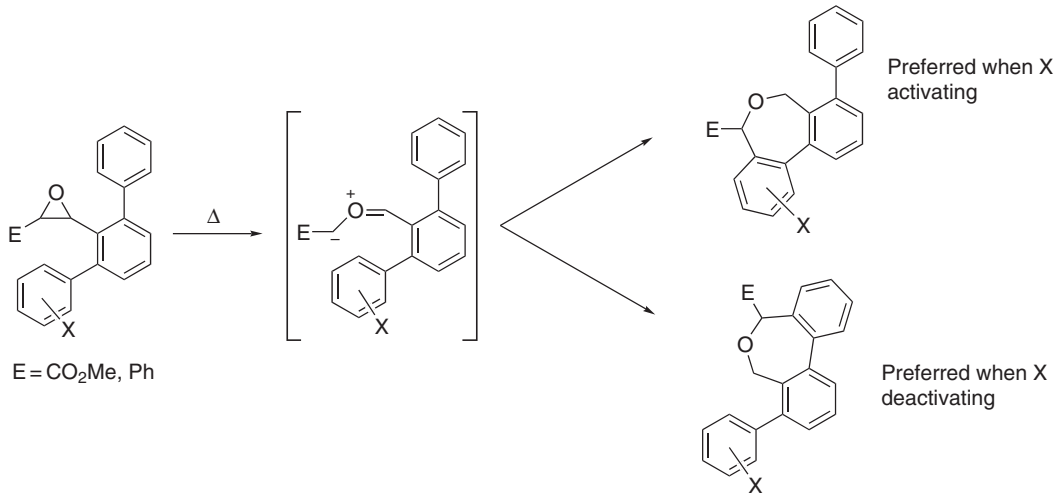
3.07.1.2.3 Electrocyclizations leading to furans and oxepines

O'Shea and Sharp <1996JCS(P1)515, 1997JCS(P1)3025> have prepared novel dihydrobenzoxepines by FVP of oxiranes at 625 °C. Both electron-rich and electron-poor dipolarophiles may be used in this system. The order of dipolarophile reactivity was found to be olefin > thiophene > benzene. Competition reactions for the cyclization of ylides with substituted or unsubstituted aromatic rings showed that *p*-substituents are always activating and that *meta*-substituents may be mildly activating or mildly deactivating toward cyclization (Scheme 4). These reactions achieve the same result as electrophilic substitution of the aromatic ring, and complement this method, as the latter only works well for electron-rich rings. Some problems with generality were caused by the polymerization of substrates under the pyrolysis conditions.

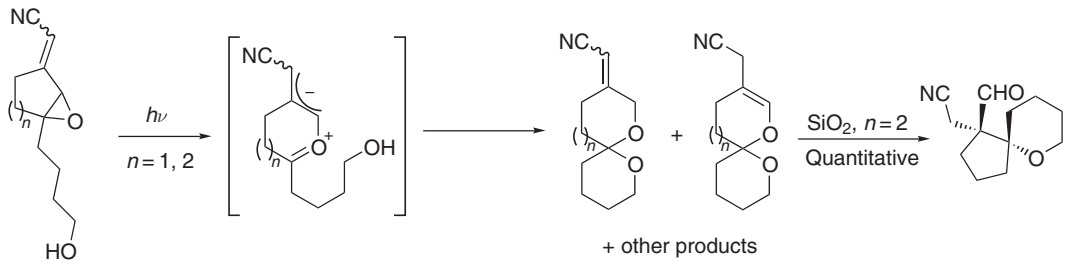
3.07.1.2.4 Trapping by hydroxyl functions leading to acetals

Ishii and co-workers <1995LA19, 1995CPB1621> have described the formation of carbonyl ylides from α,β-unsaturated-γ,δ-epoxy nitriles bearing tethered hydroxyl functionality, and their subsequent cyclization on to the hydroxyl group to form acetals (Equation (3)). Conditions could be adjusted by addition of triethylamine or oxalic acid to favor internal or external double bonds, and *cis*- or *trans*-exocyclic double bonds. In some cases, the product with an internal double bond rearranges to a spiroether on exposure to SiO_2. The effects of substitution α- to the hydroxyl and tetrasubstitution of the epoxide were investigated: the former was found to decrease the yield due to steric hindrance, and the latter gives a similar overall yield to the unsubstituted case but with a greater proportion of the spiroether product. Increasing the length of the tether to the hydroxyl decreases the yield, with the six-carbon tether giving no acetal. If the hydroxyl is replaced by an

acid function, the spirolactone with an internal double bond is formed as the only product and is stable to SiO_2. These reactions proceed diastereoselectively with substituted four- and five-carbon tethers.



Scheme 4



(3)

	Yield (%) (*E*)/(*Z*)	*Yield* (%)
$n=1$, Et_3N additive	7 (5:2)	29
$n=1$, oxalic acid additive	29 (17:12)	13
$n=2$, Et_3N additive	7 (4:3)	19
$n=2$, oxalic acid additive	11 (6:5)	14

3.07.1.2.5 Trapping by oxygen leading to ozonides

No further advances have occurred in this area since the publication of chapter 3.07.1.2 in <1995COFGT(3)313>.

3.07.1.3 Carbonyl Ylides from Carbenes

Interaction of a carbonyl oxygen lone pair with a singlet carbene, either inter- or intramolecularly, may form a carbonyl ylide. In most cases, the carbene is formed by decomposition of a diazo compound in the presence of catalytic amounts of Rh(II) dimers such as dirhodium tetraacetate, allowing a wide range of substrate functionality to be tolerated. This method has been applied to a range of diazo compounds and dipolarophiles in cycloaddition reactions, and to the synthesis of natural product skeletons. One major development since COFGT (1995) is the field of enantioselective carbonyl ylide transformations. Progress in this field has been mainly achieved using Rh(II) dimers bearing chiral ligands (chiral carboxylates, carboxamidates, or binaphthol phosphates). It is likely that the process requires an association between the carbonyl ylide and catalyst during the cycloaddition.

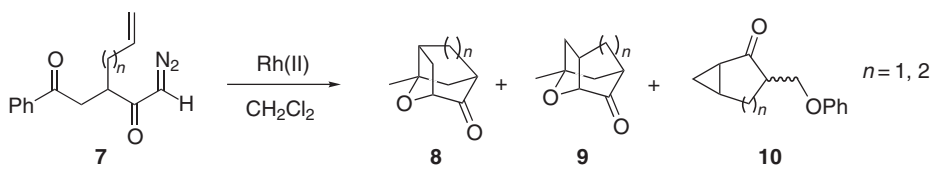
The reactions of carbonyl ylides from carbenes have been extensively reviewed; authors include: Padwa <1996CRV223, 1997TCC(189)121, B-1999MI(6)55, B-2002MI001>, Doyle <B-1998MI397, B-1999MI289, B-2000MI191>, Hodgson <2001CSR50, 2001RCC659>, Jørgensen <1998CRV863, B-2002MI002>, Chiu <1997TCC(190)3>, McKervey <B-1999MI539>, Zaragoza-Dörwald <B-1999MI206>, Charette <B-1999MI581>, Calter <1997MI37>, Clark <B-2002MI003>, Muthusamy <2002T9477>, and Karlsson <2001OPP105>.

3.07.1.3.1 Intramolecular cycloadditions: diazocarbonyl to oxygen heterocycle

(i) Racemic cycloadditions

Padwa's group have published extensively in this area. An investigation of the effects of altering the catalyst, length of tether between the ylide and the dipolarophile, and the substitution pattern on a typical substrate **7** illustrated the complex interplay of factors determining the product profile of these reactions <1996JOC63>.

With diazodione **7**, rhodium catalysts bearing electron-deficient ligands were seen to produce cycloadduct **8** predominantly, whereas more electron-rich ligands favored the production of regioisomeric cycloadduct **9**; in all cases cyclopropanation was a significant side reaction to give **10** (Equation (4)). Increasing the tether length favored cycloaddition over cyclopropanation, but did not alter the proportions of the cycloadducts **8** and **9** ($n = 2$) formed with different catalysts. The regiochemical differences observed on changing the ligands in the catalyst imply that some of the catalysts could be associated with the ylide from **7** ($n = 1$) during the cycloaddition, thereby affecting the outcome of the reaction.



7 **8** **9** **10**

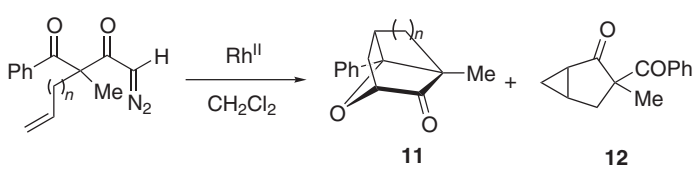
(4)

For $n = 1$:

Catalyst	*Yield*	*Ratio* **8**:**9**:*cis*-**10**:*trans*-**10**
$Rh_2(cap)_4$	94%	10:47:14:23
$Rh_2(OAc)_4$	96%	12:52:4:28
$Rh_2(pfb)_4$	87%	33:12:17:25
$Rh_2(tfa)_4$	93%	34:12:30:17

cap = caprolactamate
pfb = perfluorobutyrate

In structurally related substrates in which cyclic five-membered carbonyl ylides are generated, catalysts bearing more electron-deficient ligands favor cycloadducts **11** over cyclopropanation products **12** (Equation (5)). An increase in tether length results in the formation of the cycloadduct only; the suggested reason is the smaller loss of entropy on forming a five-membered ylide compared with cyclopropanation across the 6,7-π bond. A tethered C=O group was also successfully used as a dipolarophile, with no ligand effect observed.



11 **12**

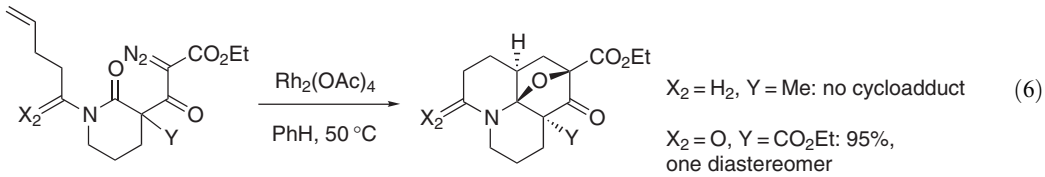
$n = 1$:	*Catalyst*	*Yield* **11**:**12**
	$Rh_2(cap)_4$	70%:28%
	$Rh_2(OAc)_4$	60%:24%
	$Rh_2(tfa)_4$	67%:0%

$n = 2$: (**11**) only, >95%.

(5)

The intramolecular cycloadditions of push-pull stabilized (isomünchnone) ylides with alkenes was also investigated (Equation (6)) <1997JOC2001>. With a tethered terminal alkene or α,β-unsaturated ester (X = H_2, Y = Me), none of the expected cycloadduct was produced, despite computational studies showing that the product formation was energetically and electronically feasible. Modelling of the transition state, however, showed that the chair–chair conformation adopted suffered from severe diaxial interactions when X = H_2, whereas the amido analog (X = O) adopted a boat–twist boat conformation in which these interactions were lessened.

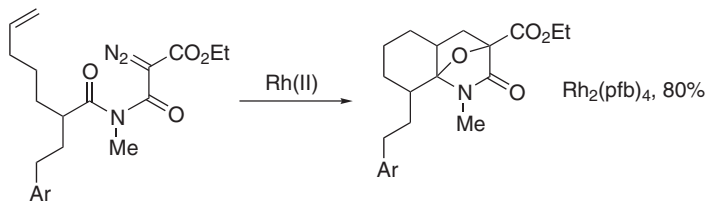
In line with this analysis, introduction of a C=O in the tether α- to the nitrogen allowed isolation of a single cycloadduct in 95% yield.



(6)

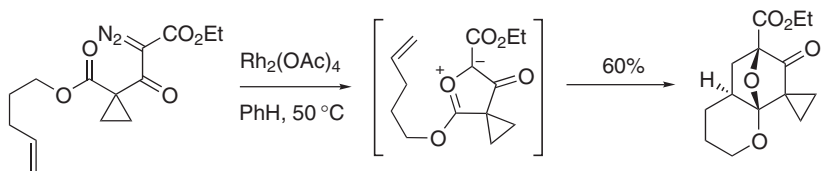
An aryl group was introduced into the tether of a similar system, in a model study toward the synthesis of lycorine <2001CJC1681>.

In another isomünchnone cycloaddition, with the tether attached to the ylide-forming carbonyl, the yield was found to depend on the catalyst used (Equation (7)) <1996T2489>; the cycloadduct was produced in 80% yield with $Rh_2(pfb)_4$ (pfb = perfluorobutyrate), and progressively lower yields were obtained with $Rh_2(tfa)_4$ and $Rh_2(OAc)_4$.



(7)

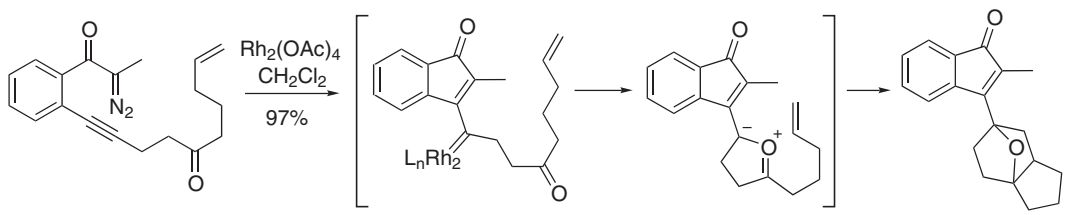
Introduction of oxygen into the tether was undertaken <1997TL3319, 2001MI1043>; the expected cycloadduct was formed in 60% yield after heating for 5 h in benzene with $Rh_2(OAc)_4$ (Equation (8)). However, stopping the reaction after 1 h led to isolation of a carbonyl ylide dimer in addition to the cycloadduct; heating of this dimer in absence of catalyst gave the cycloadduct.



(8)

Application of the method developed by Padwa to the synthesis of natural products, such as the aspidosperma alkaloids <1998JOC556> and (±)-ribosine <1999JOC4079>, has also been reported.

The formation of a vinyl metallocarbene from interaction of a metallocarbene with an alkyne, followed by carbonyl ylide formation and cycloaddition, was used to form a complex polycyclic system in 97% yield (Equation (9)) <1995JOC53>.



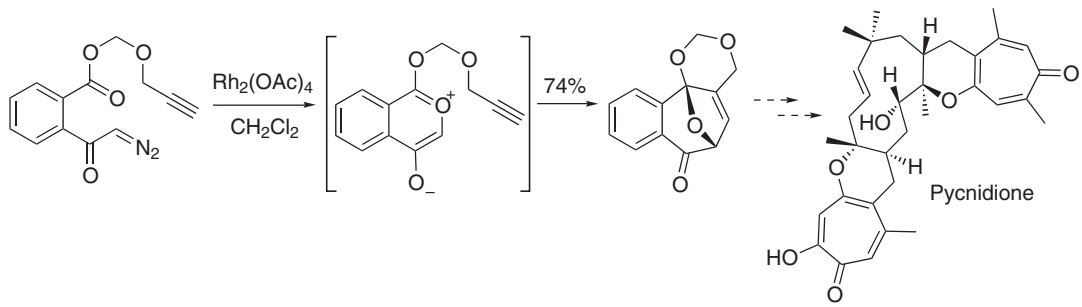
(9)

Baldwin and co-workers <1999OL1933> reported an oxidopyrylium ("aromatic" carbonyl ylide)-based study toward a biomimetic synthesis of tropolone natural products, by forming the skeleton of analogs of pycnidione and epolone B (Scheme 5).

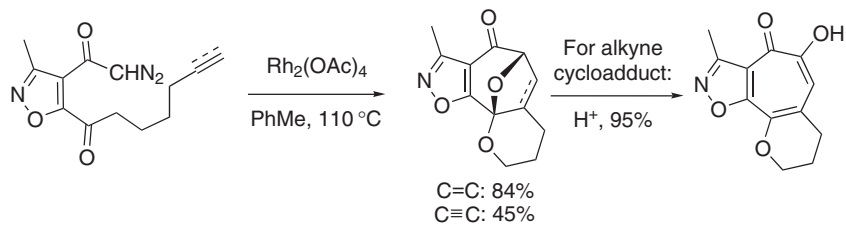
Plüg and Friedrichsen <1996JCS(P1)1035> have extended their benzotropolone-forming methodology to cycloadditions of oxidopyryliums (Scheme 6), of use in the synthesis of hetero-annulated tropolones.

Johnson and co-workers <2001SL646> have developed an approach to annulated furans by intramolecular cycloaddition of tethered alkynes with an alkoxycarbonyl sulfone-distabilized ylide (Equation (10)). After formation of the initial cycloadduct, elimination of phenylsulfinic acid proceeds under the reaction conditions to give the furans in 34–65% yields. Competition reactions

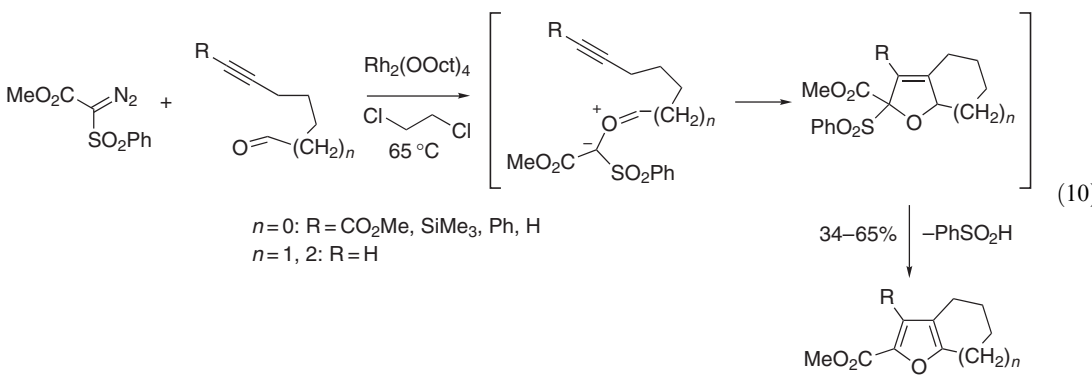
between unsaturated δ,ε- and ε,ζ-alkynals gave solely the three-carbon tether derived product, implying that the cyclization is rate determining and the intermolecular ylide formation is reversible. The use of tethered alkenes is also possible leading to moderate yields of cycloadducts.



Scheme 5



Scheme 6



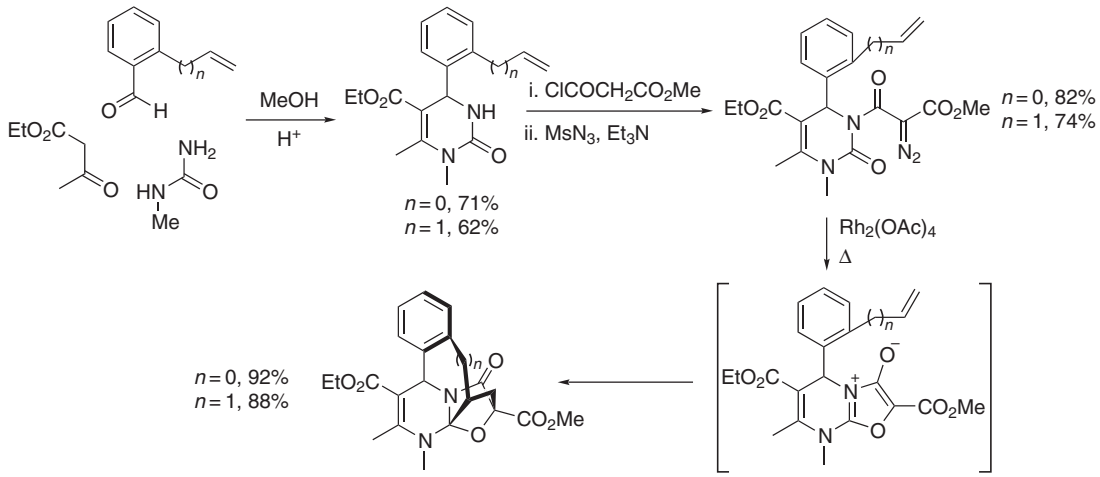
(10)

Kappe and co-workers <1997JOC3109> have used an isomünchnone cycloaddition as the key step in the synthesis of dihydropyrimidines for calcium-channel modulators (Scheme 7). Single isomers of the cycloadducts were obtained due to a pseudoaxial aryl group leading to a very favorable alignment of the π-bond over the dipole. If the substrate lacked the *N*-methyl group, the product obtained was that arising from a 1,5-H shift, and no cycloadduct was observed.

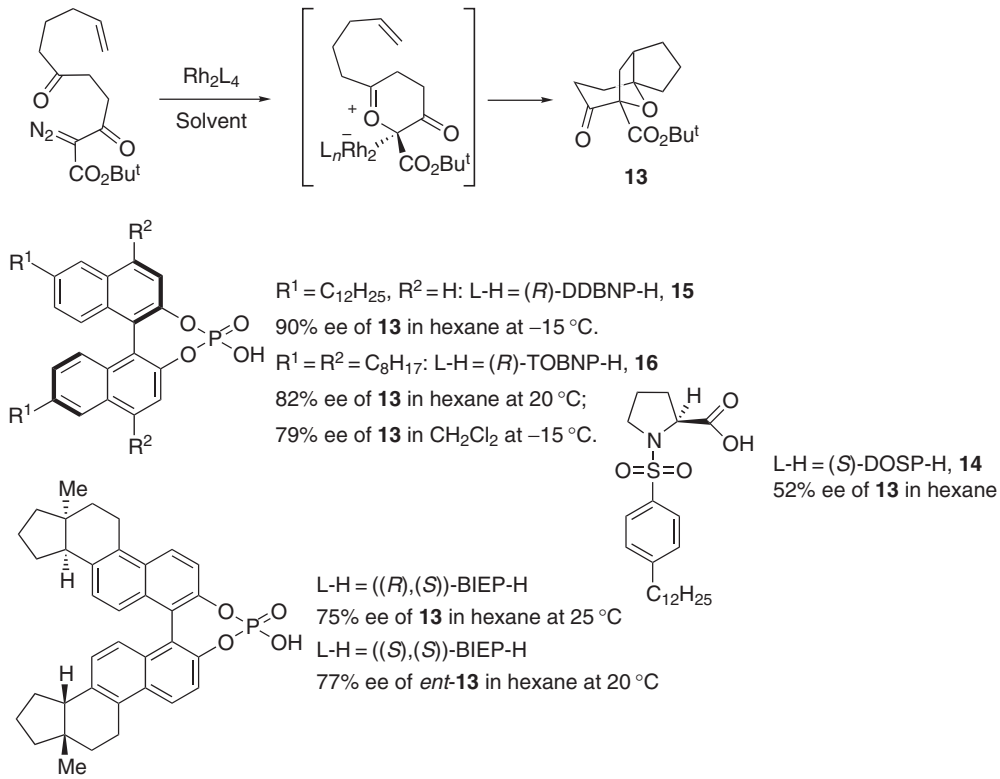
(ii) Asymmetric cycloadditions

The first example of an enantioselective carbonyl ylide cycloaddition was reported in 1997 <1997TL6471>, using Davies' prolinate catalyst Rh_2[(*S*)-DOSP]$_4$ **14**, which generated the cycloadduct **13** in 52% ee (Scheme 8). The observation of asymmetric induction supports the likelihood of an association between the catalyst and the ylide (*vide supra*, Section 3.07.1.3.1.(i)).

Further studies using substituted binaphthol phosphates as ligands in the Rh(II) catalysts led to the development of Rh_2[(*R*)-DDBNP]$_4$ **15**, a hexane-soluble analog of the previously reported unsubstituted binaphthol phosphate-derived Rh(II) catalyst; catalyst **15** gave a 90% ee of



Scheme 7

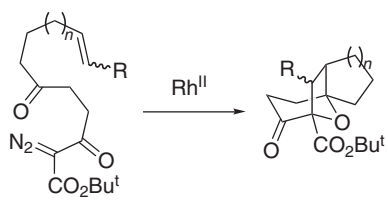


Scheme 8

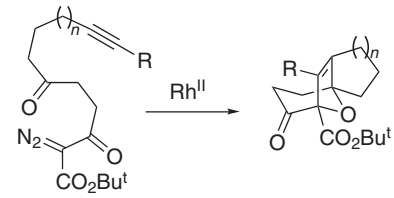
cycloadduct **13** in hexane at −15 °C <1999CC2185>. Steroidal-based binaphthol phosphate catalysts were also investigated <2001CEJ4465>, and it was found that both the backbone and axial chirality of the ligand could contribute to the asymmetric induction, with the axial chirality being dominant. Alternative positional substitution of the binaphthol phosphate framework with four octyl groups gave a catalyst (Rh_2[(*S*)-TOBNP]$_4$ **16**) producing similar ee values to Rh_2[(*R*)-DDBNP]$_4$ **15** at room temperature in hexane, though not such high ee values at lower temperatures, but giving the best ee values so far obtained in CH_2Cl_2 for cycloadduct **13** <2003TA3841>.

The scope of the intramolecular cycloadditions with α-diazo-β,ε-diketo esters was investigated by altering the nature and substitution of the dipolarophile and the length and nature of the tether connecting the dipole and dipolarophile (Scheme 9) <2003SL59, 2003JOC6153>. Use of

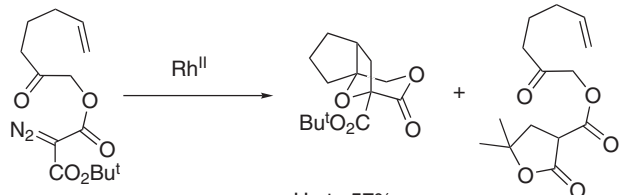
(*E*)- and (*Z*)-alkenyl tethers demonstrated that the cycloaddition was stereospecific, and that control of up to four stereocenters could be achieved. It was found that Rh_2[(*S*)-DOSP]$_4$ **14** gave a higher ee with the (*E*)-alkene and Rh_2[(*R*)-DDBNP]$_4$ **15** with the (*Z*)-alkene. Increased tether length was not detrimental to the ee unless the dipolarophile was substituted. Tethered α,β-unsaturated esters resulted in good yields of cycloadduct but poor ee values. Alkynes could be used as dipolarophiles in good yield and with the same sense of asymmetric induction as the corresponding alkenes, although the ee values were generally around 10% lower. Replacement of the ketone α- to the diazo group with an ester dramatically reduced the efficiency of the cycloaddition; upon heating, poor yields and ee values of cycloadducts were obtained along with a significant quantity of lactone by-product (Scheme 9). These last results were ascribed to a combination of inductive effects and the tendency of esters to adopt the *s-trans* conformation. It is also possible that there is greater reversibility of the ylide to metallocarbene for these substrates than for the corresponding ketones.



n = 1, 2; R = (*E*)-Me, (*Z*)-Me, (*E*)-CO_2Me
n = 1, R = (*E*)-Me: up to 65%, up to 80% ee
n = 1, R = (*Z*)-Me: up to 68%, up to 83% ee
n = 2, R = (*E*)-Me: up to 44%, up to 59% ee
n = 1, R = (*E*)-CO_2Me: up to 93%, up to 38% ee
n = 2, R = (*E*)-CO_2Me: up to 95%, up to 32% ee



n = 1, 2; R = H, Me
n = 1, R = H: up to 80%, up to 86% ee
n = 1, R = Me: up to 77%, up to 76% ee
n = 2, R = H: up to 41%, up to 86% ee
n = 2, R = Me: up to 73%, up to 79% ee

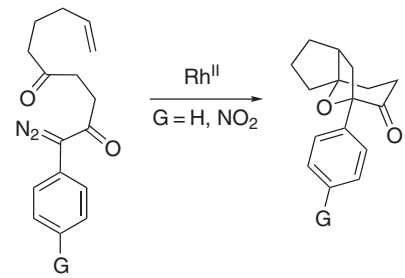


Up to 57%
Up to 43% ee

Up to 39%

Scheme 9

The effect of electronic variation at the dipole on yield and ee was probed using a series of substrates bearing *para*-substituted phenyl groups at the diazo-carbon (Equation (11)) <2003JOC581>. Some moderate differences were observed using Rh_2[(*R*)-DDBNP]$_4$ **15**, for which higher ees were obtained with a *p*-NO_2 substituted diazo compound (51%, cf 35% ee for *p*-H).

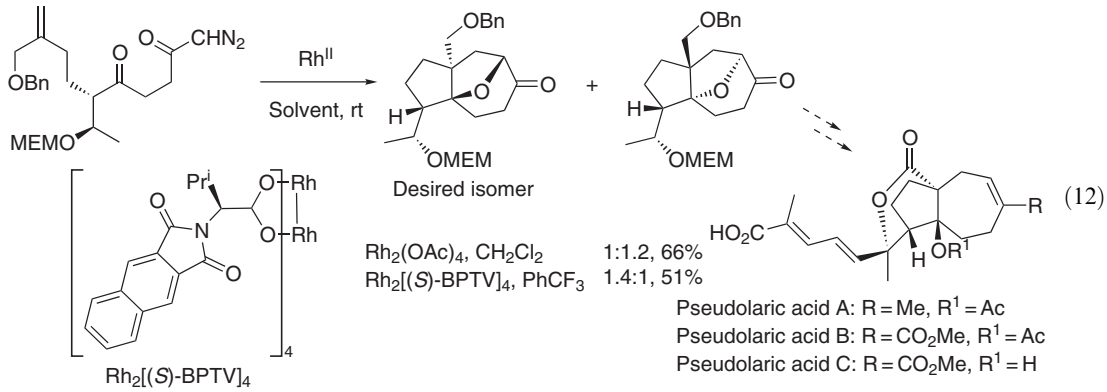


G = H: up to 87%, up to 35% ee
G = NO_2: up to 100%, up to 51% ee

(11)

Hodgson and co-workers also reported attempted enantioselective cycloadditions of oxidopyryliums generated from α-diazoketones and α-diazo-β-keto esters; however, poor ee values were obtained with a wide variety of chiral Rh(II) catalysts <2003MI49>.

Chen and co-workers have studied a carbonyl ylide cycloaddition-based approach to the pseudolaric acids <2003JOC4195, 2001OL1721>, during the course of which they investigated whether a tethered allylic ether would act as a dipolarophile and what effect, if any, the existing stereocenters would have on the cycloaddition diastereoselectivity (Equation (12)). The allylic ether was effective as a dipolarophile, but the use of an enantiomerically pure substrate gave at best a 1:1.2 ratio of isomers in favor of the undesired cycloadduct under achiral Rh(II) catalysis. An examination of chiral catalysts produced one encouraging result: $Rh_2[(S)\text{-BPTV}]_4$ gave a 1.4:1 ratio in favor of the desired product, in 51% combined yield.

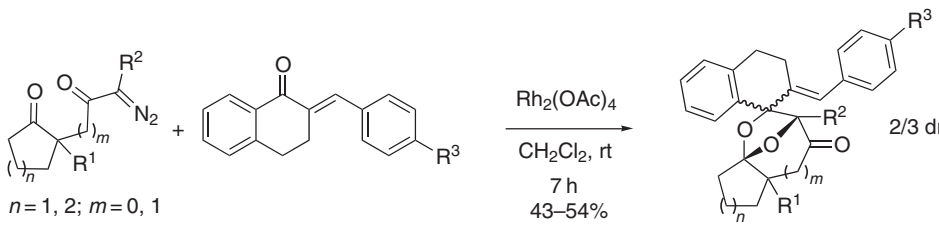


(12)

3.07.1.3.2 Intermolecular cycloadditions: carbene to oxygen heterocycle

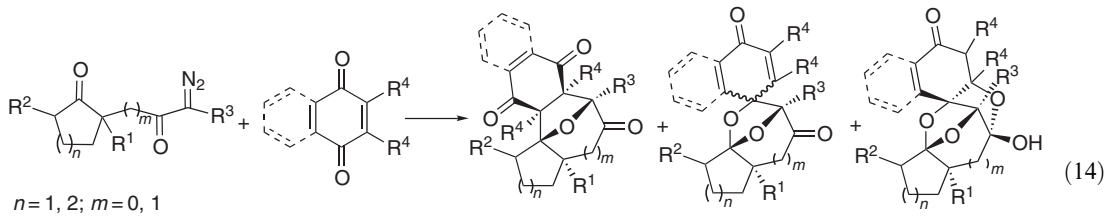
(i) Racemic cycloadditions

Muthusamy and co-workers have published extensively in the area of cycloadditions of carbonyl ylides across C=O bonds. α,β-Unsaturated tetralones were investigated as dipolarophiles <2000TL8839> and gave exclusive C=O addition; a range of diazo substrates and aryl substituents on the tetralone gave cycloadducts in 2:3 dr and moderate yields (Equation (13)).



(13)

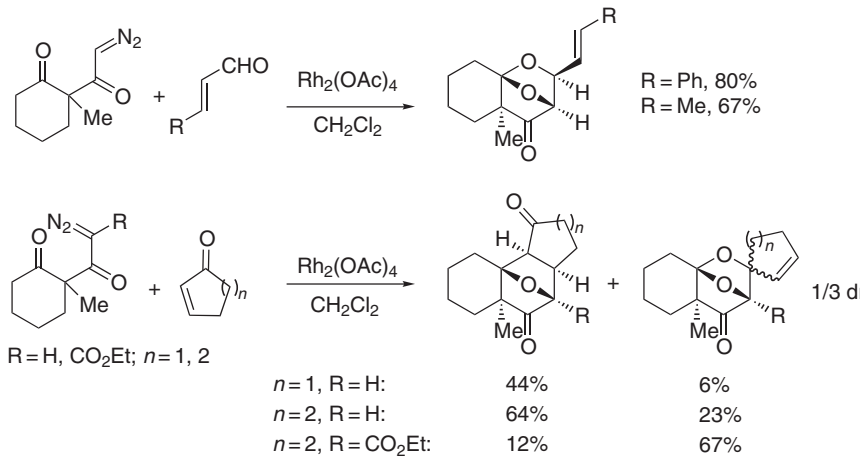
p-Quinones and 1,4-naphthoquinones gave 2 products derived from C=O cycloaddition (**17**, **18**) and one from C=C addition **16**; again a range of diazo substrates was investigated and product ratios were similar for all (*ca.* 5:15:30 **16**:**17**:**18**) <2001T7009> (Equation (14)). The product of C=C addition gives an entry to the anguacycline antibiotic skeleton.



	16	**17**	**18**
p-Quinone:	4–6%	15–18%	25–35%
Benzoquinone: R^4 = Cl:	4–5%	30–40%	0%
R^4 = H:	24–33%	5–14%	5–8%

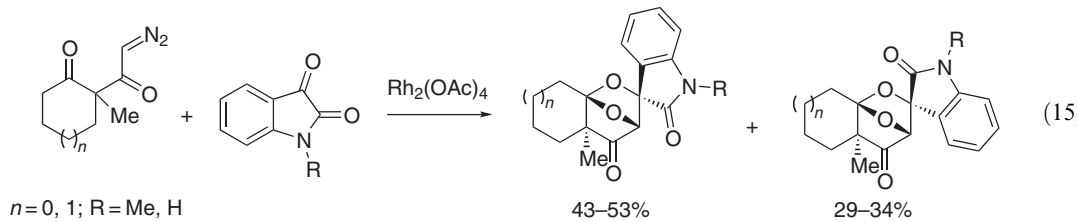
(14)

A range of α,β-unsaturated ketones and aldehydes were investigated as dipolarophiles for the synthesis of novel oxa-bridged tetrahydropyranones (Scheme 10) <2002JOC8019>. All of the aldehydes and heterocycle-substituted aldehydes examined gave exclusively C=O addition. With cyclic unsaturated ketones, the use of an α-diazoketone substrate gave predominantly C=C addition products, whereas for an α-diazo-β-keto ester, which results in a more electrophilic ylide, the products mainly arose from C=O cycloaddition. Acyclic α,β-unsaturated ketones resulted in exclusively C=C addition. However, the use of the same substrate and an α,β-unsaturated symmetrical ketone gave only C=O addition <2002TL3931>.



Scheme 10

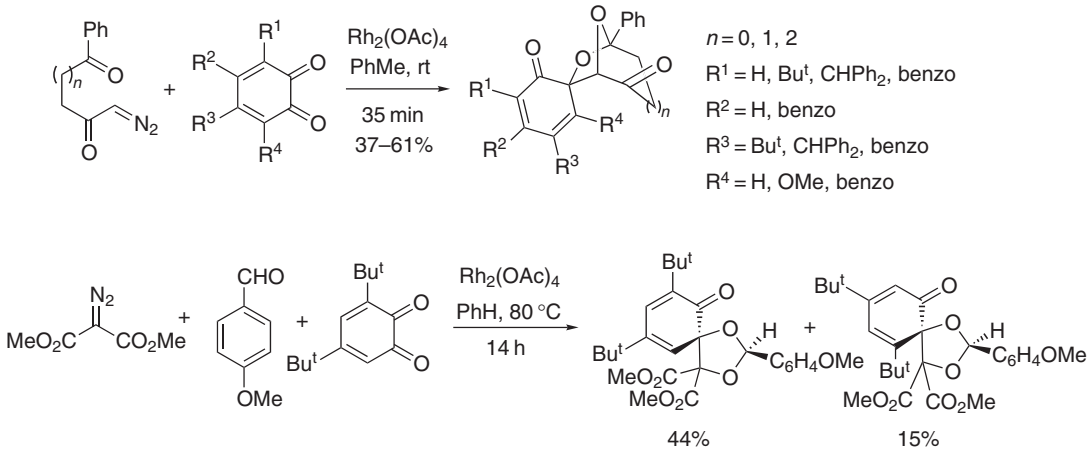
Isatins were also explored as dipolarophiles, and it was found that cycloaddition occurred exclusively across the carbonyl group β- to the nitrogen, for a range of *N*-protecting groups (Equation (15)) <2003T8117>.



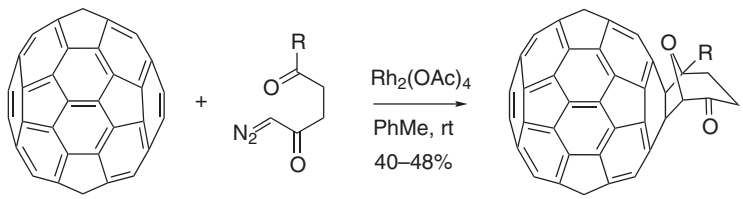
The same group has reported C=C cycloadditions with, for example, fulvenes <2001SL1407>, indoles <2001TL523>, and norbornene-based dipolarophiles <2002TL5981>. The formation of oxa-bridged cyclooctanoid rings from seven-membered carbonyl ylides in moderate yields has also been achieved <2002BCSJ801>.

Nair and co-workers have reported carbonyl ylide cycloadditions with *o*-quinones, *p*-quinone-imides, fullerenes, and 2-oxoindolinylidenes. A series of *o*-quinones were investigated <1998TL5627, 2002T4171>, and cycloaddition across the more electron-deficient of the two carbonyl groups proceeded in moderate-to-good yields with five-, six-, and seven-membered ylides (Scheme 11). An FMO study correctly rationalized the observed products. This reaction was extended to include ylides formed intermolecularly, and was found to be general for a range of aromatic aldehydes and *o*-quinones (Scheme 11) <2003TL8407>. The diastereoselectivity of the reaction was ascribed to a concerted carbonyl ylide cycloaddition step, with a preference for *trans*-ylide geometry.

The cycloadducts of aryl-, ferrocene-, and cyclopropane-substituted carbonyl ylides with buckminsterfullerene were synthesized in moderate yields (unreacted fullerene was recovered) (Equation (16)) and their redox properties explored by cyclic voltammetry <1999TL5087, 2002T3009>. The reduction potentials of the cycloadducts were more negative than those of the parent fullerene, due to the loss of a double bond.

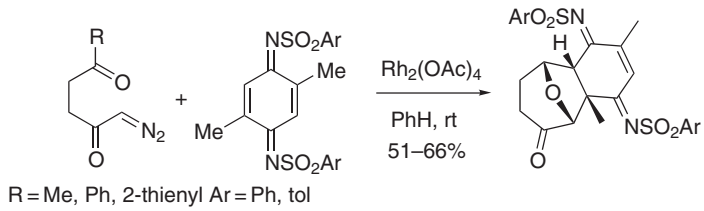


Scheme 11



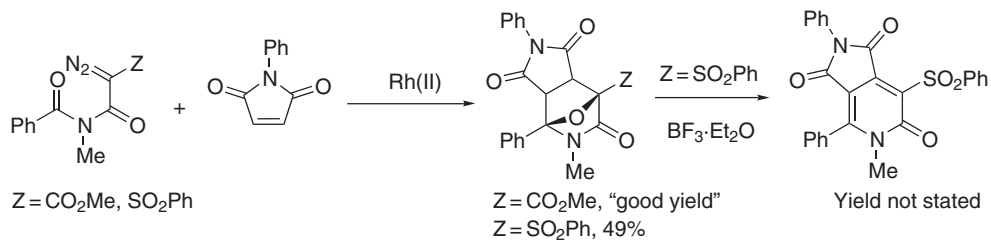
(16)

Use of *p*-quinone-imides as dipolarophiles with five- or six-membered cyclic ylides gave single regio- and stereoisomeric adducts, derived from *endo*-alkene cycloaddition <2001TL2045>. No imine addition was observed (Equation (17)).



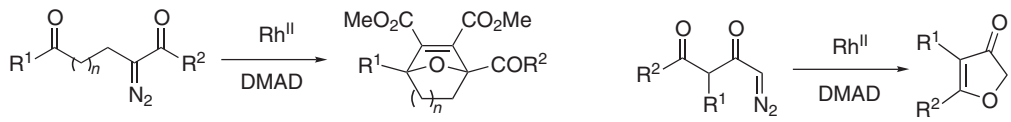
(17)

Padwa and co-workers have published cycloadditions of carbonyl ylides and isomünchnones with DMAD and *N*-phenyl maleimide, a cascade reaction of an ylide formed from a vinyl metallocarbene, and syntheses of the pterosin sesquiterpenes and illudins. *In situ*-generated isomünchnones from diazoimides underwent cycloaddition with DMAD or *N*-phenyl maleimide, and the yields obtained using catalysts with different electronic properties investigated (Equation (18)) <1996T2489, 1997JOC2001>. Where a methyl ester group was α- to the diazo function, catalysts containing the more electron-withdrawing ligands gave the cycloadducts in higher yield, whereas with a phenylsulfonyl group α- to the diazo function, the reverse was the case.



(18)

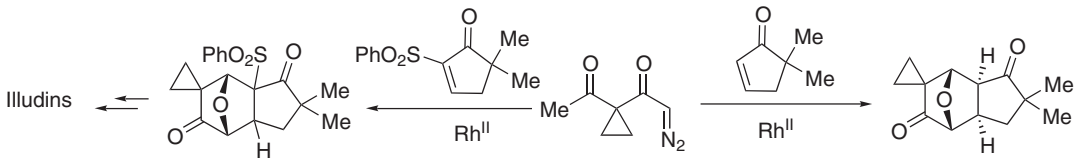
The cycloaddition of five- and six-membered cyclic ylides and fused aromatic ylides with DMAD is reported to proceed in high yields, except where [1,4]-proton transfer is more rapid than the cycloaddition (Scheme 12) <2000JOC5223>.



n = 1: R^1 = Ph, Me; R^2 = Ph, Me; 70–90%
n = 2: R^1 = R^2 = Ph, Me; 89–90%

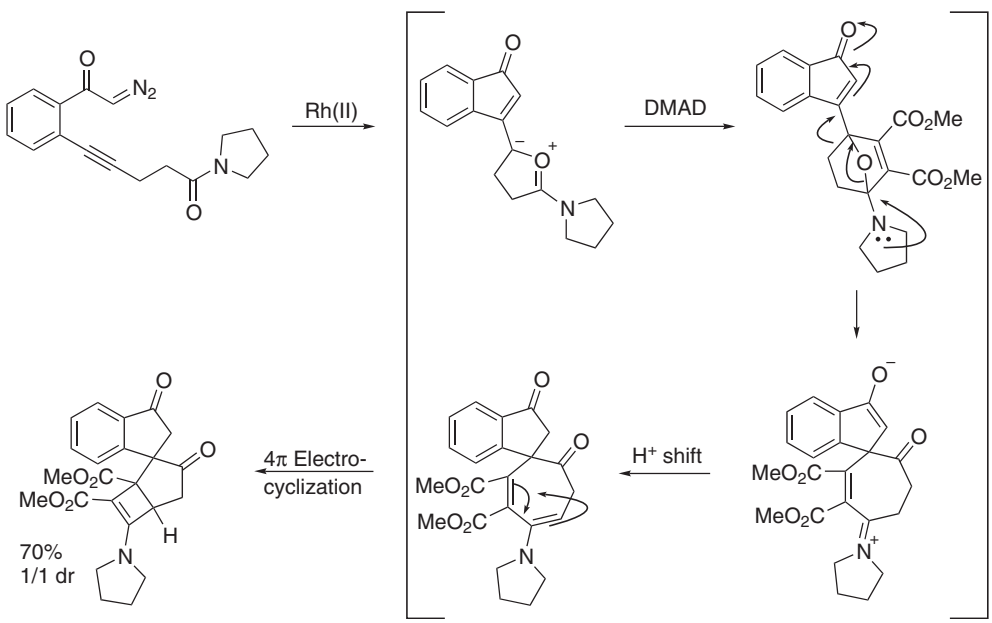
Scheme 12

Illudin M and the pterosin skeleton have been synthesized using similar key steps (Scheme 13) <1995TL1989, 1996JOC73, 1997JOC1317>.



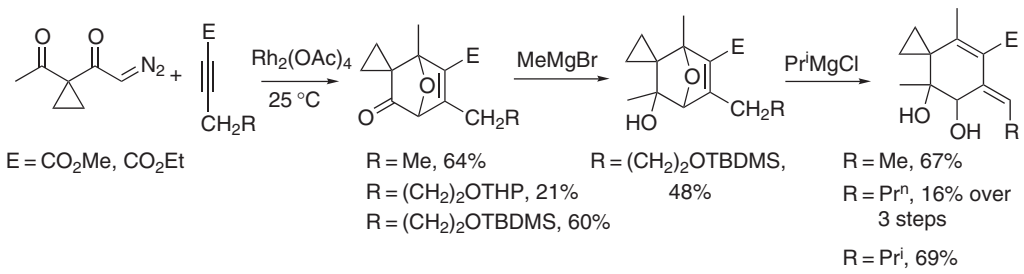
Scheme 13

The interaction of a metallocarbenoid with an adjacent triple bond, subsequent carbonyl ylide formation and cycloaddition, and then further rearrangements are reported to form complex polycyclic structures (Scheme 14) <1995JOC53>.



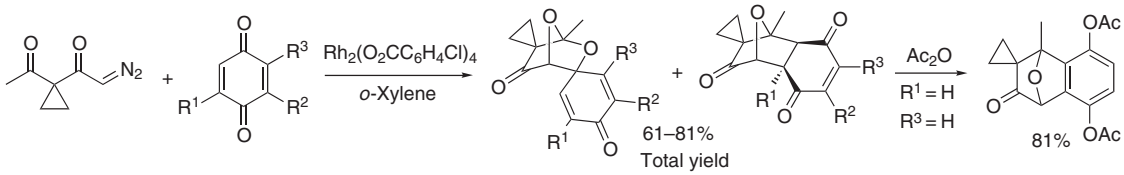
Scheme 14

Kinder and co-workers have synthesized isodehydroilludin M and the bicyclic core of dehydroilludin M <1998SC2541, 1997SC521>. The key step in the former synthesis is the same as in the approach used by Padwa (*vide supra*); in the latter, the cyclopropane-bearing five-membered ylide and an ester-substituted alkyne undergo cycloaddition (Scheme 15).



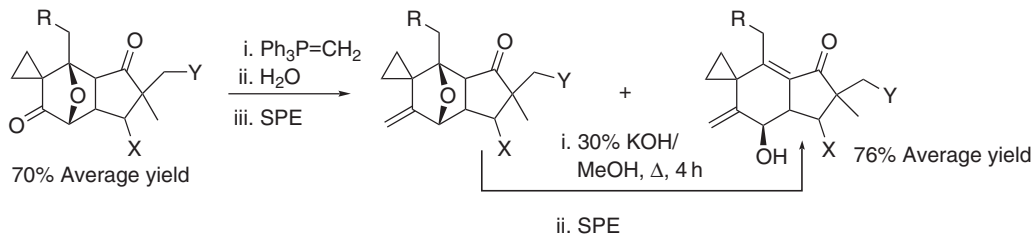
Scheme 15

Pirrung and co-workers have also reported syntheses of illudin analogs. The illudin skeleton was combined with the anthraquinone skeleton in the hope of also combining the antitumor activities of the two parent compounds <2000OL353>. A variety of diazo compounds and *p*-quinones were employed, and product ratios were found to vary with catalyst and solvent. Aromatization of the cycloadducts was carried out by treatment with acetic anhydride (Scheme 16).



Scheme 16

The synthesis of 49 illudin analogs using parallel synthesis and solid-phase extraction (SPE) techniques was also undertaken (Scheme 17) <2003OL1983>. Unusually, THF, diethyl ether, and dioxane were found to be good solvents for the cycloadditions. This was ascribed to the coordination of the catalyst by the solvent slowing the diazo decomposition, and hence the carbonyl ylide formation, such that its rate equalled the rate of the cycloaddition; thus, the ylide was not present in sufficient quantity to undergo side reactions. Three of the illudin analogs exhibited complete inhibition of H460 nonsmall cell lung tumors at 100 μM.



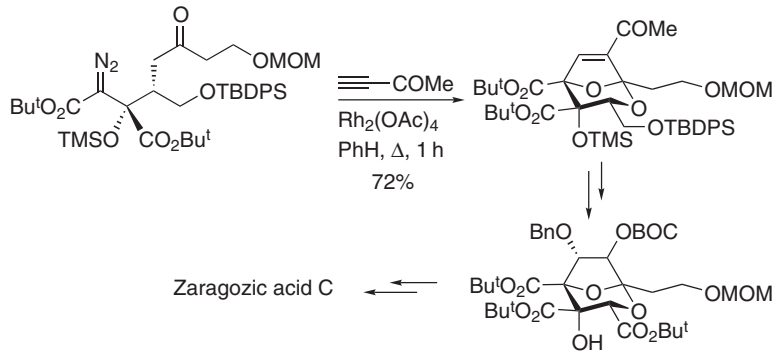
Scheme 17

Hashimoto and co-workers reported a carbonyl ylide cycloaddition-based synthesis of the core of the zaragozic acids, and subsequently a total synthesis of (+)-zaragozic acid C (Scheme 18) <1998TL2371, 2003AG(E)5351>.

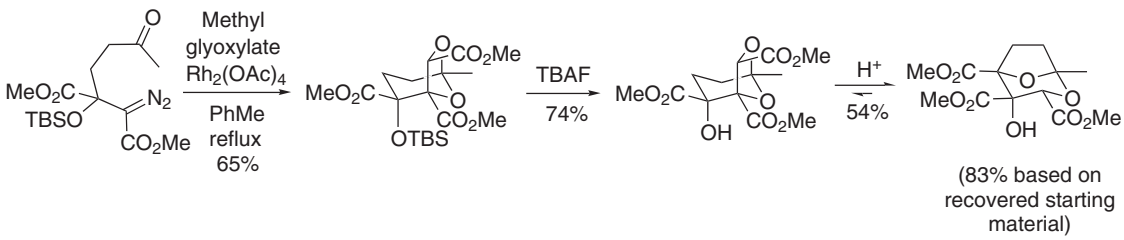
The zaragozic acid core has also been approached by Hodgson and co-workers, via a glyoxylate cycloaddition with a carbonyl ylide followed by acid-catalyzed isomerization to give the desired 2,8-dioxabicyclo[3.2.1]octane structure (Scheme 19) <2000JCS(P1)3432, 2000TL5597>.

The same group has reported concise total syntheses of *cis*-nemorensic acid and 4-hydroxy-*cis*-nemorensic acid <2002OL1809> in which the key step is regioselective cycloaddition of propargyl bromide across a cyclic carbonyl ylide generated from a levulinic acid-derived diazoketone (Scheme 20).

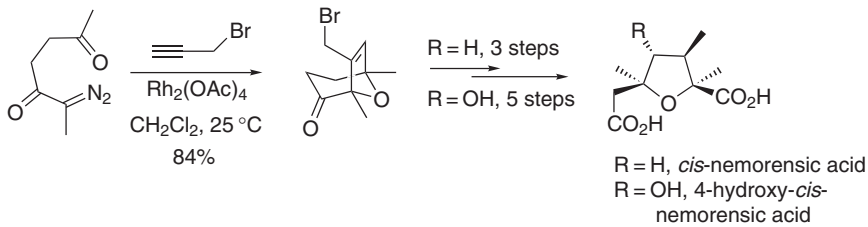
Doyle and co-workers studied carbonyl ylides formed intermolecularly from a diazo compound and an aldehyde, and subsequent cycloadditions either across the C=O bond of a second



Scheme 18

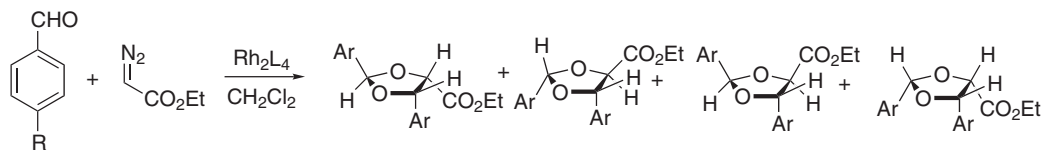


Scheme 19



Scheme 20

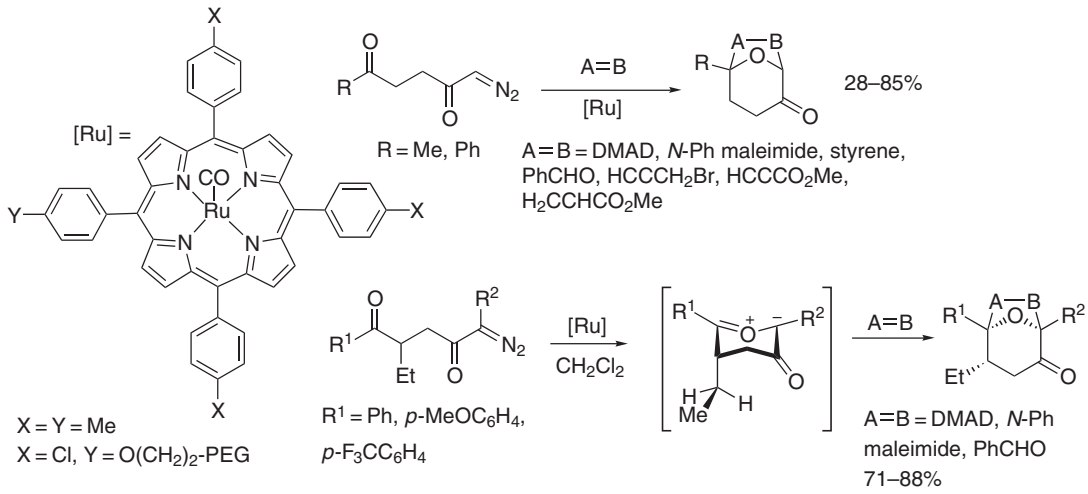
molecule of aldehyde to give 1,3-dioxolanes, or DMAD *in situ* <1997JOC7210>. A computational study of the possible isomeric ylides formed between the carbenoid and the aldehyde was carried out, and the effect of different catalysts and the electronics of the aldehyde on the product distribution were investigated. For anisaldehyde and benzaldehyde, the different catalysts examined had no effect on the product distribution, and only two of the four possible stereoisomeric cycloadducts were formed; these reactions are proposed to involve a catalyst-free ylide intermediate. However, in the cycloaddition of *p*-nitrobenzaldehyde, all four isomeric dioxolanes were produced in a ratio dependent on the catalyst, and so a catalyst-complexed ylide was invoked in the reaction mechanism (Scheme 21).



R = OMe, $Rh_2(OAc)_4$, <15%	1:1:0:0
R = H, $Rh_2(cap)_4$, 27%	1:1:0:<0.2
R = NO_2, $Rh_2(OAc)_4$, 37%	21:22:3:54
R = NO_2, $Rh_2(cap)_4$, 35%	43:41:0:16

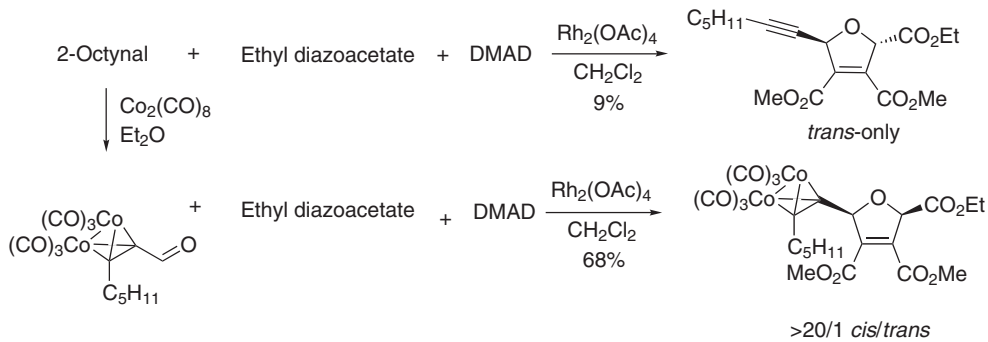
Scheme 21

Zhou and co-workers have investigated the use of Ru(II) porphyrins as diazo-decomposition catalysts in carbonyl ylide cycloadditions (Scheme 22) <2002OL3235, 2003S1403>. The catalysts have high product turnovers, and a PEG-supported variant was recyclable for seven successive reactions. A variety of diazo compounds and dipolarophiles were used; comparable activity to $Rh_2(OAc)_4$ was found. In a diastereoselectivity study, cycloadducts were predominantly formed with R^1 and Et in a *cis*-relationship, implying that the ylide is unbound or loosely bound by the catalyst, so that the stereochemistry of the ylide determines the diastereocontrol (Scheme 22). This was supported by the observation that altering the electronics or sterics of the catalyst has little effect on the diastereoselectivity of product formation.



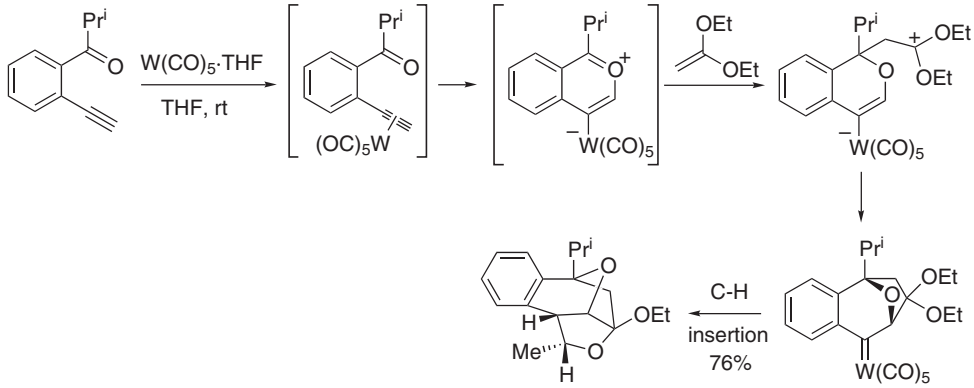
Scheme 22

Skaggs and co-workers have reported the cycloaddition of a carbonyl ylide with DMAD to form a dihydrofuran in the presence of a cobalt cluster-protected alkyne (Scheme 23) <2002OL2277>. The cobalt cluster prevents the ynal component acting as the dipolarophile, and may also have steric and electronic effects on the ylide; for example, dioxolane formation occurs in only trace amounts, whereas usually this pathway is dominant for electron-rich aldehyde dipolarophiles. The reaction is modelled as occurring on the W-form of the dipole, leading to a 2,5-*cis*-relationship in the product, and is highly *exo*-selective with respect to the Co cluster. Pauson–Khand and Nicholas reactions may be used to further elaborate the Co cluster, or it may be removed in high yield by treatment with iodine.



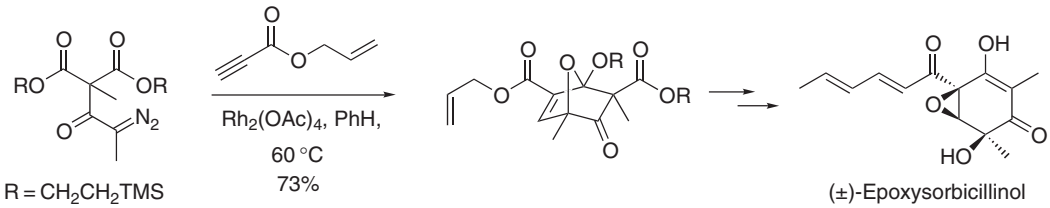
Scheme 23

Iwasawa and co-workers have formed pyryliums from the interaction of a tungsten complex with the triple bond in an *ortho*-acylated alkynylbenzene <2001JA5814>. Cycloaddition with ketene acetals and vinyl ethers *in situ* is then possible, followed by CH-insertion of the resulting tungsten carbenoid to form a tetracyclic product (Scheme 24).



Scheme 24

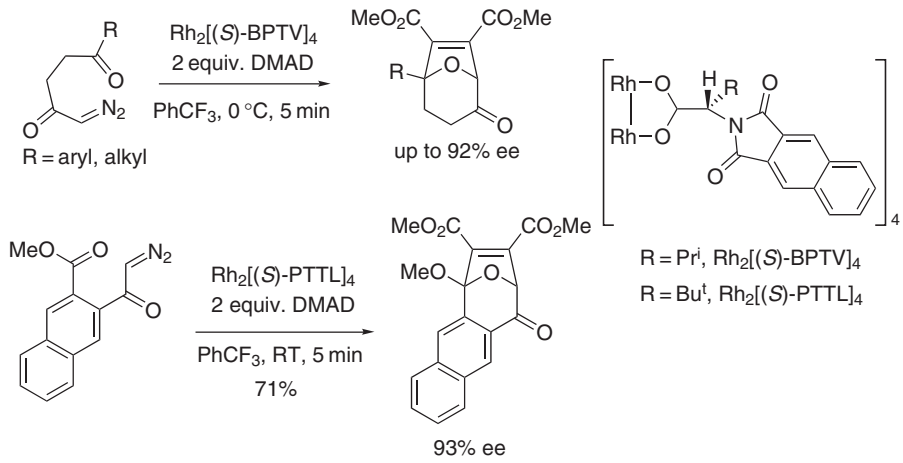
The intermolecular cycloaddition of a carbonyl ylide with an alkynyl ester has been applied to the synthesis of (±)-epoxysorbicillinol by Wood and co-workers (Scheme 25) <2001JA2097>.



Scheme 25

(ii) Enantioselective cycloadditions

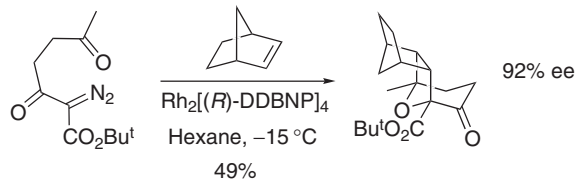
Hashimoto and co-workers have developed chiral amino acid-derived Rh(II) catalysts for enantioselective cycloadditions of α-diazodiones and α-diazoketo esters with DMAD in trifluorotoluene <1999JA1417, 2000TL5931>. Careful matching of the substrate to the catalysts can result in very high ees (Scheme 26).



Scheme 26

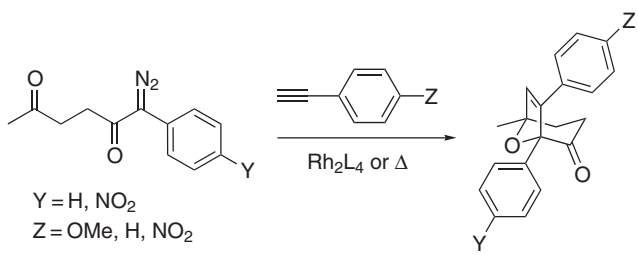
A range of enantioselective intermolecular cycloadditions of carbonyl ylides have been reported by Hodgson and co-workers. Good ee values (up to 92%) have been achieved with dipolarophiles

such as phenyl acetylene, norbornene, and norbornadiene when reacted with the cyclic ylide generated from a levulinic acid-derived α-diazo-β-keto ester (Equation (19)) <2003TA921>.



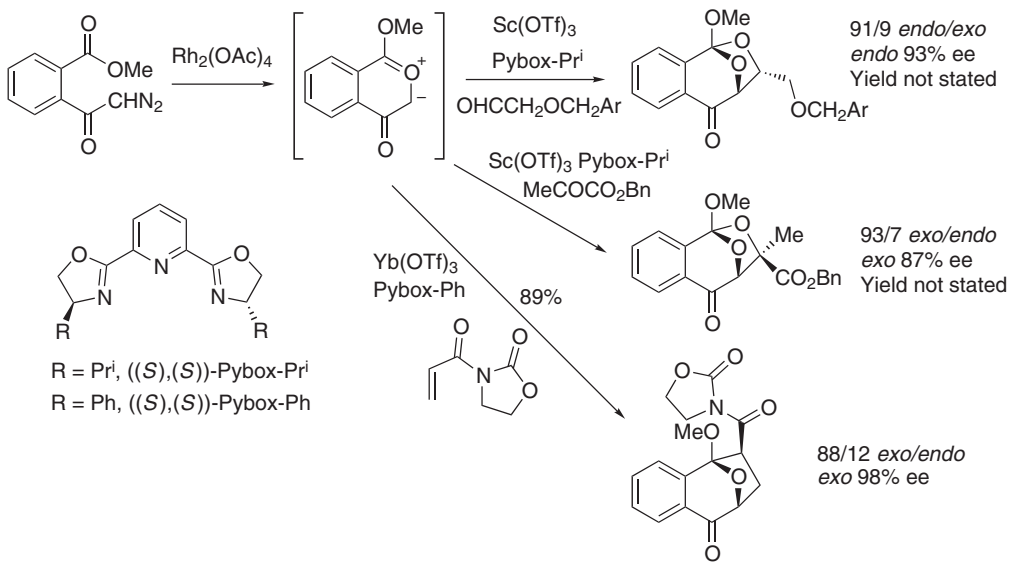
(19)

The effects on yield and ee of the dipolarophile electronics with a range of *p*-substituted aryl acetylenes and *p*-substituted aryl α-diazoketones has been investigated (Equation (20)) <2002TL3927, 2003JOC581>. In all cases, including heating in the absence of catalyst, a single cycloadduct regioisomer was obtained, possibly as a result of aryl π–π interactions in the transition state. In competing reactions in the presence of three acetylenes the catalysts are found to perturb product distributions slightly compared to the absence of catalyst. Use of asymmetric catalysts generally gave lower yields than with achiral complexes, and conclusions were that: a high cycloaddition rate does not necessarily lead to high ee values; the enantioselection is not only determined by the facial selection in the ylide formation step; and that the origin of the effect from the catalyst electronics was complex. The ee values obtained with phenyl acetylene could be improved by using phenyl acetylene as solvent.



(20)

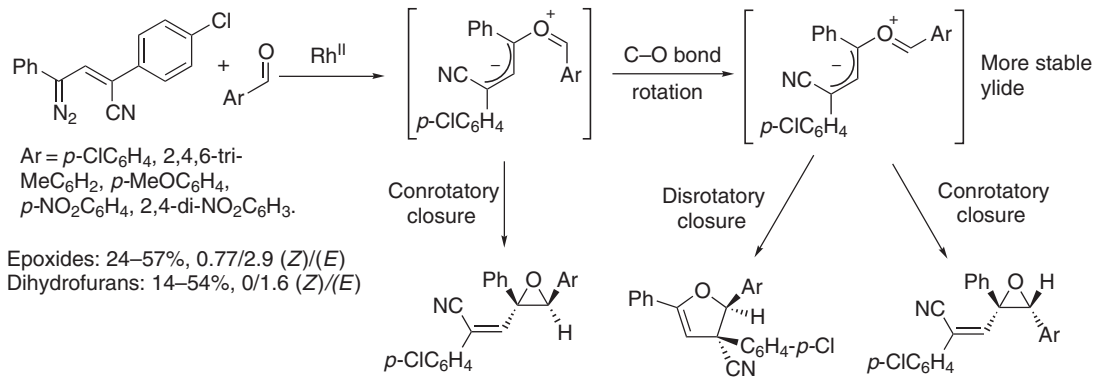
Suga and co-workers have developed a catalyst system producing high enantioselectivities from cycloaddition of an oxidopyrylium when a lanthanide triflate and a Pybox ligand are added to the reaction mixture along with $Rh_2(OAc)_4$ (Scheme 27) <1998TL3165, 2001BCSJ1115, 2003S1413, 2002JA14836>.



Scheme 27

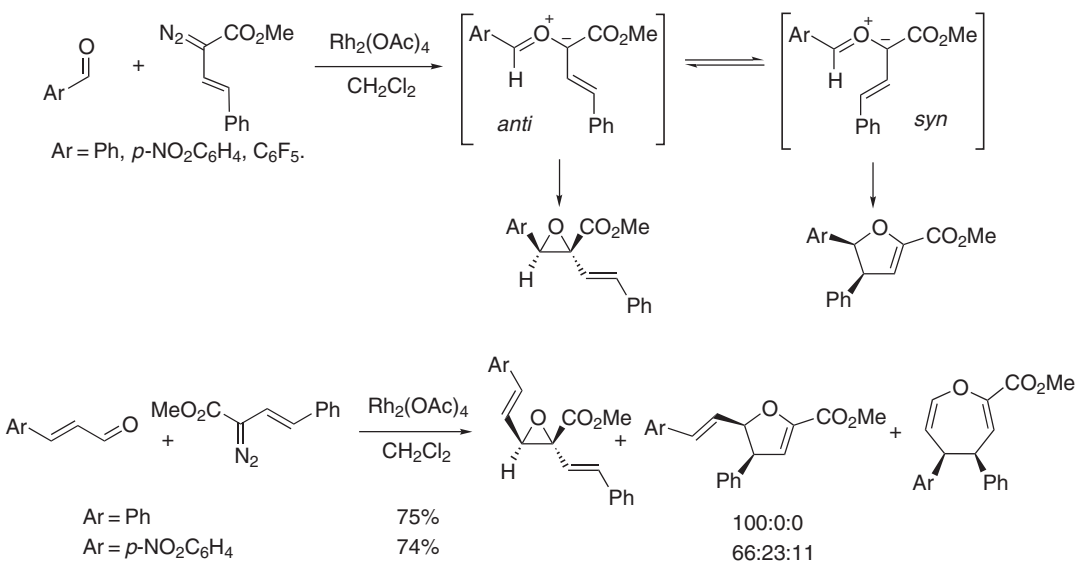
3.07.1.3.3 Electrocyclizations leading to furans and oxiranes

Hamaguchi and co-workers have investigated the mechanism of the reaction of vinyldiazo compounds with aryl aldehydes to give mixtures of oxiranes and dihydrofurans <2000TL1457, 2001JOC5395>. It was found that electron-donating groups on the aldehyde favored the formation of oxiranes, whereas electron-withdrawing groups favored dihydrofuran formation. The Woodward–Hoffman rules were used to infer the structure of the ylides leading to the different products, and subsequent addition of a dipolarophile to trap the first-formed ylide as a cycloadduct allowed the reaction scheme shown below to be proposed (Scheme 28).



Scheme 28

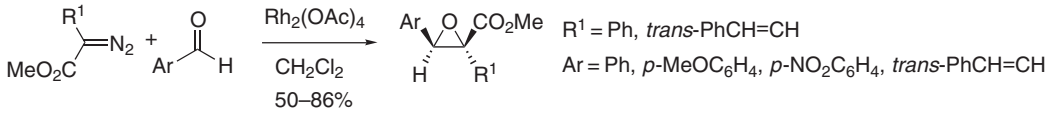
Doyle and co-workers have also reported very similar reactions <2001OL3741>, observing one oxirane and one dihydrofuran product, and proposing an equilibrium between two ylides, which may be perturbed by the electronics of the aldehyde (Scheme 29). The catalyst used was also found to affect the product distribution. The reaction was extended to imine dipolarophiles, forming pyrroles, and also to aldehydes with a conjugated double bond, leading to a mixture of oxirane, dihydrofuran, and oxepine products as single diastereomers (>20:1) (Scheme 29).



Scheme 29

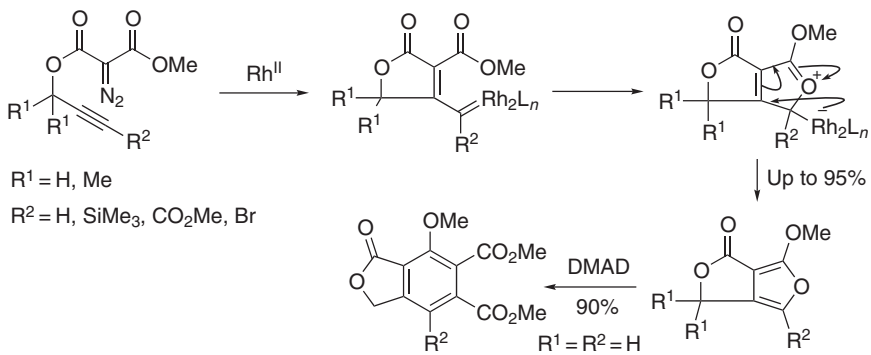
The same group also reports the stereospecific formation of (*Z*)-epoxides from diazo compounds and aryl aldehydes (Equation (21)) <2001OL933>. Use of aliphatic aldehydes led to a

complex mixture of products. Increasing ylide stability leads to a decrease in the tendency for the ylide to undergo cycloaddition across a second molecule of aldehyde. Examination of chiral catalysts yielded only racemic epoxides.



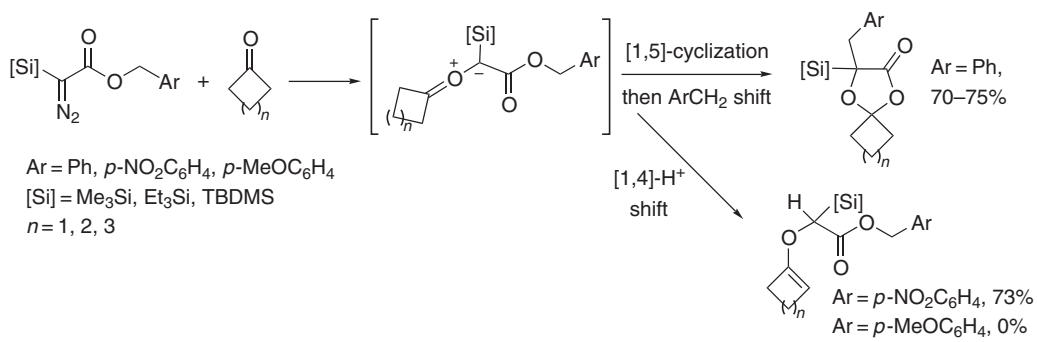
(21)

Padwa and co-workers have observed formal 6π-cyclization via a carbonyl ylide formed from the interaction of a vinyl carbenoid with an adjacent carbonyl group, and subsequent [4 + 2]-cycloadditions of the resultant furans with dienophiles such as DMAD (Scheme 30) <2003JOC227>.



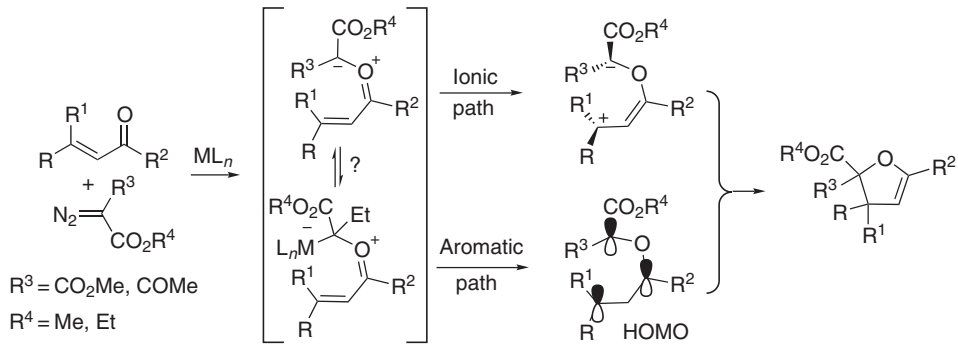
Scheme 30

Bolm and co-workers have reported the formation of dioxolanones from α-silyl diazoacetates and acyclic or cyclic ketones (Equation (22)) <2002OL4631>. The best yield was obtained with adamantanone; α-alkyl substitution of the ketone was found to reduce yields, whilst α-substitution of the benzyl group of the diazo compound did not significantly affect the yield. The use of (*R*)-(+)-1-phenylethanol in the substrate led to a 3.5:1 dr in the product. Alteration of the electronics of the benzyl group was explored, and it was found that electron-donating groups gave exclusive dioxolanone formation, whereas electron-withdrawing groups favor instead the formation of an enol ether from a [1,4]-proton shift.



(22)

Anaç and co-workers have reported the 1,5-closure of α,β-enone-derived ylides to dihydrofurans, and an investigation to support the proposal of an aromatic transition state rather than an ionic transition state (Scheme 31) <2003HCA(86)290>. It was found that the use of the *s-trans* conformation of an enone does not lead to dihydrofuran products; if the ionic mechanism operated, formation of the dihydrofuran would be possible due to bond rotation in the transition state. Two diazo compounds were used, and ethyl acetodiazoacetate (EADA) was found to favor dihydrofuran formation to a greater extent than dimethyl diazomalonate (DMDM), possibly because the

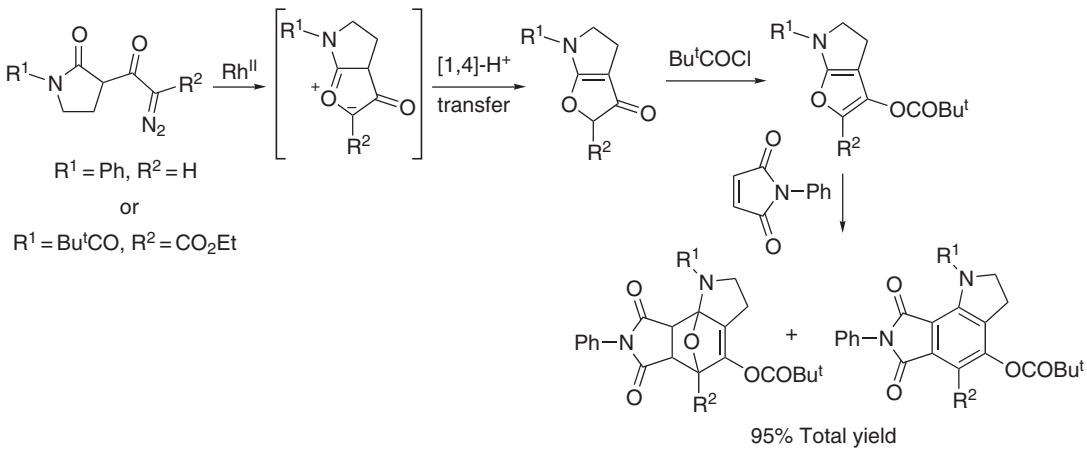


Scheme 31

conjugation in the ylide stabilizes the aromatic transition state, and because the more electrophilic carbene reacts with the carbonyl oxygen more readily than with the alkene bond.

3.07.1.3.4 Hydrogen migration leading to enol ethers

Padwa and co-workers report that the isomünchnone ylide formed as part of their approach to lycorine undergoes a fast [1,4]-proton transfer to form a dihydrofuranone, and the intermediate ylide could not be induced to undergo cycloaddition even in the presence of excess DMAD (Scheme 32) <1999TL4003, 2001CJC1681>. This dihydrofuranone could be aromatized by treatment with pivaloyl chloride, and then Diels–Alder reactions with either inter- or intramolecular dienophiles could be achieved. If acetyl chloride was used in the aromatization step, a poor yield of cycloadduct was obtained, possibly due to competitive deacylation.

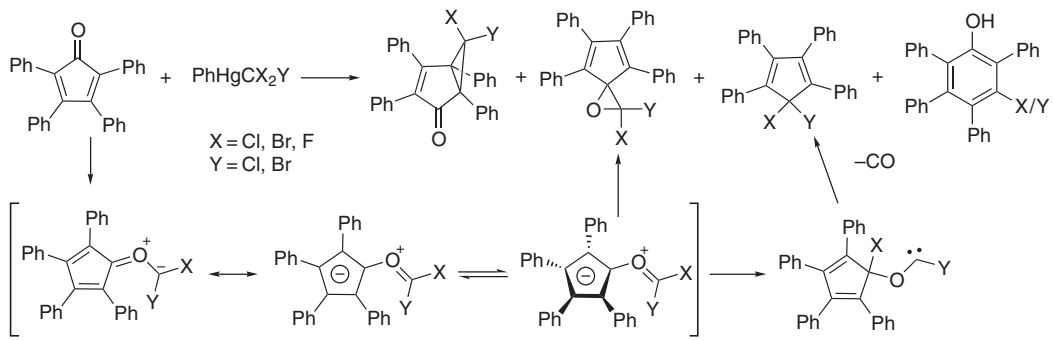


Scheme 32

The formation of enol ethers from the ylide of an α-silyl diazoester (with an electron-withdrawing aryl-substituted ester) and a ketone has been observed by Bolm and co-workers (*vide supra*, Equation (22)) <2002OL4631>.

3.07.1.3.5 Halogen migration and decarbonylation reactions

Wang and co-workers have reacted phenyl(trihalomethyl)mercury and tetraphenylcyclopentadienone and observed high levels of decarbonylation, in addition to epoxidation, cyclopropanation, and ring expansion, and propose a pathway proceeding via a carbonyl ylide (Equation (23)) <1999JCR(S)348>.

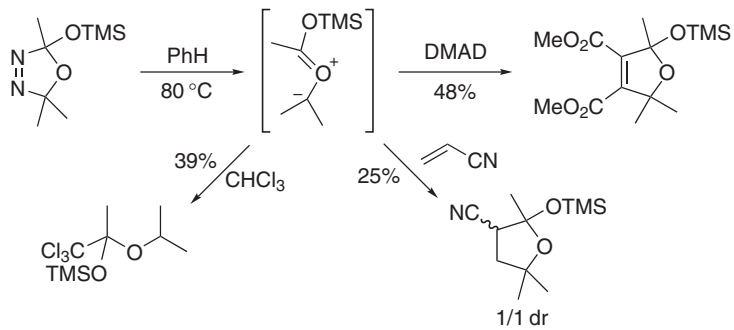


(23)

3.07.1.4 Carbonyl Ylides from Cycloreversions

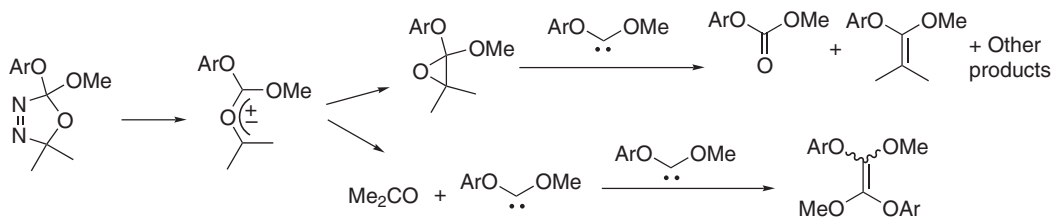
Two main methods of carbonyl ylide generation by cycloreversion have been used in the last few years: cycloreversions of oxadiazolines under thermal conditions, and cycloreversions of oxanorbornene under photolytic conditions. In the former case, products which may arise from carbonyl ylides are isolated; however, there is some debate over whether a carbonyl ylide is a true intermediate in these reactions. The area has been reviewed by Padwa <1996CRV223>.

Warkentin and co-workers have explored the products arising from the cycloreversion of oxadiazolines, and have proposed that carbonyl ylide formation is one of the pathways by which the cycloreversion can occur. Heating of a trimethylsilyloxy-substituted oxadiazoline in the presence of dipolarophiles such as DMAD and acrylonitrile gives rise to moderate yields of carbonyl ylide-derived cycloadducts; in the presence of chloroform or other carbon acids, C—H insertion products can be observed (Scheme 33) <1995TL7591>.



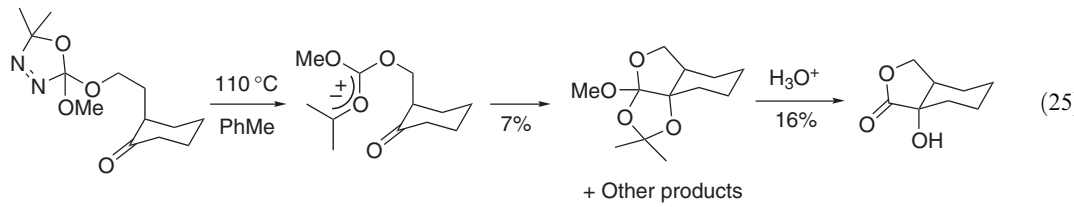
Scheme 33

Thermal cycloreversion of aryloxy–alkyloxy-substituted oxadiazolines can give rise to carbonates and ketene acetals, amongst other products; the intermediacy of carbonyl ylides and oxiranes in the major fragmentation pathway was proposed, although the oxiranes were not unambiguously detected (Equation (24)) <1997CJC326>. Later studies of diaryloxy-substituted oxadiazolines determined that the ketene acetal products could not be formed by interaction of the diaryloxycarbene and acetone formed during the reaction, as addition of acetone-d_6 did not lead to deuterium incorporation into the product; therefore, these products must arise from the carbonyl ylide <2001CJC319>.



(24)

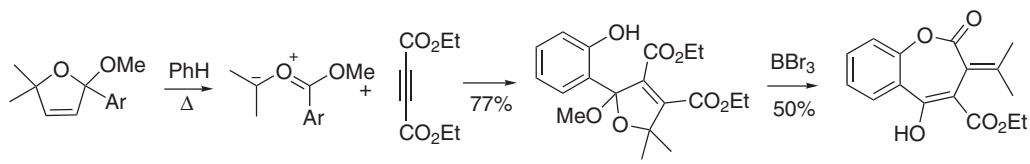
Cycloreversion of a range of spirocyclic oxadiazolines was also investigated to study the rate dependence of the process on the electronic character of the substituents <1997CJC1264>. It was found that the presence of electron-withdrawing groups increased the rate of the cycloreversion, as expected for a carbonyl ylide pathway and opposite to that expected for direct fragmentation to carbenes. An oxirane was isolated in 12% yield from the reaction mixture on thermolysis of a dimethoxy oxadiazoline, providing further support for this mechanism <2001CJC110>. The products of carbonyl ylide cycloaddition across a tethered carbonyl group were isolated, although it was not found to be possible to trap the ylide with DMAD (Equation (25)) <2003CJC598>.



(25)

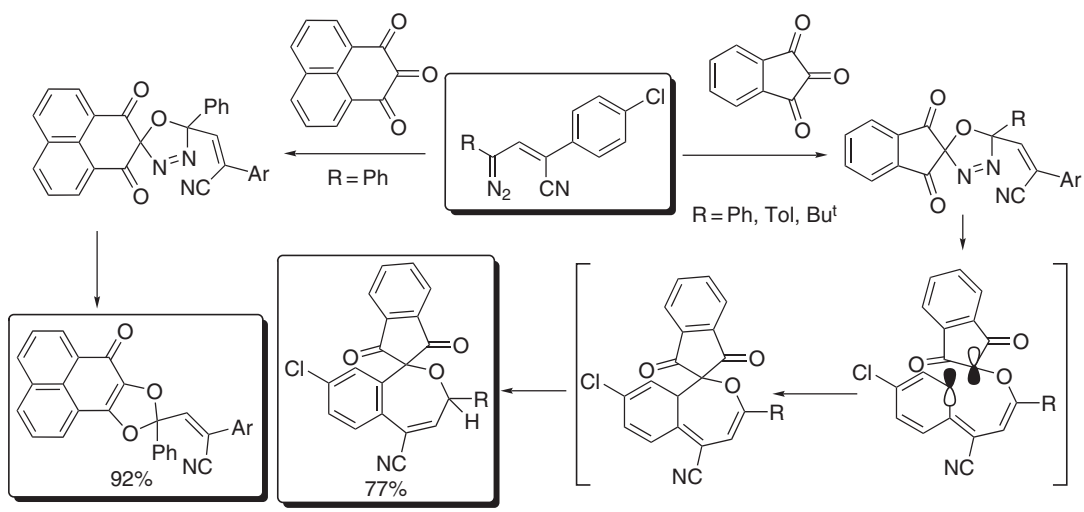
A computational study by Smith of the mechanism of these types of reaction, however, has found that carbonyl ylides are not true intermediates on the reaction coordinate <1995JOC7456>. The ylides are not computed to be stable over the range of bond angles necessary for their formation and reaction, and it is suggested that they collapse directly to a carbene and acetone. However, the studies of electronic effects on the reaction rate by Warkentin and co-workers appear to disagree with this proposal.

Rigby and Aasuml have trapped a carbonyl ylide from the cycloreversion of an oxadiazoline using diethyl acetylenedicarboxylate; in the presence of BBr_3, the cycloadduct underwent subsequent ring-expansion to form an oxepine (Scheme 34) <2003TL5029>.



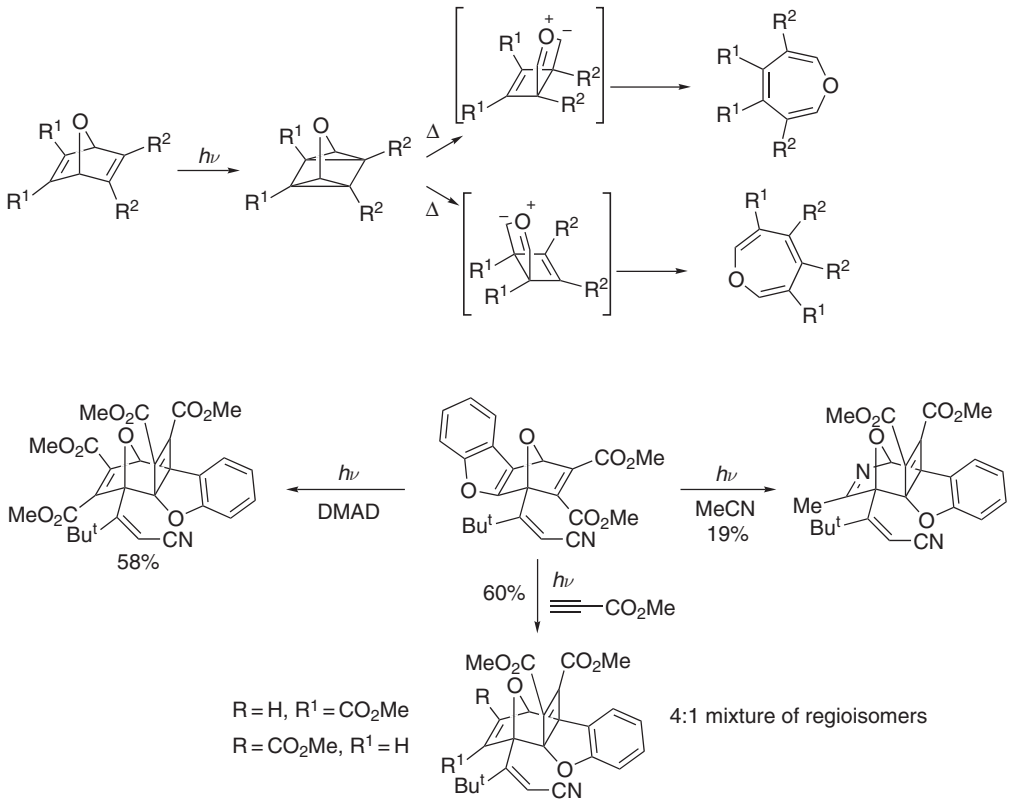
Scheme 34

Hamaguchi and co-workers have formed an oxadiazoline *in situ* by reaction of a diazo compound and a tricarbonyl compound in the absence of a diazo-decomposition catalyst <2003TL4339>. The oxadiazoline then cycloreverts with loss of N_2 to a carbonyl ylide, which, where the tricarbonyl is an indanetrione, undergoes a 1,7-cyclization followed by a 1,5-H shift to form an oxepine. Alternatively, with a six-membered ring cyclic tricarbonyl, the product is a dioxolane (Scheme 35).



Scheme 35

Bussenius and co-workers have investigated the cycloreversions of oxanorbornadienes under photochemical conditions, which produce carbonyl ylides and, after 1,5-electrocyclic ring-opening, oxepines <1995LA1503>. The use of the benzo-fused analog gives benzoxepines in only 5–10% yield. However, photolysis of the benzofuro-fused oxanorbornadiene in acetonitrile gave a 19% yield of the cycloadduct arising from addition of the ylide to the cyano group of the solvent. In the presence of other dipolarophiles, e.g., DMAD, good yields of the corresponding cycloadducts were obtained (Scheme 36). A vinyl group at the bridgehead does not participate in, for example, di-π-methane reactions.



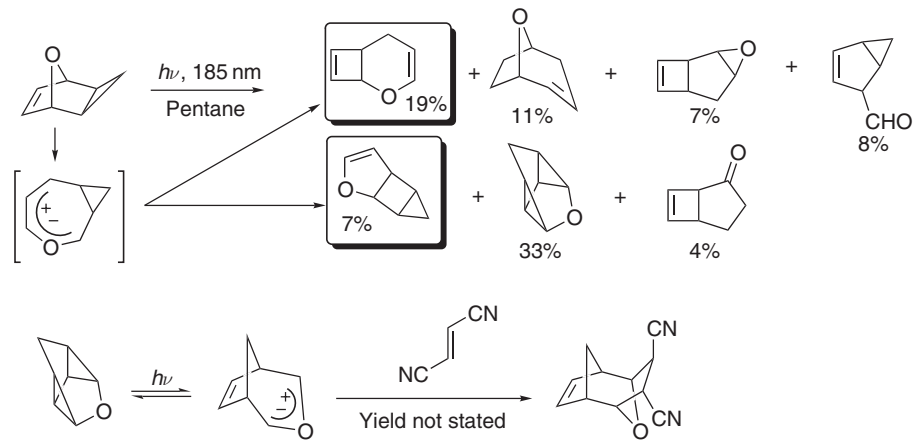
Scheme 36

Klärner and co-workers have photolyzed a cyclopropane-fused oxanorbornene at 185 nm, such that the irradiation excites both the double bond and the cyclopropane ring, and obtained seven products, two of which are attributed to electrocyclization of an intermediate carbonyl ylide (Scheme 37) <1996TL1385>. The tetracyclic product of this photolysis may also form a carbonyl ylide, which can be trapped by fumaronitrile as a cycloadduct.

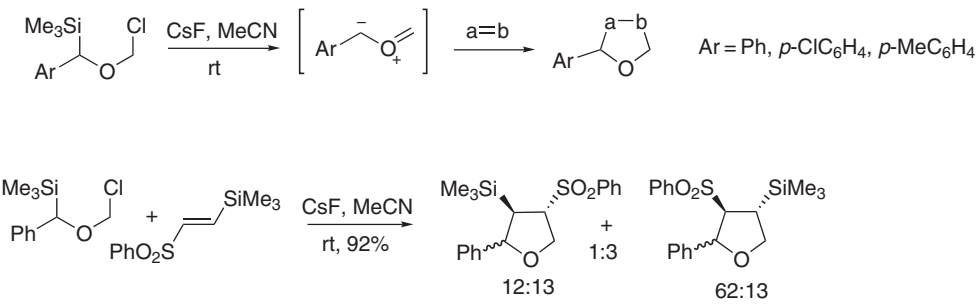
3.07.1.5 Carbonyl Ylides from Elimination Reactions

A series of mild conditions have been reported, allowing synthesis of nonstabilized symmetrical or unsymmetrical ylides, including the "parent" carbonyl ylide 2-oxatrimethylene, from halogen-substituted ethers. The area has been reviewed by Friedrichsen <B-1997MI117>.

Hojo and co-workers have reported a series of systems for the formation of nonstabilized and alkyl-substituted carbonyl ylides, including the "parent" ylide, 2-oxatrimethylene. Their initial reports use CsF to eliminate Me_3SiCl from an α-trimethylsilyl-α'-chloroether (Scheme 38) <1996SL234>. Cycloadditions with a wide range of dipolarophiles proceeded in good to high yields; a range of styrenes was used, giving cycloadducts in 62–75% yield and an 82:18 ratio of 3-aryl:4-aryl regioisomers regardless of the electronic nature of the styrene. Substituted allenes as well as C═O, C═S, C═NTs, and N═N bonds functioned as dipolarophiles. Mixtures of



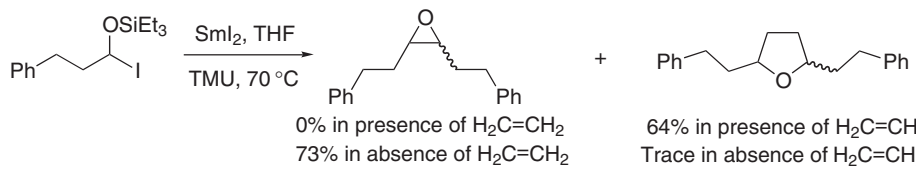
Scheme 37



Scheme 38

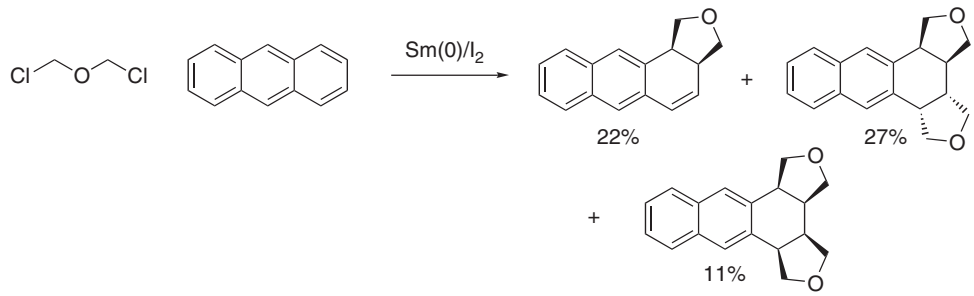
regioisomers (~75:25) in agreement with computation for the C=X bonds were observed in all cases except for ketones; in this case steric arguments are proposed to explain the complete selectivity. The method was applied to a three-step synthesis of lignan (Scheme 38).

Nonstabilized symmetrical carbonyl ylides may be generated from two molecules of 1-iodo-1-silyloxyalkanes in the presence of $Sm^0/HgCl_2$ or SmI_2/tetramethylurea (TMU) <1996JA3533>. In the absence of a dipolarophile, epoxides were formed in good yield; bubbling ethylene through the reaction mixture gave a tetrahydrofuran (Equation (26)). Extensions of the method were made to include alkyl groups on the ylide and a wide range of dipolarophiles; yields were good to excellent, and usually the reactions were highly selective for the 2,5-*trans*-isomer. Use of aldehydes as dipolarophiles resulted in moderate yields of dioxolanes, with diastereoselectivity decreasing with increasing steric bulk of the aldehyde. This latter reaction is equivalent to an intermolecular stereoselective pinacol coupling of two different aldehydes.



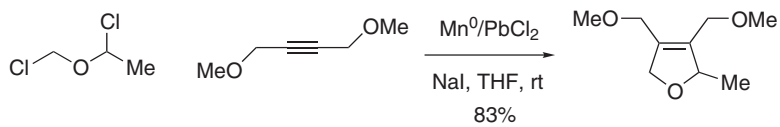
(26)

Treatment of α,α'-dichloroalkyl ethers with SmI_2 allows formation of 2-oxatrimethylene and alkyl-substituted ylides (Equation (27)) <1996TL9241>. Cycloadditions with a wide range of alkenes translated the double bond geometry into the tetrahydrofuran product, and substituted ylides gave 2,5-*trans*-stereochemistry. Use of alkynes in the presence of excess ylide gave double cycloaddition, forming fused tetrahydrofurans. Generation of the ylide from bis(iodomethyl)ether allowed cycloaddition with *t*-butyl acrylate and cyclohexanone; cycloadditions of the ylide formed from the bis-chloride were also possible with aromatic π-bonds.



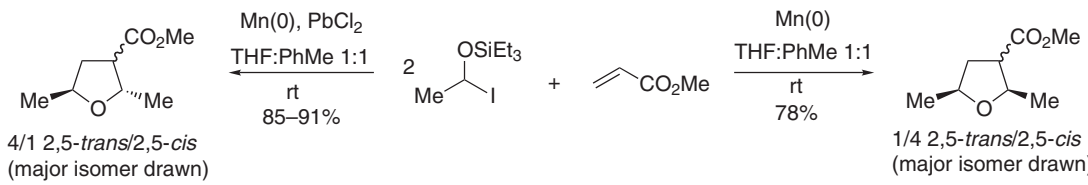
(27)

The reduction of α,α'-dichloroalkyl ethers with $Mn(0)/PbCl_2/NaI$, a milder system than those described above, allowed the use of electron-poor alkenes (which could be reduced by samarium) as dipolarophiles <1997JOC8610>. Use of a Pb/Mn-generated ylide in excess (up to fourfold) in presence of a triple bond did not lead to double addition, in contrast to the ylide generated with the samarium system. The system is applicable to the generation of nonsymmetrical ylides (Equation (28)). Ylides were reacted successfully and in high yield with unactivated, electron-rich and electron-poor alkenes, C=O bonds and C=NTs groups. Benzophenone also worked well, despite the possibility of electron transfer from the manganese to benzophenone. The rôle of the sodium iodide is suggested to be to exchange the chlorine atoms in the substrate for iodine, thereby making the substrate more reactive toward the reduction system.



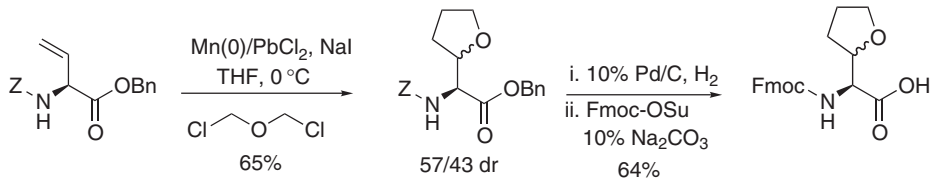
(28)

The same reduction system was simultaneously reported by Takai and co-workers <1997JOC8612>. They observe that when using acrylates as dipolarophiles, the diastereoselectivity is affected by the presence of $PbCl_2$; in its presence, the major tetrahydrofuran isomer obtained bears 2,5-*trans*-substitution, and in its absence, 2,5-*cis*-stereochemistry dominates the mixture in a 4:1 ratio (Scheme 39). The use of either 2 equiv. of 1-iodo-1-silyloxyalkane or 1 equiv. of bis(iodoalkyl)ether gives very similar results, and it is proposed that the former may be in equilibrium with the latter under the reaction conditions.



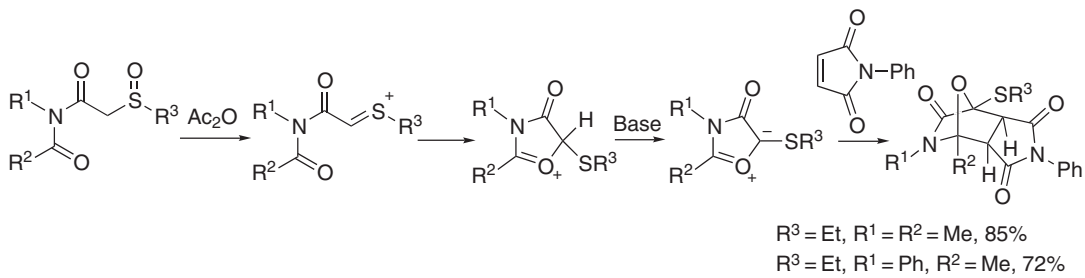
Scheme 39

Kiso and co-workers have used this reduction protocol to synthesize N^{α}-protected L-tetrahydrofuranylglycine, a key starting material for the synthesis of inhibitors of HIV-1 protease <2002BMCL3615>. Bis(chloromethyl)ether was used to generate the ylide, which then underwent cycloaddition with vinyl glycine to provide a 57:43 diastereomeric mixture of cycloadducts. Protecting group interchange then provided the required protected tetrahydrofuranylglycine in 42% overall yield (Scheme 40).



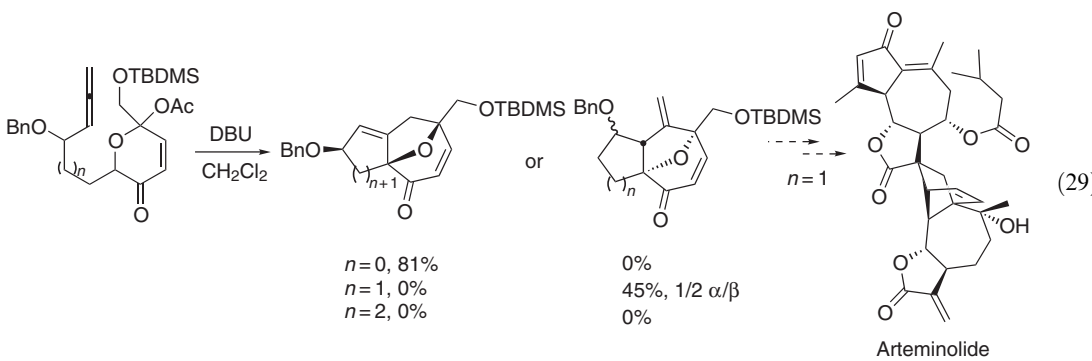
Scheme 40

Padwa and co-workers have reported the formation of isomünchnone ylides from tandem Pummerer cyclization–deprotonation, and the subsequent cycloadditions of these ylides with a range of dipolarophiles, such as DMAD, *N*-phenyl maleimide, methyl propiolate, phenyl vinylsulfone, and 1,4-naphthoquinone (C=C addition) (Scheme 41) <1999JOC2038>. The use of alkynes results in cycloadducts which lose methyl isocyanate (for R^1 = Me) to give α-thioether-substituted furans.



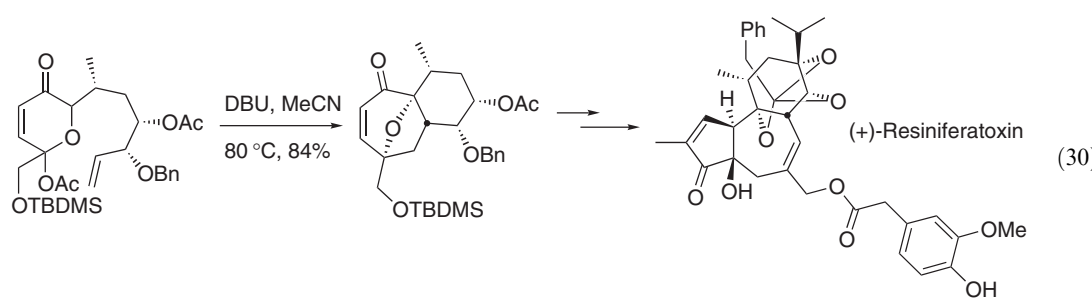
Scheme 41

During studies toward the synthesis of arteminolide, Lee and co-workers reported the cycloaddition of an oxidopyrylium with a tethered allene; either of the double bonds could potentially react, and so the effect of the tether length was investigated <2001TL1695>. It was found that a two-carbon tether gave exclusively cycloadducts arising from reaction with the terminal double bond in 81% yield; a three-carbon tether gave a 1:2 dr of the product from cycloaddition with the internal double bond, as required for the synthetic strategy, in 45% yield. Increasing the tether length to four carbons gave no cycloadducts (Equation (29)).



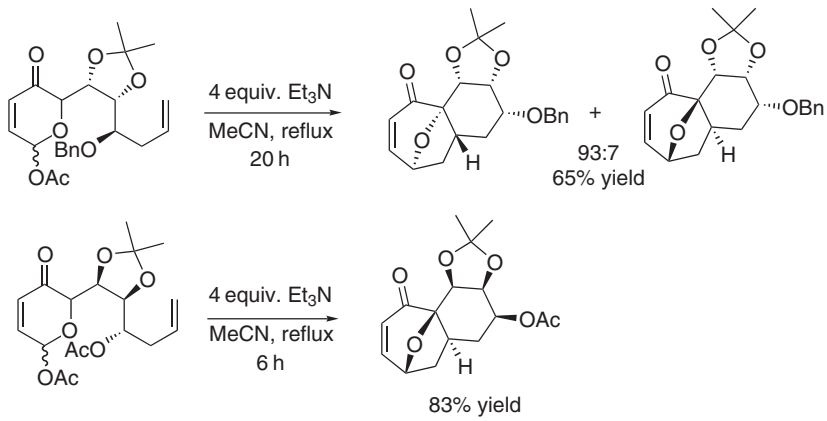
(29)

Wender and co-workers have used intramolecular oxidopyrylium cycloaddition as a key step in the synthesis of (+)-resiniferatoxin (Equation (30)) <1997JA12976>.



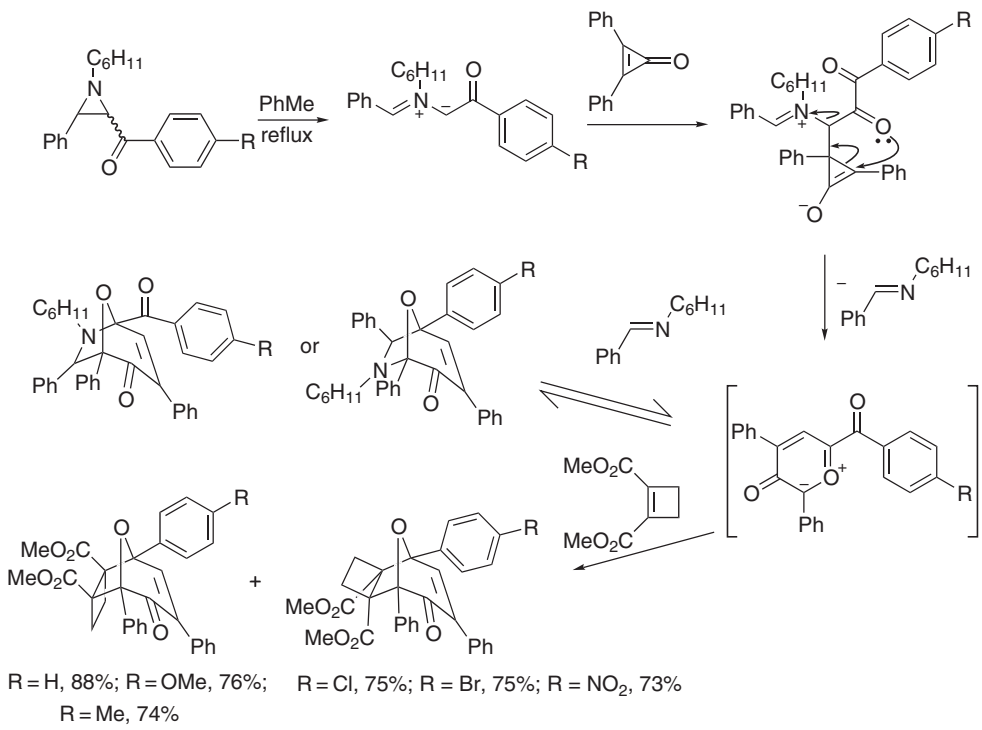
(30)

Krishna and co-workers have reported a diastereoselective oxidopyrylium cycloaddition in which the tether is derived from D-ribose, giving a 93:7 dr of cycloadduct in 65% yield (Scheme 42) <2003SL2383>. The pseudoenantiomeric substrate gives the corresponding cycloadduct in 83% yield as a single diastereomer.



Scheme 42

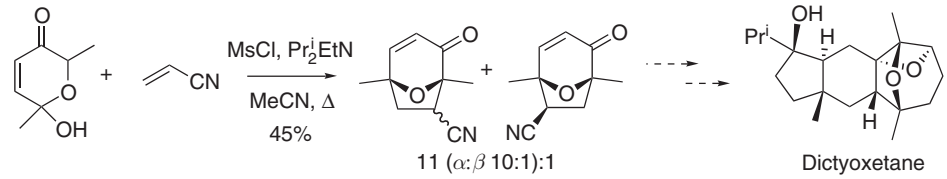
Matsumoto and co-workers have reported an ylide cascade reaction, in which an aziridine is opened to an azomethine ylide; this adds to a cyclopropenone, and the resulting intermediate rearranges to a pyrylium with elimination of an imine <1995TL5295>. This ylide may undergo cycloaddition with either the imine produced in the ylide formation step, or with cyclobutenes (73–88% yields, Scheme 43). Substitution of the starting aziridinyl ketone with an electron-rich aromatic ring leads to *exo*-cycloadducts, and with electron-poor aromatic rings leads to *endo*-cycloadducts.



Scheme 43

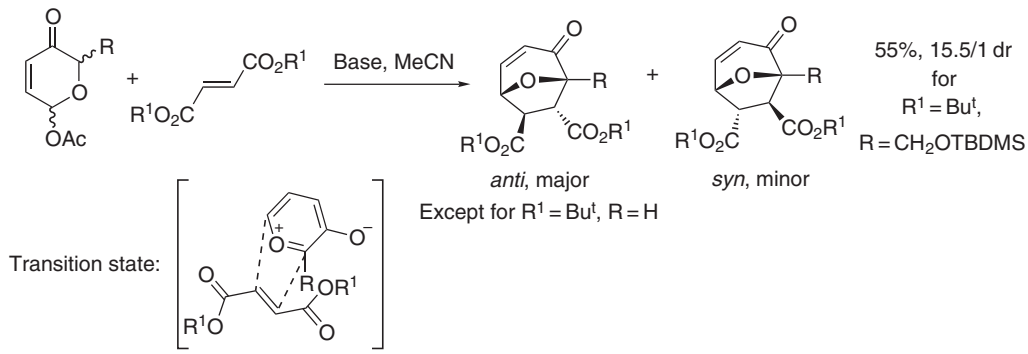
The dipolar cycloaddition of 3-oxidopyryliums and electron-poor alkenes to give 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonanes, and the application of this strategy to the total synthesis of dictyoxetane,

has been reported by Marshall and co-workers (Equation (31)) <1996JOC9135>. The use of electron-rich alkenes, such as ethyl vinyl ether, as the dipolarophilic component led to proton transfer followed by dimerization in preference to cycloaddition. The minor cycloadduct obtained from the reaction with acrylonitrile was that required for the synthesis of dictyoxetane.



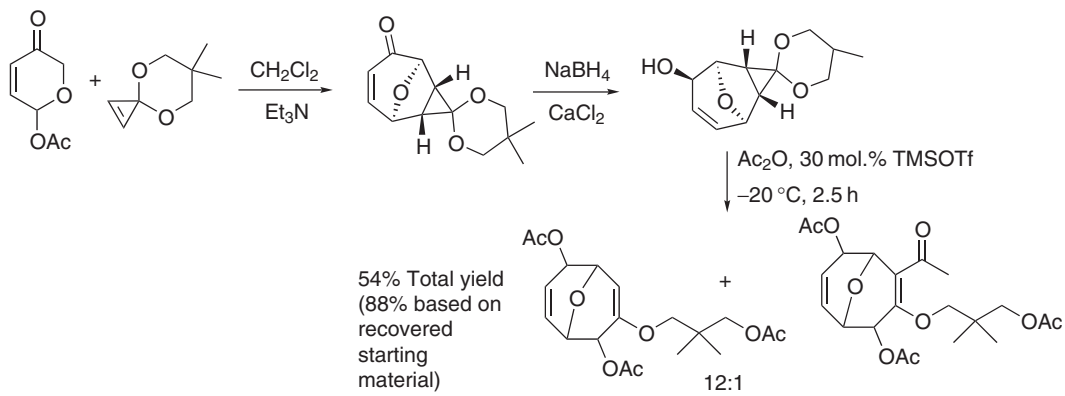
(31)

Ohmori and co-workers have reported the construction of seven-membered rings via a range of oxidopyrylium cycloadditions with dialkyl fumarates <2001CL9062>. It was found that the diastereoselectivity of the reaction was improved on increasing the size of the substituents on the oxidopyrylium and the fumarate esters, up to 15.5:1 for di-(*t*-butyl) fumarate and $CH_2OTBDMS$-substituted oxidopyrylium (Scheme 44). No *cis*-carboxylate products were obtained, suggesting that the cycloaddition was concerted despite the potential steric congestion in the suggested transition state, and no cycloadduct was isolated from dimethyl maleate. This method was applied in a route to phomoidride B <2001CC1552, 2002JCS(P1)755>.



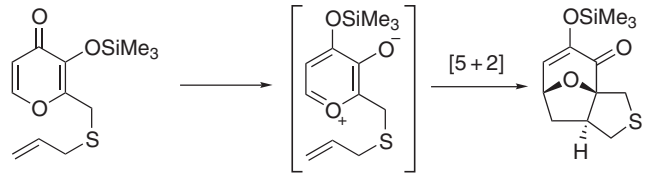
Scheme 44

The synthesis of 1,5-oxa-bridged cyclooctadienes was achieved by Delgado and co-workers via cycloaddition of 3-oxidopyryliums and a cyclopropenone acetal, followed by ring opening <2002OL3091>. A 1:12 dr of cycloadducts in 54% total yield (88% based on recovered starting material) was obtained (Scheme 45).



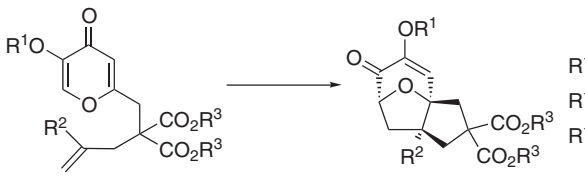
Scheme 45

Although not an elimination process, computational study of the reaction of a silyloxy-substituted pyrone bearing a tethered double bond suggests that the reaction must proceed by silyl migration to the carbonyl oxygen to form a "weak oxidopyrylium" intermediate, followed by a concerted [5 + 2]-cycloaddition (Equation (32)) <2000JOC5480>. The reaction must be both intramolecular and have the silyloxy group present in order to overcome the kinetic barriers to reaction. The constraints imposed by the tether make this a very stereoselective reaction.



(32)

Diastereoselective cycloadditions of a range of oxidopyryliums with tethered alkenes using (−)-menthyl and (−)-8-phenylmenthyl chiral auxiliaries under thermal conditions or Lewis acid catalysis have been reported by Ohmori and co-workers (Equation (33)) <1997H2097>. Benzoyl-substituted substrates undergo the cycloaddition upon heating to 130 °C in *o*-dichlorobenzene to give the cycloadducts in 70% yield and 27–33% de; under $ZnCl_2$ catalysis at 40 °C, 23–64% yield, and 53–59% de were obtained. Silyloxy-substituted substrates in the presence of TBDMSOTf and 2,6-lutidine at 20 °C gave the cycloadducts in high yields and 75% de.



(33)

3.07.2 CARBONYL OXIDES

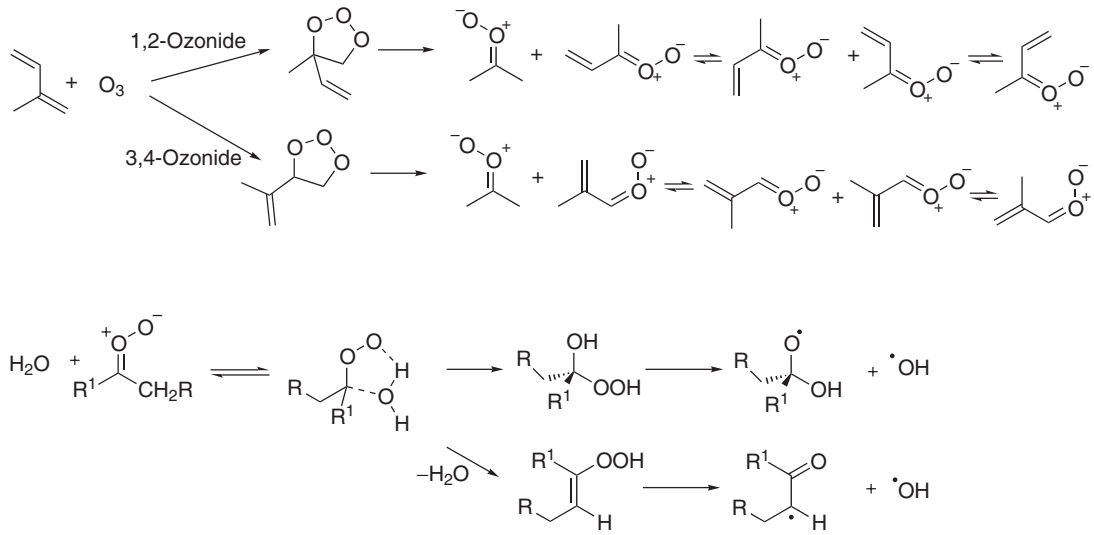
Carbonyl oxides may be generated by ozonolysis of alkenes and alkynes, by interaction of a carbene with molecular oxygen, or cycloaddition with $^1O_2$ and subsequent cycloreversion. This area has been reviewed by Ishiguro <1997JPO787, 2000BCSJ535>, Horie and Moortgat <1998ACR387>, and McCullough and Nojima <B-1992MI661>.

3.07.2.1 Carbonyl Oxides from Ozonolysis

3.07.2.1.1 Ozonolysis of alkenes

The ozonolysis of alkenes is the most common source of carbonyl oxides. 1,3-Dipolar cycloaddition of ozone with an alkene forms the primary ozonide (POZ) which may undergo cycloreversion to an aldehyde or ketone together with a carbonyl oxide. Under normal ozonolysis conditions, these will recombine to form the secondary ozonide (SOZ), which is usually then treated with an appropriate reagent to obtain the desired products. However, a more reactive carbonyl compound may intercept the carbonyl oxide to form a different SOZ. Under atmospheric conditions, for which a great deal of research has been undertaken, the carbonyl oxide may also participate in a range of decomposition routes: loss of O (^3P) to give a ketone and (in the presence of O_2) O_3; isomerization to dioxiranes; intramolecular abstraction of an α-H to give a hydroperoxide, which decomposes to a hydroxyl radical. This last process is important in the atmosphere, and there have been a large number of computational and mechanistic studies for a range of alkenes in order to determine the atmospheric sources of hydroxyl radicals <1996JA4636, 1997JA7330, 1999CEJ1809, 1999JPC(A)2050, 1999MI3981, 1999JPC(A)7656, 2000JPC(A)7821, 2001JPC(A)4446, 2002CPL171, 2002JA2692>. For unsymmetrical dienes, such as isoprene, it is found that both possible POZs, and therefore nine different carbonyl oxides, are formed (Scheme 46) <2003JPC(A)5812, 2003JPC(A)5798>. All are formed in a vibrationally excited

state, and are therefore able to undergo unimolecular decomposition, or may be collisionally stabilized to allow reaction with other species, such as water vapor (Scheme 46). The presence of water vapor to catalyze the hydroperoxide decomposition is predicted to increase the hydroxyl radical yield by around 5% <2002MI215>; however, other studies indicate that there is very little dependence of the hydroxyl yield on relative humidity <2003JPC(A)6176>.



Scheme 46

The yield of hydroxyl radical is dependent on the *syn*:*anti* ratio of the monosubstituted carbonyl oxides formed, as the *syn*-carbonyl oxide has the O^- positioned to abstract the α-hydrogen to form the hydroperoxide necessary for hydroxyl radical generation <1997JA7330>. For *syn*-carbonyl oxides, isomerization to dioxiranes is slower than the hydrogen abstraction; for CH_2OO, the yield of dioxirane is high and that of the hydroxyl radical low, as there is no α-hydrogen to abstract.

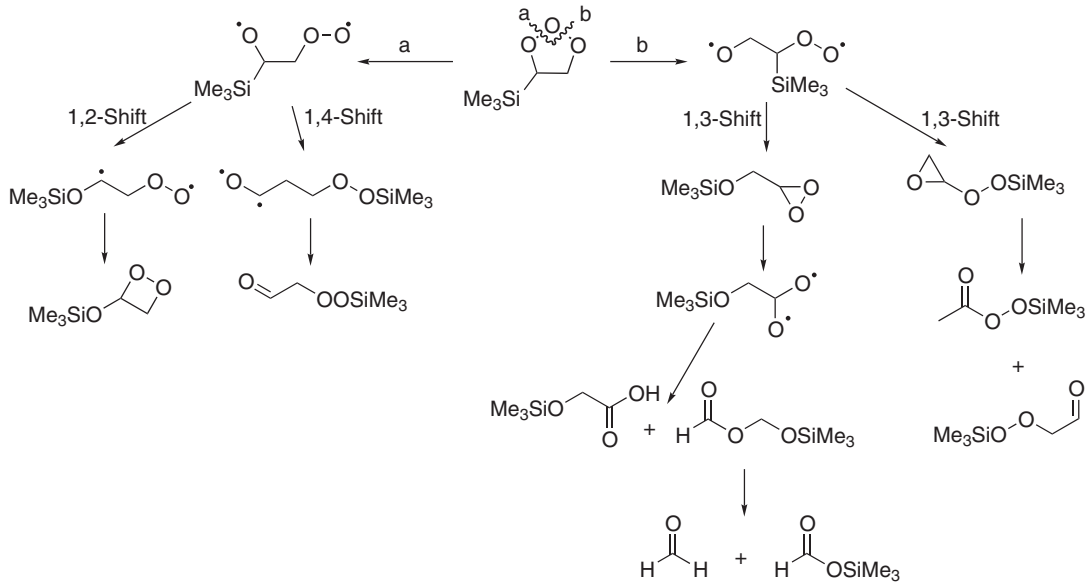
The study of density functional theory (DFT) of carbonyl oxides <1998CPL669>—the parent oxide CH_2OO, *syn*-MeC(H)OO, *anti*-MeC(H)OO, and Me_2COO were examined—showed that the dipolar character of the carbonyl oxide increased with the number of methyl groups, and that the ionic resonance form was stabilized in more polar solvents, leading to a weakened O—O bond and increased double bond character for C—O. The *syn*-Me carbonyl oxide was calculated to be more stable than the *anti*-isomer in both nonpolar and polar solvents, due to a long-range interaction of the terminal oxygen atom and the methyl group. The calculations also indicate that the O—O bond may be an efficient oxygen-atom donor in solution phase.

The ozonolysis of terminal alkenes was found to yield a 1:1 ratio of formaldehyde to alkyl aldehyde, unless the alkyl group was branched, in which case formation of the more substituted carbonyl oxide was favored in an ~65:35 ratio <1999JPC(A)8125>. The yield of hydroxyl radical decreased with increasing alkyl chain length, perhaps due to the easier redistribution of the excess vibrational energy throughout the larger molecule, reducing the propensity for unimolecular decomposition.

Trimethylsilyl-substituted alkenes were ozonolyzed in the gas phase to give trimethylsilyl-substituted carbonyl oxides, which decompose exclusively through the mechanisms shown below (Scheme 47); the intermediates may be tracked as migration of the TMS group is possible in 1,3-diradicals, and the results indicate that the POZ cycloreversion is nonconcerted <2001JOC6977>.

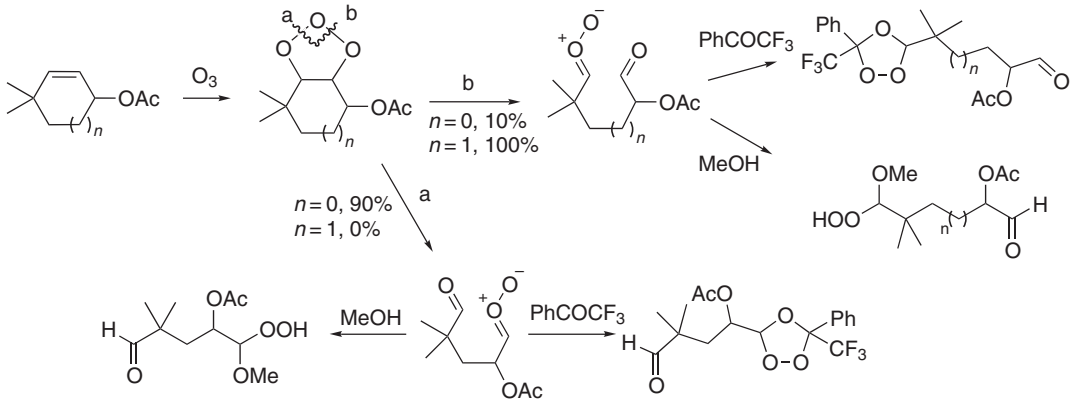
The ozonolysis of atmospherically produced 4,5-dihydro-2-methylfuran (DHMF, from the oxidation of hydrocarbons) has been studied <2002JPC(A)11492>. It is proposed that both possible fragmentation pathways of the POZ to carbonyl oxides are operational. A 50% yield of CO_2 suggested that one pathway is dominant, but only a 3% yield of the co-product, ethyl acetate, was isolated.

The directing effect of substituent sterics and electronics on POZ cleavage was investigated by conducting the ozonolysis of a cyclic alkene in the presence of trifluoroacetophenone <1996JOC5953>. The carbonyl oxide generated from an electron-rich alkene combined exclusively with trifluoroacetophenone, whereas that from an electron-poor alkene recombines with the carbonyl group produced from cycloreversion to give the expected SOZ. An allylic acetoxy group



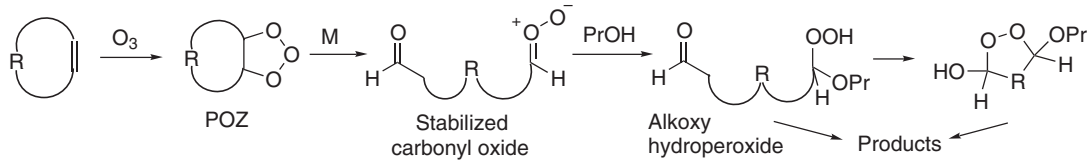
Scheme 47

favors formation of the carbonyl oxide most remote from the acetoxy group (Scheme 48). Use of a five-membered ring substrate with an acetoxy group led to the increased steric congestion overriding the electronic effect of the acetoxy group.



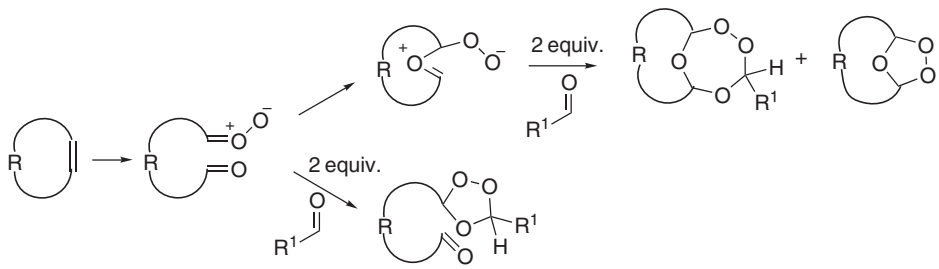
Scheme 48

A mass spectrometric investigation of the ozonolysis of cyclic alkenes in the presence of an alcohol showed that hydroperoxyl and carbonyl groups may react thermally in the gas phase to form a cyclic peroxyhemiacetal (Scheme 49) <2003JPC(A)2048>. Intermolecular peroxyhemiacetal formation was also possible between hydroperoxides with no tethered carbonyl group and the carbonyl group formed from POZ cycloreversion. This is not expected to be a major atmospheric process as $[ROH] << [H_2O]$.



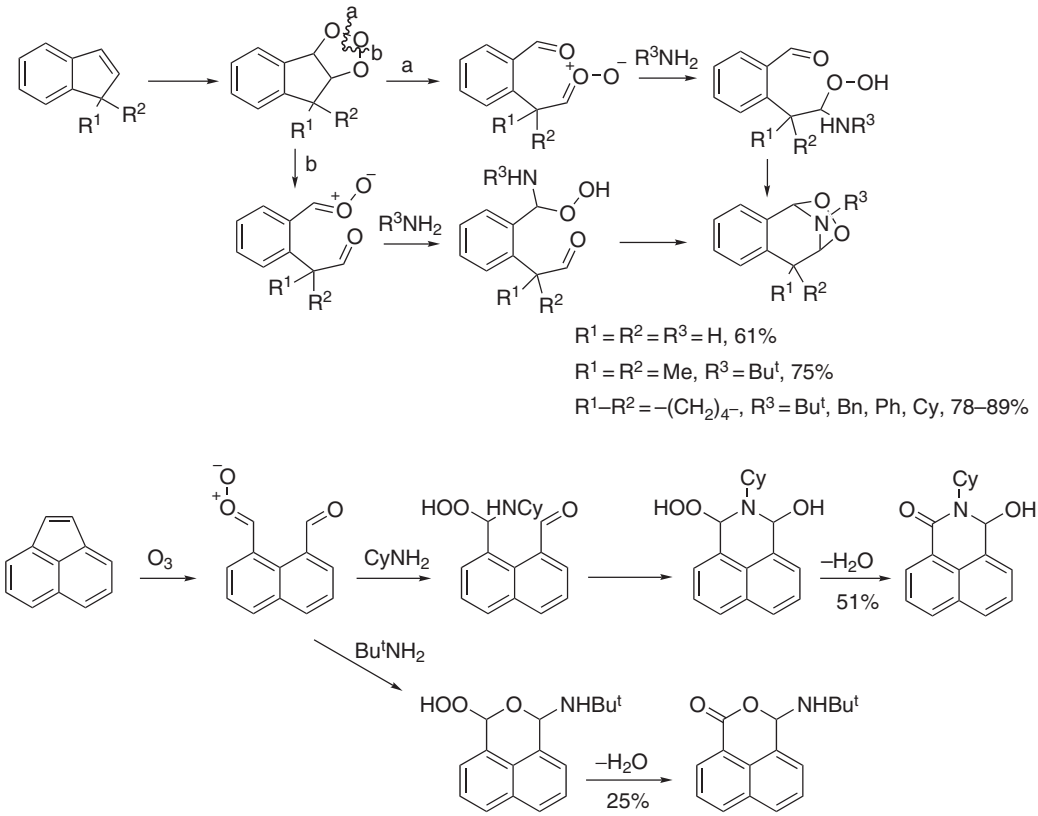
Scheme 49

Another investigation of the ozonolysis of cyclic alkenes, and trapping with external aldehydes, was reported as a route to bicyclic 1,2,4,6-tetraoxepines in moderate-to-low yields, decreasing for increased ring size <1999MI775>. Two secondary ozonide products were also observed (Scheme 50).



Scheme 50

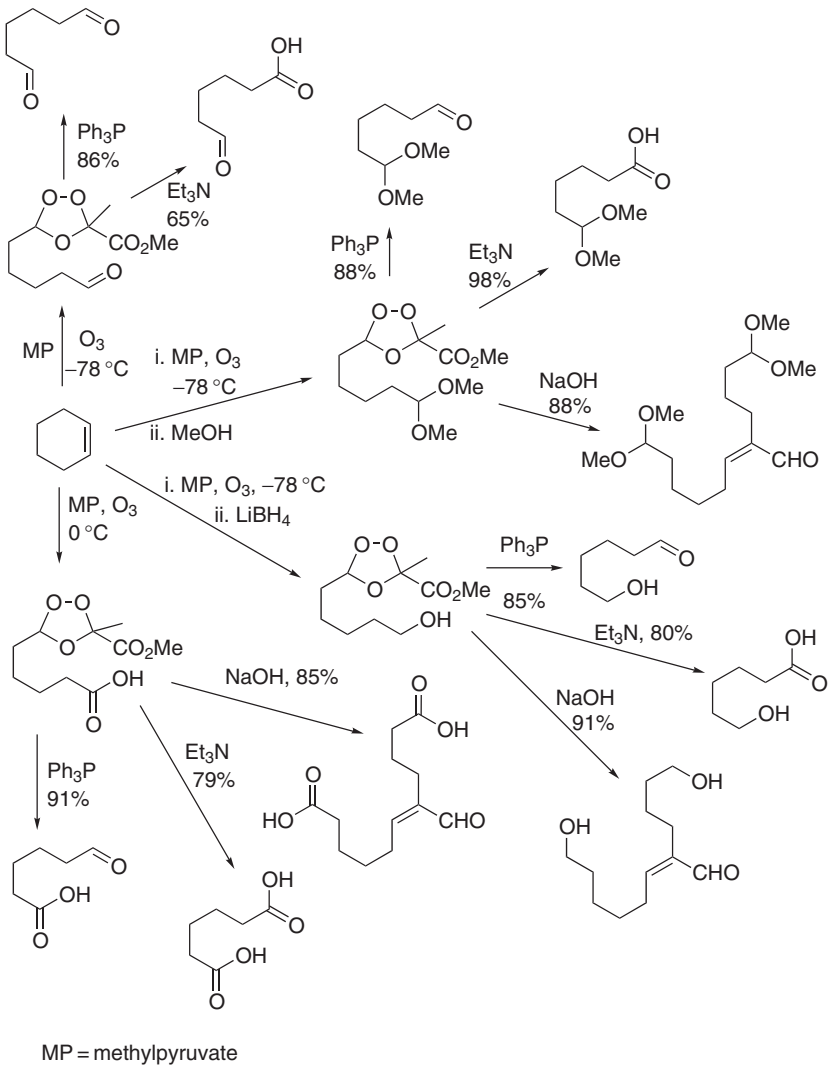
The ozonolysis of indenes in the presence of primary amines produced dioxazolidines, in a similar fashion to the reaction of carbonyl oxides and alcohols to give alkoxyalkyl hydroperoxides (Scheme 51) <1997JCS(P1)1939>. The use of ammonia gave 61% yield of an isoquinoline, presumably from co-condensation of ammonia with the dialdehyde produced from the ozonolysis. Secondary amines gave no trapping product and quantitative recovery of the indene, suggesting that ozone and secondary amines react together more rapidly than ozone reacts with indene. Acenaphthylene also reacts with ozone and a primary amine to give an amino-substituted lactone or hydroxylactam, depending on the amine used; the proposed mechanism is shown below (Scheme 51).



Scheme 51

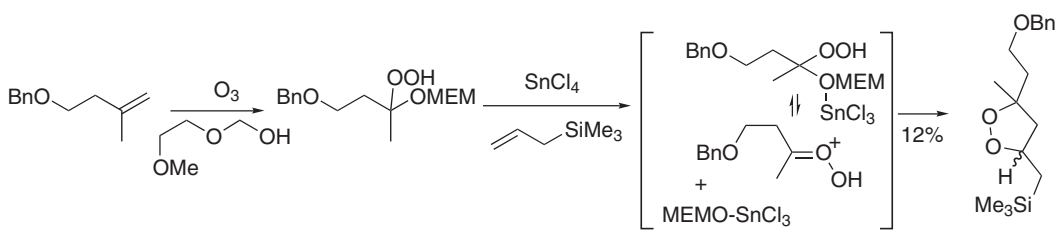
A range of reaction conditions for ozonolysis of alkenes in the presence of methyl pyruvate (MP) have been reported, which allow selective production of 10 different products from one alkene. The

chemistry exploits the three different reactive sites of the ozonide: the peroxide bond, the ozonide ring proton, and the MP-derived methoxycarbonyl group (Scheme 52) <1997T5217>. Triphenylphosphine is used to attack the O—O bond, Et_3N to abstract the ring proton, and hydroxide to hydrolyze and decarboxylate the ester and catalyze an aldol condensation.



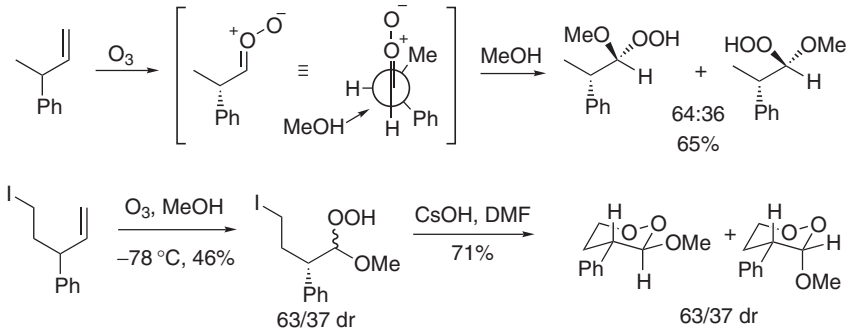
Scheme 52

The formation of protonated carbonyl oxides, or peroxycarbenium ions, have been reported from hydroperoxyketals (ozonolysis products in the presence of alcohols) <1995TL3655>, or directly from SOZ <1999TL6553>. These may undergo addition of allylsilanes in the presence of Lewis acids such as $SnCl_4$; the best results were obtained when the ozonolysis was carried out in the presence of MEM alcohol. The protocol was used in the synthesis of plakinic acid, albeit in low yield (Scheme 53).



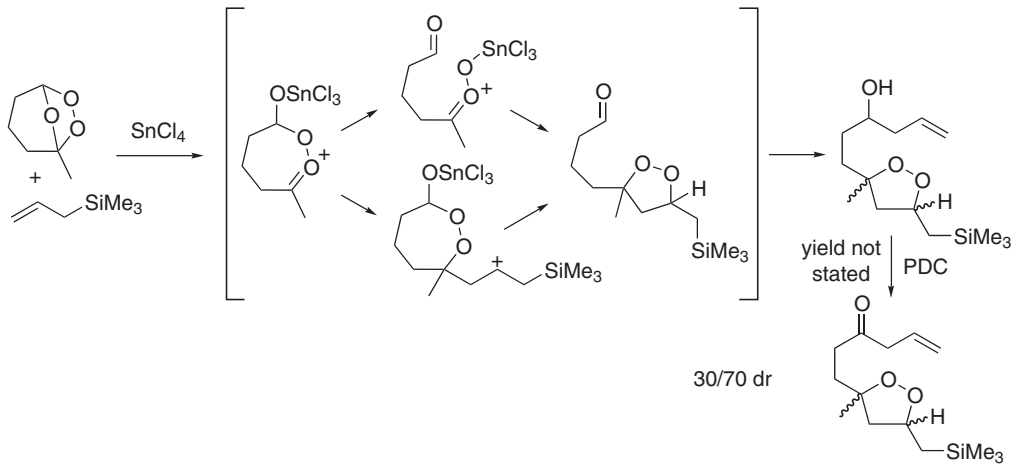
Scheme 53

It was established that the addition of an alcohol to a carbonyl oxide proceeds via a Felkin–Ahn-type transition state by observing the diastereomeric ratio of hydroperoxyketals obtained with substrates bearing a stereogenic center α- to the carbonyl oxide (Scheme 54) <1995JOC8218>. Equilibration of the hydroperoxy ketals to the observed ratio is excluded by the conditions, which are not acidic enough to allow this equilibration. Cyclization of the product to a 1,2-dioxane may be achieved if an iodoalkene is used as the initial substrate (Scheme 54). *Syn*- and *anti*-carbonyl oxides gave rise to the same product ratio; use of more bulky alcohols allowed the dr to be increased from 65:35 for MeOH to 82:18 for Bu^{t}OH, though the latter gave a poor yield due to its low solubility in the reaction mixture. An attempt was made to improve the dr through chelation control with a neighboring hydrogen bond donor, but both *syn*- and 1:1 *syn*:*anti*-carbonyl oxides gave a 1:1 dr in the presence of a large excess of MeOH. However, with 5 equiv. of methanol, the pure *syn*- and pure *anti*-carbonyl oxides each gave a 4:1 dr, although the lower methanol concentration allowed the formation of carbonyl oxide dimers and other by-products. Only the *syn*-carbonyl oxide is expected to be able to participate in chelation control, but the (*E*)- and (*Z*)-substrates give the same result despite giving rise to the *syn*- and *anti*-carbonyl oxides, respectively.



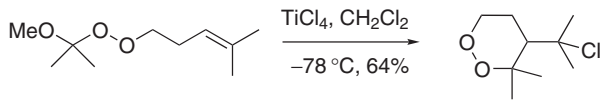
Scheme 54

1,2-Dioxanes may be formed directly from an SOZ by treatment with $SnCl_4$ and allyltrimethylsilane (Scheme 55) <1999TL6553>. In general this reaction seems not to be regioselective, but the SOZ from 1-methylcyclopentene led to a single dioxolane regioisomer arising from allylation at the less-substituted ozonide carbon; the product was a 30:70 *cis*:*trans*-mixture with a 1:1 mixture of epimers at the exocyclic carbinol.



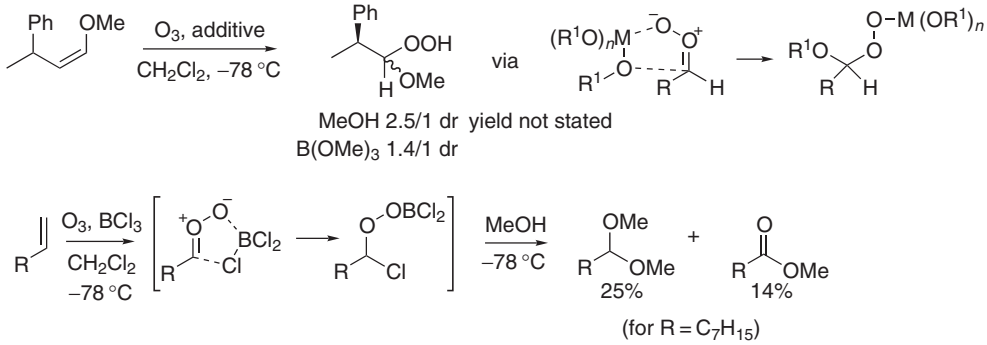
Scheme 55

1,2-Dioxanes can also be synthesized via olefin cyclization to peroxycarbenium ions formed from hydroperoxyacetals, either intermolecularly or intramolecularly to form six-membered and larger rings (Equation (34)) <2000JOC8407>.



(34)

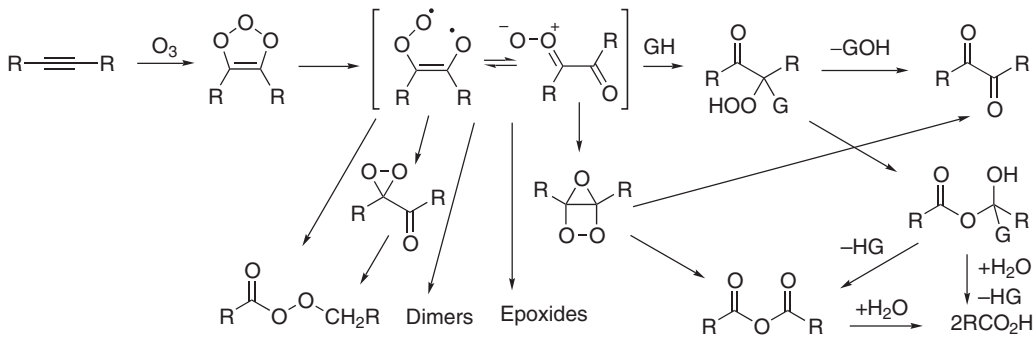
The product distribution of alkene ozonolysis may be altered by delivery of an alkoxide anion to a Lewis acid-complexed carbonyl oxide to give hydroperoxyacetals under aprotic conditions (Scheme 56) <2000OL3377>. As before, the diastereoselection using a chiral substrate was found to follow from a Felkin–Ahn transition state. Using a boron halide as the Lewis acid gave products that suggested an intermediate acyl chloride.



Scheme 56

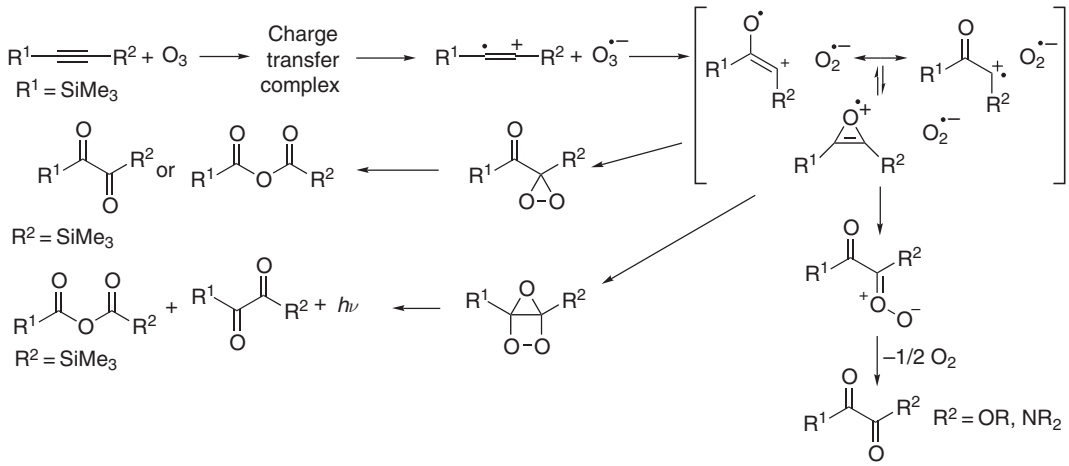
3.07.2.1.2 Ozonolysis of alkynes

Similarly, to the ozonolysis of alkenes, the ozonolysis of alkynes has been investigated computationally with reference to its importance in atmospheric chemistry. One study suggests that the mechanism of alkyne ozonolysis proceeds via a van der Waals complex between the alkyne and ozone, followed by a concerted [3 + 2]-cycloaddition to the POZ, which has an 8π-antiaromatic system and is vibrationally excited, resulting in cycloreversion to an α-ketocarbonyl oxide (Scheme 57) <2001JA6127>. The *trans, anti*-conformation of the carbonyl oxide is predicted to be the most stable, with a longer lifetime than the parent carbonyl oxide CH_2COO, but again, this is formed in a vibrationally excited state, and in the gas phase may undergo a variety of reactions: O_2 loss to give a triplet carbene and triplet O_2 and thence a ketone, or glyoxal formation from O—O cleavage are possible; cyclization to a 3-keto-1,2-dioxetane which fragments to formaldehyde and CO_2, and cyclization to 2,3,5-trioxabicyclo[2.1.0]pentane, which rearranges to form anhydride and then to CO and formic acid are also suggested. The enthalpy barriers for loss of atomic oxygen from the carbonyl oxide are less than that for rearrangement, suggesting that in solution the oxide could act as an oxygen-atom-transfer reagent.



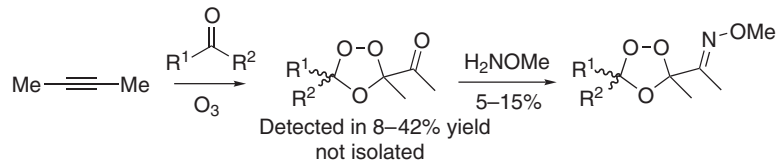
Scheme 57

The ozonolysis of electron-rich alkynes, and the observation of chemiluminescence for the reaction of a symmetrical alkyne, is reported to form α,β-diketo esters and diesters <2000HCA1611>. The authors propose a mechanism avoiding the classical cycloaddition step for formation of a primary ozonide and hence the formation of an antiaromatic system (Scheme 58).



Scheme 58

The interception of carbonyl oxides by external carbonyl compound to form an SOZ, and the subsequent stabilization of the SOZ by derivatization as an *O*-methyl oxime has been reported (Equation (35)) <1997JOC6129>. A range of carbonyl compounds, including aldehydes, ketones, esters, and acyl cyanides, have been used to trap the carbonyl oxides, and the trapping of the α-oxo-ozonides has also been carried out using diazomethane to yield epoxyozonides. The detected yields of the α-oxo-ozonides were in the range 8–42%; however, the *O*-methyl oximes were isolated in only 5–15% yield. Where an intramolecular secondary ozonide formation was possible, such as in the ozonolysis of diacyloxy butynes, the carbonyl oxide could not be intercepted by acetone. The rate of intramolecular SOZ formation is reported to be competitive with the rate of dioxirane formation.

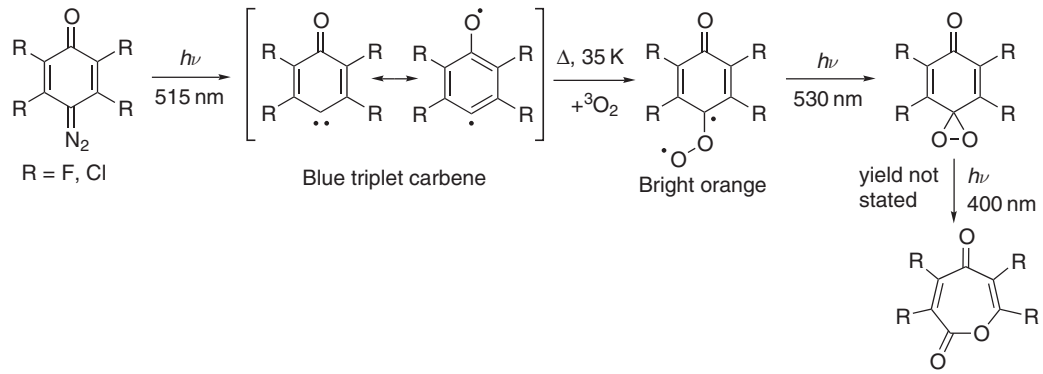


(35)

3.07.2.2 Carbonyl Oxides from Interaction of Carbenes with Molecular Oxygen

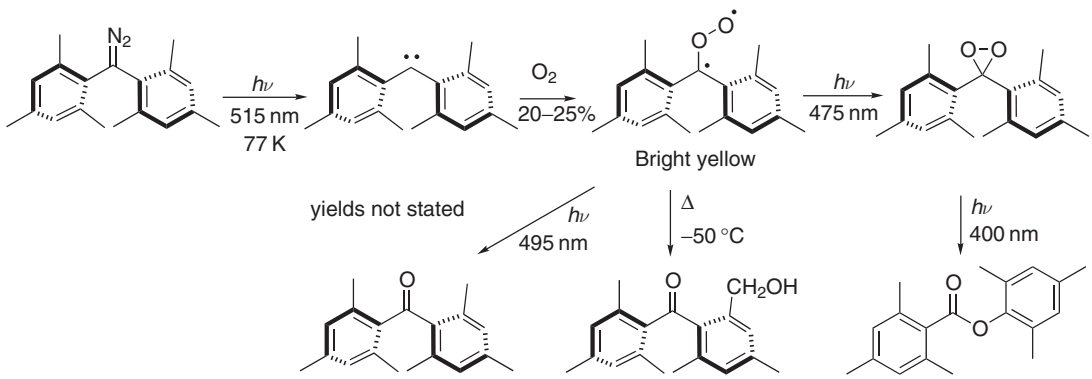
Triplet carbenes may be reacted with triplet oxygen, or singlet carbenes with singlet oxygen, to form carbonyl oxides, which may undergo oxygen atom loss to form ketones, sometimes with concomitant oxidation of, for example, sulfides, ring-expansion reactions, or rearrangements to esters.

The formation of a very electrophilic triplet carbene and its reaction with O_2 to give a carbonyl oxide which may rearrange to a ring-expanded product has been achieved in an O_2-doped argon matrix at 35 K (Equation (36)) <2000CEJ4567>.



(36)

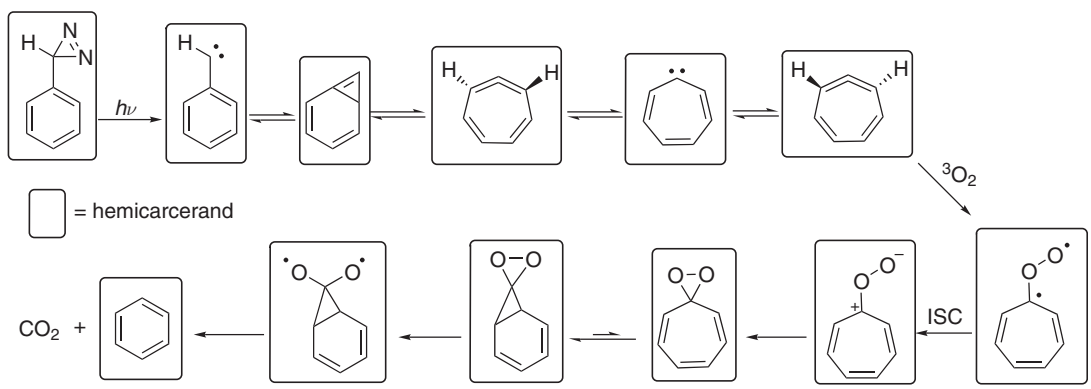
The formation and reaction of dimesityl ketone-*O*-oxide from $^3O_2$ and the photolysis of dimesityl diazomethane at 140 K has been reported; attempted reaction of the carbene with $^1O_2$ also gave the carbonyl oxide (Scheme 59) <2001JA2618>. The carbonyl oxide was characterized by UV–vis, IR, ^{13}C NMR, and ^1H NMR spectroscopy, which showed that there is no rapid rotation of the mesityl rings, although the ring *anti*- to the terminal oxygen rotates more rapidly than that *syn*, and there is no *syn–anti* conversion of the carbonyl oxide.



Scheme 59

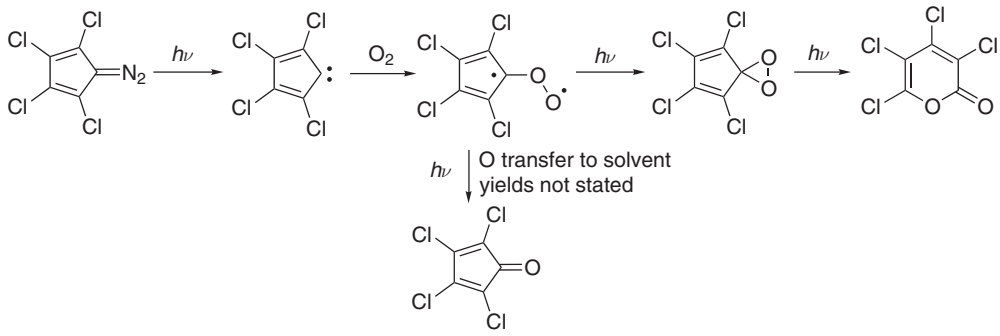
Several similar carbenes and carbonyl oxides to those above have been generated and the effect of sterics and electronics on the rate of formation of the carbonyl oxides has been studied <1997JA1582, 2000JOC8797, 2001BCSJ2207, 2002JA474>.

The photolysis of phenyldiazine inside a hemicarcerand formed a carbene, which rearranges to cycloheptatetraene, which then reacts with O_2 via a carbonyl oxide (proposed from computational studies) and a dioxirane (detected) to form a benzene hemicarciplex and carbon dioxide (Scheme 60) <2001CEJ1209>.



Scheme 60

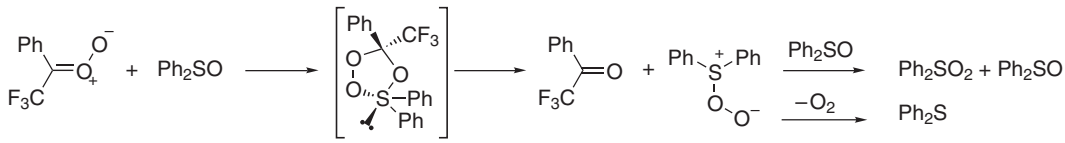
Generation of the carbene from tetrachlorodiazodicyclopentadiene under photolytic conditions in the presence of a triplet sensitizer, followed by reaction with O_2, produces the corresponding ketone and ring-expanded lactone products (Scheme 61); the carbonyl oxide intermediate may act as an oxygen-atom-transfer agent in the presence of, e.g., cyclohexene <1995MI157>.



Scheme 61

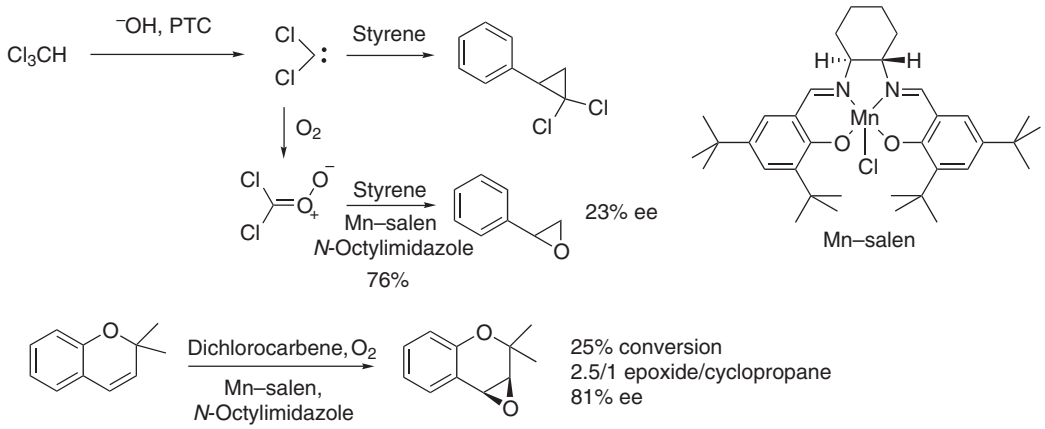
The mechanism of the photochemical reaction of aryl diazomethanes and $^1O_2$ in the presence of a triplet sensitizer has been investigated by Nojima and co-workers <1997JOC6911>. There was no solvent effect on the yield of the carbonyl oxide, and so the photolysis is suggested to proceed via a dioxadiazole which can cyclorevert to either the aromatic aldehyde and N_2O, or the carbonyl oxide and N_2, depending on the stability of the carbonyl oxide formed. Increased electron-donating character of the diazo compound gives a higher proportion of carbonyl oxide.

A comparison of the behavior of trifluoromethyl-substituted carbonyl oxides with those oxides without electron-withdrawing groups toward diphenyl sulfides and diphenyl sulfoxides has been reported <1997JOC2387>. The photolysis of the precursor diazo compound is carried out and the yield of trifluoromethyl-substituted carbonyl oxide is estimated as 40% based on the amounts of N_2 and N_2O formed. The carbonyl oxide will oxidize sulfides to sulfoxides, as for the more electron-rich analogs, but removes oxygen atoms from sulfoxides to form sulfides. At low concentrations of Ph_2SO, the main reaction is oxidation, and at high concentrations of Ph_2SO, the main reaction is deoxygenation. The mechanism proposed from ^{18}O-labeling studies is shown (Scheme 62). In the presence of styrene, the carbonyl oxide forms 9.1% styrene oxide, and no C—C cleavage products (e.g., benzaldehyde); it is proposed that this takes place via the dioxirane as the reaction characteristics are more similar to those for DMDO than for carbonyl oxides. The rate of oxidation is increased when using an electron-rich styrene, indicating an electrophilic attack by the oxygen atom-transfer reagent.



Scheme 62

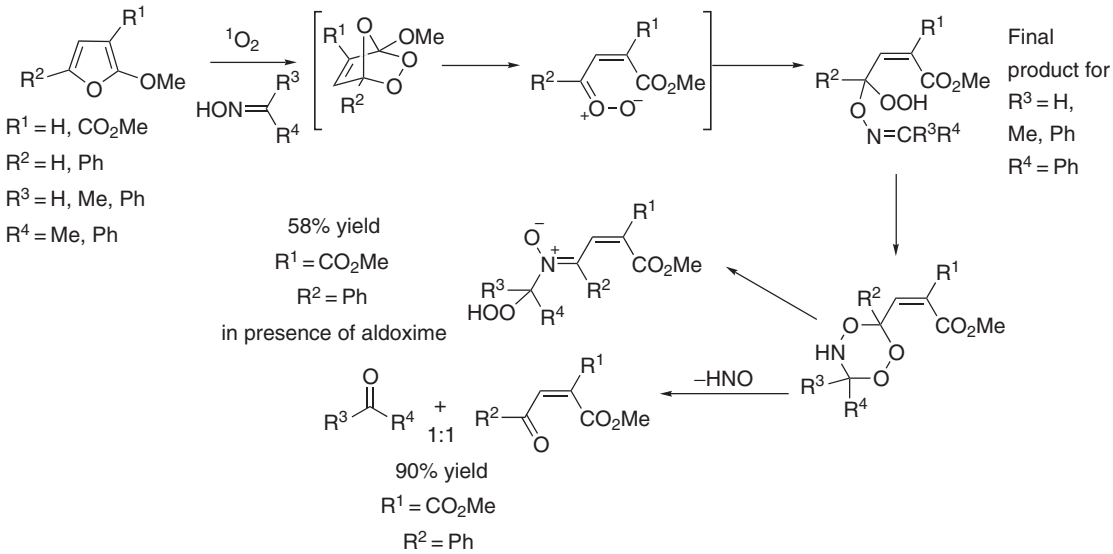
Enantioselective epoxidations of alkenes have been carried out using a chiral manganese(III)–salen complex, which abstracts the terminal oxygen atom from a carbonyl oxide to form the reactive Mn=O species <1997MI796>. Using dichlorocarbene and styrene, in the absence of the metal complex the sole product is the dichlorocyclopropane, whereas in the presence of the Mn^{III} complex, a trace of the epoxide is also formed. The addition of *N*-octyl imidazole, which improves the formation of the metal–oxo complex by donation of electron density to the metal complex, allowed isolation of styrene oxide in 76% yield, and 23% ee (Scheme 63). The best ee result was 81% for the chromene shown (Scheme 63); trisubstituted alkenes give up to 58% ee. The sense of asymmetric induction observed was the same as that reported by Jacobsen with the same salen complex, and so the Mn=O intermediate is assumed.



Scheme 63

3.07.2.3 Carbonyl Oxides from Cycloaddition—Cycloreversion of $^1O_2$

The oxidation of 2-alkoxyfurans by $^1O_2$ in the presence of aldo- and keto-oximes has been reported by Iesce and co-workers <1998JOC9528>. [4 + 2] Cycloaddition of $^1O_2$ with the furan and cycloreversion to the carbonyl oxide followed by reaction with the oxime, led to nitrones (for aldoximes), a 1:1 mixture of ketone and α,β-unsaturated ketone, or an oxime peroxide, depending on the furan substitution (Scheme 64).



Scheme 64

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Biographical sketch

Deborah Selden was born in Nottingham in 1977. She studied at Merton College, Oxford, where she obtained an M.Chem. in 2000, including a year's research project under the supervision of Dr. Mark Moloney. She is currently completing her D.Phil. studies in the area of chiral rhodium(II) catalysts for asymmetric carbonyl ylide cycloadditions under the direction of Dr. David Hodgson at Oxford University; in autumn 2004 she will take up a position as a trainee patent attorney at W. H. Beck Greener & Co., London.

David Hodgson obtained his first degree in Chemistry at Bath University. After a Ph.D. at Southampton University in the field of natural product synthesis (with P. J. Parsons) and a research position at Schering, he was appointed in 1990 to a lecturership at Reading University. In 1995 he moved to the Chemistry Department at Oxford University. He received a Glaxo Wellcome Award for Innovative Organic Chemistry in 1999, a Pfizer Academic Award and an AstraZeneca Research Award in Organic Chemistry in 2000 and the Liebig Lectureship of the German Chemical Society for 2001. His research interests are broadly in the development and application of synthetic methods, particularly asymmetric generation and transformations of carbenoids.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 309–353

3.08
Thioaldehydes and Thioketones

N. J. COOPER
Dstl Porton Down, Salisbury, UK

3.08.1 INTRODUCTION

Thioaldehydes and thioketones are similar to the corresponding carbonyl compounds, but there are significant differences: for example, simple thioaldehydes and thioketones are generally unstable, and can only be isolated in the gas phase or at low temperatures. Additionally, as the C═S bond is less polarized than the C═O bond, nucleophilic addition may, in certain circumstances, occur at the thiocarbonylsulfur and not at the carbon atom, as might be expected.

Thioaldehydes and thioketones have high reactivities associated with the poor orbital overlap of the (*C*-2*p*, *S*-3*p*) π-bond. Only a few stable, isolable thioketones have been made, and the greater reactivity of thioaldehydes mean that there are even fewer examples of stable compounds. Thiocarbonyl compounds tend to spontaneously oligomerize unless there is electronic stabilization (thioamides, thionoesters, and thionoacids are usually fairly stable) or steric stabilization (thioaldehydes and thioketones need bulky substituents if they are to be isolable) present.

Thioaldehydes and thioketones usually react more rapidly than their carbonyl counterparts due to the instability of the C—S π-bond. They undergo cycloaddition reactions much faster than carbonyl compounds. Thus, Diels–Alder [4 + 2]-cycloaddition between a diene and a thioketone, or thioaldehyde, gives stable cycloadducts. Indeed, transient thiocarbonyls are usually characterized as such cycloadducts.

Also, as the C═S double bond is weaker than the C═O double bond, the balance between the two tautomeric forms (thione and enethiol) is altered. For thiocarbonyl compounds, the enethiol form is often the most stable tautomer.

Thioaldehydes and thioketones are generally formed by thionation of the carbonyl compound. A variety of reagents exist for this transformation, some of which have only recently come into prominence.

The synthesis of thioaldehydes and thioketones and their reactions has recently been reviewed <2002SR209>.

This article covers advances since COFGT (1995), and reviews the literature published between 1995 and 2003.

3.08.2 THIOALDEHYDES

As mentioned earlier, thioaldehydes are usually unstable and are not isolated but immediately reacted *in situ* to give a variety of adducts. The generally high reactivity of thioxo derivatives, that renders such compounds versatile as intermediates in the synthesis of complex natural products, has hampered their investigation, though substantial work has recently been devoted to the development of novel synthetic methodologies for their preparation and synthetic applications.

In this context, thioaldehydes are particularly attractive, but have been considered elusive until recently, owing to their tendency to give cyclic or linear polymers through further reaction of the C═S bond. Numerous attempts to prepare monomeric thioaldehydes have revealed that simple thioaldehydes can only be detected spectroscopically or by chemical trapping. Only a relatively limited number of stable thioaldehydes are known: those stabilized by a mesomeric effect through heteroatoms (thermodynamic stabilization) and those stabilized for steric reasons (kinetic stabilization).

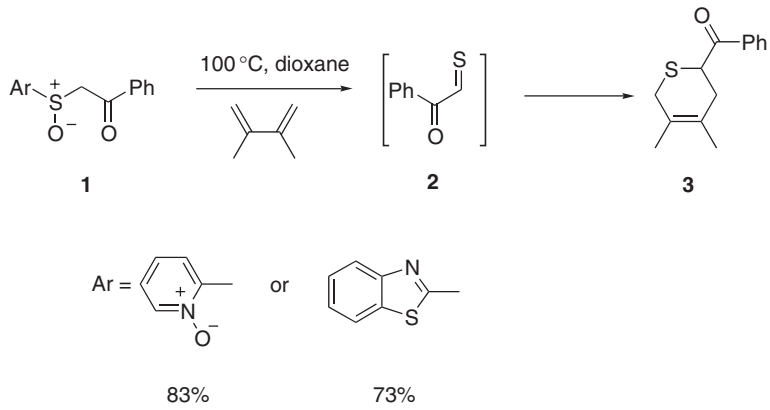
Various strategies exist for the formation of stable and unstable thioaldehydes; thionation of the corresponding carbonyl compound is the most widely used. Hexamethyldisilathiane (HMDST) has often been used to accomplish the direct thionation of ketones and aldehydes, the driving force behind this reaction being the formation of the strong Si—O bond. Usually, only mild conditions are necessary: HMDST reacts with carbonyl compounds to give the thiocarbonyls at 50–80 °C with the concomitant formation of hexamethyldisiloxane (HMDSO). HMDST is normally used with an acid catalyst, such as $CoCl_2 \cdot 6H_2O$ or $CF_3SO_3SiMe_3$; hydrogen chloride has also been used <2000EJO2171>. Thioformyl silanes have been the subject of recent investigation and can be used as a synthetic equivalent of a thioaldehyde, following a subsequent deprotection step.

3.08.2.1 Alkyl Thioaldehydes

3.08.2.1.1 Thermal decomposition of phenacyl sulfoxides

In COFGT (1995), the photolysis of phenacyl sulfides was reviewed. No new material has since been published, which reports the synthesis of thioaldehydes by this route. The synthesis of

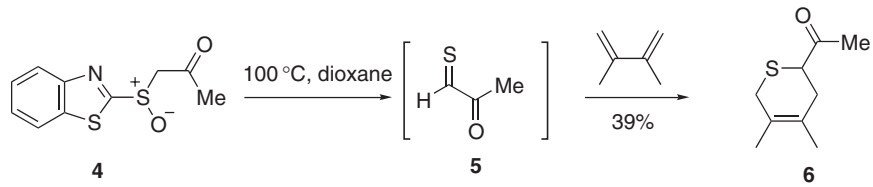
thioketones by photolysis of phenacyl sulfides has been reported. However, the thermolysis of phenacyl sulfoxides has been used as a route to thioaldehydes. Morita and co-workers <1996TL3739> recently reported that thermolysis of phenacyl sulfoxide **1** bearing a range of nitrogen-containing heterocycles in the presence of 2,3-dimethyl-1,3-butadiene led to 2*H*-thiapyran **3**. The products were thought to result from Diels–Alder reaction of the diene and thioaldehyde **2** formed from decomposition of the sulfoxide. It was expected that the sulfine may form by abstraction of the α-hydrogen by the *N*-oxide group, but this was not the case. The two cycloadducts were obtained in good yields (Scheme 1).



1 **2** **3**

Scheme 1

The same group later reported that a wider range of cycloadducts were accessible in yields of 10–85% <1997JOC9018>. Phenacyl sulfoxides bearing a 2-pyridyl, 4-pyridyl and 2-pyrimidyl group were accessed and the cycloadducts obtained in yields of 10%, 19%, and 26% respectively. Use of a thiophene substituent was also attempted but no product was obtained. Additionally, other groups were used in place of the benzoyl substituent on the sulfoxide, and the synthesis of thioaldehydes bearing a phenyl, nitrile, ester, or ketone substituent attempted. However, only in the case of the methyl ketone **4** was any of the hetero-Diels–Alder product **6** obtained via thioaldehyde **5** and the yield was only modest (Scheme 2).



4 **5** **6**

Scheme 2

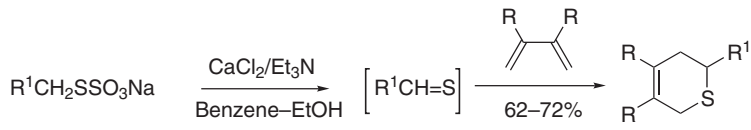
3.08.2.1.2 Formation of the α-C—C bond

Since the publication of COFGT (1995), no syntheses of thioaldehydes via this approach have been published. Addition of an appropriate organolithium compound to, for example, ethyl thionoformate is an example of this approach, and was discussed in COFGT (1995).

3.08.2.1.3 1,2-Elimination reactions

A variety of thioaldehydes have been made by base-induced 1,2-elimination from suitable sulfides and trapped *in situ*, usually to give the Diels–Alder cycloadducts.

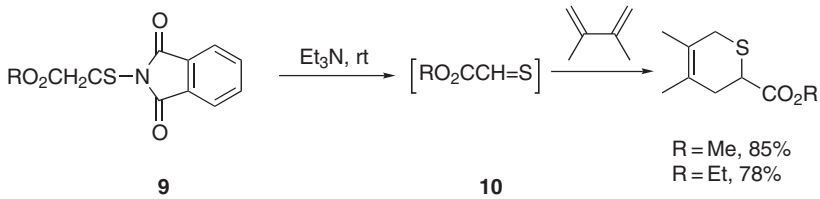
Using this approach, Shimizu and co-workers <2001JCS(P1)2269> prepared some cycloadducts from Bunte salts **7**, by trapping intermediate thioaldehyde **8** with different dienes (Scheme 3).



7 8

Scheme 3

Kirby and co-workers <1996JCS(P1)977> started from phthalimide **9**. Treatment of ethyl and methyl phthalimidosulfanylacetate with triethylamine at room temperature gave the transient thioaldehydes, ethyl, and methyl thioxoacetate **10**, which were trapped with 2,3-dimethylbuta-1,3-diene to yield the cycloadducts (Scheme 4). Those of ethyl thioxoacetate and anthracene, cyclohexa-1,3-diene, and cyclopentadiene were obtained similarly in high yield.



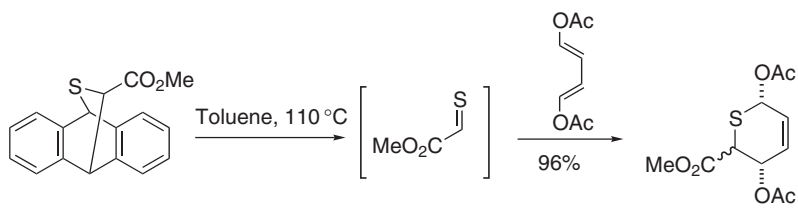
9 10

Scheme 4

3.08.2.1.4 Cycloreversion and related reactions

Pyrolysis is usually only used to generate transient thioaldehydes, from thermally labile adducts, which are a convenient means of storing such reactive compounds. A common pyrolytic method for producing thioaldehydes is the retro-Diels–Alder reaction.

Grierson and co-workers <2000SL658> prepared the carbethoxy-substituted thioaldehyde **12**, previously prepared by Kirby, during the synthesis of a sulfone analog of the Esperamicin-A_1 aglycone. The thioaldehyde **12** was formed by *in situ* thermolysis of sulfide **11**, in a retro-Diels–Alder process, and trapped to give the cycloadduct in almost quantitative yield (Scheme 5). The cycloadduct was transformed into the target compound in several further steps.



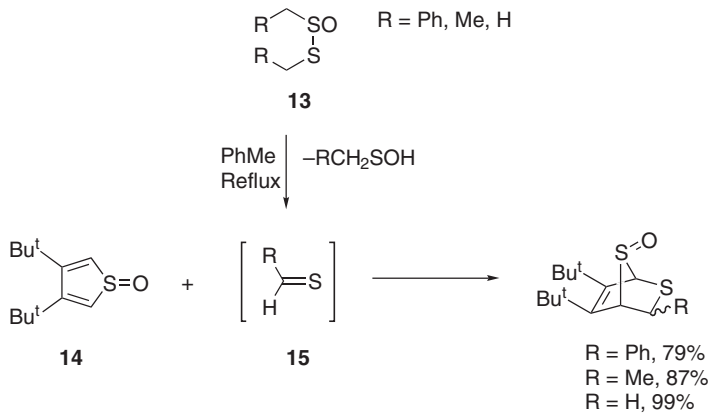
11 12

Scheme 5

Nakayama and co-workers <2003TL5159> have recently reported 3,4-di-*t*-butylthiophene-1-oxide **14** as a trapping reagent for thioaldehydes and thioketones. Thioaldehydes **15** were prepared by thermolysis of the corresponding thiosulfinate **13** in refluxing toluene and trapped as the Diels–Alder cycloadducts in very good yield (79–99%). Even thioformaldehyde could be efficiently formed and trapped in high yield (Scheme 6).

3.08.2.1.5 Sulfuration of aldehydes and derivatives

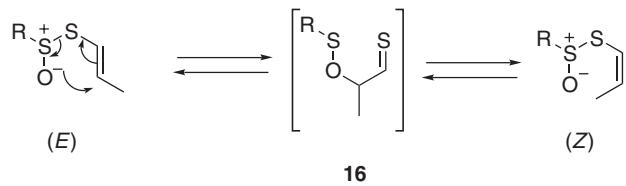
Since the publication of COFGT (1995), no new material has been published which refers to the sulfuration of aldehydes and their derivatives to alkyl thioaldehydes. Sulfuration has been used for the synthesis of unsaturated thioaldehydes, and especially thioketones, and these developments are discussed in more detail below.



Scheme 6

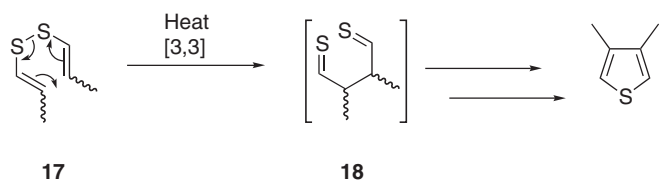
3.08.2.1.6 Other methods

During research into *Allium* chemistry, Block and co-workers <1996JACS2799> observed that attempts to isolate pure samples of (*E*)- or (*Z*)-sulfoxide always led to mixtures. This could be explained by a [2,3]-sigmatropic rearrangement via the intermediate thioaldehyde **16** (Scheme 7). However, it was not possible to trap this species with 2,3-dimethyl-1,3-butadiene.



Scheme 7

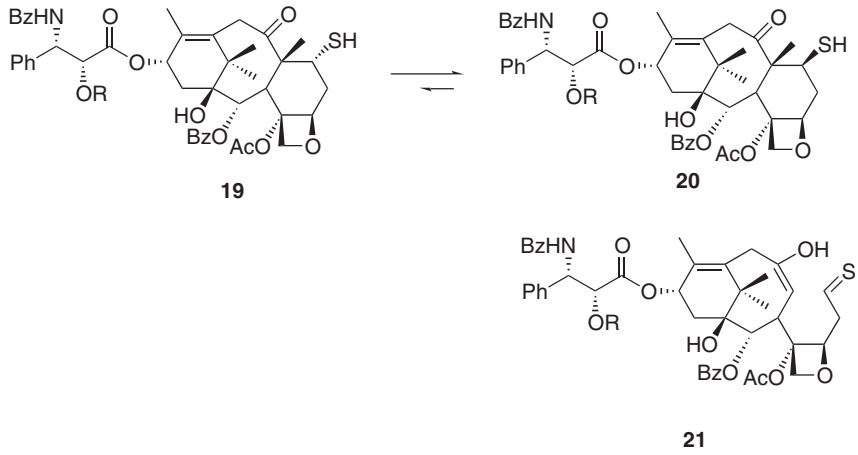
Further research led to the observation that pyrolysis of the disulfide **17** at 150–200 °C gave 3,4-dimethylthiophene as the major product. Block and co-workers suggested that the dithioaldehyde **18** was an intermediate, and could be formed by [3,3]-dithio-Claisen rearrangement of the disulfide (Scheme 8).



Scheme 8

The same group also reported the formation of a thioaldehyde–sulfine compound as an intermediate in the formation of a 2-oxa-3,7-dithiabicyclo[2.2.1]heptane derivative <1996JACS6570>.

Mastalerz and co-workers <2001OL1613> have suggested the formation of a thioaldehyde intermediate in the epimerization of sulfur analogs of paclitaxel. Reaction of a triflate derivative with potassium thioacetate gave the thioacetate, which could be transformed into the thiol **19** by selective hydrolysis with NH_3 in ethanol. The thiol underwent base-catalyzed epimerization to **20** when it was heated in toluene at 90 °C in the presence of excess DBU. By analogy with its oxygen counterpart, an aldol-type equilibrium proceeding through the thioaldehyde intermediate **21** was suggested (Equation (1)).



19 20 21 (1)

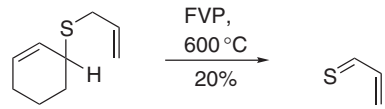
3.08.2.2 α,β-Unsaturated Thioaldehydes

α,β-Unsaturated thioaldehydes, e.g., alkyl thioaldehydes, are generally unstable compounds and immediately undergo further reaction, either dimerization or polymerization or they react with an added diene in a hetero-Diels–Alder manner. Usually, the thioaldehydes are characterized as cycloadducts following cycloaddition, although it has proven possible to confirm the presence of the C=S bond by infrared spectroscopy, and it is possible to observe the thioaldehydes by mass spectrometry.

3.08.2.2.1 Thioaldehydes bearing an α,β-alkenic bond

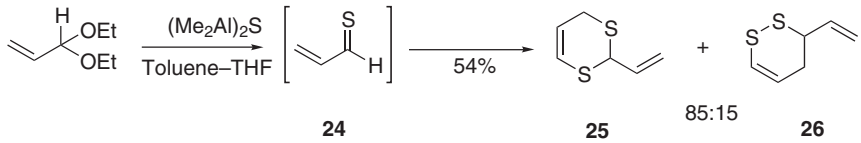
(i) Simple alkenyl thioaldehydes

Flash vacuum pyrolysis (FVP) is an efficient way of generating (in the gas phase) transient species for spectroscopic or chemical investigations at high temperatures, which can be captured at low temperature with matrix isolation. In general, temperatures over 600 °C and pressures of less than 10^{-4} mbar are necessary. The thioaldehydes are usually isolated in a liquid nitrogen trap or argon matrix. Ripoll and co-workers <1997TL8707> utilized the technique of FVP and found that sulfide **22** underwent retro-ene reaction upon heating to 600 °C to give thioacrolein **23** in 20% yield (Equation (2)).



22 23 (2)

The availability of carbonyl compounds makes direct thionation attractive and many reagents have been developed to carry out this transformation. For example, propenethial **24** has recently been prepared by thionation of acrolein diethyl acetal with bis(dimethylaluminum) sulfide in toluene–tetrahydrofuran <2000JOC6601>. The intermediate thioaldehyde was not isolated, but underwent an *in situ* [4 + 2]-cycloaddition to give an 85:15 mixture of the products **25** and **26** (Scheme 9).

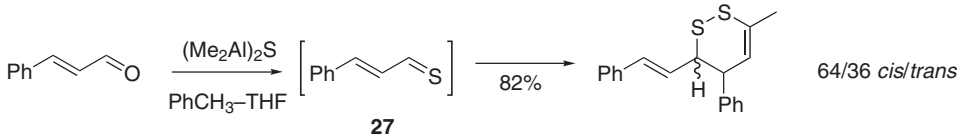


24 25 26

Scheme 9

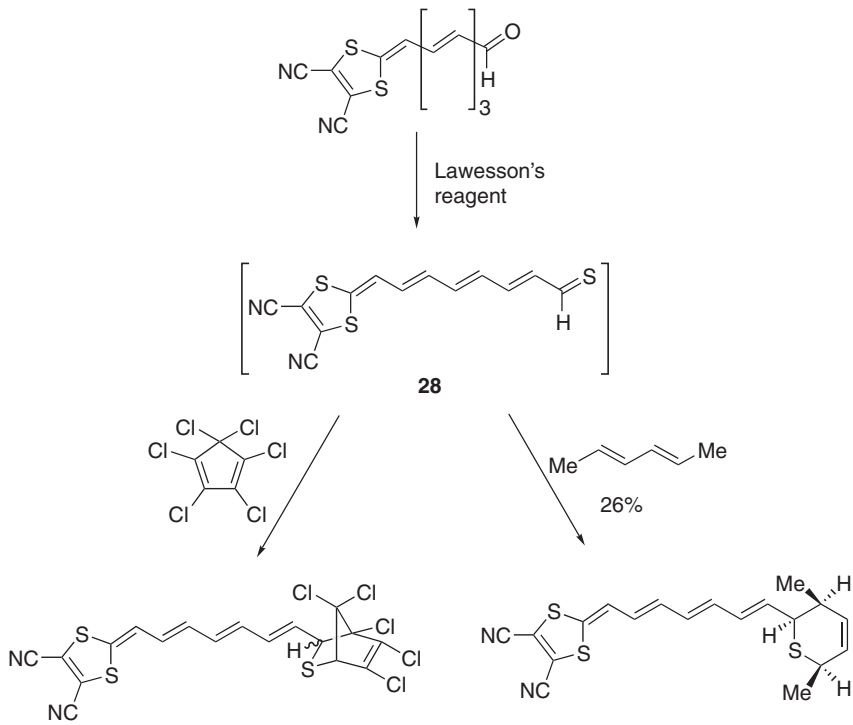
Direct conversion of a carbonyl compound into the thiocarbonyl was demonstrated by the same reseachers, who showed that aldehyde **27** could be prepared by treating cinnamaldehyde

with bis(dimethylaluminum) sulfide. The thioaldehyde dimerized in a [4 + 2] manner to give the disulfide in good yield, as a mixture of diastereoisomers (Scheme 10).



Scheme 10

Very recently, Markl and co-workers <2003HCA2589> reported the dimerization of aldehydes via thioaldehydes, giving 1,3-dithietanes which then extruded sulfur to yield alkenes. This approach was used to make tetrathiafulvenes with polymethine spacers. Thionation of the aldehyde with Lawesson's reagent was the method of choice and the intermediate thioaldehyde **28** could be trapped with perchlorocyclopentadiene or 2,4-hexadiene (Scheme 11).



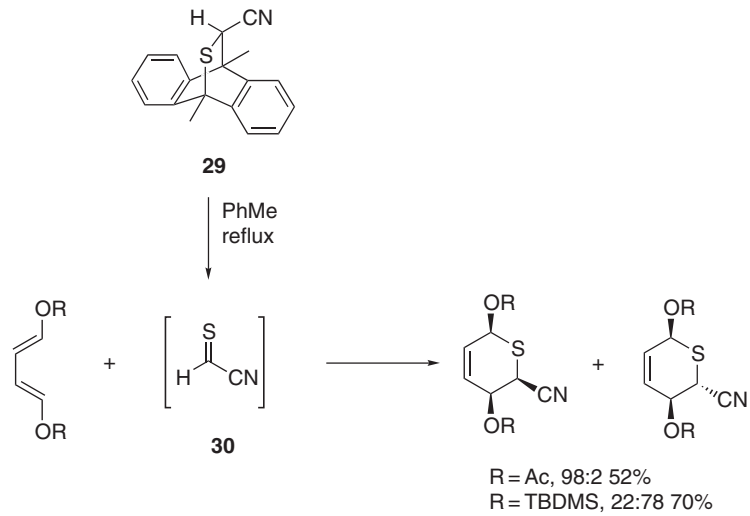
Scheme 11

The retro-Diels–Alder approach has proven successful for generating thioaldehydes: Infact, the thioaldehyde **30** bearing a nitrile substituent was accessed simply by heating the nitrile **29** in refluxing toluene (Scheme 12). Trapping of the thioaldehyde with several dienes led predominantly to the all *cis*-cycloadduct, when R = acetyl, and a mixture of the *cis*- and *trans*-cycloadducts when R was the *t*-butyldimethylsilyl (TBDMS) protecting group <1997PS245>.

3.08.2.2.2 Thioaldehydes bearing an α,β-aryl or hetaryl substituent

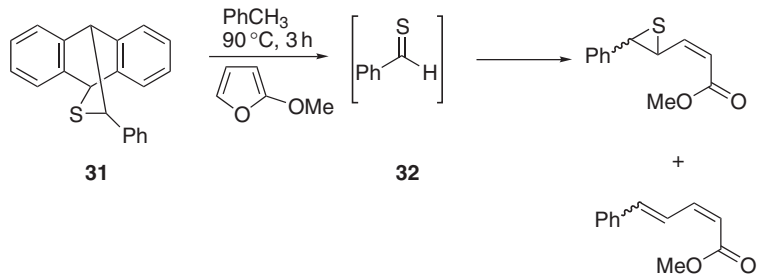
(i) Simple aryl thioaldehydes

The thioaldehyde–anthracene cycloadduct **31** when heated with 2-methoxyfuran in toluene gave via thioaldehyde **32** a mixture of *cis*- and *trans*-isomers together with 2(*Z*)-penta-2,4-dienoate



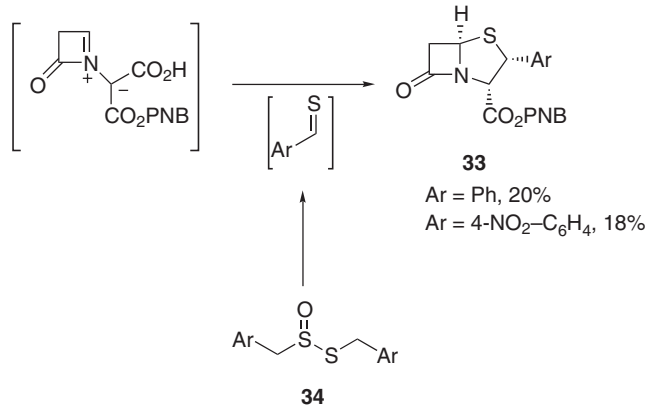
Scheme 12

(Scheme 13). A similar procedure carried out with the corresponding seleno–anthracene adduct also gave the penta-2,4-dienoate <2003TL1179>.



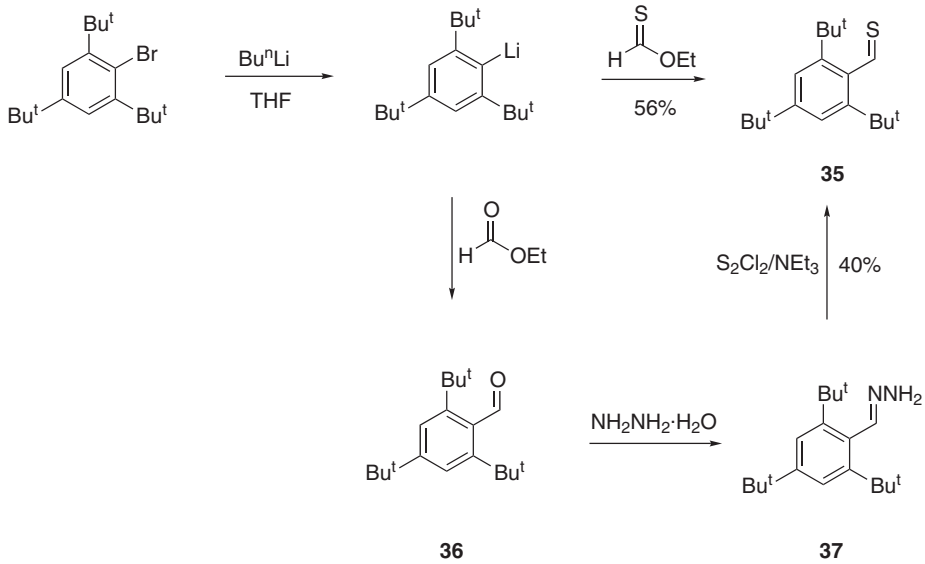
Scheme 13

Gallagher and co-workers <2001JCS(P1)1897> have utilized a process similar to that employed by Baldwin and Lopez, whereby heating a solution of the methanethiosulfinate **34** in acetonitrile generated the thioaldehyde, which was trapped with the azomethine ylide to give the penams **33** (Scheme 14).



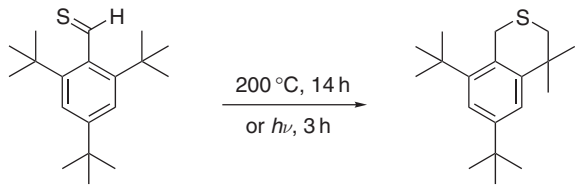
Scheme 14

Okazaki and co-workers recently reported the first stable aromatic thioaldehyde, namely (2,4,6-tri-*t*-butyl)thiobenzaldehyde. Two approaches from the same starting material were used, and both proved successful. Treatment of the bromobenzene with butyllithium gave the aryllithium compound, which was reacted with *O*-ethylthioformate at −78 °C in THF, to give the thioaldehyde **35** in 56% yield (Scheme 15). A similar reaction using ethyl formate gave 2,4,6-tri-*t*-butylbenzaldehyde **36** in 47% yield, which was converted into the hydrazone **37**. The reaction of the hydrazone with disulfur dichloride and triethylamine gave the same thioaldehyde in slightly lower yield <1996BCJ709>.



Scheme 15

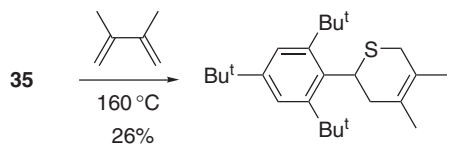
Thioaldehyde **35** is remarkably stable, and can be stored as a solid at room temperature for several years. Heating at higher temperatures (200 °C) in a solution of degassed benzene, caused the thioaldehyde to undergo an intramolecular cyclization with the *o*-*t*-butyl group to give a dehydrothiopyran in almost quantitative yield (Equation (3)).



(3)

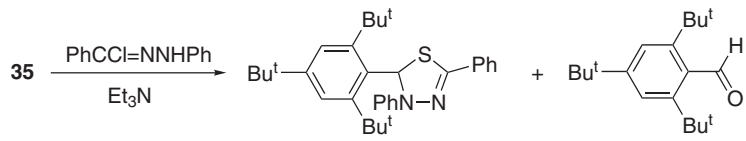
38

The thioaldehyde undergoes [4 + 2]-cycloaddition with 2,3-dimethyl-1,3-butadiene at 160 °C to give the adduct **39** and [3 + 2]-cycloadditions with diphenylnitrilimine to give product **40** and mesitonitrile oxide at room temperature (Equations (4) and (5)). Further reactions were also reported.



(4)

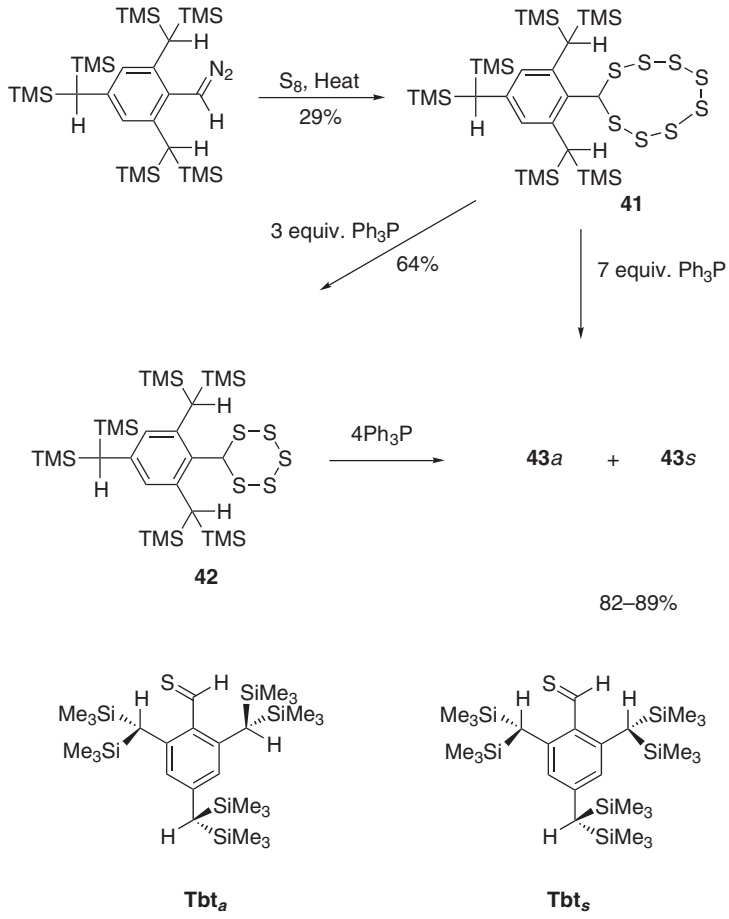
39



(5)

40

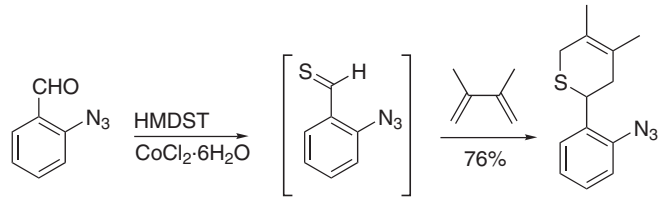
Desulfurization of polysulfides with triphenylphosphine or hexamethylphosphorus triamide (HMPT) has recently been reported, and provides a novel approach to the synthesis of alkyl thioaldehydes. 2,4,6-Tris[bis(trimethylsilyl)methyl]phenyl (Tbt)-substituted octathionane **41** was treated with 7 equiv. of triphenylphosphine in refluxing THF to give a clear blue solution (a characteristic of thiocarbonyl compounds), which was found to be due to the two thioaldehydes **43** Tbt_a and Tbt_s (Scheme 16) <1997CEJ62>. The isomeric thioaldehydes are stable compounds and were stored for several months without decomposition.



Scheme 16

Treatment of the pentathionane **42** with 4 equiv. of triphenylphosphine in refluxing THF gave a mixture of the two isomeric thioaldehydes, with a slight increase in the yield of the Tbt_s-substituted thioaldehyde. Also the Tbt_s-substituted thioaldehyde could be formed exclusively, and in good yield by the addition of HMPT (15 equiv.) to a solution of the octathionane in THF at low temperature.

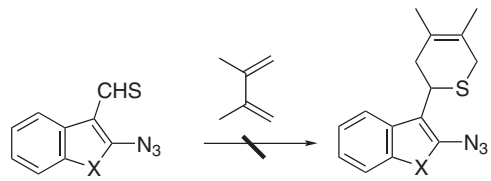
Degl'Innocenti and co-workers <1995CL147> utilized thionation of *o*-azidobenzaldehyde with HMDST and cobalt(II) chloride hexahydrate to access the transient *o*-azidothioaldehyde **44**, which could be trapped with a fivefold excess of a variety of dienes to give the Diels–Alder cycloadducts (Scheme 17, Table 1). Yields for this process ranged from 41–76%, depending on the diene used.



44

Scheme 17

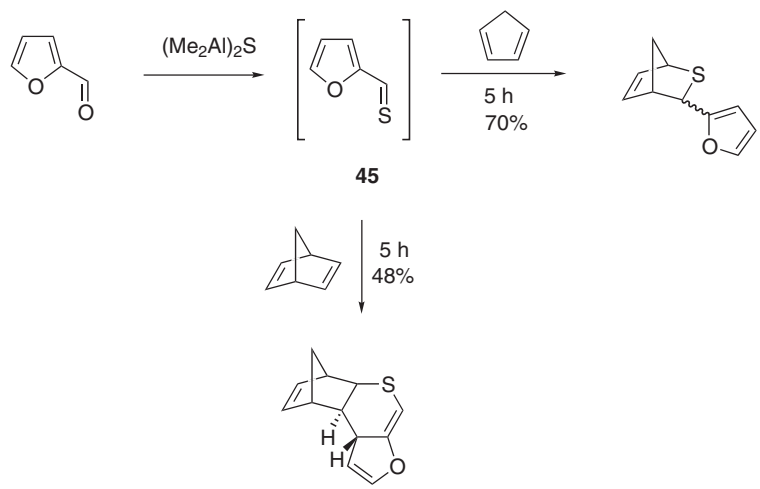
2-Azido-3-formylbenzothiophene and benzofuran gave none of the desired cycloadducts when reacted in the presence of 2,3-dimethyl-1,3-butadiene. In such cases only unidentified products were formed and it was suggested that they arose from ring-cleavage of the azido adducts initially formed (Equation (6)).



X = O or S

(6)

Thionation was also used to transform 2-formyl furan into the thioaldehyde **45** (Scheme 18). Bis(dimethylaluminum) sulfide was used, and the unstable thioaldehyde underwent smooth hetero-Diels–Alder reaction with cyclopentadiene or norbornadiene to give the cycloadducts in moderate-to-good yield <2000JOC6601>.



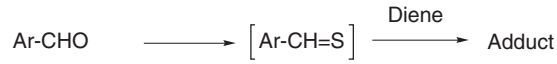
45

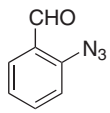
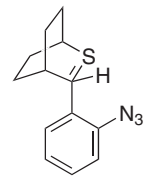
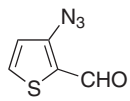
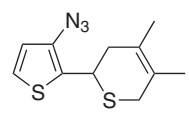
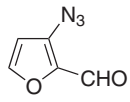
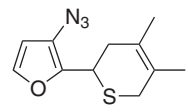
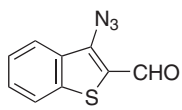
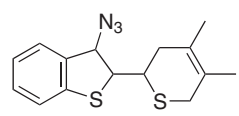
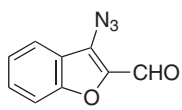
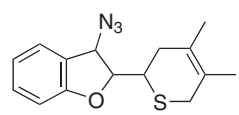
Scheme 18

(ii) Electronically stabilized aryl thioaldehydes

Unlike the unstable simple aryl and hetaryl thioaldehydes, electronically stabilized thioaldehydes are, generally, stable due to favorable interaction of the nitrogen lone pair electrons. Thioaldehydes based on the 6-amino-5-thioformyluracil structure are perfectly stable, and have been prepared by Hirota and co-workers <1996T9971>. Treatment of the aminouracil derivative with DMF—$POCl_3$ gave Vilsmeier salts **46**, which could be converted into the thioaldehydes **47** by treatment with sodium sulfide. The products were formed in yields of 23–98% (Scheme 19) and could be recrystallized from ethanol or benzene and stored at room temperature for several

Table 1 Arylthioaldehydes prepared using HMDST

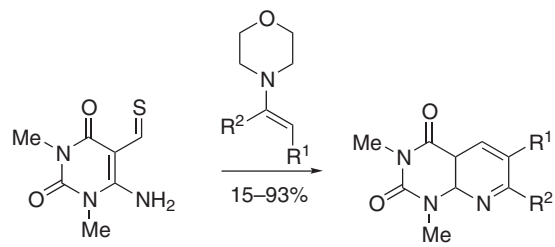


Ar-CHO	*Diene*	*Adduct*	*Yield* (%)
			71
			59
			55
			45
			41

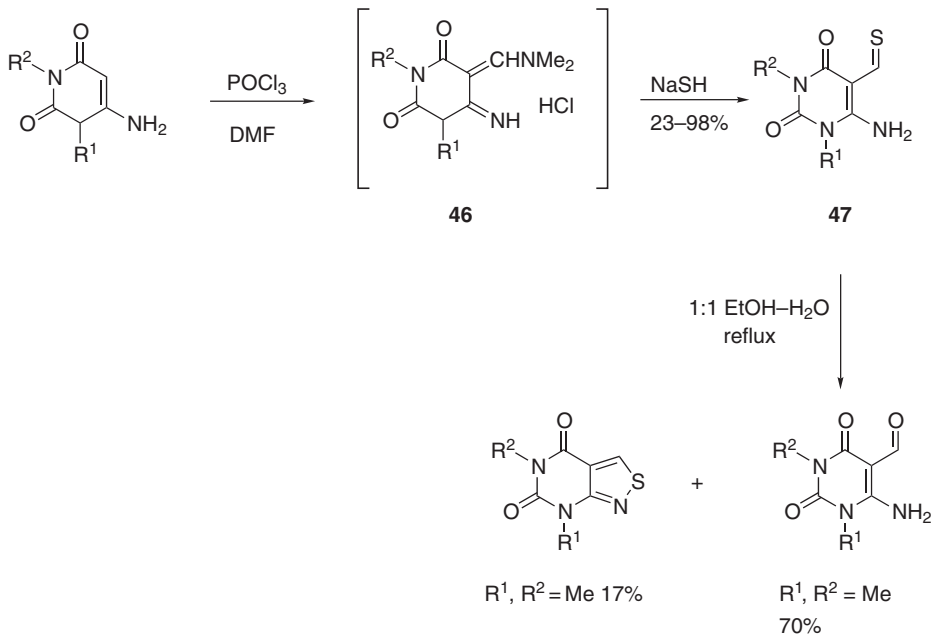
Reproduced by permission of The Chemical Society of Japan from *Chem. Lett.*, **1995**, 147–148 (<1995CL147>).

years. Hydrolysis of the thioaldehyde in refluxing ethanol gave the corresponding aldehyde (70%) and isothiazolo[3,4-*d*]pyrimidines (17%). A novel uracil derivative could be obtained by the reaction of thioaldehyde with amines or phosphorus ylides.

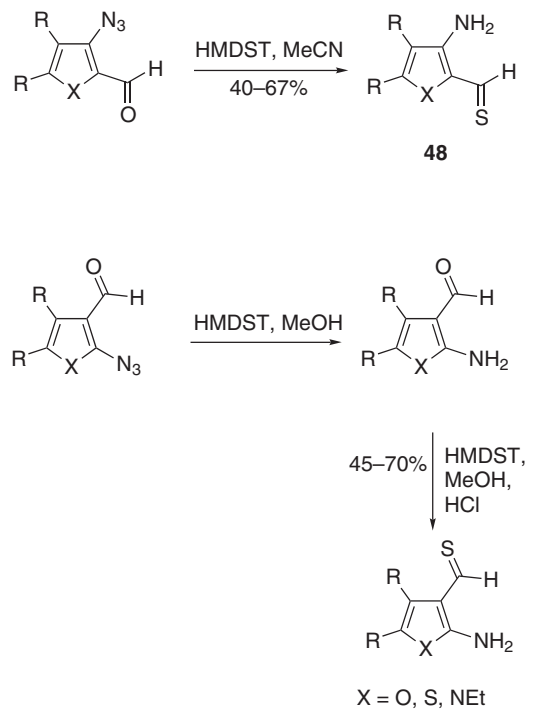
Hirota and co-workers <1997JOC2999> have also carried out further reactions on these thioaldehydes, notably with morpholino enamines to give desulfurized cyclic products via elimination of hydrogen sulfide. This route provided a method for the regiospecific synthesis of pyrido[2,3-*d*]pyrimidine derivatives (Equation (7)).



The thionating reagent HMDST has also been used to prepare a range of stable *o*-amino thioaldehydes (Scheme 20) <1996S1185>. 2-Azido and 2-azidothioaldehydes **48** derived from the corresponding formyl compounds, have been accessed using either methanol or acetonitrile



Scheme 19

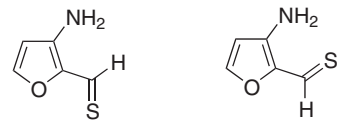


Scheme 20

as solvent. The formyl moiety in the 2-azidoaldehydes showed lower reactivity, and use of excess HMDST delivered only the corresponding amino aldehyde. It was found that subsequent addition of HCl to a methanolic solution of the aldehydes and HMDST gave the desired thioaldehydes. With one exception the *o*-amino thioaldehydes were found to be stable orange to red compounds.

HMDST was found to convert 2-azido-1-ethyl-3-formylindole into the isolable amino thioaldehyde in good yield. This suggests that HMDST can act as a valid substitute for H_2S in the transformation of five-membered heteroaromatic *o*-azidoaldehydes to *o*-amino thioaldehydes.

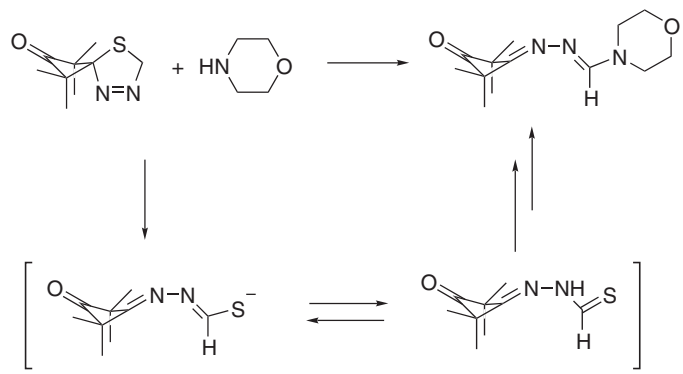
Conformational studies were carried out on the thioaldehyde **49** whose ^{1}H-NMR spectrum in DMSO displays, at room temperature, the signals corresponding to a pair of rotational conformers (rotamers) in an approximately 3.5:1 ratio (Equation (8)). The major rotamer was suggested by NOE interactions to have (*E*)-stereochemistry <1997JOC2263>.



(*Z*)-Minor (*E*)-Major (8)

49

Mloston and co-workers <1997HCA230> have reported that base-catalyzed ring opening of spirocyclic 2,5-dihydro-1,3,4-thiadiazoles with secondary amines gave *N*-alkylidenehydrazone, via an intermediate thioaldehyde **50** (Scheme 21).



50

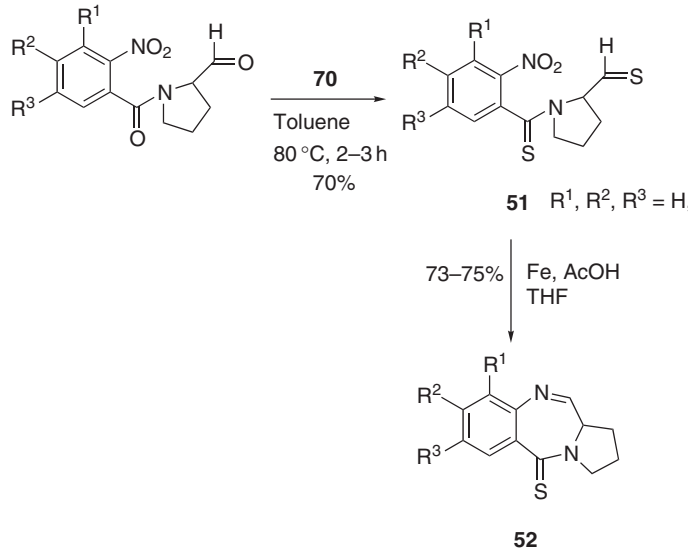
Scheme 21

Kamal and co-workers <1996TL2281> have prepared the thioaldehyde **51** as part of a synthesis of the antibiotic DC-81 and its thio-analog. Direct thionation with Lawesson's reagent converted the aldehyde into the thioaldehyde and the amide into the thioamide (Scheme 22). Reductive cyclization with iron and acetic acid in THF afforded the desired 5-thiodiazepine **52** in good yield.

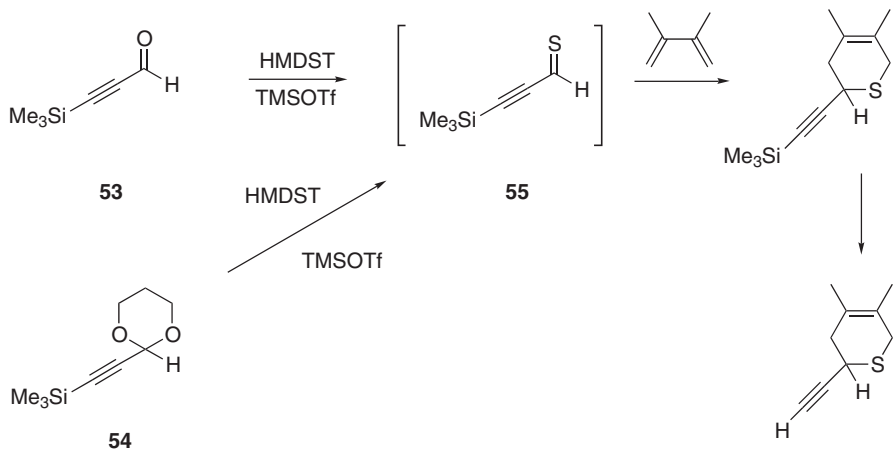
3.08.2.2.3 Thioaldehydes bearing an α,β-alkynic bond

Recently, one of only a few examples of a thioaldehyde bearing an α,β-alkynic bond has been reported by Capperucci and co-workers <1999SL1739>. Treatment of the trimethylsilyl-protected alkyne **53** with HMDST and trimethylsilyl triflate gave the thioaldehyde **55**, which was trapped with 2,3-dimethyl-1,3-butadiene to give the cycloadduct (Scheme 23). The yield was not noted. Additionally, the acetal **54** could be converted into the same thioaldehyde with HMDST and TMSOTf. Deprotection with TBAF gave the desilylated product.

When the thioaldehyde was trapped with cyclohexadiene, four molar equivalents of HMDST gave a 1:1 mixture of *exo* and *endo*-isomers. 2 equiv. gave an improved *exo*:*endo* ratio of 3:1. For more information on thioacyl functions linked to sulfur see COFGT (1995) (Chapter 5.16): Thioacyl functions linked to a metalloid (Si, Ge, or B) or metal; and their seleno and telluro analogs.



Scheme 22



Scheme 23

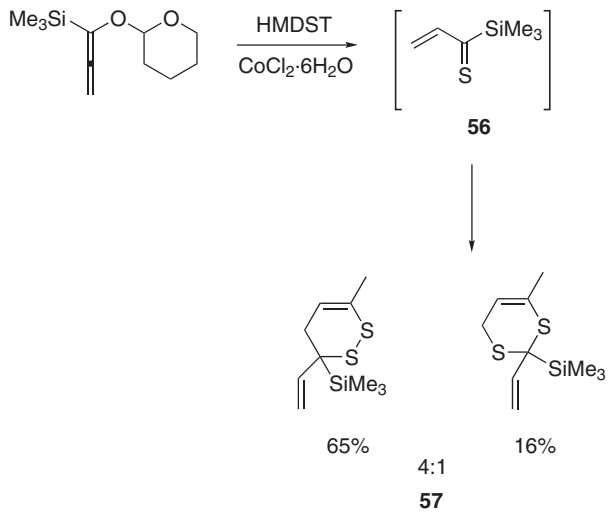
3.08.2.3 Silyl Thioaldehydes

Thioacyl silanes can be regarded as synthetic equivalents of thioaldehydes, since the silyl moiety can be easily removed in a subsequent deprotection step. Thioacyl silanes are usually generated by direct thionation of a range of starting materials. Allenes and acetals have been transformed into thioacyl silanes with HMDST and $CoCl_2 \cdot 6H_2O$.

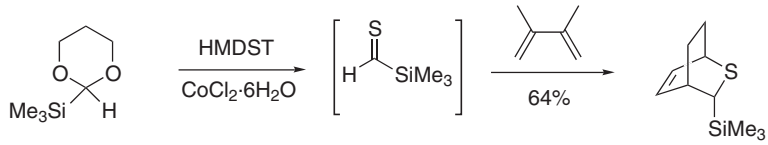
A range of allenes treated with HMDST in acetonitrile gave the intermediate thioacylsilanes **56**, which self-dimerized to afford polyfunctionalized 1,2-dithiins **57** as the major products (Scheme 24) <2003TL2831>.

Treatment of a range of silylated acetals, obtained via transacetalization from the corresponding silyl dithianes, with the same reagents gave the corresponding thioformylsilanes **58** which were trapped to give adducts **59** in modest to good yield (37–64%) depending upon the diene used (Scheme 25) <1997SL361>.

Additionally, Katritzky and co-workers <2000JOC9206> have reported that benzotriaziole (Bt) derivatives reacted with HMDST in the presence of TMSOTf or cobalt dichloride hexahydrate as a Lewis acid to afford the corresponding thioacylsilanes **60** (Scheme 26). These could

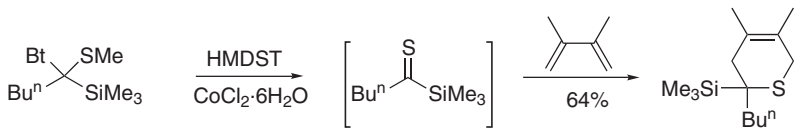


Scheme 24



Scheme 25

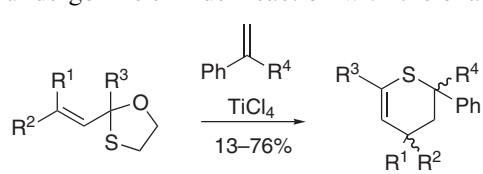
be smoothly transformed into the cycloadducts **61** by reaction with 1,3-dimethyl-2,3-butadiene. This methodology has the advantage that the starting materials are readily available.



Scheme 26

3.08.2.4 Thioaldehyde Synthetic Equivalents

α,β-Unsaturated oxathioacetals have recently been shown to react with alkenes in a Diels–Alder type process, and thereby act as synthetic equivalents of thioaldehydes. The oxathiolanes were stirred with 1 equiv. of titanium(IV) chloride and 2–3 molar equivalents of styrene to give, after hydrolysis by potassium hydroxide, the corresponding thiapyrans (Equation (9)) <2003TL853>. A range of other alkenes were later found to undergo Diels–Alder reaction with the oxathioacetals <2003T1859>.



(9)

R^1 = H, Me
R^2 = Ph, Me
R^3 = H, Me, Ph
R^4 = H, Me

3.08.3 THIOKETONES

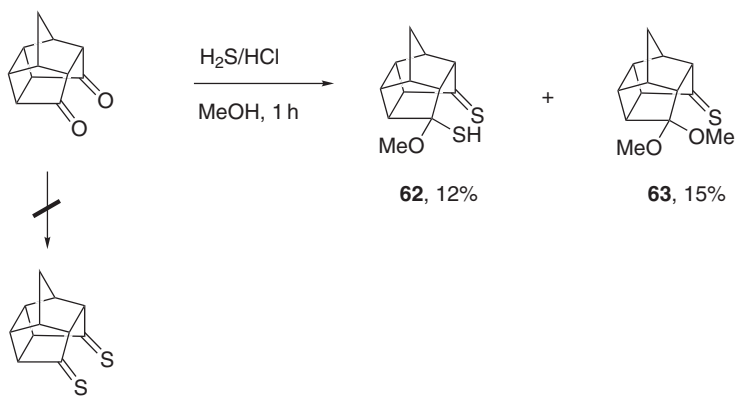
Thioketones are usually more stable than thioaldehydes, especially diaryl thioketones, or thioketones flanked by a heterocycle. Direct thionation of a ketone is a popular method for the synthesis of thioketones and the use of microwave irradiation has proven successful for this transformation (*vide infra*).

3.08.3.1 Dialkyl Thioketones

3.08.3.1.1 Dialkyl thioketones by sulfuration of ketones

(i) Using hydrogen sulfide

The use of hydrogen sulfide in the presence of an acid catalyst is a method for the generation of thiocarbonyl groups, which has been used for over a century. The acid catalyst is usually hydrogen chloride, which reversibly protonates the carbonyl group, facilitating addition of H_2S, and subsequent dehydration to give the thiocarbonyl. The use of hydrogen sulfide has been overshadowed by phosphorus-based reagents (most notably Lawesson's reagent) and HMDST. However, hydrogen sulfide does generally give good yields and clean products. In conjunction with their research into the thionation of cage ketones, Romanski and Mloston <2002S1355> found that the thioketones **62** and **63** were formed from the ketone using H_2S/HCl in methanol (Scheme 27).

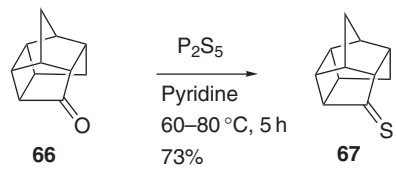


Scheme 27

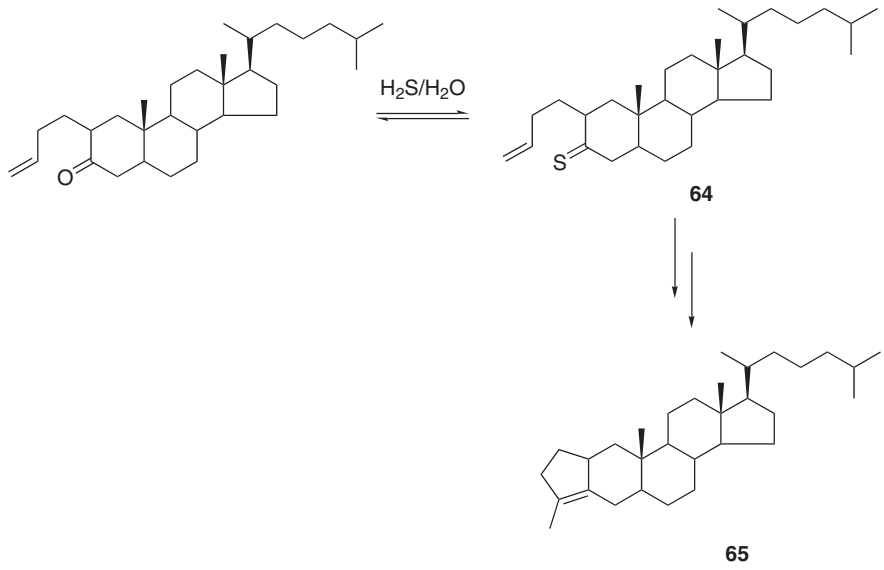
Additionally, reaction of the steroidal ketone with aqueous H_2S gave the thioketone **64**, which was converted via a series of one electron transfers into alkene **65**, the ultimate product of the reaction sequence <1998TL447> (Scheme 28).

(ii) Using phosphorus-based reagents

Phosphorus pentasulfide is another popular thionating reagent. The most commonly used conditions involve heating a solution of the ketone in pyridine with phosphorus pentasulfide. Good yields can be achieved, but excess can cause product decomposition. Use of a more polar solvent such as diglyme usually results in an increase in the thionation rate. Romanski and Mloston <2002S1355> used phosphorus pentasulfide to thionate the cage ketone **66**. The product, thioketone **67**, was formed in good yield by simply heating a solution of the cage ketone with P_2S_5 in pyridine (Equation (10)).

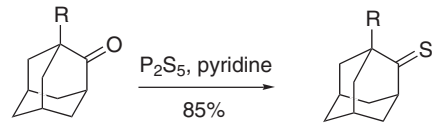


(10)



Scheme 28

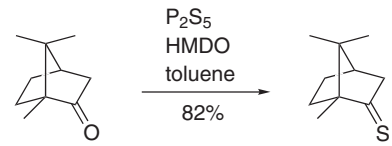
In a similar manner, P_2S_5 has been used to access the adamantane thione **68** (Equation (11)).



(11)

68

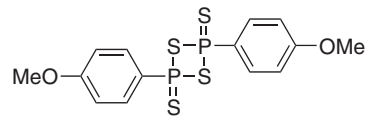
Curphey <2002JOC6461> has developed an effective combination of phosphorus pentasulfide and HMDSO. Thionation of camphor in refluxing toluene gave thiocamphor **69** in 82% yield as determined by HPLC (Equation (12)).



(12)

69

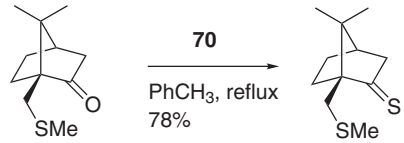
Another successful phosphorus-based reagent is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetane-2,4-disulfide, known as Lawesson's reagent **70**. It is accessed by the reaction of anisole with phosphorus pentasulfide, and can be considered to be an organic analog of P_4S_{10}.



70

It is soluble in benzene, toluene, and xylene and is used routinely in these solvents. One drawback, however, is that the products of thionation usually require chromatographic purification to remove anisole-related by-products.

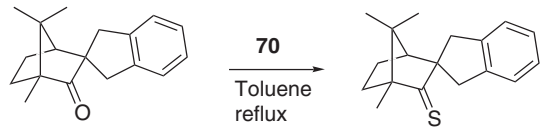
Lawesson's reagent is the most popular choice for the direct thionation of ketones and has been used by Montenegro and co-workers <1996TA3553> in their synthesis of 10-methylthiocamphorthione **71** from 10-methylthiocamphor (Equation (13)).



(13)

71

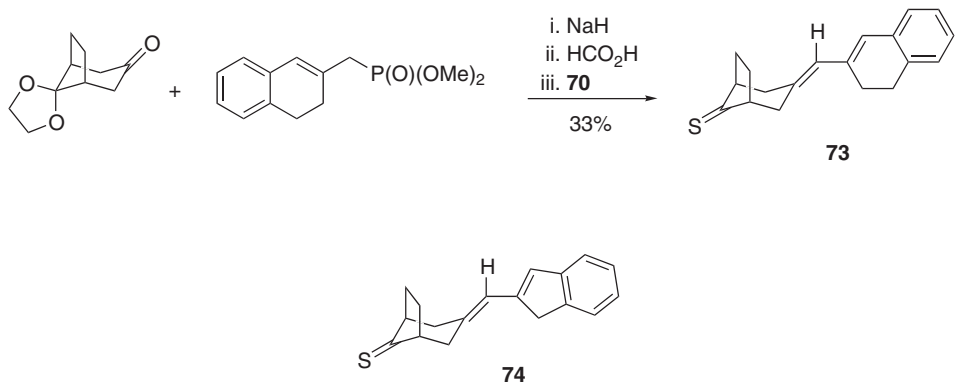
Additionally, Shimada and co-workers <1999CL695> have reported a new synthesis of sterically crowded thiones derived from D-camphor (Equation (14)). Direct thionation with Lawesson's reagent **70** was utilized to carry out the transformation of the ketone into the thioketone **72**.



(14)

72

During investigations into bicyclic thioketones as triggers for liquid crystal optical switches, the axially chiral bicyclic thioketones **73** and **74** were prepared <2003JOC1075>. The starting tricyclic compound was extended via ketone function using a Wadsworth–Emmons reaction, and the acetal deprotected to give the ketone, which was thionated using Lawesson's reagent **70** (Scheme 29).



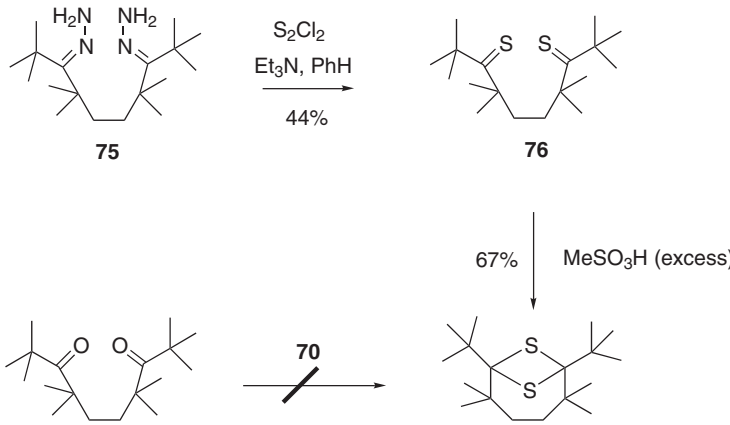
Scheme 29

3.08.3.1.2 Dialkyl thioketones by direct sulfuration of other compounds

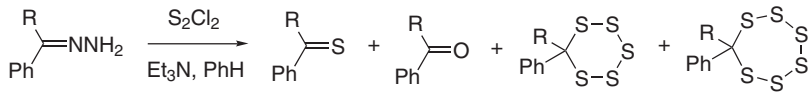
(i) Hydrazones

Hydrazones are easily prepared by reaction of a ketone with hydrazine and can be efficiently transformed into thiocarbonyl compounds by treatment with disulfur dichloride, probably via an unstable thiosulfinate, which immediately eliminates sulfur. During work on the synthesis of sterically congested cycloalkanes, Nakayama and co-workers <2000JOC1799> prepared the thioketone **76** by treatment of the dihydrazone **75** with S_2Cl_2 and triethylamine (Scheme 30). Under acid conditions, this dimerized to yield the dithietane. It was noted that direct thionation of the corresponding diketone with Lawesson's reagent did not give the required compound.

Nakayama and co-workers reinvestigated the mechanism of thionation with the hope of isolating a dithiirane intermediate. The products were not the presumed dithiiranes, but thioketones, ketones, and cyclic polysulfides (Scheme 31). The proportion of products depended on the nature of the substituent on the phenylhydrazone starting material.



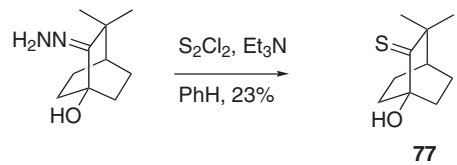
Scheme 30



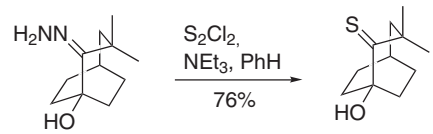
R = 1-Ad	50%	15%	11%	6%
R = Bu^t	10%	63%	7%	3%
R = Ph	17%	47%	4%	7%

Scheme 31

Similarly, Takeuchi and co-workers <1998JOC2209> isolated the thioketones **77** and **78** by treatment of the hydrazones with S_2Cl_2 and triethylamine in benzene (Equations (15) and (16)).

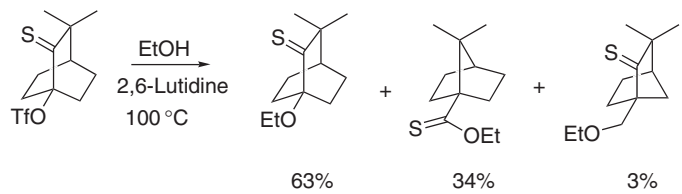


77 (15)



78 (16)

The alcohols **77** and **78** were converted into the triflate and the tresylate respectively, and were subjected to solvolysis in ethanol to give a range of products. Ethanolysis of the triflate gave a mixture of compounds, including a ring-contracted thioketone as a minor component (Scheme 32).



63% 34% 3%

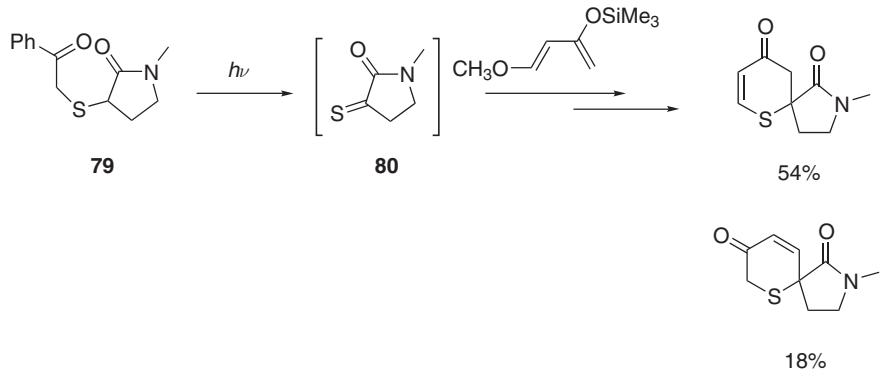
Scheme 32

Ethanolysis of the tresylate gave a mixture of five products, one of which was the thioketone with the tresylate group replaced with an ethoxy group.

3.08.3.1.3 Dialkyl thioketones by other methods

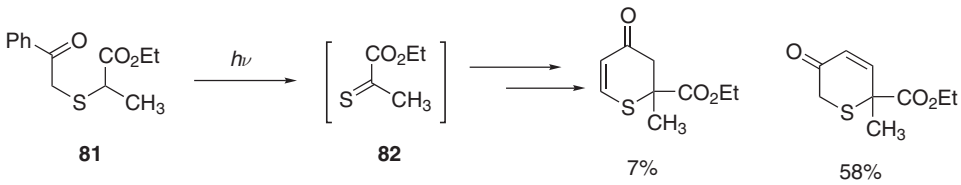
(i) Photolytic cleavage of phenacyl sulfides

Vedejs and co-workers originally developed the Norrish type II photolytic cleavage of phenacyl sulfides into a versatile method for the synthesis of thioaldehydes, and have recently reported a synthesis of otonecine using the photolytic cleavage of a variety of phenacyl sulfides into the corresponding thioketones, as a key step (Scheme 33). Lactam thioketone **80** was generated by the photochemical cleavage of the corresponding phenacyl sulfide **79**. Sun-lamp irradiation of **79** in the presence of the Danishefky diene gave the two enones <1998JACS3613>.

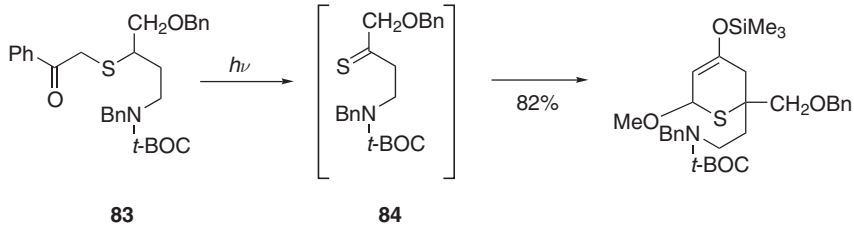


Scheme 33

Methyl thionopyruvate **82** was accessed in a similar manner by sun-lamp irradiation of the phenacyl sulfide **81** (Equation (17)), as was thioketone **84**, obtained from phenacyl sulfide **83** (Scheme 34).



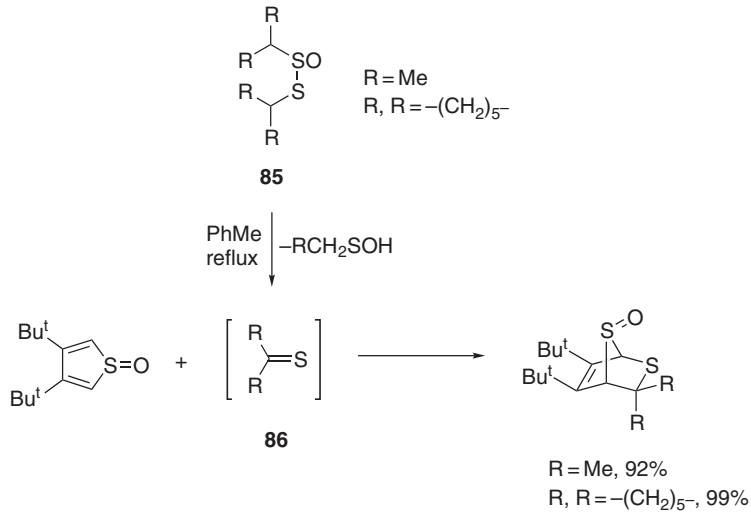
(17)



Scheme 34

(ii) Pyrolytic methods

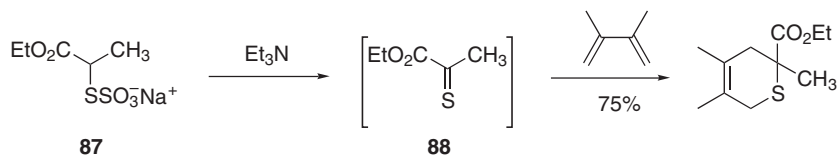
In an analogous manner to the synthesis and trapping of thioaldehydes, Nakayama and co-workers <2003TL5159> successfully trapped a variety of thioketones **86** with 3,4-di-*t*-butylthiophene 1-oxide (Scheme 35). The thioketones were obtained by thermolysis of the disulfides **85**, and the cycloadducts were formed in excellent yield (92% and 99%).



Scheme 35

(iii) From Bunte salts

Larsen and co-workers synthesized a range of thioketones by a modification of the Kirby protocol <1996JOC4725>. The crude Bunte salts **87** were diluted with the appropriate diene and subjected to slow addition of triethylamine, which resulted in smooth formation of thioketones (e.g., **88**). Subsequent cycloaddition afforded 3,6-dihydro-2*H*-thiopyrans in yields of 12–86% (Scheme 36).



Scheme 36

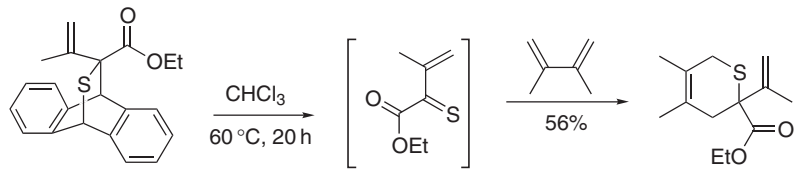
3.08.3.2 α,β-Unsaturated Thioketones

α,β-Unsaturated thioketones are generally more stable than dialkyl thioketones and are usually furnished by thionation of the carbonyl compound, and are trapped *in situ* with suitable dieneophiles. There are several other methods and FVP has proven successful.

3.08.3.2.1 Thioketones bearing an α,β-alkenic bond

(i) Simple alkenyl thioketones

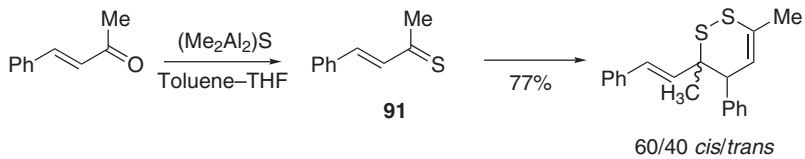
Sometimes thionation of the corresponding unsaturated ketones is unsuccessful due to a sterically hindered moiety or the tendency for self-condensation. Capozzi and co-workers developed a useful method for the synthesis of α,β-unsaturated thioketones by transformation of the ketone group of the thione-cycloadducts into the corresponding methylenic group, which was thermally decomposed to α,β-unsaturated thioketones <2001S409>. Heating a solution of the ester **89** in chloroform generated the thioketone **90**, which was trapped with either electron-rich or electron-poor alkenes to give the corresponding 3,4-dihydrothiopyrans in yields of 42–56% (Scheme 37).



89 **90**

Scheme 37

α,β-Unsaturated thioketone **91** was accessed by direct thionation of the ketone with bis(dimethylaluminum) sulfide <2000JOC6601>. The thioketone underwent [4 + 2] self-dimerization in which one molecule served as the dienophile, to afford a mixture of isomeric diithins (Scheme 38). The thioketone could also be trapped with cyclopentadiene or norbornadiene.

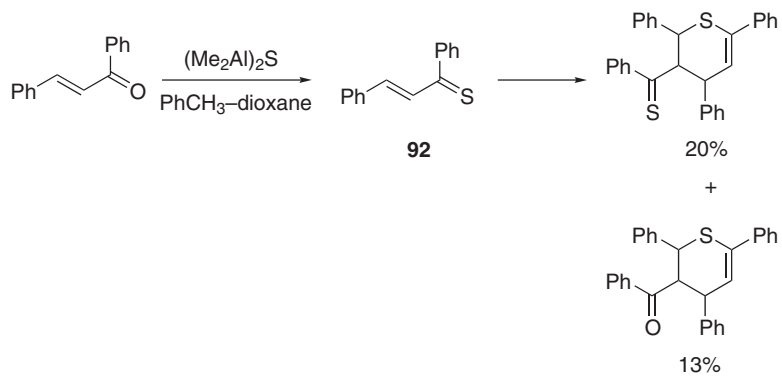


91

60/40 *cis*/*trans*

Scheme 38

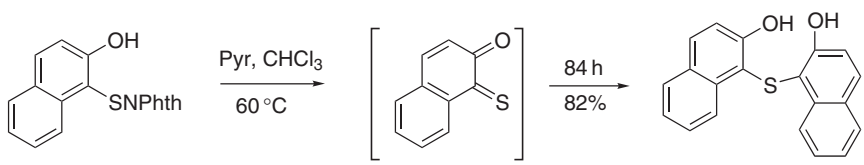
Reaction of a chalcone with bis(dimethylaluminum) sulfide in toluene–dioxane gave the unstable thiochalcone **92**, which yielded a different type of dimer. Here the C=C double bond acted as the 2π-dienophile (Scheme 39). It was suggested that the C=S bond of this thioketone is greatly stabilized by the combined resonance and steric effects of the phenyl group.



92

Scheme 39

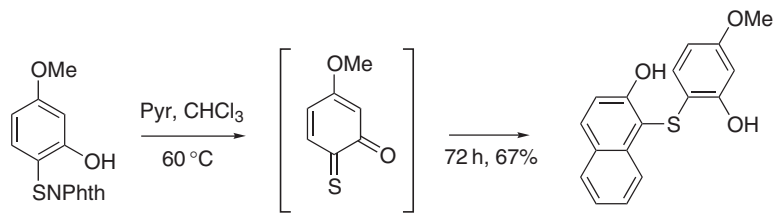
Capozzi and co-workers <2000EJO3653> prepared thioketone **93** by the treatment of thiophthalimide with pyridine in refluxing chloroform (Scheme 40). This was trapped with several activated arenes to give diaryl sulfides in moderate-to-good yields.



93

Scheme 40

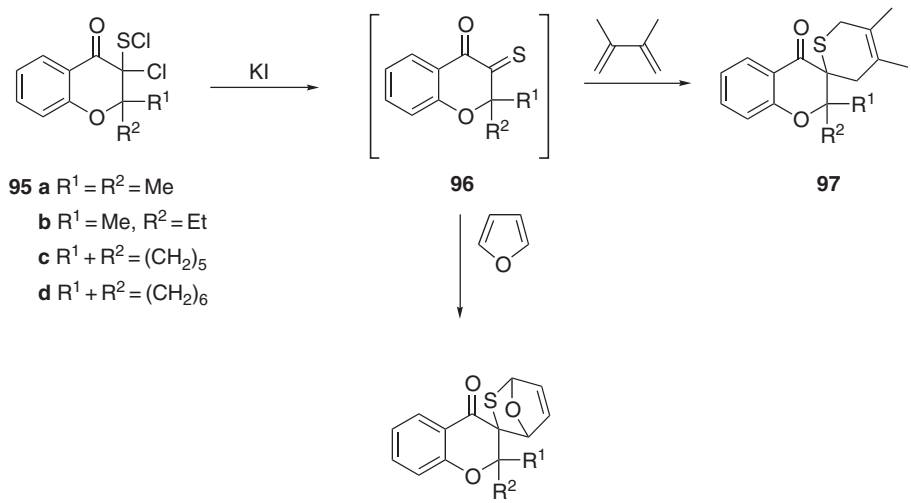
Similarly, the thioquinone **94** was obtained from the thiophthalimide and reacted with β-naphthol (Scheme 41).



94

Scheme 41

Compounds (**95a–95d**), when treated with potassium iodide in the presence of 2,3-dimethyl-1,3-butadiene, gave the cycloadducts **97**, via the intermediate α-*oxo*-thioketones **96** (Scheme 42). Several of the intermediate thioketones also underwent hetero-Diels–Alder reaction with furan to give the cycloadducts **98**.



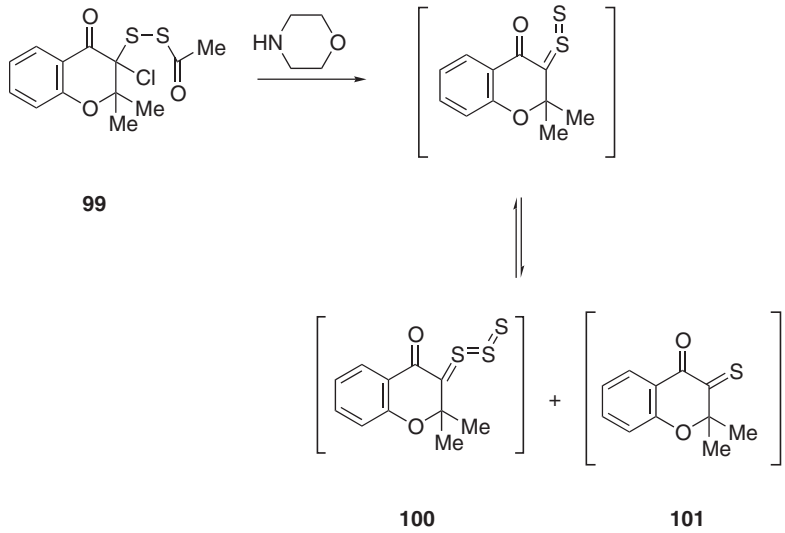
Scheme 42

Senning and co-workers <1998JOC9840> reported a trithiolane synthesis from the reaction of α-chlorosulfenyl disulfide with morpholine (Scheme 43). The thiosulfine underwent a disproportionation reaction to give the thione **101** and thione disulfide **100**, which combine to form the trithiolanes.

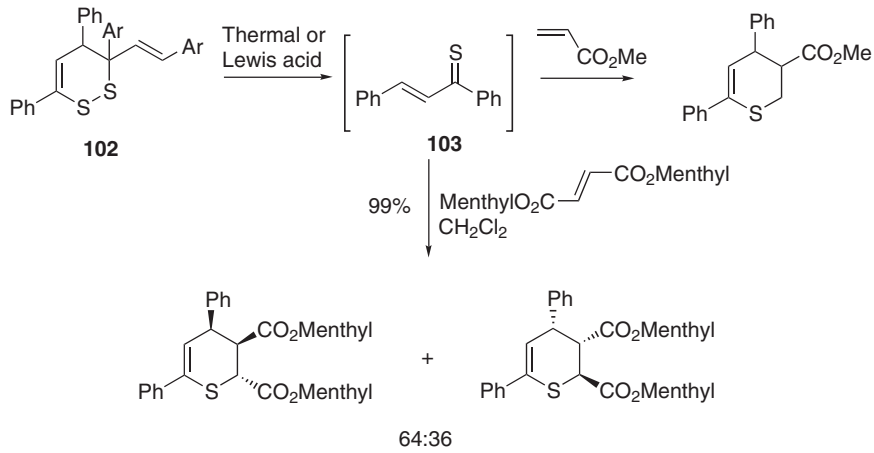
Thermal and Lewis -acid-promoted reaction of thiochalcones **103**, obtained from the disulfide **102** with dimethyl or dimenthyl fumarate gave two 3,4-*cis*-cycloadducts in good yield. The diastereoselectivities were, however, modest (Scheme 44) <1996JCS(P1)1897, 1996JCS(P1)1359>.

Alkenyl thioketones have been accessed by flash vacuum pyrolysis (FVP) of alkenyl, allyl, or propargyl sulfides <1999EJO869>. Thus, FVP of the sulfide **104** at 800 °C generated the thioketone **105** by a retro-ene pathway. The β,γ-unsaturated thioketone isomerized to the thermodynamically more stable α,β-unsaturated product **106** (Scheme 45). Similarly, the cyclohexenyl sulfide **107** at 700 °C gave, after expulsion of propene in a retro-ene step, the unsaturated thioketone **108**, which tautomerized to the more stable conjugated enethiol form (Scheme 46).

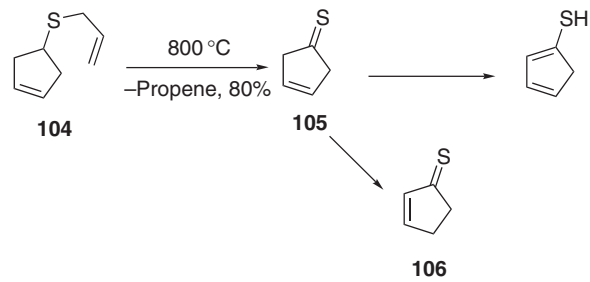
The α,β-unsaturated thioketone **111** was prepared by FVP of either the allyl **109** or propargyl **110** sulfides (Scheme 47). Heating the allyl sulfide at 600 °C gave, after retro-ene reaction, the cyclohexenyl thioketone, also furnished from the propargyl sulfide after the explusion of allene at 550 °C <1997TL8707>.



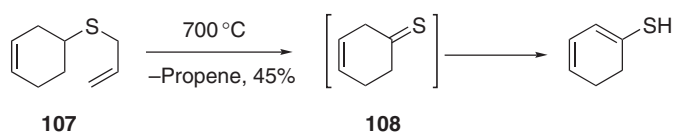
Scheme 43



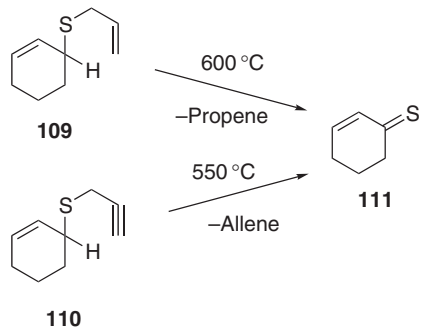
Scheme 44



Scheme 45

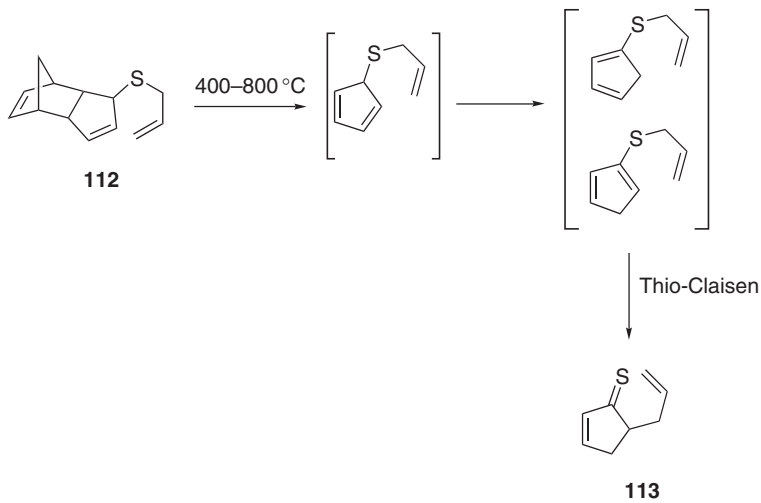


Scheme 46



Scheme 47

Thermolysis of sulfide **112** was reported to be extremely easy with 50% of the starting material already cleaved at the modest FVP temperature of 400 °C (Scheme 48). Cyclopentadiene was quantatively obtained and the absence of propene at any temperature between 400 and 800 °C, ruled out a pathway leading to cyclopentadienethione by retro-Diels–Alder and retro-ene reactions. An intense purple color, which rapidly faded upon warming, was observed during the FVP, and characterization of the product revealed it to be 5-allylcyclopent-2-enethione **113**. Presumably, the initially formed sulfide isomerizes into the more stable isomers, one of which undergoes in turn a thio-Claisen rearrangement.

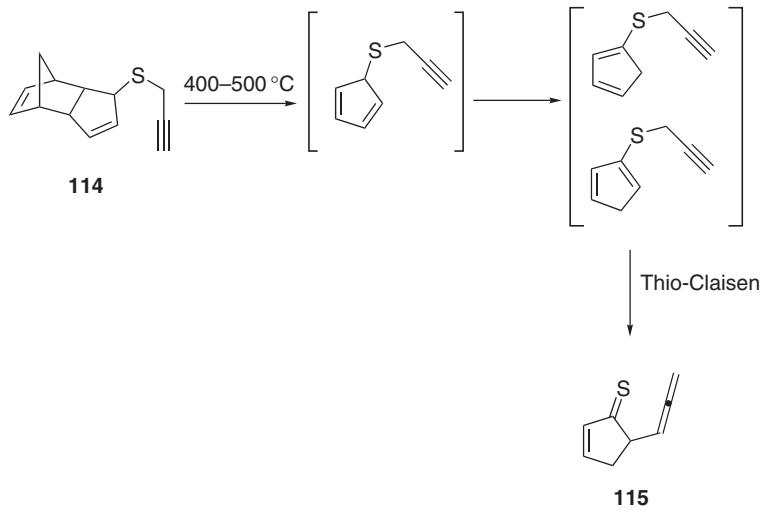


Scheme 48

Propargylic sulfide **114** behaved similarly to the allylic one (Scheme 49). The retro-Diels–Alder cleavage was reported to be even easier (75% after FVP at 400 °C) and retro-ene cleavage was not noted since the formation of allene was not detected. FVP was complete at 500 °C and 5-allenylcyclopent-2-enethione **115** was obtained <2000PS135>.

3.08.3.2.2 Thioketones bearing an α,β-aryl or hetaryl substituent

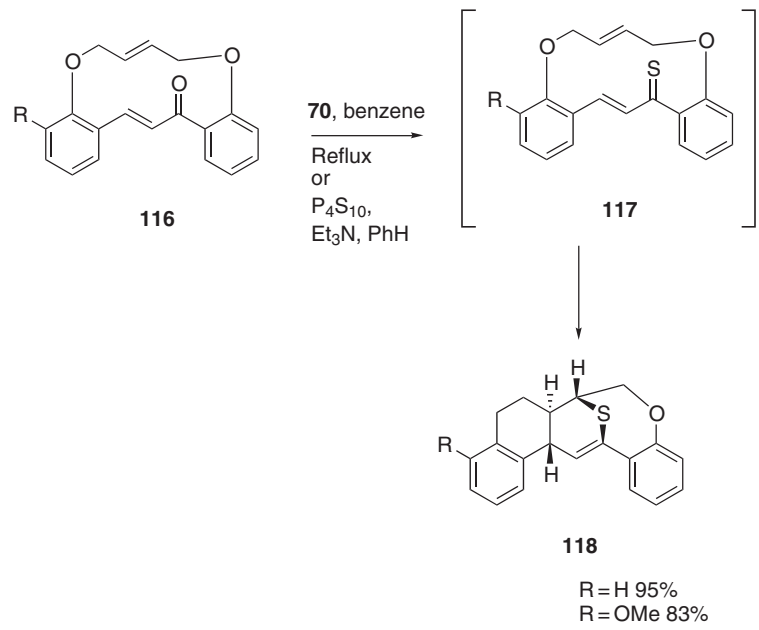
Alkyl aryl thioketones are less stable than diaryl thioketones, but both are usually formed by direct thionation. Lawesson's reagent is a popular choice, and recently a range of diaryl thioketones have been rapidly accessed using microwave activation.



Scheme 49

(i) Simple alkenyl aryl thioketones

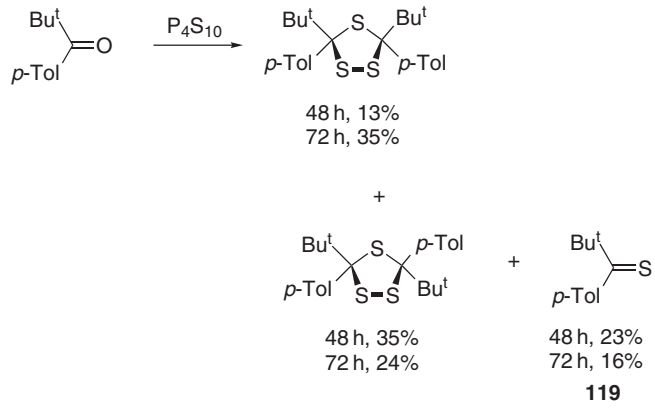
Macrocyclic thioketone **117** was generated by thionation of the corresponding ketone **116** with **70** in refluxing benzene, and immediately underwent a transannular hetero-Diels–Alder reaction to afford the cycloadduct **118** in 95% yield (Scheme 50).



Scheme 50

Ketone **116** (R = OMe) was converted into the thioketone with P_4S_{10} and a catalytic amount of triethylamine since unwanted side reactions occurred with **70**. The cycloadduct was formed in 83% yield <1996SL72>.

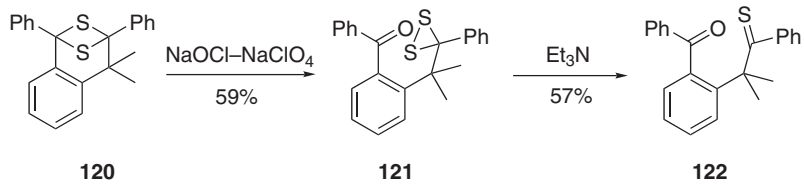
Thiopivalophenone **119** was synthesized by sulfurization of pivalophenones with tetraphosphorus decasulfide (Scheme 51). Investigation of this reaction suggested the formation



Scheme 51

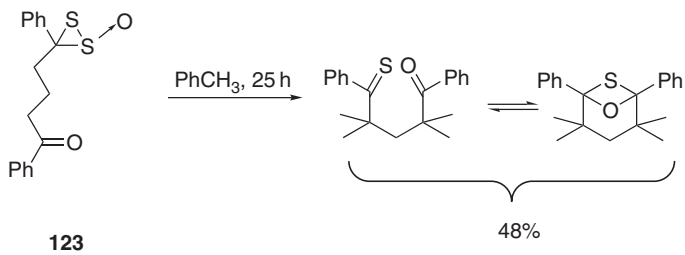
of *cis*- and *trans*-1,2,4-trithiolanes. Prolonged heating resulted in the formation of *trans*-trithiolane. It was suggested that both the isomers interconvert in refluxing toluene via a thione-*S*-sulfide intermediate <2000CC1535>.

The aryl-substituted thioketone **122** was accessed from the unsymmetrical bicyclic 1,3-dithietane **120** by first converting it into the dithiirane **121** with sodium hypochlorite-sodium chlorate, and then treating this compound with triethylamine (Scheme 52) <1997BCJ509>.



Scheme 52

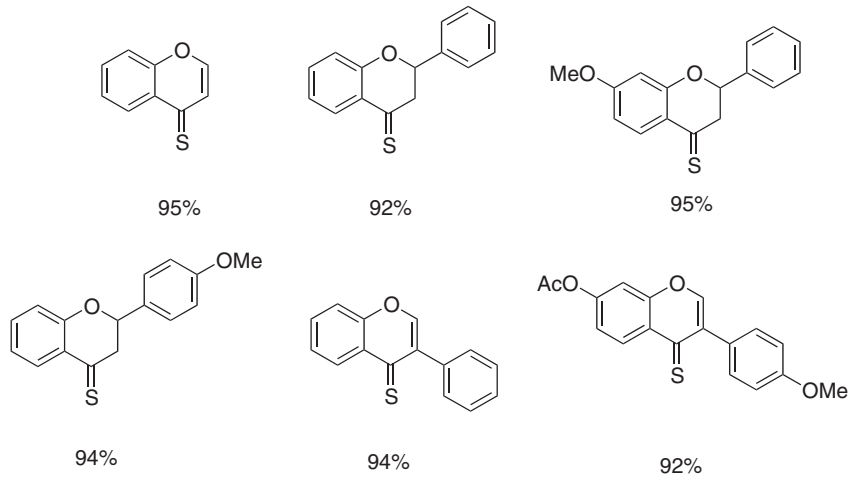
Additionally, the same group found that heating a solution of the dithiirane oxide **123** in toluene for 25 h gave the thioketone and the 6-oxa-7-thiobicyclo[3.3.1]heptane, which are in equilibrium with one another (Equation (18)).



(18)

(ii) Cross-conjugated, electronically stabilized aryl thioketones

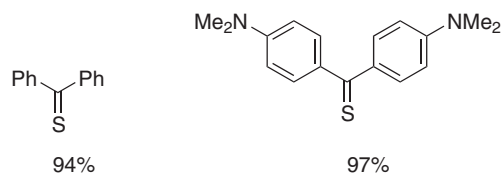
Varma and Kumar <1999OL697> have reported that microwave irradiation is extremely effective for the direct sulfuration of a series of carbonyl compounds (Equation (19)). In addition, solvent-free conditions were employed and the carbonyl compound was simply mixed with Lawesson's reagent **70** and heated in a microwave for only 3–4 min.



(19)

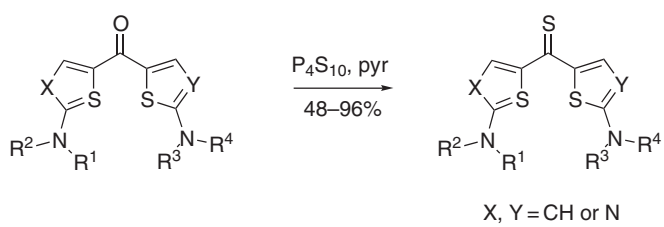
(iii) Diaryl thioketones

(a) Sulfuration of aryl ketones. The direct conversion of a carbonyl into a thiocarbonyl group is widely used for the preparation of aryl thioketones. Lawesson's reagent **70** is a popular choice, as is phosphorus pentasulfide. Curphey <2002JOC6461> showed that combination of phosphorus pentasulfide and HMDSO efficiently converted benzophenone and Michler's ketone into their thio-analogs (Equation (20)). Yields were almost identical to those obtained with Lawesson's reagent, and superior to those obtained with P_4S_{10}. Additionally, it was noted that the P_4S_{10} and HMDSO combination reaction gave products that were easier to purify (generally by column chromatography), than the products obtained by thionation with Lawesson's reagent.



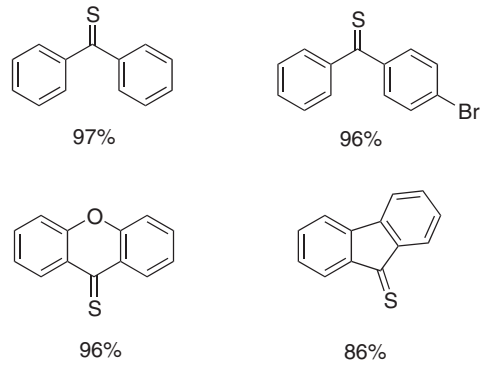
(20)

P_4S_{10} alone was used to convert several *N,N′*-persubstituted bis(2-amino-5-thienyl)ketones and their thiazole analogs, into their thioketone analogs (Equation (21)). Yields of the direct thionation were generally good <2001PS185>.



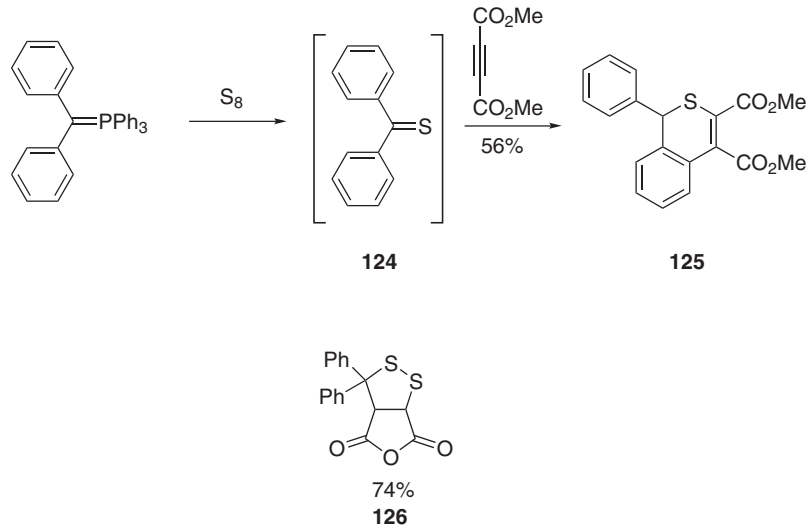
(21)

The use of microwaves has become an area of interest for the synthesis of a wide variety of compounds and efficient functional group transformations under solvent-free conditions. Varma and Kumar <1999OL697> accessed a variety of thioketones by simply mixing the carbonyl compound with Lawesson's reagent (0.5 equiv.) and then irradiating the mixture under solvent-free conditions. The desired thioketones were obtained in only 3–4 min and in excellent yield (>90%) (Equation (22)).



(22)

(b) Sulfuration of aryl ketone derivatives. Okuma and co-workers <2000H2753> synthesized thiobenzophenone **124** by the reaction of triphenylphosphorane with excess sulfur. The product **124** was trapped with dimethylacetylene dicarboxylate to give the cycloadduct **125** (Scheme 53). However, this result appears anomalous since reaction of the triphenylphosphorane with elemental sulfur gave the disulfide **126** when the transient thioketone was trapped with maleic anhydride: this was postulated to be formed from the thiocarbonyl-*S*-sulfide.



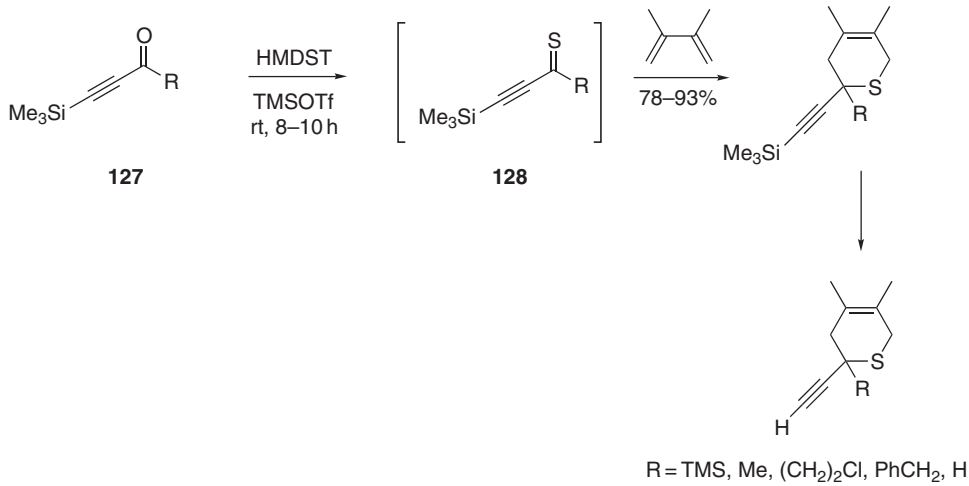
Scheme 53

3.08.3.2.3 Thioketones bearing an α,β-alkynic bond

In addition to reporting the first synthesis of a thioaldehyde bearing an α,β-alkynic bond, Capperucci and co-workers <1999SL1739> also prepared a series of thioketones with α,β-alkynic bonds. Thus, treatment of the ketone **127** with HMDST in the presence of TMSOTf furnished the thioketone **128**, which could be trapped with 2,3-dimethyl-1,3-butadiene or cyclohexadiene to give the cycloadducts in good yield (78–93%) (Scheme 54). It was noted that the use of $CoCl_2{\cdot}6H_2O$ gave a complex mixture of products and was therefore not used.

3.08.4 THIOALDEHYDE AND THIOKETONE FUNCTIONS FURTHER SUBSTITUTED ON SULFUR

As a consequence of the availability of sulfur *d*-orbitals to participate in bonding, a range of compounds exist in which the sulfur atom of the thiocarbonyl group is further substituted. As with COFGT (1995), only those compounds for which the usual representation contains a C═S bond will be discussed.



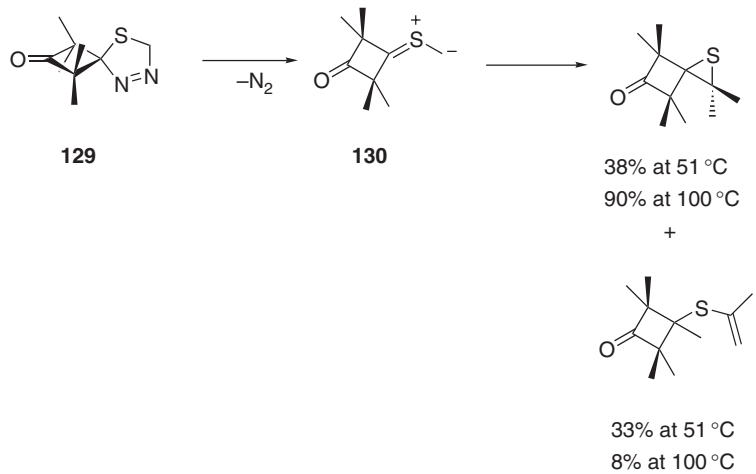
Scheme 54

3.08.4.1 Two-coordinate Sulfur Functions

3.08.4.1.1 Thiocarbonyl ylides

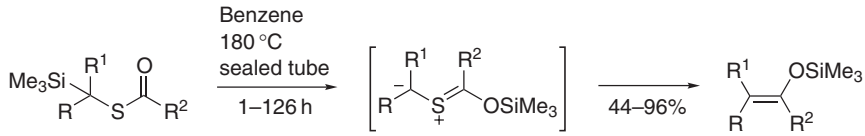
Thiocarbonyl ylides are active 1,3-dipoles in cycloadditions. A general synthesis consists of the thermal elimination of nitrogen from 2,5-dihydro-1,3,4-thiadiazoles, which are accessible by 1,3-dipolar cycloadditions of diazoalkanes to C=S double bonds. This approach is limited since thioaldehydes are generally too reactive to be used. Thiocarbonyl ylides can be prepared from silylated precursors, and thioformaldehyde-*S*-methylide has been prepared and intercepted. 1,3,4-Thiadiazoles prepared from aliphatic thioketones can be isolated, and extrusion of nitrogen carried out in the presence of a dipolarophile <2000EJO1695>. Treatment of a vinyldiazo compound with $Rh_2(OAc)_4$ in the presence of a thioketone is a method for generating vinylthiocarbonyl ylides <1999TL8117>.

Mloston has explored the synthesis and reactions of thiocarbonyl ylides <1999PJC635, 2000H475, 1997HCA1992, 1998HCA285, 2002HCA1644>. Extrusion of nitrogen from thiadiazoles is also a popular approach, for example, thiocarbonyl ylide **130** can be generated from the thiadiazole **129** (Equation (23)) <2001HCA1805>.



(23)

Another method of thiocarbonyl ylide generation was described by Komatsu and co-workers <2003JOC6164>, and involves the 1,4-silatropy of *S*-silylbenzyl thioesters (Scheme 55). Thus, heating a solution of the thioester **131** in benzene at 180 °C in a sealed tube gave, via the intermediate thiocarbonylylides **132**, a range of silyl enol ethers.



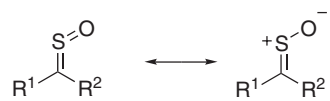
131 132

Scheme 55

Huisgen <2003CEJ2256> has recently published work on the regiochemistry of 1,3-dithiolanes obtained from thiocarbonyl ylides and thiones.

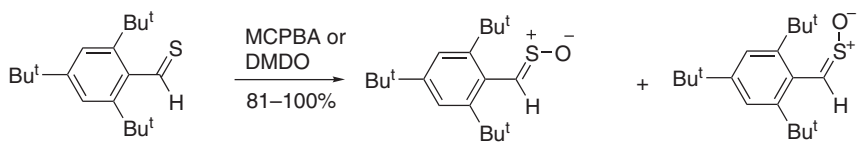
3.08.4.1.2 Sulfines

Sulfines, also known as thiocarbonyl-*S*-oxides, are usually prepared by direct oxidation of the corresponding thioketone. The heterocumulene structure **133** is used by some authors, but it is assumed from theoretical considerations that the thione *S*-oxide structure **134** is a better description.



133 **134**

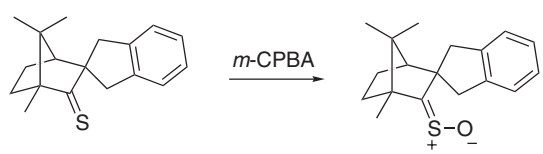
A variety of oxidizing agents have been employed; MCPBA is the most commonly used <1999CL695> but ozone and *N*-sulfonyloxaziridines have also been successfully applied. The first stable aromatic thioaldehyde, 2,4,6-tri-*t*-butylthiobenzaldehyde has been prepared (*vide supra*) and was treated with MCPBA to give a mixture of isomeric sulfines (*E*)/(*Z*)-**135** (Scheme 56).



(*E*)-**135** (*Z*)-**135**

Scheme 56

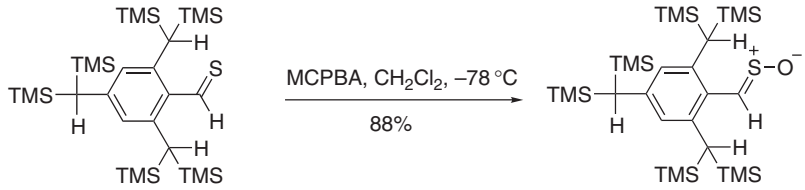
Shimida and co-workers furnished the camphor-based sulfine **136**, by direct oxidation of the thioketone (Equation (24)).



(24)

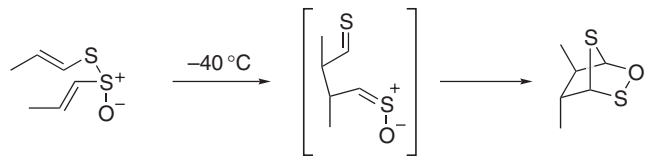
136

MCPBA has also been used to form the sulfine **137** from the thioaldehyde. A solution of the aldehyde in dichloromethane was oxidized to the (*E*)-sulfine at −78 °C in excellent yield (Equation (25)) <1997CEJ62>. Formation of only the (*E*)-sulfine was rationalized on the basis that it is the kinetic product, since (*Z*)-sulfines are thermodynamically more stable than (*E*)-sulfines.



137

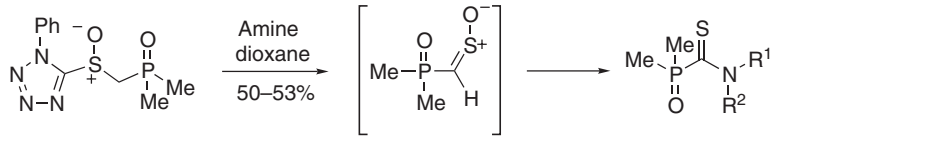
The reagent combination of hydrogen peroxide with a catalytic amount of methyltrioxorhenium (MTO) oxidizes a range of aromatic thioketones, generally with yields of over 90% <1999JOC6935, 1999JOC6374>. Recently, Block and co-workers in their investigations into *Allium* chemistry, found that flow pyrolysis of 2-methyl-2-propyl-1′-propenyl sulfoxide gave a 98:2 mixture of (*Z*)- and (*E*)-propanethial *S*-oxide <1996JACS7492>. Block and co-workers also obtained the ((*E*),(*E*))-thiosulfinate **138**, and suggested that thio-Claisen rearrangement gave the (*Z*)-sulfine **139**, which underwent 1,3-dipolar cycloaddition onto the thioaldehyde to give the observed product (Scheme 57).



138 **139**

Scheme 57

Morita and co-workers <1999JOC6730, 1999TL2327> found that thermolysis of phenacyl sulfoxides bearing heterocycles such as thiadiazole, triazole, or tetrazole gave the corresponding sulfines **140**, which reacted with an added amine to give the thioamide product (Scheme 58). Yields for this reaction were variable: typically the thioamide was formed in ~50% yield when the amine used was aniline, benzylamine, piperidine, morpholine, or pyrrole, whereas none of the thioamide was observed when diisopropylamine or imidazole was used.

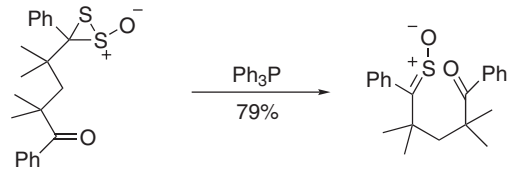


140

Amine = $PhNH_2$, $PhCH_2NH_2$, $(Pr^i)_2NH$
piperidine, morpholine, pyrrole, imidazole

Scheme 58

Nakayama and co-workers <1997BCJ509> have reported that the divalent sulfur atom of the dithiirane-*S*-oxide was readily eliminated by the treatment with 1.5 equiv. of Ph_3P in dichloromethane at room temperature to give the sulfine **141** in 79% yield, along with $Ph_3P{=}S$ (Equation (26)). The sulfine could also be accessed by heating a solution of the dithiirane in toluene for 25 h. However, the latter approach furnished the sulfine in only 14% yield.



(26)

141

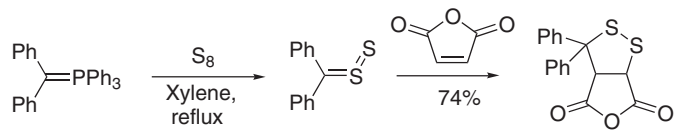
A theoretical study of sulfines and sulfenes with a view to establish their similarities and differences in structure and reactivity has recently been published <1997PS441>, and additionally the 1,3-dipolar activity of an aliphatic sulfine in cycloadditions has been studied <1996JOC6570>.

Kappert and co-workers <1997LAR2519> have reported on the synthesis, structure, conformation, and thermochemistry of dimesityl sulfine, obtained by MCPBA oxidation of the thioketone. The sulfine was found to be fairly stable, and isolated as a crystalline solid.

Metzner and co-workers have reported on the chemoselective synthesis of aliphatic sulfines by direct oxidation of dithioesters <1995BSF67> and reviewed new sulfines and their chemistry <1996PAC863>.

3.08.4.1.3 Thiosulfines

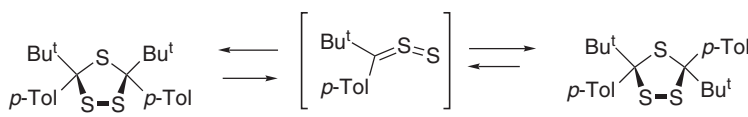
Thiosulfines, or thiocarbonyl-*S*-sulfides, are highly reactive species which can be accessed in a convienient "unzipping" reaction of α-chloroalkanesulfenyl chlorides with morpholine via acetyl-α-chloroalkyl disulfides <1996MFC909, 1998JOC9840>. As mentioned earlier, Okuma and co-workers found that the treatment of triphenylphosphorane with excess elemental sulfur, and trapping the intermediate with maleic anhydride, gave the cycloadduct **126**, which was proposed to be formed from the intermediate thiosulfine **142** (Equation (27)).



(27)

142 **126**

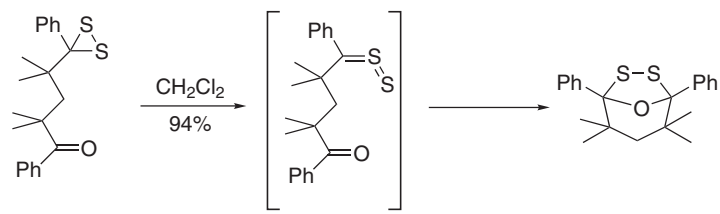
As mentioned above, the *cis*- and *trans*-isomers of the 1,2,4-trithiolanes interconvert via the thiosulfine **143** (Scheme 59).



143

Scheme 59

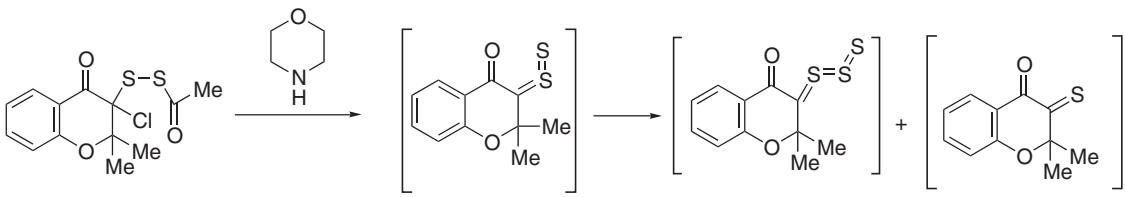
Additionally, a thiosulfine intermediate has been suggested for the formation of the 1,3,4-oxadithiolane **146** from the dithiirane **144**. It was suggested that the product arose by cycloaddition of the thiosulfine onto the ketone moiety (Scheme 60). Even though the concentration of the thiosulfine is low, the reaction is presumed to occur because the product is far more thermodynamically stable than the dithiirane <1997BCJ509>.



144 **145** **146**

Scheme 60

A thiosulfine intermediate **147** has also been postulated for the formation of the thioketone **101** and the *S*-disulfide **100** from the disulfide **99**, after treatment with morpholine (Scheme 61) <1998JOC9840>.



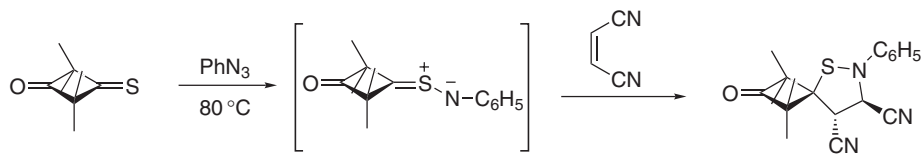
147 **100** **101**

Scheme 61

The formation and chemistry of thiosulfines has recently been reviewed <1997T939>.

3.08.4.1.4 Thiocarbonyl-S-imides

Very little has been published on the synthesis of thiocarbonyl-*S*-imides in recent years. One approach, used by Mloston and co-workers, utilized the reaction of the thioketone **148** with phenyl azide, which generated the thiocarbonyl-*S*-imide **149** which was trapped with dimethyl acetylenedicarboxylate to give spiro-product **150** (Scheme 62). Mloston has published several papers on the reactivity of thiocarbonyl-*S*-imides <1996PJC880, 1997PS463, 1999PJC683>.



148 **149** **150**

Scheme 62

Mloston has also investigated the reactions of thioketones with methyl azidoacetate which gave, after extrusion of nitrogen, a glycinate product and trithiolane **151** and dithiazolidine **152**. A mechanism involving an intermediate thiocarbonyl-*S*-sulfide and a thiocarbonyl-*S*-imide was postulated (Scheme 63).

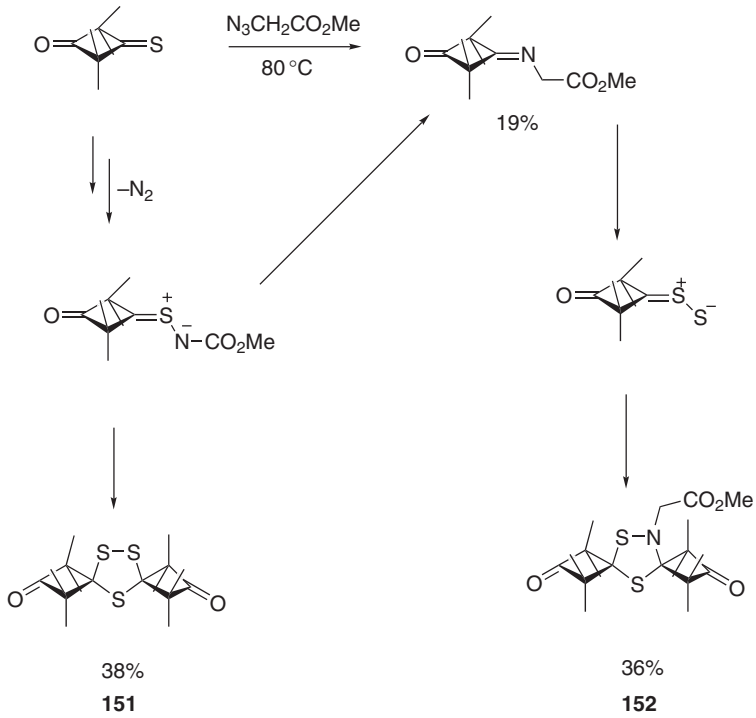
Mloston has also reported on the reactivity of a fluorinated thiocarbonyl-*S*-imide <2000T4231>.

3.08.4.1.5 Metal complexes of thioaldehydes and thioketones

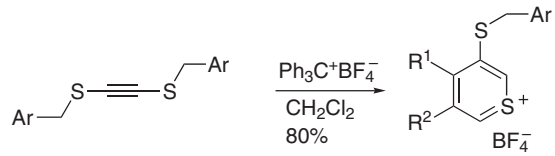
No new material has been published in this area during the scope of this review and, as with COFGT (1995), a detailed discussion of their preparation is inappropriate for this review.

3.08.4.1.6 Thiopyrylium salts

Thiopyrylium salts are usually stable and can be accessed from thiopyrans by hydride abstraction, by a disproportionation or by *S*-methylation of thiopyran-4-thiones. Zimmerman and co-workers have published work on the chemistry of thiopyrylium salts <1996JHC1717, 1999JHC813>. Such salts have been obtained by intramolecular cyclization of bis(arylmethylthio)acetylenes (Equation (28)). For example, treatment of dithioacetylenes with tritylium tetrafluoroborate gave the thiopyrylium salts in good yield in a one-pot process <1999PS433>.



Scheme 63



(28)

3.08.4.2 Three-coordinate Sulfur Functions

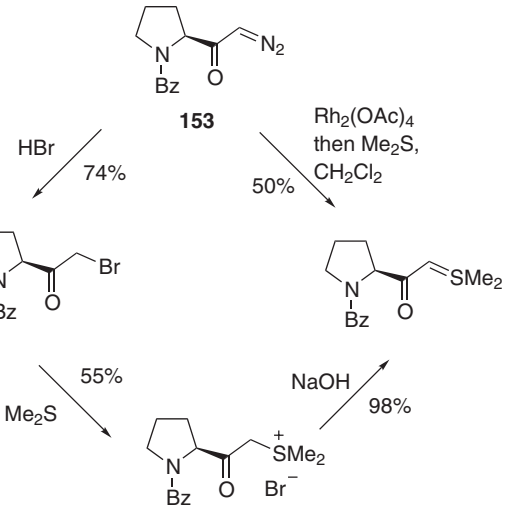
3.08.4.2.1 Sulfonium ylides

A widely used method for the synthesis of sulfonium ylides is the reaction of a diazo compound with a sulfide under photolytic, thermal, or base-catalyzed conditions. Direct nucleophilic displacement of an α-bromoketone with dimethyl sulfide, and elimination of HBr from the resulting salt is another method <1996MI156, 1997MI1904, 2002MI189, 1998MI2304>.

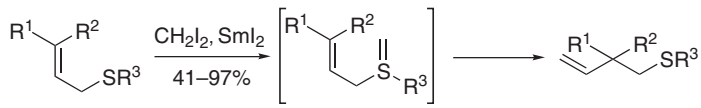
A Russian group has shown that the diazo compound **153** (obtained by the addition of diazomethane to the corresponding ester or acid chloride) gave the thiocarbonyl ylide via two related routes (Scheme 64). Treatment of the diazo ketone with $Rh_2(OAc)_4$ and Me_2S in dichloromethane at 40 °C gave a 50% yield of the ylide directly. Alternatively, the diazo compound could be treated with HBr and then Me_2S to give the same compound in similar overall yield <2002MI2230>.

Recently, Kunishima and co-workers <1998SL1366> have prepared sulfonium ylides by the treatment of allylic sulfides with diiodomethane and samarium(II) iodide. [2,3]-Rearrangement led to the sulfides in yields of 41–97% (Scheme 65).

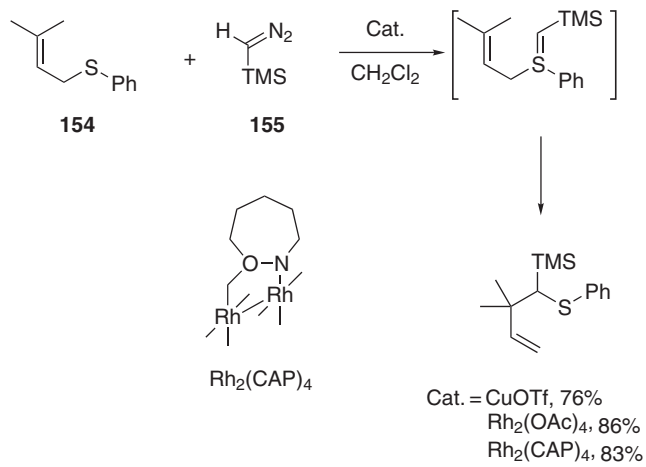
Vranken and Carter have reported on the metal-catalyzed formation, and subsequent [2,3]-sigmatropic rearrangement of sulfonium ylides. The best yields were obtained for the allylic sulfide **154** and the diazo compound **155** in the presence of copper(I) triflate. Various rhodium catalysts were also used, with the best yields of product obtained with Rh_2OAc_4 and $Rh_2(CAP)_4$ (Scheme 66) <1999TL1617>.



Scheme 64



Scheme 65

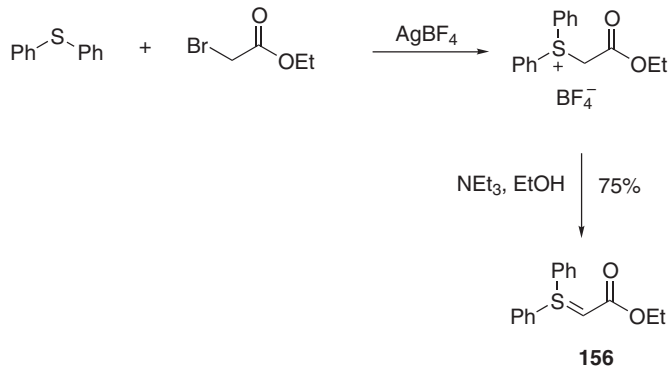


Scheme 66

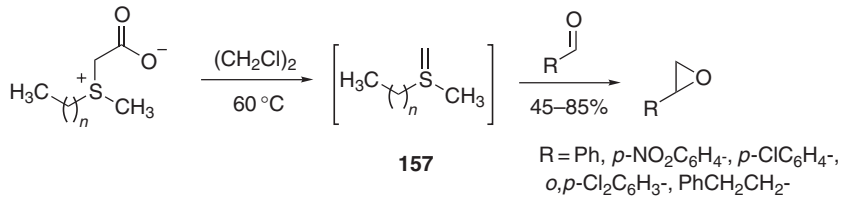
Mloston has utilized a modification of an approach used by Nozaki and co-workers. Reaction of diphenyl sulfide with ethyl bromoacetate in the presence of $AgBF_4$ in the dark afforded the sulfonium salt, which was deprotonated with triethylamine in ethanol at 0 °C to give the ylide **156** in 75% yield (Scheme 67) <1999HCA935>.

Recently, Forbes and co-workers have published a novel protocol for the generation of sulfonium ylides via the decarboxylation of a carboxymethylsulfonium betaine (Scheme 68). The so-formed ylide was reacted with an aldehyde to give the corresponding terminal epoxide. Heating the betaine in dichloroethane at 60 °C led to the expulsion of CO_2 and concomitant formation of the ylide, which reacted *in situ* with the added aldehyde to furnish the desired epoxide <2003OL2283>.

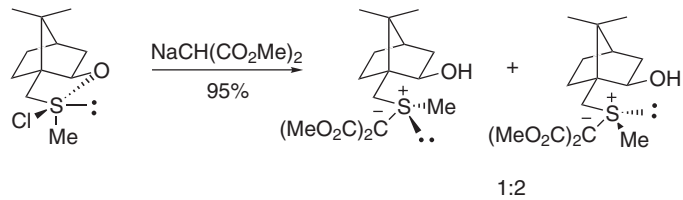
A thiocarbonyl ylide bearing a dimethyl malonate substituent was prepared by nucleophilic addition of the anion onto the chlorosulfurane (Scheme 69). The product was obtained as a mixture of inseparable diastereomers <1997H325>.



Scheme 67



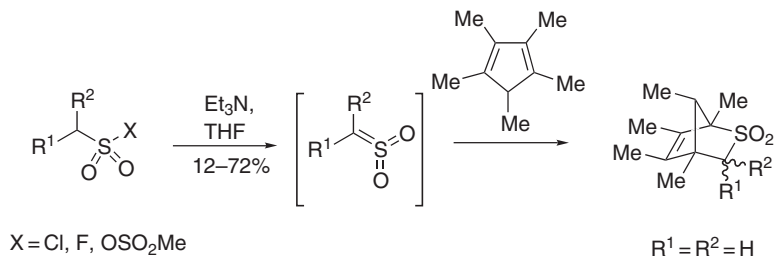
Scheme 68



Scheme 69

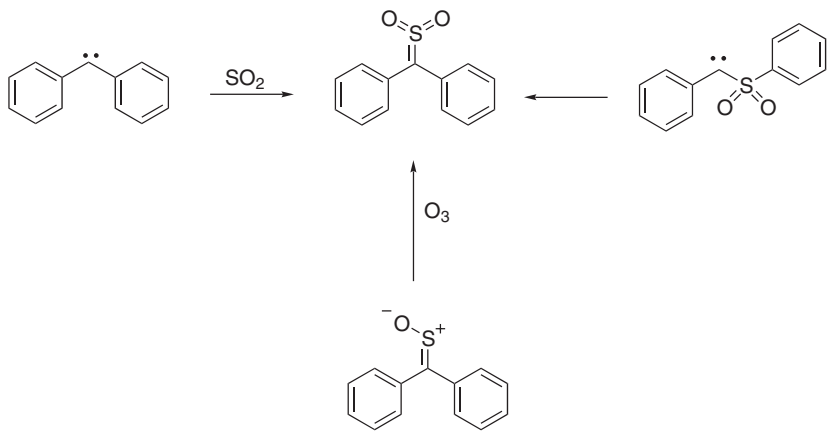
3.08.4.2.2 Sulfenes

Sulfenes are very short-lived species and all attempts to generate a sulfene directly observable by NMR spectroscopy have been unsuccessful. King and co-workers <2000CJC1642> have reported on the preparation of bis(trimethylsilyl)methanesulfonyl and tris(trimethylsilyl)methanesulfonyl chlorides, and their reactions with nucleophiles and bases leading to products formed via the intermediate sulfenes. Opitz and co-workers <1995LA2137> have reported that sulfenes generated *in situ* from sulfonyl chlorides and triethylamine can be trapped with 1,2,3,4,5-pentamethylcyclopentadiene to give the cycloadducts (Scheme 70).



Scheme 70

Sander and co-workers have reported on the synthesis and matrix isolation of diphenylsulfene. Three routes were used: one involved the thermal reaction of diphenylcarbene and SO_2, the second a photochemically induced Wolff rearrangement of a sulfonylcarbene, and the third oxygen-transfer from ozone to diphenylsulfine (Scheme 71) <1997JACS981>.

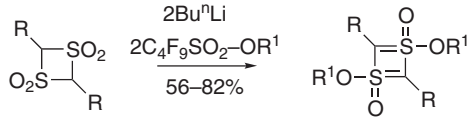


Scheme 71

3.08.4.3 Four-coordinate Sulfur Functions

3.08.4.3.1 Sulfoxonium ylides

The usual methods for the formation of sulfoxonium ylides are similar to those used to generate sulfonium ylides. Sundermeyer and Walch <1996CB161> prepared a range of sulfoxonium ylides by silylation of cyclic methylene disulfones with the silylating agents silyl nonafluorobutanesulfonates (Equation (29)).



R^1 = TBDMS
R^2 = TBDMS or TIPS

(29)

Gais and co-workers <2002JACS10427> have utilized sulfoxonium ylides in their asymmetric synthesis of antihomopropargylic alcohols.

3.08.4.4 Five-coordinate Sulfur Functions

No new examples of five-coordinate sulfur compounds have been reported during the period covered by this review.

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Biographical sketch

Nicholas J. Cooper was born in Pontypool, South Wales in 1978 and gained his B.Sc. degree in chemistry and biochemistry from Cardiff University in 1999. He then undertook a Ph.D. at Cardiff on the reverse-Cope cyclization under the supervision of Prof. David W. Knight. Upon completion of his Ph.D. he joined the Defence Science and Technology Laboratory [DSTL] at Porton Down as a synthetic organic chemist.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 355–396

3.09
Seleno- and Telluroaldehydes and -ketones

L. J. GUZIEC and F. S. GUZIEC Jr.,
Southwestern University, Georgetown, TX, USA

3.09.1 OVERVIEW

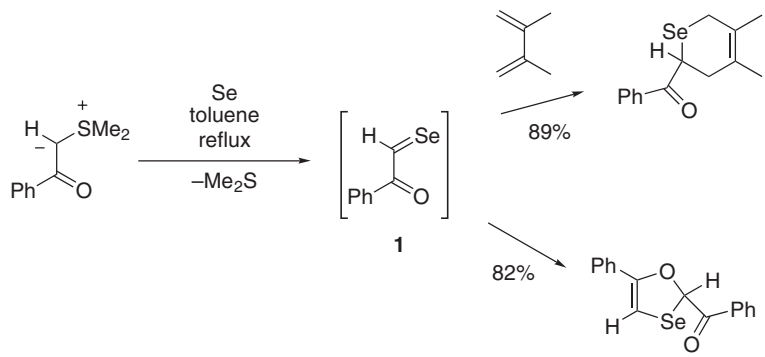
Until relatively recently reports on the chemistry of selenium and tellurium analogs of aldehydes and ketones were quite rare <1995COFGT(3)381>. Since the 1990s significant synthetic advances have made these compounds much more available for study. New reagents have been described which allow for the direct preparation of these selenium and tellurium analogs from the parent oxygen compounds. Some reactions such as the Staudinger chalcogenation have emerged as powerful methods for the preparation of a variety of selones whose cycloaddition chemistry has now been intensively studied. It should be noted that the use of incorrect or ambiguous nomenclature still leads to significant problems in searching the literature for these compounds. Recommended unambiguous nomenclature—selenal, tellural, selone, and tellone—is used throughout this chapter.

3.09.2 SELENOALDEHYDES (SELENALS), RHC=Se

Selenals, the selenium analogs of aldehydes, are much less widely described in the literature than the corresponding oxygen or sulfur analogs. It was only in the mid-1980s that general methods for the generation of these compounds became available. The selenal moiety is extremely reactive, but the selenocarbonyl moiety can be often stabilized by association with metals or conjugatively. Because of the extreme reactivity of unstabilized selenals, these compounds have been typically generated *in situ* and trapped, often as cycloadducts.

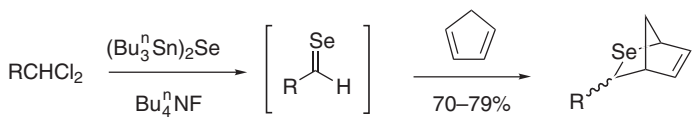
3.09.2.1 Simple Selenals

The most general method for the generation of unstabilized selenals still appears to be the base-promoted elimination of α-silylselenocyanates <1995COFGT(3)381>. A number of related base-promoted methods may also prove to be useful in the preparation of selenals. α-Oxoselenals **1** can be prepared by reaction of carbonyl-stabilized sulfur ylides with elemental selenium followed by *in situ* elimination of dimethyl sulfide. The resulting unstable selenals can be readily trapped by dienes. In the absence of added trapping agents, the selenals react further with the sulfur ylide to afford oxaselenoles (Scheme 1) <1987TL4423>.



Scheme 1

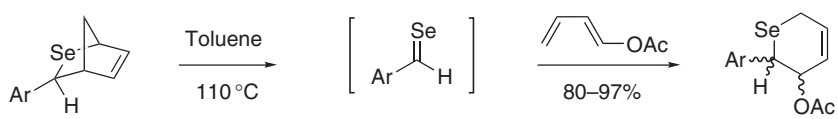
Selenals substituted with electron-withdrawing groups can be prepared by the reaction of the corresponding geminal dihalides with selenium dianion. The most convenient preparative method involves *in situ* generation of Se^{2-} via reaction of bis(tributyltin)selenide with tetrabutylammonium fluoride. The generated selenals were isolated as their cyclopentadiene or 1,3-cyclohexadiene adducts (Equation (1)) <1991TL7427>. Selenobenzaldehyde has been generated and trapped in a similar manner <1996BCJ2235>.



(1)

R = MeO_2C, MeCO, PhCO, NC

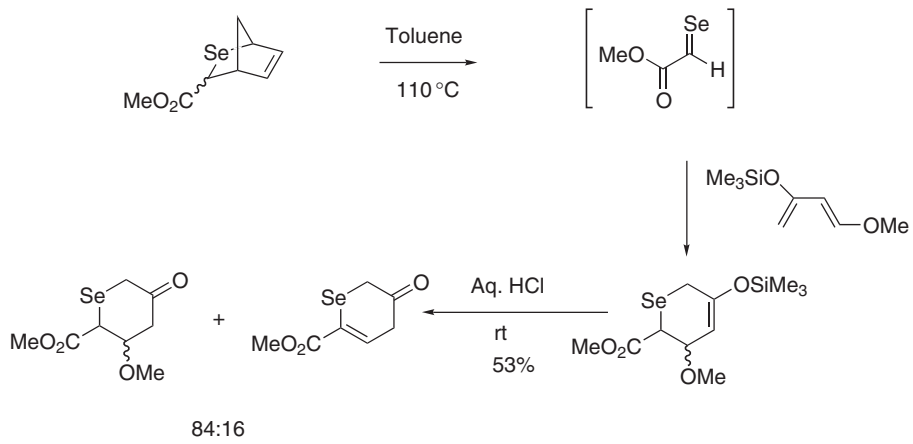
Thermal retrocyclization of selenal cycloadducts can be used to regenerate selenals <1993TL4925>. These compounds can be trapped by electron-rich conjugated dienes such as 1-acetoxy-1,3-butadiene regioselectively and in high yield (Equation (2)). Danishefsky's diene and 1,4-diacetoxy-1,3-butadiene react similarly (Scheme 2) <1998PS599>.



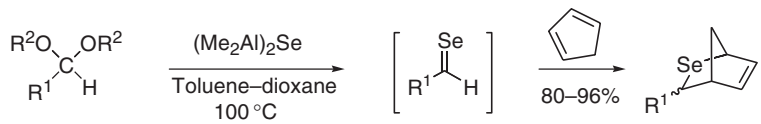
(2)

Ar = Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$

A number of new selenating reagents have also been used for the preparation of selenals. Treatment of aldehyde-derived acetals with bis(dimethylaluminum) selenide at elevated temperatures generates the corresponding selenals which can be trapped as Diels–Alder adducts in good-to-excellent yields (Equation (3)) <1992TL7865>.



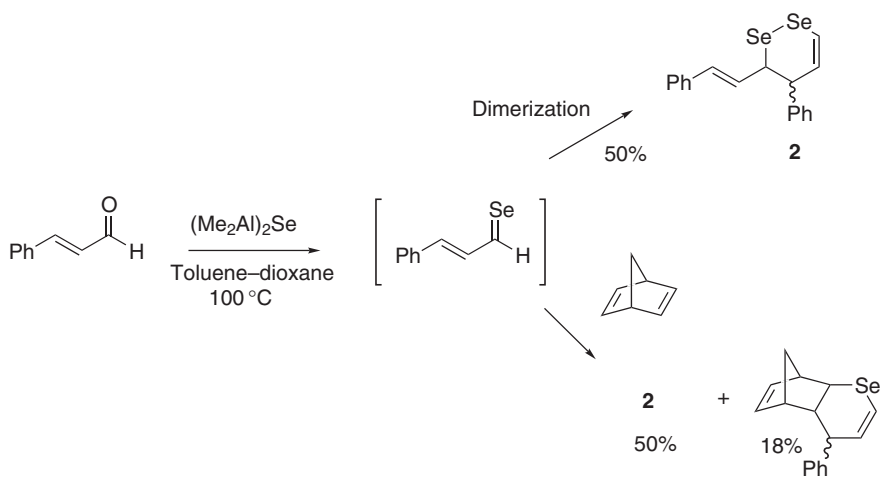
Scheme 2



(3)

R^1 = Ph, $PhCH_2$, Pr^i, n-C_7H_{15}
R^2 = Me, Et

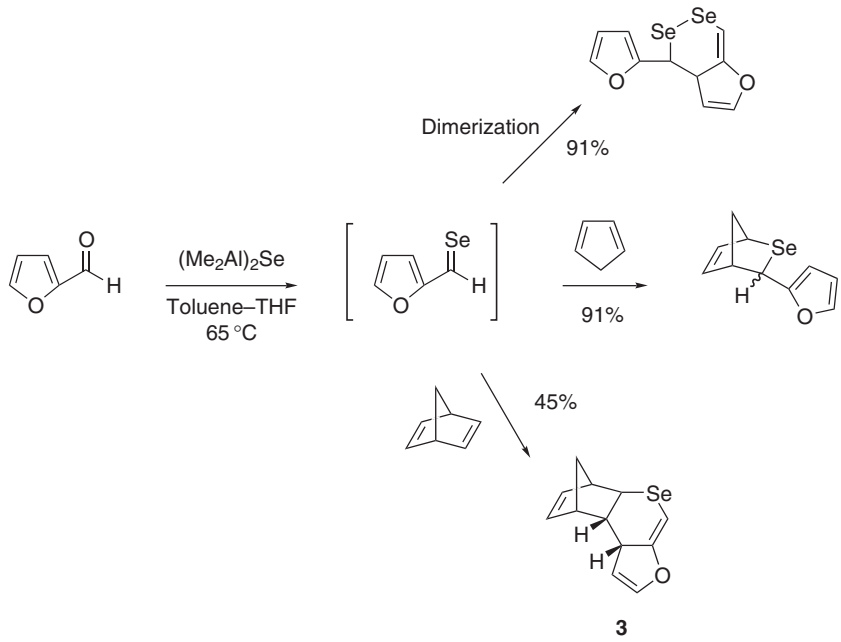
When α,β-unsaturated aldehydes are treated with bis(dimethylaluminum) selenide at elevated temperatures, the resulting selenals undergo [4 + 2]-dimerization to afford diselenin derivatives **2**. This dimerization is regioselective and occurs in a "head-to-head" fashion (Scheme 3) <1992TL3515, 1999JOC1565>. The intermediate selenal can also be trapped by norbornadiene. The selenals derived from furfural and 2-thiophenaldehyde can be generated and trapped as cycloadducts in three different reaction modes (Scheme 4). Besides the above-mentioned dimerization, these selenals react normally with cyclopentadiene at the selenocarbonyl moiety as dienophiles, but with norbornadiene as 4π heterodienes affording tricyclic derivatives such as **3**. Upon heating the dimer retrocyclizes to afford the selenal, which can again be trapped via cycloadditions.



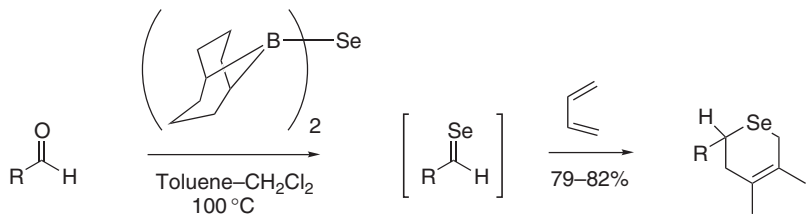
Scheme 3

Treatment of benzaldehyde or *p*-tolualdehyde with bis(1,5-cyclooctanediylboryl) selenide at an elevated temperature in a sealed tube afforded the corresponding selenals, again isolated as their cycloadducts, in good yield. Acetaldehyde required a significantly higher temperature (150 °C) for

the reaction to occur and the selenoacetaldehyde adduct was isolated in much lower yield (32%) (Equation (4)) <1992CL1843>.



Scheme 4

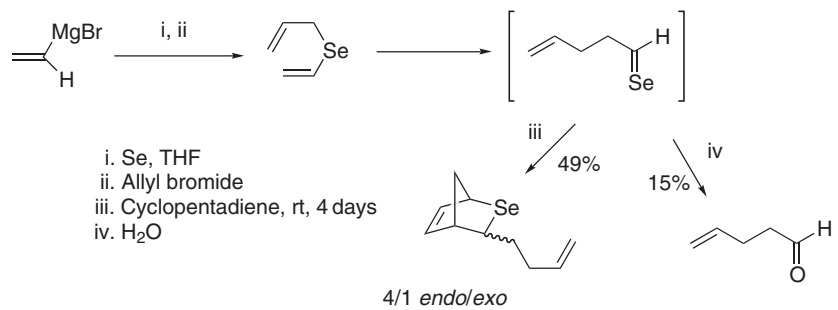


(4)

R = Ph, 4-MeC_6H_4

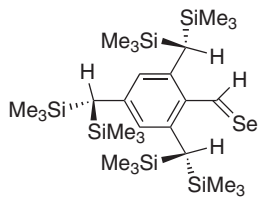
Ω-H-Perfluoroalkanals are reported to react with trimethylselenophosphate at 80 °C to form selenals which co-polymerize with the starting aldehydes. The selenals can be trapped in modest yields as their corresponding cycloadducts <1991JOU348>.

The seleno-Claisen rearrangement of allyl vinyl selenide affords the intermediate unsaturated selenal which can be trapped as a diene adduct or hydrolyzed to 4-butenal (Scheme 5) <1992CC1680>. This heteroatom-assisted [3,3]-sigmatropic rearrangement has been extended to other allyl alkenyl selenides and tellurides (cf. Section 3.09.3) <1995CL135>.

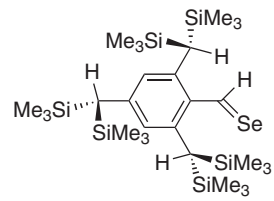


Scheme 5

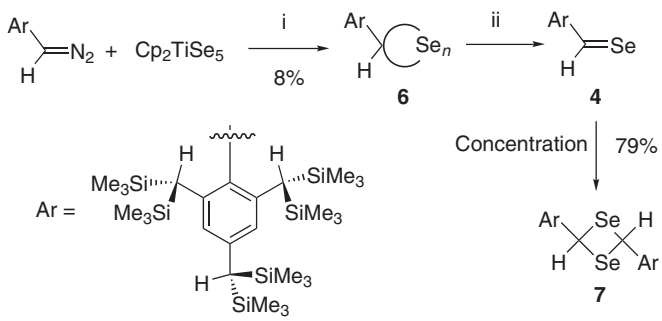
Very few simple selenals are stable enough to be isolated. These stable selenals have the selenocarbonyl moiety shielded by an extremely sterically hindered group (chapter 3.09.2.1 of <1995COFGT(3)381>). Stable rotational isomers of 2,4,6-tris[bis(trimethylsilyl)methylbenzaldehyde] **4** and **5** have been recently isolated <1996AG(E)660, 1997T12167, 1998PS633>. Treatment of the substituted diazo compound with titanocene pentaselenide and a catalytic amount of CuCl afforded a mixture of cyclic polyselenides **6** in low yield. Deselenation of **6** using triphenylphosphine at room temperature afforded the selenal **4**, which dimerized to a 1,3-diselenetane **7** upon concentration (Scheme 6). Heating the dimer at 45 °C in THF afforded an equilibrium mixture containing both **4** and its rotamer **5** (Scheme 7). Rotamer **5** could be isolated by flash chromatography at −20 °C in 15% yield. It is stable as a solid even in open air but slowly isomerizes to rotamer **4** in solution. Rotamer **4** (and also the equilibrium mixture of rotamers) reacts with both 2,3-dimethyl-1,3-butadiene and mesitonitrile oxide to afford cycloadducts derived from reaction of **4** (Scheme 8). When the rotamer mixture was heated in deuterated benzene, quantitative intramolecular cyclization to the benzoselenolane **8** was observed. This is analogous to the reaction previously observed in the case of 2,4,6-tri-*t*-butylselenobenzaldehyde. The increased stability of **5** apparently is due to more efficient shielding of the selenocarbonyl group by the rotation of the two bulky trimethylsilyl groups at an elevated temperature.



4

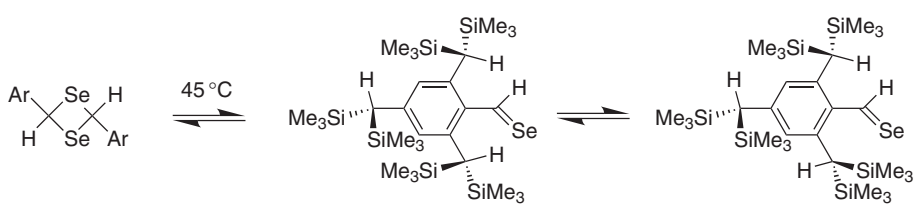


5



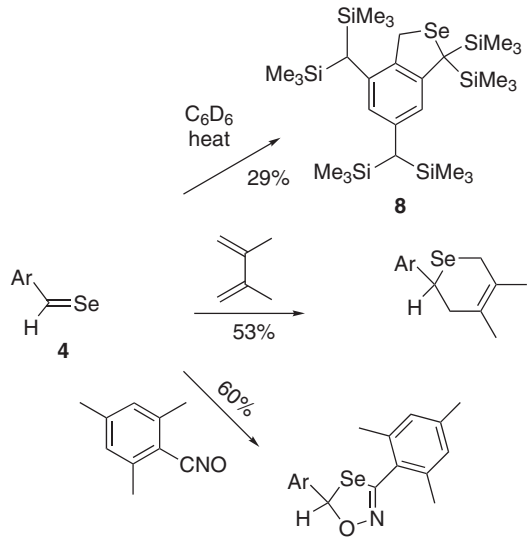
i. CuCl (cat.), THF, rt; ii. Ph_3P, THF, rt

Scheme 6



4 **5**

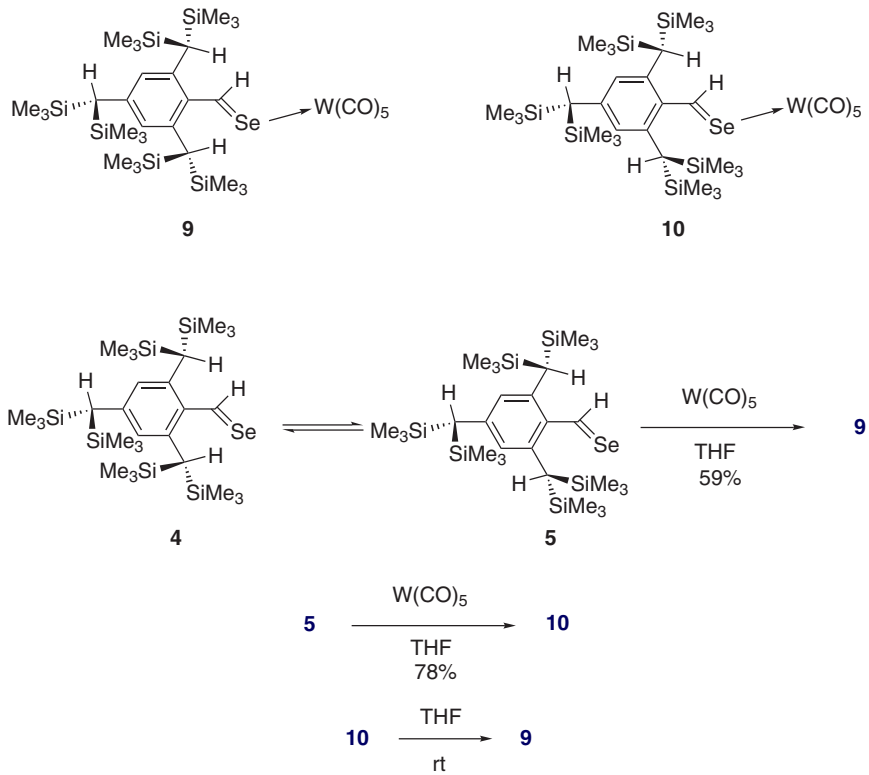
Scheme 7



Scheme 8

3.09.2.2 Metal-stabilized Selenals

Metal complexation can significantly stabilize the selenocarbonyl group. The preparations of a number of new metal complexes of selenals have been reported. These include tungsten complexes **9** and **10** of the previously mentioned sterically hindered selenals **4** and **5** <1996AG(E)660, 1997T12167, 1998PS633>. Complex **9** could be prepared by reaction of selenal **4** or the equilibrium mixture of **4** and **5** with the THF complex of tungsten pentacarbonyl (Scheme 9). Both crystalline complexes show significantly increased stability relative to the uncomplexed selenals. Complex **10** almost completely isomerized to **9** when dissolved in THF at room temperature.

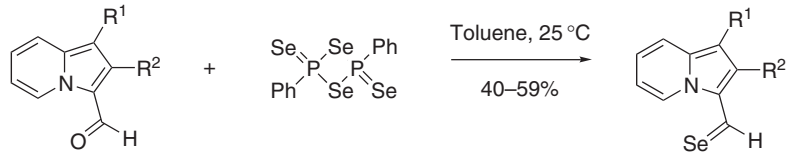


Scheme 9

Even resonance-stabilized selenals show increased stability as their tungsten complexes (see Section 3.09.2.3) <1989JCS(P1)1241>. Novel insertion reactions of tungsten-stabilized selenobenzaldehyde have also been reported <1995CB1149, 1996CB1169>.

3.09.2.3 Conjugatively Stabilized Selenals

A selenating agent structurally similar to the Lawesson thionating reagent converts a number of heterocyclic formyl derivatives to their corresponding resonance-stabilized indolizine selenals **11** (Equation (5)) <2001TL5949>. Using this reagent these selenations occur more slowly and in lower yield than the corresponding reactions using the previously described $PhP(Se)Cl_2$ <1988CC1494>.

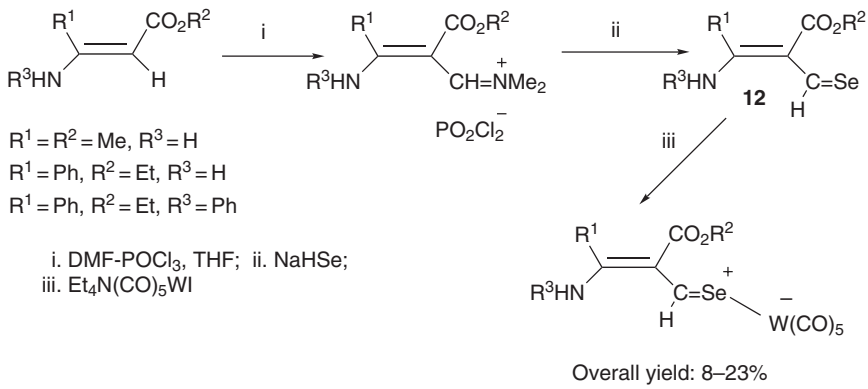


$R^1 = H$, $R^2 = Me$
$R^1 = H$, $R^2 = Bu^t$
$R^1 = Me$, $R^2 = Bu^t$

11

(5)

Another description of the preparation of stabilized selenals **12** via a Vilsmeier salt (cf. chapter 3.09.2.3 of <1995COFGT(3)381>) has been reported (Scheme 10). These were stable for a short time in benzene solution, but could be converted into their much more stable tungsten complexes <1989JCS(P1)1241>. These resonance-stabilized complexes proved to be much more stable than the selenobenzaldehyde tungsten pentacarbonyl complex.



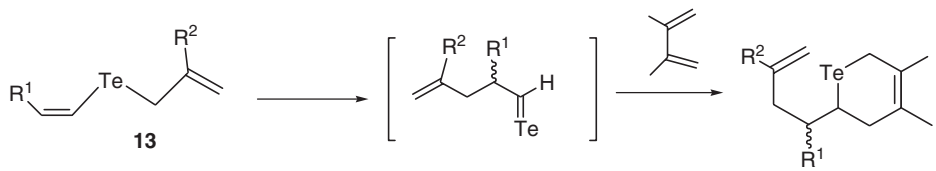
$R^1 = R^2 = Me$, $R^3 = H$
$R^1 = Ph$, $R^2 = Et$, $R^3 = H$
$R^1 = Ph$, $R^2 = Et$, $R^3 = Ph$

i. DMF-$POCl_3$, THF; ii. NaHSe;
iii. $Et_4N(CO)_5WI$

Scheme 10

3.09.3 TELLUROALDEHYDES (TELLURALS), RHC═Te

The chemistry of telluroaldehydes (tellurals) very much parallels that of the corresponding selenium compounds, although the tellurium compounds appear even less frequently in the literature. The tellurals have previously been generated by the reaction of tellurating agents with aldehydes, thermal reaction of Wittig reagents with tellurium, or by insertion of tellurium into metal—carbene complexes <1995COFGT(3)381>. A recent new preparation of tellurals involves [3,3]-sigmatropic rearrangements of allyl alkenyl tellurides **13** (Equation (6)) <1995CL135>. The unstable tellurals can be trapped as cycloadducts with 2,3-dimethyl-1,3-butadiene (cf. Section 3.09.2.1, Scheme 5).



$R^1 = Ph$, 4-$CF_3C_6H_4$, $R^2 = H$
$R^1 = MeO_2C$, $R^2 = Me$

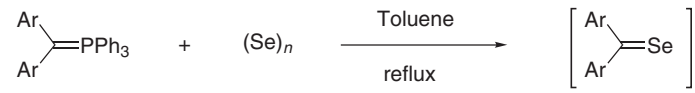
(6)

3.09.4 SELENOKETONES (SELONES), $R_2C{=}Se$

Selones, like the previously described selenals, are much less stable than the corresponding ketones and thiones. Like selenals, selones are highly reactive species and generally cannot be isolated unless stabilized sterically, conjugatively, or by association with metal complexes. Stable sterically hindered selones have most often been prepared by pyrolysis of the corresponding triphenylphosphanylidene hydrazone with selenium or by reaction of a ketone hydrazone with a selenium halide in the presence of an amine base. Unstabilized selones can be generated *in situ* by base-promoted elimination of the corresponding selenocyanates, by direct reaction of the corresponding ketone with a selenating agent or by reaction of an ylide with elemental selenium. Many isolable "selones" are in fact vinylogously stabilized selenoamides or esters. These are often best prepared by direct displacement of activated halides by sodium hydrogen selenide. Metal-stabilized selones are most often prepared by selenium insertion into the corresponding metal–carbene complexes (chapter 3.09.4.2 of <1995COFGT(3)381>. Recent examples of these transformations are discussed below.

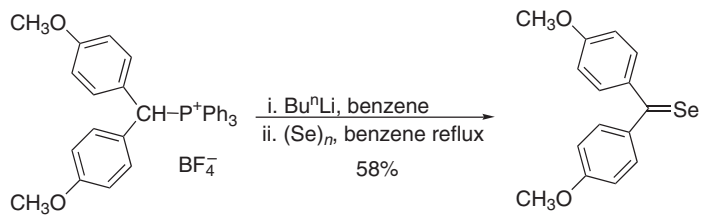
3.09.4.1 Simple Selones

The reaction of diarylmethylene triphenylphosphine ylides **14** with elemental selenium, recently termed "Staudinger chalcogenation," has emerged as a particularly convenient method for the generation of diaryl selones (Equation (7)). A wide variety of substituted diaryl selones have been generated *in situ* and trapped using this method. Reactions of selones with dienes <1990H2107, 1992TL1333, 1993CB1895, 1995JA10922>, dimethylacetylene dicarboxylate <1992TL1333>, other acetylenic esters <2000JOC2090>, diazoalkanes <1993PS259>, and alkenes <1992TL1333, 1995TL8813, 1998PS583> have been reported using this chalcogenation method. Of the diarylselones 4,4′-dimethoxybenzophenone selone **15** can be readily prepared using a variation of this method (Equation (8)). It is easily isolable and especially stable and its reactions with dipolarophiles have been particularly well studied <1994JCS(P1)2151>.



(7)

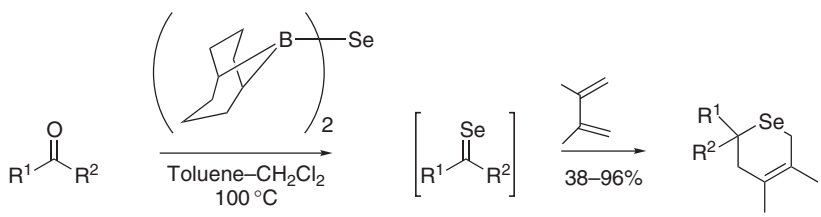
14



(8)

15

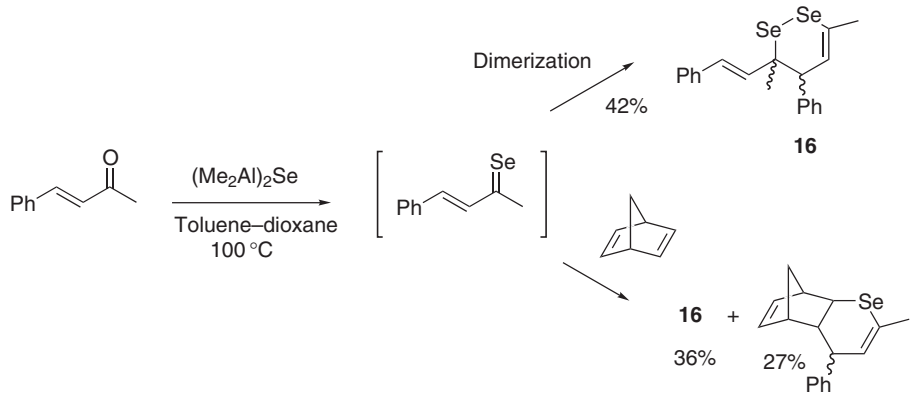
Selenating reagents have also been used for the direct preparation of selones (cf. Section 3.09.2.1, and Equations (3) and (4)). Treatment of a variety of ketones with bis(1,5-cyclooctanediylboryl) selenide at an elevated temperature in a sealed tube afforded the corresponding selones isolated as their Diels–Alder adducts, in moderate-to-good yield (Equation (9)) <1992CL1843>.



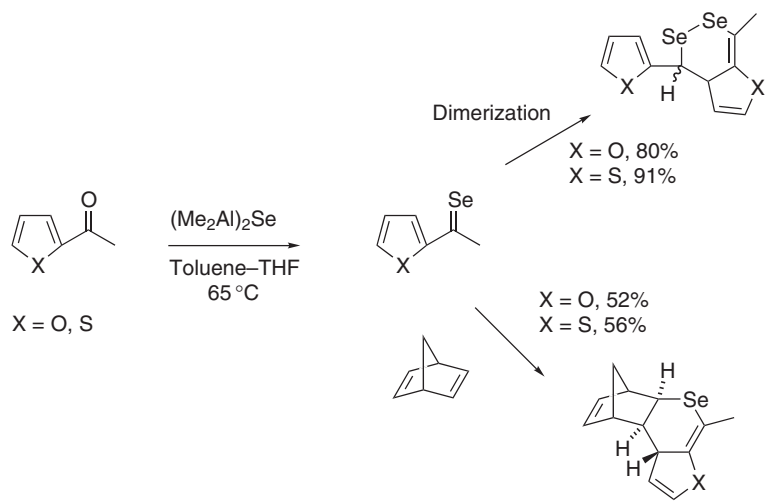
(9)

R^1 = Ph, R^2 = Me, Et, Ph
R^1 = Pr^i, R^2 = Me
R^1, R^2 = fluorenone, $-(CH_2)_5-$

Bis(dimethylaluminum) selenide has been used for the direct preparation of the unstable diferrocenylselone from the corresponding ketone. <1993JOM53>. When α,β-unsaturated ketones are treated with bis(dimethylaluminum) selenide at elevated temperatures, the resulting selones undergo [4 + 2]-dimerization to afford diselenin derivatives **16**. This dimerization is regioselective and occurs in a "head-to-head" fashion (Scheme 11) <1992TL3515, 1999JOC1565> (cf. Section 3.09.2.1 and Scheme 3). The intermediate selones can also be trapped by norbornadiene. Selones derived from 2-acetylfurfural and 2-acetylthiophene react similarly (Scheme 12).

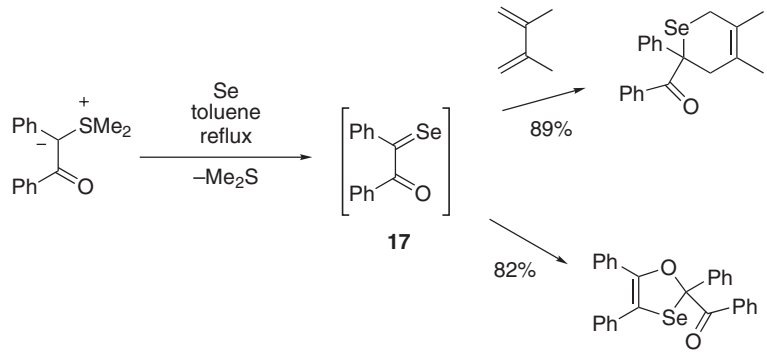


Scheme 11

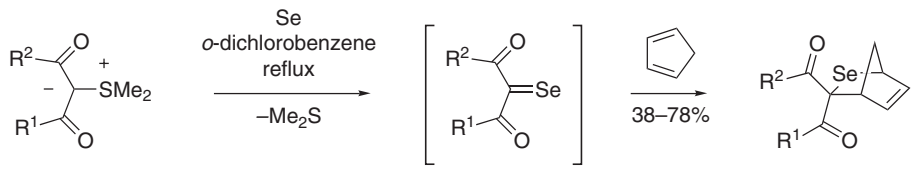


Scheme 12

Base-promoted methods involving stabilized anionic species also appear to be useful for the preparation of selones. Sulfur ylides appear to be particularly well suited as precursors for these reactions. Monoselenobenzil **17** can be readily prepared from the sulfur ylide in very good yield and trapped as its Diels–Alder adduct (Scheme 13) <1987TL4423>. When the selone is generated without added diene, the oxaselenole is formed by further reaction with the starting ylide (cf. Section 3.09.2.1). 1,3-Dicarbonyl-2-selone systems can also readily be prepared and trapped using this sulfur ylide method (Equation (10)).



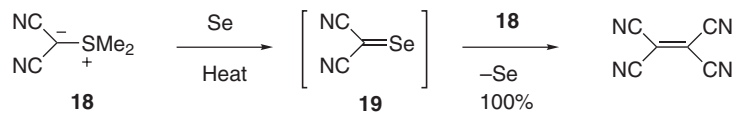
Scheme 13



(10)

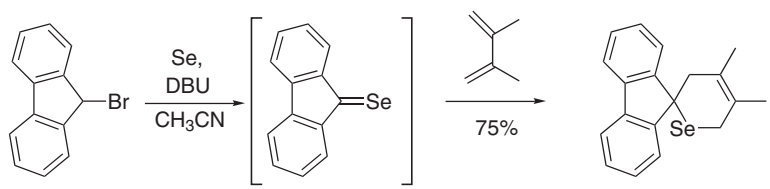
$R^1 = R^2 = Me$
$R^1 = R^2 = EtO$
$R^1 = Me$, $R^2 = EtO$

When dimethylsulfonium dicyanomethylide **18** is heated in the presence of selenium, tetracyanoethylene is generated in near quantitative yield. Selone **19** is the presumed intermediate in this reaction (Equation (11)) <1988JPO53>. Bifluoranylidene can also be directly prepared in good yield by reaction of the sulfur ylide with elemental selenium, again presumably via the intermediate selone.

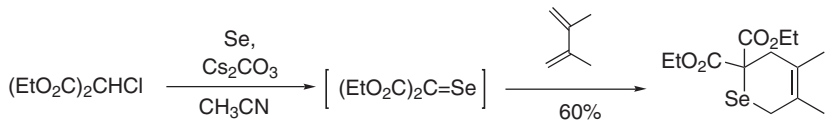


(11)

Selones can also be generated in moderate yields by the reactions of stabilized α-halo anions with elemental selenium. The most successful of these transformations involved the use of 9-bromofluorene (Equation (12)) <1991TL7389>. Similarly, the preparation of other selones containing attached electron-withdrawing groups involves caesium carbonate-promoted elimination of α-chloro compounds (Equation (13)).



(12)

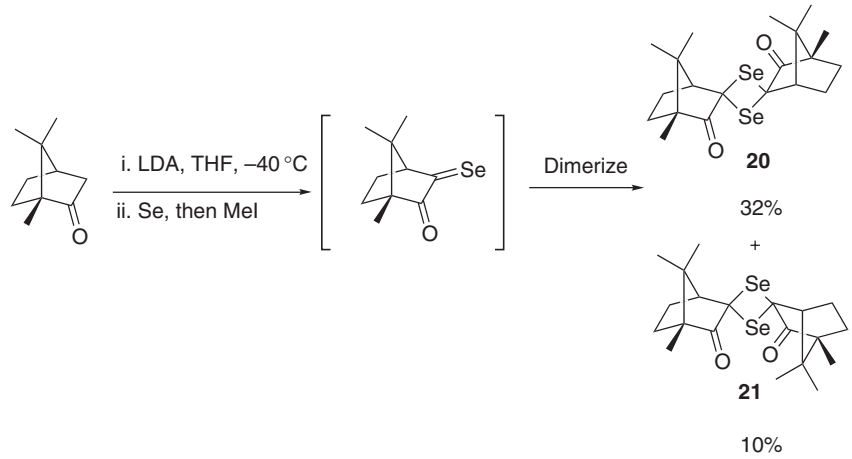


(13)

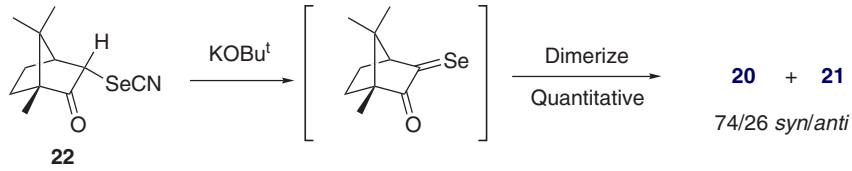
Treatment of the enolate of camphor with elemental selenium at −40 °C followed by addition of methyl iodide affords a mixture of *syn*- and *anti*-diseletanes **20** and **21**, presumably via the intermediate selone (Scheme 14) <1995JOC703>. Similarly treatment of the selenocyanate **22** with potassium *t*-butoxide quantitatively affords the same diseletanes, again via the selone (Scheme 15).

A novel photochemical approach allows for the generation of the unusual 1-selone-2-thione and 1,2-diselone systems <1987TL4833, 1987TL5699>. Treatment of the sterically hindered 1,2,3-selenadiazole **23** with molten sulfur affords the 1,2,3,4-tetrathia-5-selenepin **24**, which can

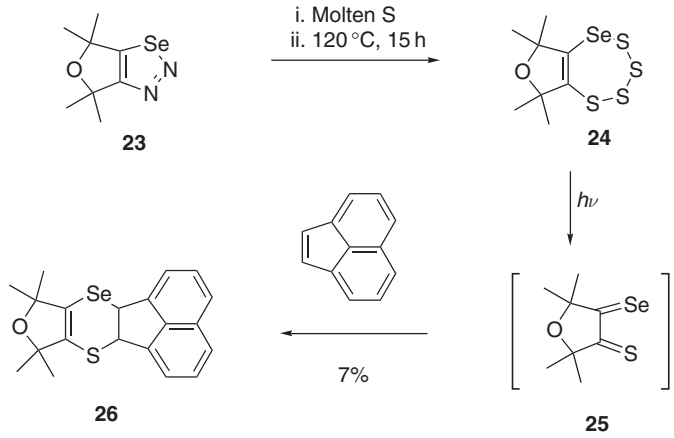
be photochemically cleaved with extrusion of sulfur to the unstable 1-selone-2-thione **25**. This very reactive molecule can be trapped by a number of alkenes in a cycloaddition reaction (Scheme 16). Upon irradiation the acenaphthene adduct **26** can regenerate the 1-selone-2-thione, which can be trapped by norbornene quantitatively (Equation (14))



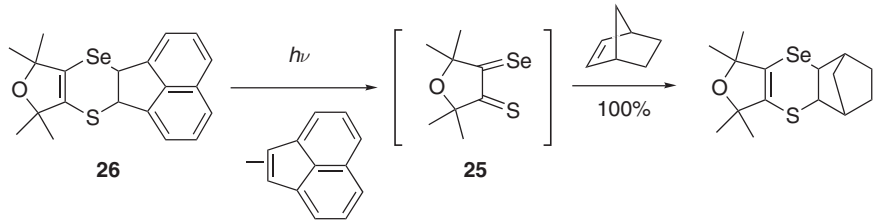
Scheme 14



Scheme 15

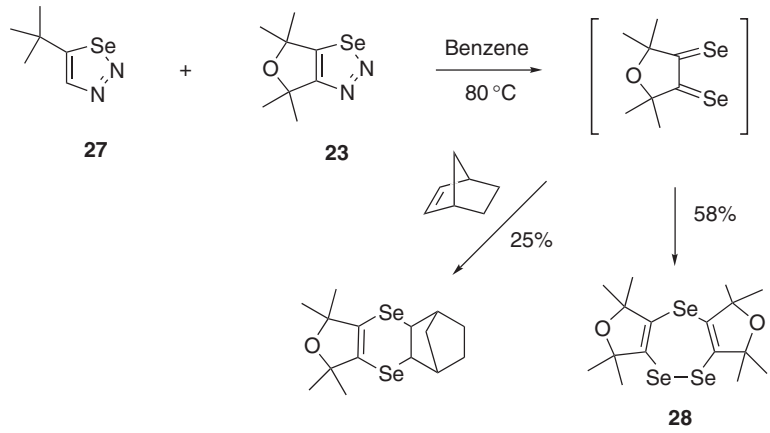


Scheme 16



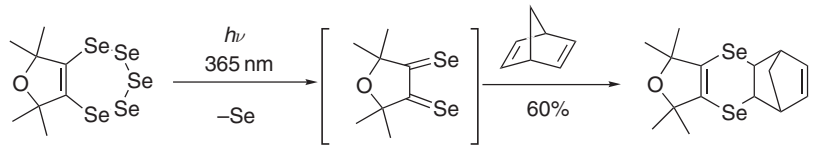
(14)

Because of the lower reactivity of elemental selenium relative to sulfur, a different approach was required for the preparation of the precursor to the 1,2-diselone. Treatment of the 1,2,3-selenadiazole **23** at 80 °C with 4-*t*-butyl-1,2,3-selenadiazole **27** as a selenium atom source afforded the 1,2,5-triselenepin **28** in good yield, presumably via a 1,2-diselone intermediate (Scheme 17) <1987TL5699>. If the reaction is carried out in the presence of an olefin such as norbornene, the cycloadduct of the 1,2-diselone can be isolated. Irradiation of the 1,2,3,4,5-pentaselenepin **29** (formed as a by-product in the attempted trapping of the diselone with acenaphthene) in the presence of norbornadiene afforded the corresponding 1,2-diselone cycloadduct in good yield (Equation (15)).



27 **23** **28**

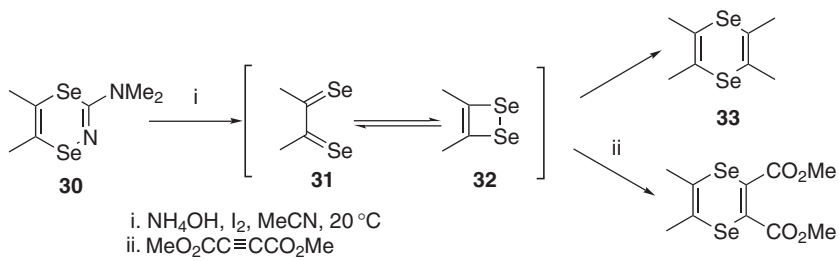
Scheme 17



29 (15)

Similar reactions have been noted in the case of another sterically hindered 1,2,3-selenadiazole <1988CL657, 1989TL2955>.

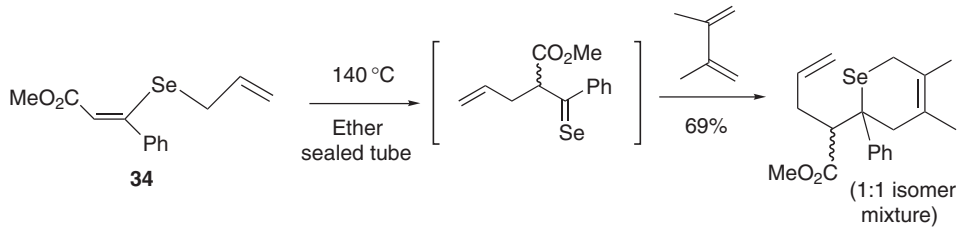
Fragmentation of the 1,4,2-diselenazine ring system **30** affords the unstable 2,3-butane diselone **31**, possibly in equilibrium with the corresponding 1,2-diselenete **32** (Scheme 18) <1996CC2375>. The unstable selone reacts further with extrusion of selenium to afford the 1,4-diselenin **33**. In the presence of a dienophile the intermediate selone can also be trapped as its cycloaddition product.



30 **31** **32** **33**

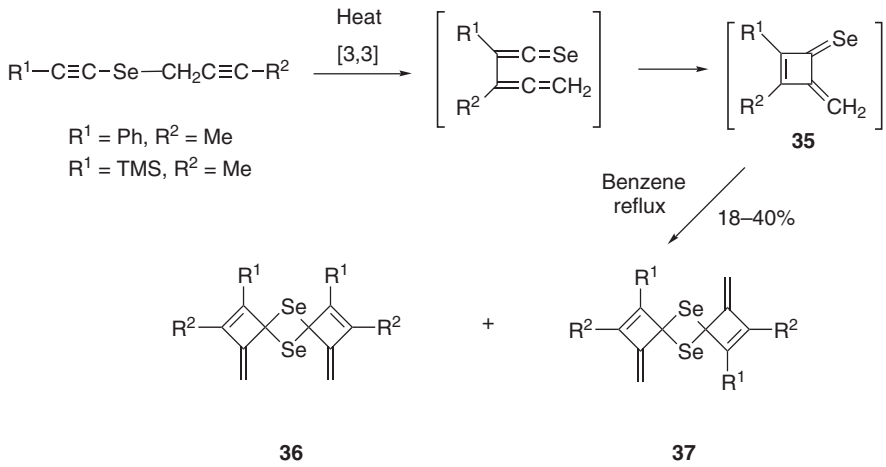
Scheme 18

Intermediate selones have been proposed as intermediates in the seleno-Claisen rearrangement <1992CC1680>. A recent method for the generation of selones involves the [3,3]-sigmatropic rearrangement of allyl alkenyl selenides (Equation (16)) <1995CL135>.

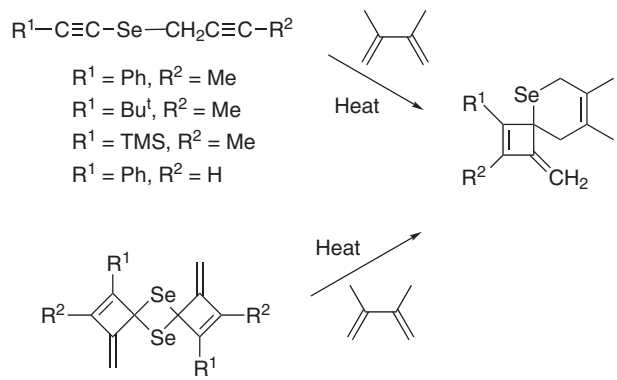


(16)

Heating of alkynyl propargyl selenides affords unstable intermediate 2-methylene-3-cyclobutene-1-selones **35** via [3,3]-sigmatropic rearrangements. Without additional trapping reagents the generated selones react further affording stereoisomeric mixtures of dimers **36** and **37** (Scheme 19) <1994CL2283>. Upon heating these dimers cyclorevert to the selones, which can be trapped by dienes (Scheme 20). The initially formed selones can also be directly trapped *in situ* by reaction with dienes in similar yields.

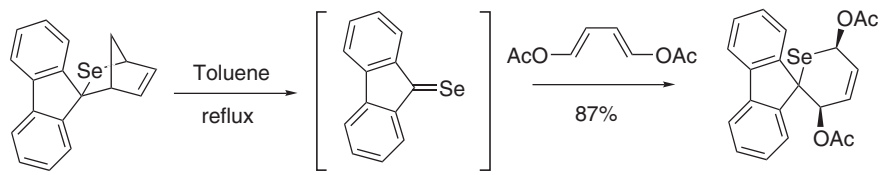


Scheme 19



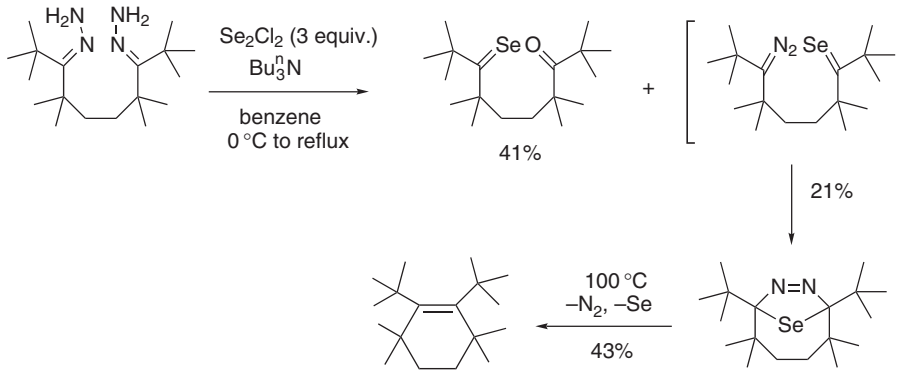
Scheme 20

Thermal retrocyclization of other selone cycloadducts can be used to regenerate selones which can be trapped by electron-rich conjugated dienes (Equation (17)) <1998PS599>.

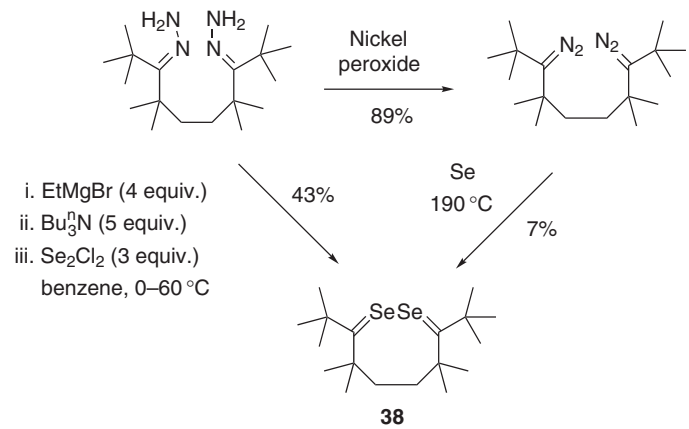


(17)

The reaction of a hindered ketone hydrazone with a selenium halide remains a convenient method for the preparation of extremely sterically hindered selones (chapter 3.09.4.1 of <1995COFGT(3)381>). Sterically hindered selones prepared in this manner are important intermediates in the preparation of extremely sterically hindered alkenes via twofold extrusion reactions (Scheme 21) <2000JOC1799, 1993JOC5900>. The use of ethylmagnesium bromide and tri-*n*-butylamine as bases in this reaction allows for the effective preparation of the diselone **38** (Scheme 22) <2002HAC351>. This diselone can also be directly prepared in modest yield by reaction of the bis-diazo compound with elemental selenium at elevated temperature.



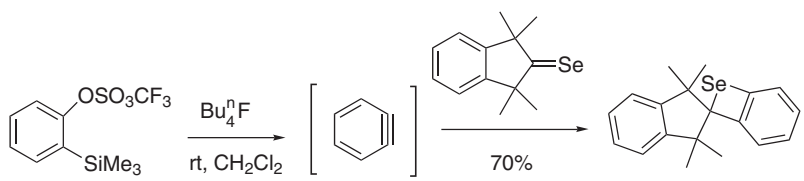
Scheme 21



Scheme 22

Sterically hindered stable selones also behave as dipolarophiles in reactions with azomethine ylides <2000T5579>.

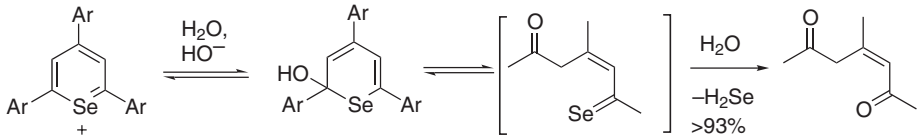
Reaction of 1,1,3,3-tetramethylindan-2-selone with benzyne generated from *o*-trimethylsilylphenyl trifluoromethanesulfonate and tetrabutylammonium fluoride afforded the first reported isolable 2H-benzoselenete (Equation (18)) <2001JA7166>. The 2H-benzoselenete **39** is a tautomeric form of selenoquinone methide **40** and had been previously postulated as a photochemical intermediate <1989JOC240>. Di-*t*-butylselone also affords a benzoselenete under these conditions.



(18)

39 **40**

Selones have also been proposed as intermediates in the hydrolysis of selenopyrylium ions (Equation (19)) <1998JOC5716, 1999JMC3942>.



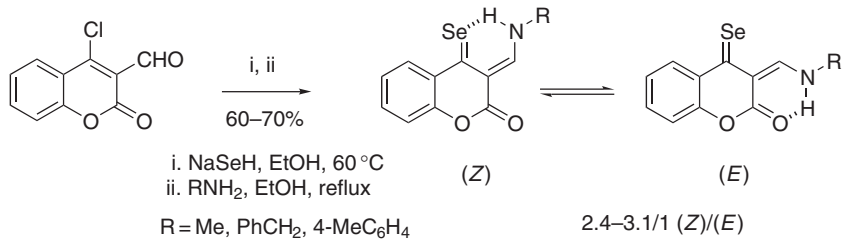
(19)

3.09.4.2 Metal-stabilized Selones

Metals have been shown to stabilize the selenocarbonyl group (chapter 3.09.4.2 of <1995COFGT(3)381>) (cf. Section 3.09.2.2). Similar to other selones, the unstable diferrocenylselone can be stabilized by complexation to tungsten pentacarbonyl <1993JOM53>.

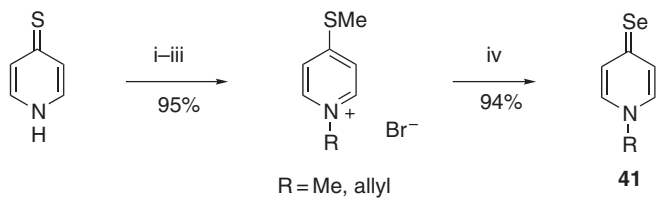
3.09.4.3 Conjugatively-stabilized Selones

Many compounds, which have selone-like structures, are actually conjugatively stabilized vinylogous amides and esters <1995COFGT(3)381>. Recent examples of this type of compound have been reported. Treatment of 4-chloro-3-formylcoumarin with sodium hydrogen selenide, followed by addition of various aliphatic primary amines, afforded the corresponding isomeric selones. These selones were stabilized not only by vinylogous effects, but also by intramolecular hydrogen bonding. It is interesting to note that the favored (*Z*)-tautomer involved a hydrogen bond to the selenium atom of the selone (Scheme 23) <1993JCS(P2)2423>.

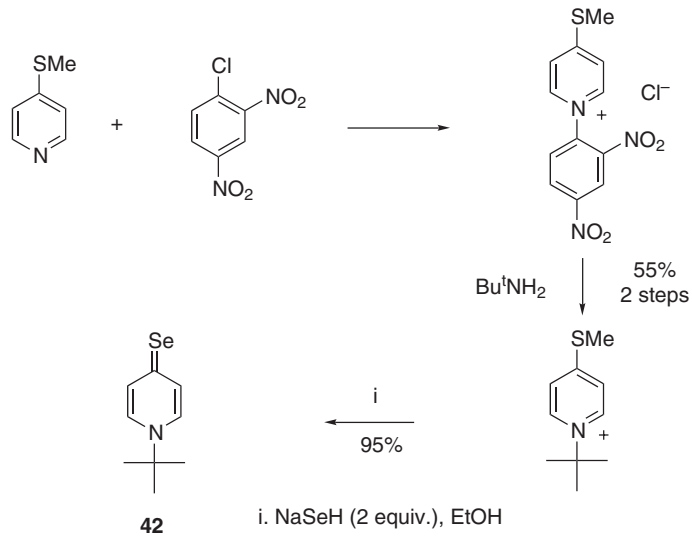


Scheme 23

N-Substituted selenopyridones **41** and quinolones can be conveniently prepared from the corresponding *N*-unsubstituted thiones by a dialkylation-displacement sequence (Scheme 24) <1998S99>. *N*-*t*-Butylselenopyridone **42** could be similarly prepared via an intermediate Zincke salt (Scheme 25).

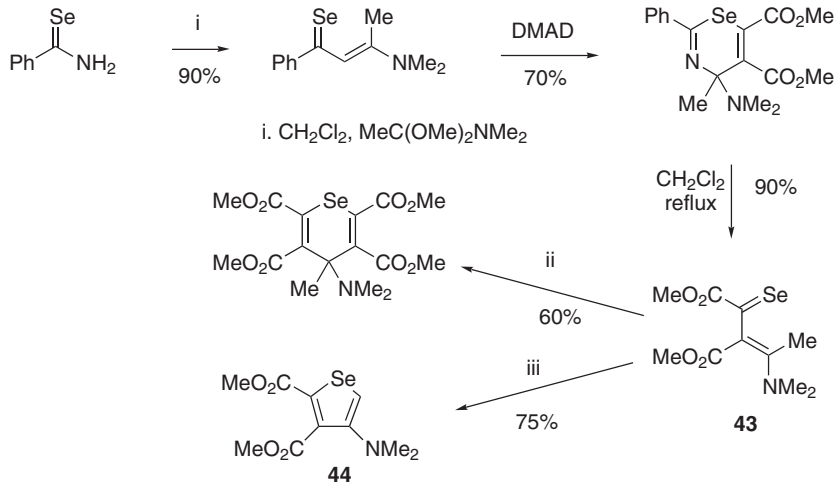


Scheme 24



Scheme 25

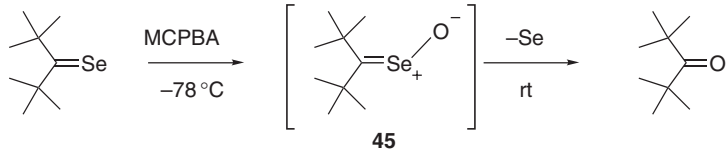
Resonance-stabilized selones can also be obtained by retrocyclization reactions. Mild heating of the 4H-1,3-selenazine affords the vinylogous selenoamide **43** in high yield. This selone reacts with excess dimethylacetylenedicarboxylate to afford the 9H-selenopyran. Upon heating **43** in the presence of oxygen selenophene **44** is obtained (Scheme 26) <1998T2545>. This method has also been used for the synthesis of a similar formyl-substituted selenophene <1998SC301>.



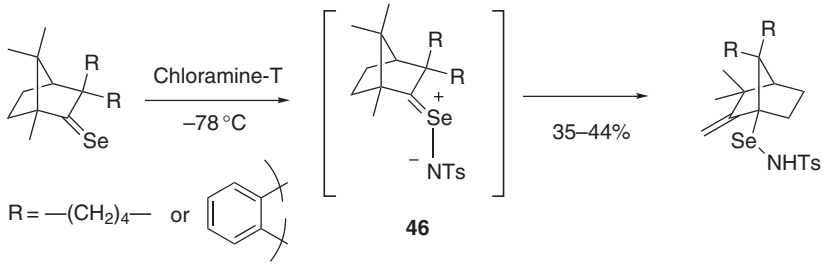
Scheme 26

3.09.4.4 "Hypervalent" Selones

Treatment of sterically hindered selones with oxidizing agents affords unstable "hypervalent" selone derivatives. Treatment of di-*t*-butylselone with a peracid affords an unstable selone Se-oxide (selenine) **45**, which loses elemental selenium to afford the corresponding ketone (Equation (20)) <1984MI001>. Similarly reactions of bornane-derived selones with chloramine-T afford the corresponding selone Se-imides **46** as unstable intermediates. These rearrange to seleneamides upon warming to room temperature (Equation (21)) <2000TL6833>.



(20)

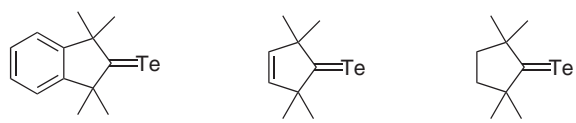


(21)

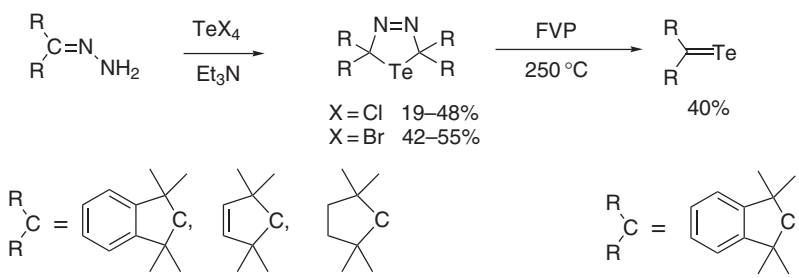
3.09.5 TELLUROKETONES (TELLONES), $R_2C{=}Te$

Telluroketones (tellones) have not been particularly well documented in the literature. The early reported description of the preparation of a telluroketone by addition of hydrogen telluride to a ketone is certainly incorrect. Presumably any intermediate telluroketone would react further with the excellent reducing agent hydrogen telluride, analogous to the selenium case <1995COFGT(3)381>.

Descriptions of the preparations of a number of isolable telluroketones **47**–**49** have recently been reported. These sterically hindered cyclic nonenolizable tellones are formed by the thermal decomposition of heterocyclic 1,3,4-telluradiazolines (Scheme 27) <1993JA7019, 1997TL2501, 1998PS549>. The required 1,3,4-telluradiazolines may be prepared by reaction of the corresponding sterically hindered hydrazone with $TeCl_2$, $TeCl_4$, or $TeBr_4$ in the presence of triethylamine. The more stable Te(IV) halides proved to be more effective in these reactions <1997T8137>. It should be noted that these reactions of tellurium halides with hydrazones differ markedly from the corresponding selenium reactions, which afford selenoketones directly under similar conditions <1995COFGT(3)381> (cf. Section 3.09.4.1, and Schemes 21 and 22).



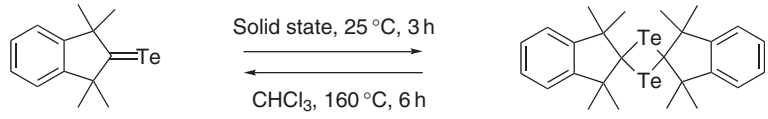
47 **48** **49**



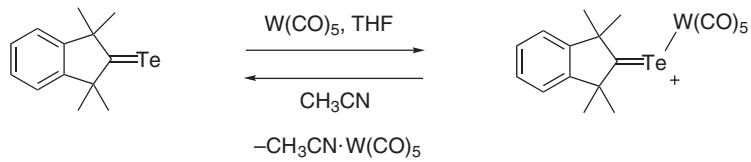
Scheme 27

The 1,1,3,3-tetramethylindanone tellone **47** has proved to be especially stable <1997TL2501, 1998PS549>. In the solid state this tellone rapidly converts to the corresponding dimeric 1,3-ditelluretane **50**. This process is readily reversed in solution at elevated temperature. Remarkably, dimerization of **47** does not occur in solution (Equation (22)). An air-stable tungsten complex of

the indanone telluroketone has also been prepared (Equation (23)) <1996CC123, 1998PS549>. Regeneration of the tellone occurs via ligand exchange with acetonitrile at elevated temperature, possibly making this metal complex a convenient and stable source of the free telluroketone.

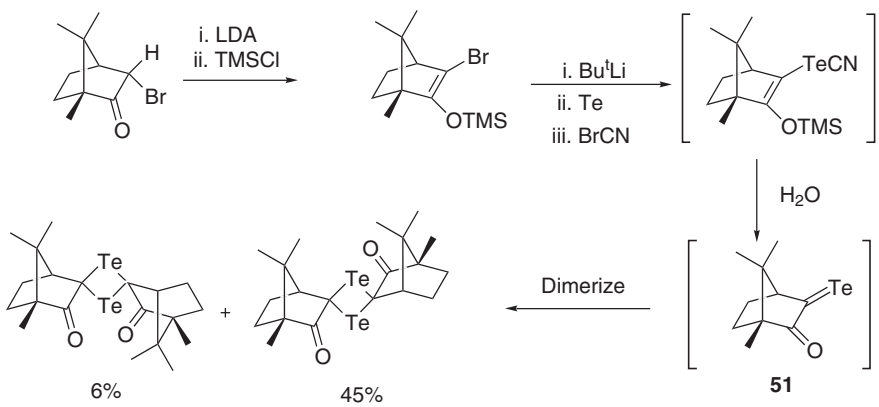


47 50 (22)



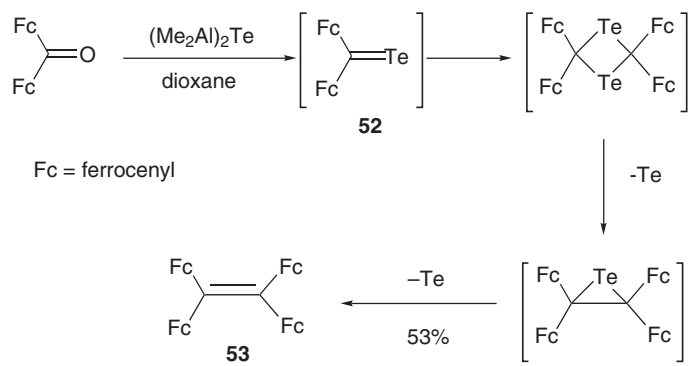
(23)

The unstable (1R)-3-telluroxocamphor **51** can be generated by hydrolysis of the trimethylsilyloxyvinyltellurocyanate (Scheme 28) <1995JOC4657>. The telluroketone rapidly dimerizes to a mixture of *syn*- and *anti*-telluretanes. It should be noted that this procedure contrasts with those used for the previously described preparations of the corresponding selones (Section 3.09.2.1, Scheme 15) due to the apparent instability of the α-bromoketone-derived tellurocyanate which decomposes to the telluride and $Te(CN)_2$.



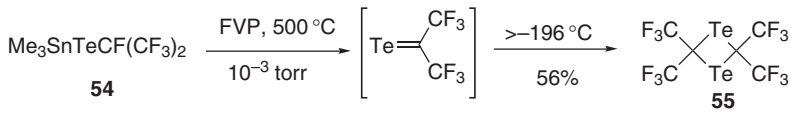
Scheme 28

Diferrocenyltellone **52** can be generated from the corresponding ketone by reaction with bis-dimethylaluminum telluride. Heating **52** led to extrusion of tellurium and formation of the olefin tetraferrocenylethylene **53** (Scheme 29) <1995OM4334>.

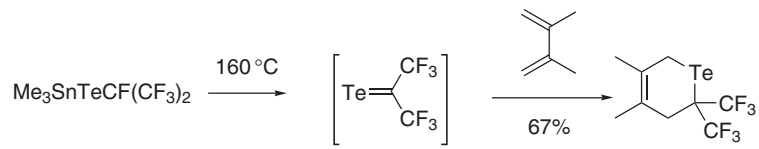


Scheme 29

The cyclic dimer of hexafluorotelluroacetone has been prepared by flash vacuum pyrolysis of the tin telluride **54** (Equation (24)) <2000JCS(D)11>. The parent tellone is extremely unstable and condensed at −196 °C already in its dimeric form; however, it could be trapped as its cycloadduct with 2,3-dimethyl-1,3-butadiene (Equation (25)).

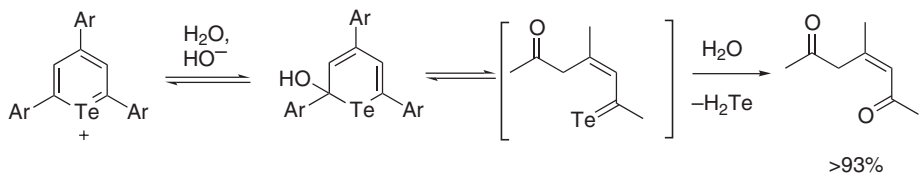


(24)



(25)

Unstable telluroketone intermediates have also been proposed in the hydrolysis of a number of telluropyrylium dyes (Equation (26)) <1998JOC5716, 1998PS549> (cf. Section 3.09.4.1, Equation (19)).



(26)

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Biographical sketch

Lynn James Guziec was born in Long Beach, California; studied at Russell Sage College, Troy, NY where she received her B.A., special honors in chemistry, in 1979. She received her Ph.D. in 1988 from New Mexico State University under the direction of Frank Guziec, Jr., She remained as a College Professor at New Mexico State University until 1995. She has worked at her present position at Southwestern University as Assistant Professor since 1996. In 1998 she received an M.Sc. in Biological Sciences from the University of Warwick, UK. Her interests include heterocycles, organosulfur and organoselenium compounds, as well as the synthesis of medicinal and anticancer compounds.

Frank Guziec was born in Chicago, studied at Loyola University of Chicago where he received a B.S. (Honors) degree in 1968. He received his Ph.D. degree in 1972 at MIT under the direction of Professor John C. Sheehan. He carried out postdoctoral work at Imperial College, London with Professor D.H.R. Barton, at MIT with H. G. Khorana, and at Wesleyan University with Max Tishler. He has served on the Chemistry faculties of Tufts University, New Mexico State University and is currently Dishman Professor of Science at Southwestern University. He carried out sabbatical research in the Pharmaceutical Sciences Department at DeMontfort University, Leicester, UK with Laurence Patterson under a Fulbright Fellowship and with Henk Hiemstra at the University of Amsterdam. His scientific interests include the chemistry of organoselenium compounds, extrusion reactions, functionalizing deamination reactions, and sterically hindered molecules. Collaborating with his wife Professor Lynn Guziec he is also involved in the design and synthesis of anticancer compounds.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 397–417

3.10 Imines and Their *N*-Substituted Derivatives: NH, NR, and *N*-Haloimines

A. P. DOBBS
University of Exeter, Exeter, UK
and
S. ROSSITER
University College London, London, UK

3.10.1 IMINES

Several ongoing series of reviews describe the chemistry of imines and related compounds, their synthesis and reactions, and the reader is directed to <1995COFGT(3)403, 1997MI183, 1997MI517, 2000JCS(P1)125>. The stability and chemistry of various meta-stable enamines has been described <2001JACS11083>.

3.10.2 *N*-H IMINES

An efficient method for preparing *N*-unsubstituted imines, stable at room temperature, as organoborane adducts has been reported <2000JACS4217>.

There have been several reports on the generation, reactions, and stability of iminyl radicals <1995JOC1276, 1997JOC559, 1997JOC2050, 1997JOC5846>.

The enzymatic deracemization of α-methylbenzylamine has been described using an amine oxidase obtained by *in vitro* evolution <2002AG(E)3177>.

3.10.2.1 *N*-H Aldimines

There are numerous examples of the reduction of nitriles to *N*-H aldimines and the reader is directed to these purely representative examples, e.g., using HCl(g) <1995JMC34, 2001T2597>, using DIBAL-H, often in the presence of many other functionalities <1995TL1385, 1996T14103, 1999JACS7582, 2001MI4423>, using palladium catalysis <2003H161>, and using phosphorus(V) reagents <1999MI1201>. Azides have also been reduced to *N*-H aldimines <1995JOC6368>. Aldehydes may be converted to the corresponding nitrile by reaction with ammonia and aqueous hydrogen peroxide in the presence of copper salts under mild conditions <2000TL6749>. The intermediate *N*-H aldimine may be isolated prior to oxidation. The reaction with ammonia may also be promoted using 4 Å molecular sieves <2002H2129>. Enamines may isomerize to *N*-H-aldimines in the presence of a rhodium catalyst <2001JACS11083>. Aldehydes also react with lithium bis(trimethylsilyl)amide to give *N*-H aldimines <2001TA439, 2002CPB423>. The thermal decomposition of 3,6-dialkyl 1,2,3,6-tetrahydro-[1,2,4,5]tetrazines at 500 °C generates the corresponding *N*-H aldimine <1998MI189>.

Similarly, there are a number of methods for the oxidation of amines to *N*-H aldimines. For example, using manganese-based oxidants <2003JCR(M)218>, phase transfer oxidants <2002IJC(A)541, 2002JPO103>, or the enzymatic oxidation of amines <1996T6725, 2002AG(E)3309>.

The diastereoselective alkylation of the aldimine/oxazolidine derived from phenylglycinol has been used in the asymmetric synthesis of diarylmethylamines, key intermediates in a program aimed at the preparation of selective opioid delta receptor ligands <1998TA3969>.

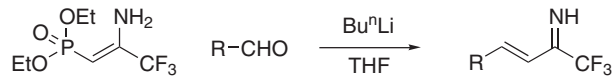
3.10.2.2 *N*-H Ketimines

There are numerous examples of both Grignard reagents and organolithium reagents which add to nitriles, often in the presence of other functionalities, to give *N*-H ketimines <1996T13783, 1998CC2405, 1998S1167, 1999TL1095, 1999T11077, 2003OPP231>. Organosodium <1997JOC2050>, organozinc <1997JMC2922>, and organozirconium <1995JACS3422> reagents may also undergo addition to nitrile groups. 9-Methyl-9-BBN/methyllithium also adds to nitriles to give the *N*-H-ketimine–borane complex <2000JACS4217>. The reductive coupling/dimerization of trifluoroacetonitrile by $[(\eta^5\text{-}C_5H_5)_2TiCl]_2$ has been reported <1999TL8523>.

The addition of ammonia to ketones has been used to prepare *N*-H-ketimines <1997ACS351, 2003BMC1549>.

There have been many examples, frequently in total syntheses, of the reduction of nitriles, ultimately to aldehydes, using primarily DIBAL-H as the reducing agent and the reader is directed to these representative examples <1996T14103, 1996TL4099, 1999T11077, 2000TL2181, 2003T367>. In many cases, isolation of the intermediate imine is possible. Chiral cyanohydrins have been converted to chiral nitrones (47–99% yield, >97% ee) using a related transimination reaction <1997TA1061>.

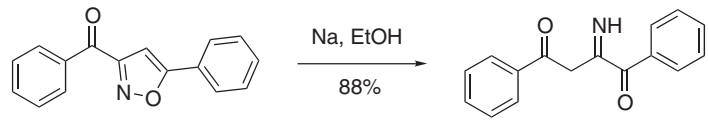
The Wadsworth–Emmons reaction has been employed using enamines to prepare α,β-unsaturated *N*-H-ketimines (Scheme 1) <2002OL769>.



R = Ar, HetAr, *o*-C_6H_{11}, ArCH=CH

Scheme 1

The ring-opening of isoxazoles by sodium metal to give *N*-H-ketimines has been reported (Scheme 2) <1998ZOR684>.



Scheme 2

N,*N*-Dihaloamines give *N*-H-ketimines in high yields on treatment with potassium hydroxide <2001JPC(A)2085, 2001MI337>. The kinetics of the elimination of *N*-haloamines to *N*-H-ketimines has been studied (Scheme 3) <1997T12615, 1999CJC997>.

Scheme 3

3.10.3 *N*-CARBON-SUBSTITUTED IMINES

A review of the methods available for the synthesis of organofluorine nitrogenated derivatives has appeared <2004JFC621>.

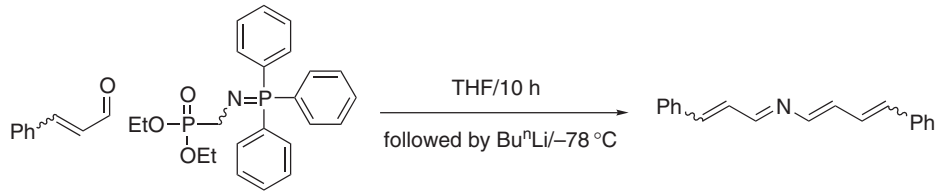
Grignard reagents add to *N*-carbon-substituted aldimines and ketimines in excellent yields <1998T12571>.

Many *N*-carbon substituted imines have been prepared both as speculative ligands <2002JHC829, 2003OBC2164> and used as chelating ligands for a range of metals, e.g., palladium <2002NJC105>, copper in both Diels–Alder reactions <1999JACS7582> and cyclopropanation reactions <1999TL2973>, and iron <1999TL4615>. The mechanism of methane elimination in $B(C_6F_5)_3$-initiated monocyclopentadienyl-ketimide titanium and related olefin polymerization catalysts has been studied <2000JACS5499>.

Imines have been used as the nucleophilic component in palladium-catalyzed cross-coupling reactions. 3,4-Disubstituted isoquinolines have been prepared by the palladium-catalyzed cross-coupling of *N*-*t*-butyl-2-(1-alkynyl)benzaldimines with aryl, allylic, benzylic, and alkynyl halides <2003JOC920>.

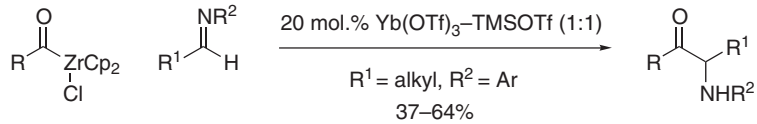
3.10.3.1 *N*-Carbon-substituted Aldimines

The reaction of amines with aldehydes remains the preferred method for the preparation of *N*-carbon substituted aldimines <1995T2929, 1996T489, 1999H119>. Both the aza-Horner–Wadsworth–Emmons <1994JOC4556> and aza-Wittig <1996TL6379> reactions have been employed in the preparation of conjugated aza-polyenes (Scheme 4).



Scheme 4

Tetrahydroquinolines may be prepared by the Lewis acid-promoted [4 + 2]-annulation of allyl silanes or allylgermane with aldimines <2000H529>. Functionalized β-thiolactams have been prepared by the Lewis acid-catalyzed addition of alkynylsilyl sulfides to imines <1997S942>. It is possible to prepare α-amino ketones in good yield by the addition of acylzirconocene chlorides to imines catalyzed by $Yb(OTf)_3$/TMSOTf <2003MI116>. A three-component variation, describing the reaction of acylzirconocene chlorides, aldehydes, and amines is also described (Scheme 5).



Scheme 5

The zirconium-mediated cross metathesis of imines has been reported <2000JACS751> and the addition of masked allylic zinc reagents to *N*-carbon substituted aldimines has been described <1998CC2405>.

The reactions of CF_3-*N*-arylaldimines, particularly in Diels–Alder reactions, have been described <2000JOC5009>.

N-Silicon substituted aldimines have been used as the dienophile component in aza-Diels–Alder reactions for the preparation of pipecolic acid derivatives <1998JOC3918>. *N*-Silylimines may be deprotected to the *N*-H-aldimine or ketimine with HCl in quantitative yield <2000JACS5499>.

3.10.3.2 *N*-Carbon-substituted Ketimines

3.10.3.2.1 Formation of N-carbon-substituted ketimines via condensation reactions

The reaction of amines with ketones remains the preferred method for the preparation of *N*-carbon substituted ketimines <2001CPB979, 2003CPB667>. Reaction of 2 equiv. of an amine <2001SC2405> or aniline <2000MI753, 2001JACS3229> with a 1,3-dicarbonyl compound rapidly leads to symmetrical 1,3-di-*N*-C-substituted ketimines in excellent yields.

3.10.3.2.2 Formation of N-carbon-substituted ketimines via rearrangement reactions

The base-promoted rearrangement of conjugated imino-iminium iodides gives *N*-substituted ketimines <1996T10095>. Similar base-promoted elimination of 5-chloro-3-azahex-3-enes gives *N*-substituted ketimines <1998ZOB573>.

3.10.3.2.3 Formation of N-carbon-substituted ketimines via oxidation or reduction reactions

Detailed mechanistic studies have been performed on the oxidative dealkylation of tertiary amines <2000JCS(P2)2328>.

A copper bromide/copper acetate/*t*-butylbenzoylperoxide mixture has been used to reduce a secondary amine to the corresponding *N*-carbon substituted ketimine <2001T2031>.

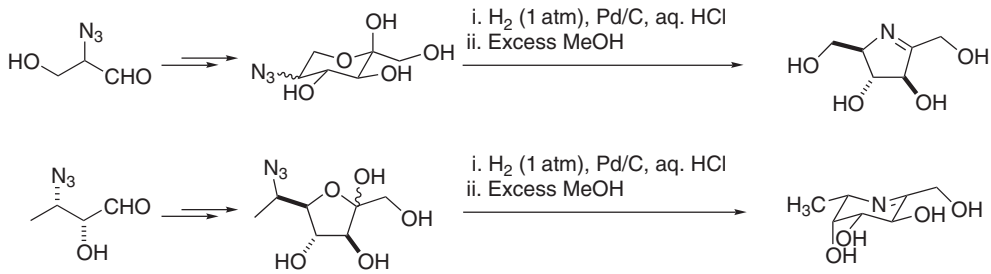
The aerobic dehydrogenation of amines, ultimately to nitriles, by a *bis*(benzylamine) ruthenium(II) porphyrin complex has been described <1996CC2343>.

N-(2-Imino-1-oxypropyl)glycine has been found as an intermediate in the base-catalyzed decomposition of (*N*-halo)-Ala-Gly <1997T12615>.

3.10.3.3 Cyclic Imines

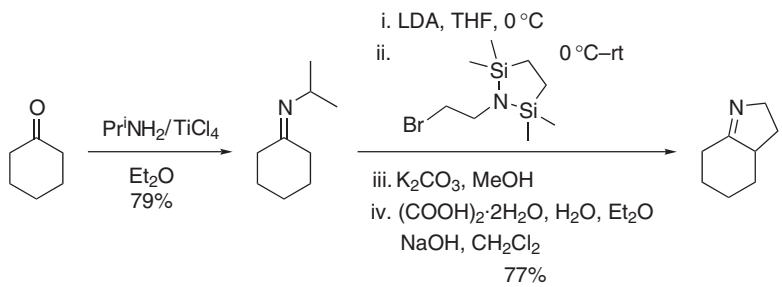
Cyclic imines continue to attract attention, primarily due to the number of natural products isolated during this period containing either cyclic imines or cyclic iminium ions.

Novel cyclic imine sugars have been prepared by a chemoenzymatic strategy, first involving an enzymatic aldol reaction to prepare an azido-sugar followed by acidic hydrogenation to give the cyclic imine sugar (Scheme 6) <1997JACS8146>.



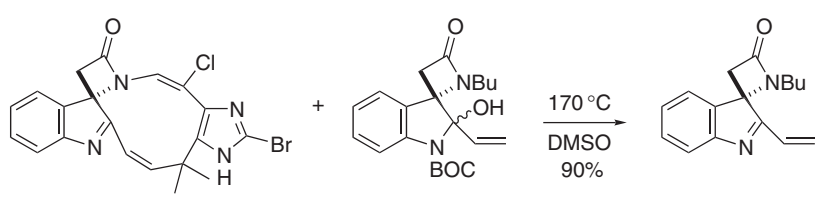
Scheme 6

A novel route to aza-heterocycles of varying oxidation levels (indoles, indolines, quinolines, and tetrahydroquinolines) has been developed from *N*-(cyclohexylidene)amines (Scheme 7) <1996T3705>.



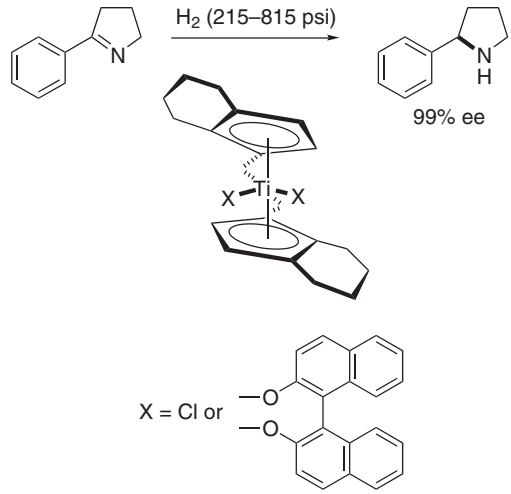
Scheme 7

Model studies toward the synthesis of the spirocyclic β-lactam alkaloids, the chartellines, have included a novel synthesis of cyclic imines from α-hydroxyamines (Scheme 8) <2001TL2631>.



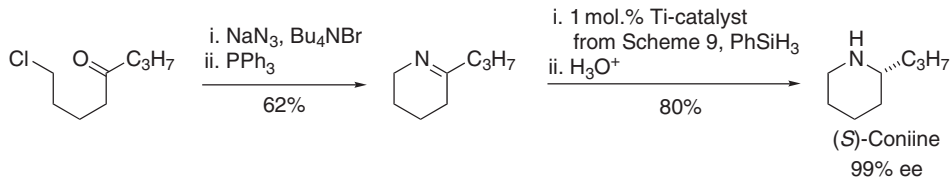
Scheme 8

The catalytic asymmetric hydrogenation of cyclic imines has received considerable attention. Buchwald has developed a titanocene catalyst for the asymmetric hydrogenation of both cyclic and acyclic imines and has performed detailed kinetic studies <1994JACS11703>. Excellent yields and ee >99% are recorded (Scheme 9).



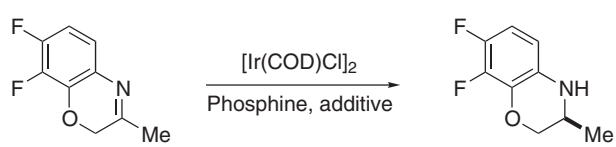
Scheme 9

The same titanocene catalyst (with X = F) has been utilized in asymmetric hydrosilylation reactions, with excellent yields and ee % <1996JACS6784>, and also as part of the total synthesis of (*S*)-coniine (Scheme 10) and (2(*R*),6(*R*))-*trans*-solenopsin A <1998JOC6344>.



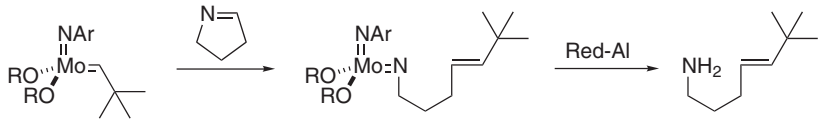
Scheme 10

As part of the synthesis of the antibacterial agent levofloxacin, an iridium complex has been developed as a novel asymmetric hydrogenation catalyst. Starting from $[Ir(COD)Cl]_2$, after screening many chiral phosphine ligands and additives, the optimum conditions were found to be (2(*S*),4(*S*))-*N*-(*t*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]-pyrrolidine (BPPM) with bismuth(III) iodide in a mixed benzene/methanol solvent (Scheme 11). Chemical yields of 96% and enantiomeric purity up to 90% are recorded <1998TA2657>.



Scheme 11

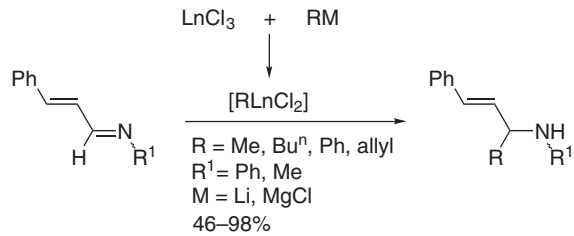
There have been two reports of cyclic imines, such as pyrroline, undergoing ring-opening metathesis (ROMP) using alkylidene Mo(=CHR′)(=NAr)$(OR)_2$ complexes. An intermediate pyrroline-bound complex has been crystallized and characterized, which, on reduction with Red-Al gave the reductively cleaved ligand X (Scheme 12) <1999OM4250, 2000OM3562>.



Scheme 12

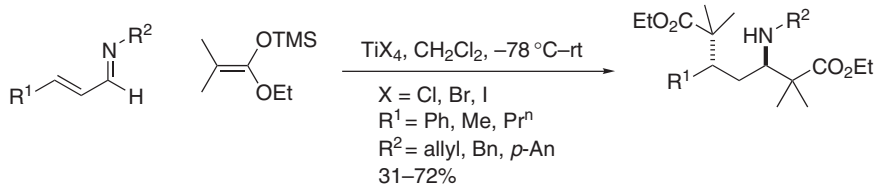
3.10.3.4 α,β-Unsaturated Imines

The control of 1,2- or 1,4-nucleophilic addition to α,β-unsaturated imines has received considerable attention. Electronic and steric effects have been investigated in the regioselective addition of organolithium reagents to imines derived from both naphthalene-1-carbaldehyde and acyclic α,β-unsaturated aldehydes <2001JOC7051>. Organolanthanum reagents [$RLaCl_2$] generated from $LaCl_3$ and an alkyllithium or Grignard reagent add in a highly regioselective 1,2-manner to *N*-alkyl α,β-unsaturated imines (Scheme 13). The use of a chiral auxiliary on nitrogen leads to high diastereoselectivity (90%) <1997JOM143>.



Scheme 13

It is possible to perform a double 1,4- followed by 1,2-nucleophilic addition to α,β-unsaturated imines using ketene silyl acetals and 0.5 equiv. of TiX_4 (Scheme 14) <1999TL8401>. It is also possible to perform a mixed double addition, using a ketene silyl acetal and allyltributylstannane, in which case the acetal always underwent initial 1,4-addition to give an enamine, which rearranged back to an imine allowing for the second stannane addition.



Scheme 14

A general method for the oxidation of cyclic β-enaminoamides and β-enaminoesters to α,β-unsaturated imines, azadienes, and aniline derivatives has been reported using manganese(III) acetate and copper(II) acetate in varying yields <1999T6483>.

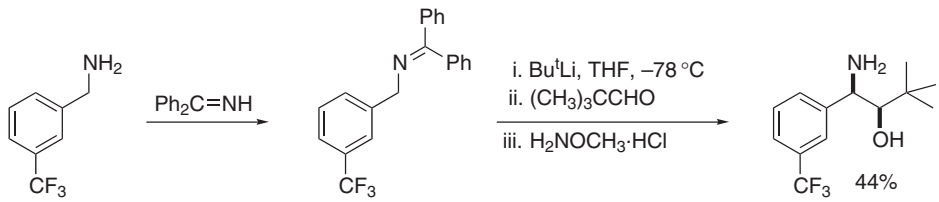
3.10.3.4.1 Arylaldimines

Many of the methods described in COFGT 1995 and earlier in this article are also the main methods for the preparation of arylaldimines and ketimines <1997H555, 1998CPB918, 2001TA439, 2000TL6749, 2002NJC105> and the corresponding heteroaromatic variants <1999TL4615, 2000JOC1516, 2002JHC829, 2003BMC1523>. Several oxidative methods from benylamines have been reported <2000JACS4217, 2002AG(E)3177, 2002IJC(A)541, 2002JPO103, 2003JCR(M)218>. Further oxidation gives nitriles <1999T13265, 2000TL6749>.

Lewis acids, such as boron trifluoride etherate promote the addition of *N*-H-arylaldimines to benzodiazaphosphole-2-oxides <1995MI171>. Allylboranes add in high yields to *N*-H-arylaldimines <2002CPB423>. The silver triflate-promoted Diels–Alder reaction of *N*-H-arylaldimines with Danishefsky's diene has been reported <2003MI475>.

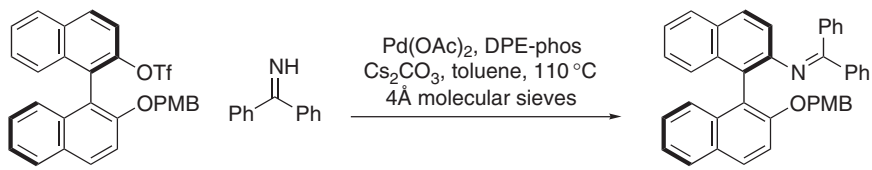
3.10.3.4.2 Arylketimines

Diarylketimines have been prepared by the reduction of benzhydryl azide <1995CC1607> and amine condensation reactions <2001T7501, 2002JCS(P1)2699> as well as by numerous examples of the addition of aryl organometallics to (substituted) benzonitriles, of which there are far too many to cite herein <1995JHC1683, 1998S1167, 1999TL1095, 2002SL113>. Various benzylamines have been reacted with benzophenone imine to give the benzophenone transfer product (Scheme 15) <1996TL945>. The product was then transformed to a β-aryl-β-aminoalcohol.



Scheme 15

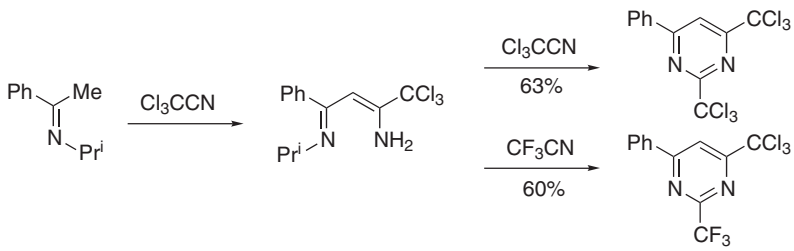
Benzophenone imine and other arylimines react well in palladium-catalyzed amination reactions with 2-triflato-2′-(4-methoxybenzyloxy)-1,1′-binaphthyl and the products readily undergo hydrolysis of the imine and hydrogenolysis of the benzyl group to afford 2-amino-2′-hydroxy-1,1′-binaphthyl (82% over the 3 steps, Scheme 16) <1999TL1095>.



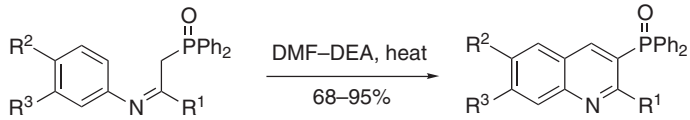
Scheme 16

The 1-azabutadiene derived from *N*-isopropyl-(1-phenylethylidene)amine and trichloroacetonitrile undergoes a double addition reaction with a variety of halonitriles to afford fluoro- and chloro-containing pyrimidines (Scheme 17).

Heating *N*-arylimines, derived from phosphine oxides with dimethyl formamide diethyl acetal (DMF-DEA) gave good yields of quinolinylphosphine oxides (Scheme 18) <2002MI4131>.



Scheme 17



Scheme 18

The reaction of 2-aza-3-trimethylsilyloxy-1,3-butadiene with carbon dienophiles has been described <2001TA439>.

3.10.3.4.3 Aza-1,3-dienes

As in the previous edition, COFGT (1995), the majority of work has focused on the cycloaddition and related chemistry of aza-1,3-dienes.

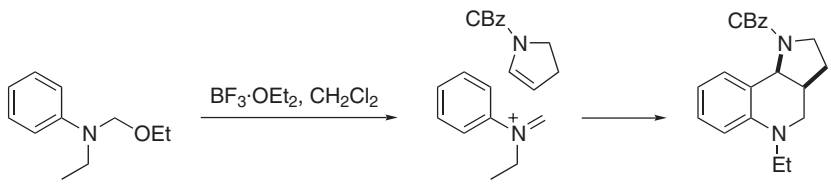
A review on the imino ene reaction has been published <1995S347>.

The aza-Diels–Alder reaction, involving both 1-aza and 2-azabutadienes, has been the prominent synthetic step in many natural product syntheses.

1-Acetylamino- and 1-dimethylamino-1-azadienes react with bromobenzoquinone to give mixtures of 1,8-diaza-9,10-anthraquinone and 1,5-diaza-9,10-anthraquinone, while reaction with 2,6-dibromobenzoquinone gave symmetrically substituted 1,8-diaza-9,10-anthraquinone derivatives <2000T1561>. A similar reaction between 4-methoxy-2-phenylquinoline-5,8-dione and 3-methyl-1-dimethylamino-1-aza-1,3-butadiene has also been used to generate 1,8-diazaanthraquinones <2000H315>. Such fused ring systems occur in several families of antitumor natural products, including the anthracyclines, pluramycins, and some enediyne antibiotics. Polygodial dimethylhydrazone takes part in hetero-Diels–Alder reactions with haloquinones under an air atmosphere to generate a quinolinequinone skeleton <2002TL2127>.

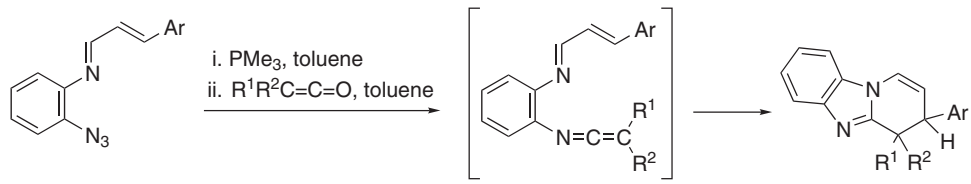
Δ^2-Piperidines have been prepared by the intramolecular Diels–Alder reaction of *O*-vinyl-substituted 2-cyano-1-azadienes <1999TL7211>. A hetero-Diels–Alder reaction of 2-cyano-1-azadienes has also been employed in the synthesis of tricyclic 1,4-benzodiazepines <1998TL4283>.

A cationic 1-azadiene was utilized in a [$4\pi^+ + 2\pi$]-cyclocondensation to prepare the pyrroloquinoline core of the potent antibiotic martinelline (Scheme 19) <2002SL1500>.



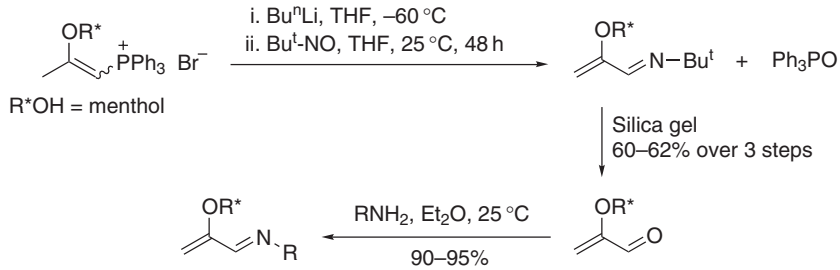
Scheme 19

Ketenimines have been employed for the first time as the 2π electron component in an intramolecular [$4\pi + 2\pi$]-cycloaddition with 1-azadiene (Scheme 20) <2000TL7029>.



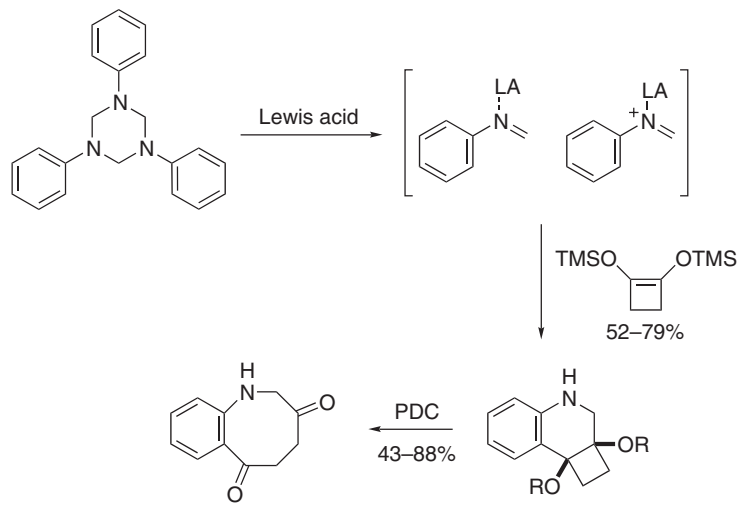
Scheme 20

Chiral 2-alkoxy-1-aza-1,3-dienes have been prepared via an aza-Wittig reaction with dimethylnitrosoethane, although the initial product was unstable to oxidation on purification with silica gel chromatography, forming a 1-oxa-1,3-diene, which could then be reacted with a primary amine to form a variety of 1-aza-1,3-butadienes in excellent yield (Scheme 21). A variety of chiral groups at the 2-position could be incorporated <1997S967>.



Scheme 21

A high level *ab initio* and density functional theoretical study of the aza-Diels–Alder reaction of 2-azabutadienes with aldehydes has suggested that this is a concerted reaction, in good agreement with the experimental evidence <1997JOC3919>. *N*-Methyleneaniline equivalents have been generated from 1,3,5-triphenylhexahydro-1,3,5-triazenes and used in cycloaddition reactions with electron-rich olefins, such as 1,2-bistrimethylsilyloxycyclobutene (Scheme 22) <2000JOC8384, 2002SC1495>.



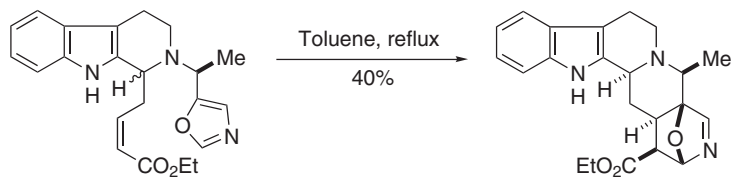
Scheme 22

A novel synthesis of isothiazoles from primary enamines, involving an α,β-unsaturated *N*-H-imine intermediate has been described <1998JCS(P1)77>.

Cationic 2-azabutadienes have also been prepared from α-arylaminosulfones and α-arylaminonitriles by treatment with $SnCl_4$, and participate in intermolecular polar $[4\pi^+ + 2\pi]$-cycloadditions with electron-rich dienophiles in excellent yields <1996SL34>.

Novel 2-aza-1,3-dienes with 1- and 3-electron-donating substituents have been prepared from *N*-thioacylacetamidines (through deprotonation of *N*-ylidene acetamidinium iodides) and trapped *in situ* with heterodienophiles to form pyrimidines in good yields <1996T10095>. 1,4-Bisaryl-2-aza-1,3-dienes may be conveniently prepared from a 1,2-monoazabisylide equivalent <1994JOC4556>. Both enantiopure 1,3-imidazolidines and 1,-benzyl-2,3-disubstituted piperazines may be prepared through the diastereoselective condensation reaction of *p*-tolylsulfinimines and glycine iminoester enolate in the presence of boron trifluoride etherate <2002SL755>. The synthesis and reactivity of imines derived from bisphosphonates and 3-phosphorylated 2-aza-1,3-dienes has been described <2000T6319>. The bisphosphonylalkylimino compounds are useful synthetic intermediates both in the preparation of aminoalkylbisphosphonate derivatives, by reduction of the imine with sodium triacetoxyborohydride, and in the synthesis of 2-aza-1,3-butadienes via olefination reactions. An extended phosphorylated 2-aza-1,3,5-triene undergoes electrocyclization to give 2-phosphorylated pyridines.

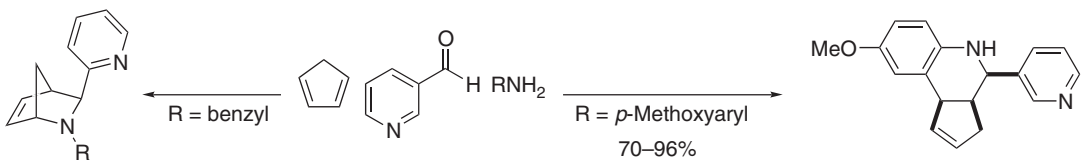
Oxazoles have been employed as effective 2-azadienes for hetero-Diels–Alder reactions, as part of the total synthesis of the alkaloid normalindine, giving moderate-to-good yields of the cycloadduct (Scheme 23) <2000T7751>.



Scheme 23

The aza-Diels–Alder reaction has also been investigated in highly fluorinated (or fluorous) media, employing hexafluoroisopropanol as the reaction solvent <2003TL217>. It was found that *N*-arylaldimines underwent an imino-Diels–Alder reaction with alkyl vinyl ethers to generate tetrahydroquinolines in good yields (70–96%) without the need for a Lewis acid and under mild, neutral conditions.

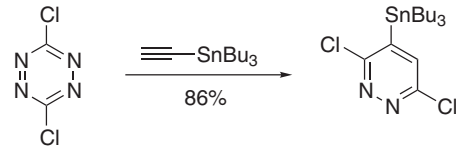
It is worthwhile mentioning that the function of heteroaromatic imines as a diene or dienophile component in the Lewis acid-mediated Diels–Alder reaction may be subtly switched by the nature of the substituent on the imine (Scheme 24) <1999TL8447>.



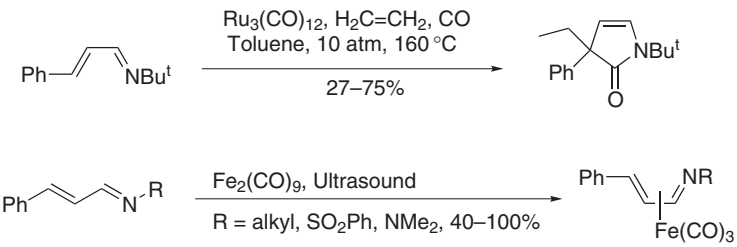
Scheme 24

The first examples of asymmetric quinoline syntheses by inverse electron demand Diels–Alder reactions have been reported using chiral titanium(IV) complexes <2001OL1973>. 3,6-Dichloro-[1,2,4,5]tetrazine has been found to act as an efficient azadiene equivalent in inverse electron demand [4 + 2]-cyclizations with a range of alkenes or alkynes in good yields, to give functionalized pyridazines (Scheme 25) <1998TL5873>.

1-Azadienes have been employed in various metal-promoted cycloadditions. Ruthenium catalyzes the reaction of α,β-unsaturated imines with carbon monoxide and alkenes in a three-component coupling reaction to give α,α-disubstituted β,γ-unsaturated γ-butyrolactams (Scheme 26) <2002JOC7014>.

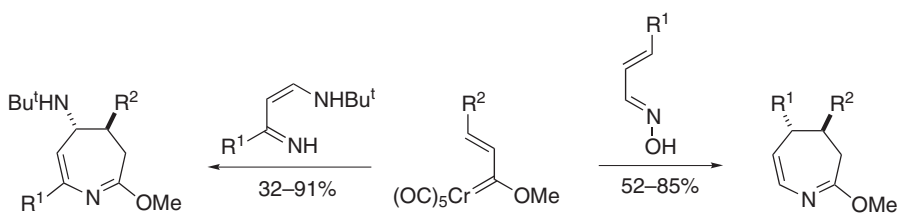


Scheme 25



Scheme 26

It has been found that 1-aza-4-aryldienes readily form tricarbonyliron complexes and that these readily act as tricarbonyliron transfer reagents <2000T2259>. 4-Amino-1-azadienes react with α,β-unsaturated Fischer carbene complexes to give a variety of substituted 3*H*-4,5-dihydroazepines and 1-hydroxy-1-azadienes give azepines in the same reaction (Scheme 27) <1996MI88>.



Scheme 27

The reaction of various vinylidene $Cp'(CO)_2Mn{=}C{=}CH(R)$, cationic carbyne $[Cp'(CO)_2Mn{\equiv}CCH_2R]^+$, and anionic carbene $[Cp'(CO)_2Mn{=}C(OEt)CHR]^-$ complexes toward 1,4-diphenyl-1-azabutadiene in either [2 + 2]- or [4 + 2]-cycloaddition reactions has been reported <1996JOM133>. It has been demonstrated that heteroarylchlorocarbenes react with 1-azabuta-1,3-dienes to give azomethine ylide intermediates under laser flash photolysis, which then undergo 1,5-intramolecular cyclization to give 2,2′-heteroarylpyrroles <1999TL7163>. A one-pot procedure for the transformation of 3-silyloxy-2-aza-1,3-dienes to α-silylated-α,β-unsaturated secondary amides has been described, employing a Zr-mediated retro-Brook rearrangement followed by trapping with an electrophile <2000T4467>.

Miscellaneous syntheses and reactions of aza-1,3-dienes that have been reported include the stereoselective synthesis of allylic amines via reduction of 1-azadienes <2000T8179>. The same researchers have reported a high-yielding synthesis of both racemic and optically active 1-azabutadienes from γ-amino esters via olefination of alkyl glyoxylates and functionalized phosphonium salts <2001T3131>. Upon reduction with hydride, these azadienes gave (*E*)-γ-amino-α,β-unsaturated esters. The synthesis of b-trifluoromethyl 1-azadienes has been reported <1995JFC1>. As a route to the 2-azadienes, the same group have also reported the aza-Wittig reaction of *N*-vinylic phosphazenes, themselves formed from diphenylmethylphosphine and carbonyl compounds <1996TL6379>. 3-Phosphorylated-2-aza-1,3-dienes may also be prepared by a similar method from imines and bisphosphonates <1999TL2411>. Dimerization gives substituted dihydropyridines or further aza-Wittig reaction with unsaturated aldehydes gave 3-azatrienes. Further development of this methodology has given routes to synthetically useful

N-phosphorylalkylimines and *N*-phosphorylalkyl-*N*′-phenylcarbodiimides via aza-Wittig reactions of phosphazenes, themselves derived from aminophosphonates with carbonyl compounds and phenyl isocyanate <2003T2617>.

The reaction of acetylenic esters with *N*-functionalized phosphazenes yields conjugated imines-phosphorus ylides, believed to be derived from the [2 + 2]-cycloaddition of P═N with the triple bond, followed by ring opening of the azaphosphate <2003OBC1112>.

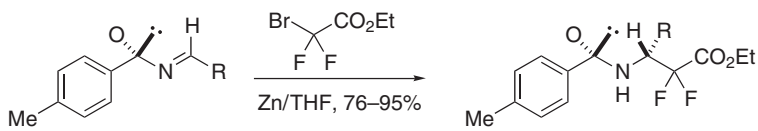
3.10.3.5 Chiral Imines

Chiral *N*-H-aldimines have been prepared by DIBAL-H reduction of chiral nitriles without affecting the α-chiral center <1997TA1061>.

The use of enantiopure imines in many different reactions has rapidly increased over the period of this review. Two major reviews on the asymmetric synthesis of amines via nucleophilic 1,2-addition of organometallic reagents to the C═N double bonds of imines, hydrazones, oxime ethers, and nitrones have been published and the reader is directed to these <1997TA1895, 2002SL651>.

Many different chiral auxiliaries have been employed on nitrogen to control the stereochemistry of a wide range of reactions, e.g., addition reactions of chiral imines to crotonic and methacrylic esters <1995TA1795>; asymmetric Michael-type alkylation reactions <1997TA1963, 2000TA4975, 2001TA1683>, Michael-type conjugate addition reactions <1998TL2675>, and Michael-type additions involving nitroalkenes <1999TA2015> or substituted acrylonitriles <1998MI2897, 2003MI2488>; Lewis acid-promoted additions of silylketene acetals <1995TL5227> and silyl enol ethers <1998SL489> to chiral imines; asymmetric synthesis of β-amino cyclic ethers via Lewis acid-mediated intramolecular cyclization of alkoxyallylstannanes with chiral imines <1998TL1791> and in the addition of alkyl radicals to the acyclic glyoxylate imines <1998SL780>. Chloral and its hydrate undergoes C—C bond formation with a range of optically active imines in the absence of any additives to give, after hydrolysis, β-trichloromethyl-β-hydroxy ketones in good yields (36–83%) and excellent stereoselectivity <2003OL2059>.

Heteroatom-based chiral auxiliaries have also become more popular. A review has been published on the asymmetric synthesis of amino acids using sulfinimines, including the synthesis and use of chiral sulfinimines <1998CSR13>. Enantiopure *p*-toluenesulfinimines have also been employed as efficient chiral imine equivalents in Reformatsky-type reactions with $BrZnCF_2COOEt$ in a high-yielding approach to enantiomerically pure α,α-difluoro-β-amino acids (Scheme 28) <2002TL5445>. Allylzinc reagents have also been shown to add to chiral imines in good yield and excellent diastereoselectivity <2001SL1747>; this method was employed in the synthesis of a broad spectrum carbapenem. Chiral imines prepared from (4(*S*),5(*S*))-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane have been used to direct the enantioselective addition of diethylzinc to arylaldehydes <1998SL965>. The asymmetric synthesis of α-aminophosphonates has been achieved using a three-component reaction of homochiral (1(*S*))-(+)-camphorsulfonamide-derived carbamates, aldehydes, and diethyl phosphite <1996TA21>.

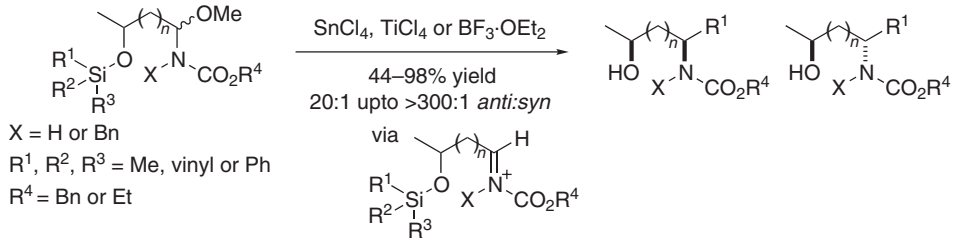


Scheme 28

Computational studies have also been performed on many of these reactions. For example, the addition of boron enolates to imines in aldol-type reactions has been studied using *ab initio* MO methods (3-21G basis set) <1997T7705>.

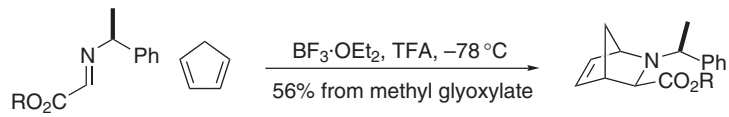
The intramolecular amidoalkylation of chiral imines and iminium ions has been reported as a high-yielding route to anti-1,2- and -1,3-aminoalcohols (Scheme 29) <1995TL2289>.

The chiral imine derived from methylglyoxylate and (*S*)-(−)-1-phenylethylamine has been employed as a versatile dienophile for the aza-Diels–Alder reaction with, for example, furan, with excellent *exo* selectivity and de's between 80 and 98% <2002TA447>. Chiral imines bearing



Scheme 29

a chiral auxiliary derived from tartaric acid react with the Danishefsky diene to give 2,3-dehydropiperidin-4-ones in high yields and excellent enantioselectivity <2000H137>. The method was applied to the total synthesis of (*S*)-coniine.

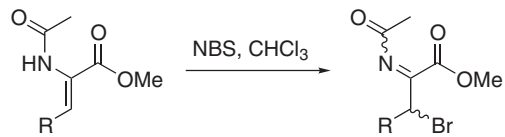


Scheme 30

Chiral imines have played an important role in natural product total syntheses. A new route to enantiomerically pure β-hydroxylated piperidines has been developed from *N*-BOC-2-acyloxazolidines <1998T8783> and applied to the total syntheses of (−)-deoxoprosopinine and (−)-pseudoconhydrine. Both (2(*S*),4(*R*))- and (2(*R*),4(*S*))-4-hydroxypipecolic acid have been prepared from (*S*)- or (*R*)-glycidol and involving a stereoselective hydrogenation of a six-membered cyclic imine <1999TA4231>. Novel pipecolic acid derivatives have been obtained via a modified Strecker reaction <2001JCS(P1)1581>. A formal total synthesis of (+)-vincamine has been achieved by a deracemizing alkylation reaction of a chiral imine <1999TA297>. The chiral imine derived from (L)-malic acid with acid chlorides from glycine derivatives in the presence of triethylamine gave rise to optically active *cis*-β-lactams, which were utilized in the synthesis of a carmonam precursor <1995SL1067>.

3.10.3.6 α- and β-Haloimines

Both aza-Wittig/Staudinger <2000JOC2965> and Horner–Wadsworth–Emmons <2002OL769> reactions have been used to prepare α-trifluoromethylimines. Similar α-trifluoromethyl-*N*-H-imines have been prepared by the condensation of 1,1,1-trifluoro-3-phenylacetone with methylchloroaluminum amide <1995TL4035>. The addition of bromine (from *N*-bromosuccinimide) to *N*-acylvinylamines gives α-bromo-*N*-acylimines (Scheme 31) <1996T5751, 1997T16313, 1999JACS9088>.

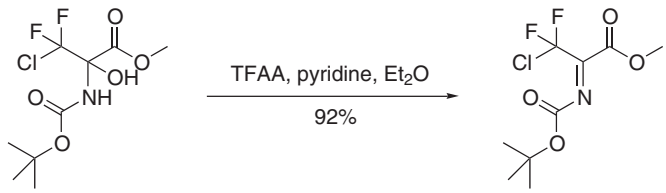


Scheme 31

3.10.3.7 Acylimines

3.10.3.7.1 N-Acylimines

The reader is directed to COFGT (1995) for the general methods of preparation of *N*-acylimines. The addition of bromine to *N*-acylvinylamines utilizing *N*-bromosuccinimide gives *N*-acylimines <1996T5751, 1997T16313>. *N*-Acylimines are generated by the reaction of dimethylcyanamide with butane-2,3-dione <1996T3939>. The elimination of 1,1-hydroxyamines has generated *N*-BOC imines (Scheme 32) <1996JOC7521>.

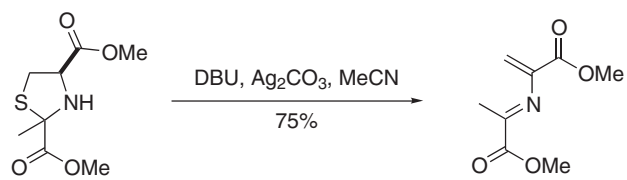


Scheme 32

N-(α-Methoxyalkyl)amides have been used as synthetic equivalents of *N*-acylimines in asymmetric heterocycloaddition processes to form β-benzamido aldehydes <2003JOC4338>.

3.10.3.7.2 α-Acylimines

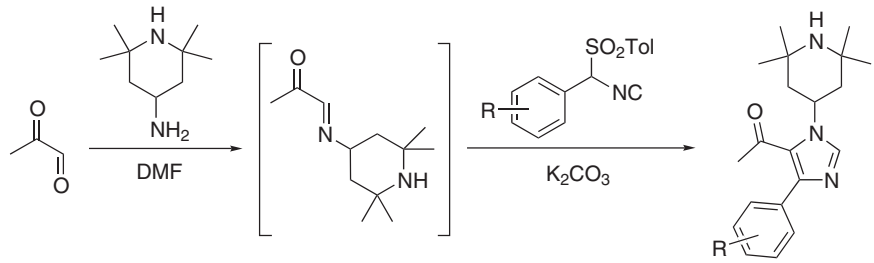
The reader is directed to COFGT (1995) for the general methods of preparation of α-acylimines. Direct amination of butane-2,3-dione in the presence of 3 Å molecular sieves has given α-acylimines in moderate yields <1996M967>. The zinc-mediated Barbier-type propargylation of cyclic imides has been reported <2000TL6479>. The aza-Wittig reaction employing oxomalonic acid diethyl ester and related compounds gives α,α'-diacylimines <1995JOC2384, 1996TL861, 1999JOC8731>. The same oxomalonic acid diethyl ester has been used in direct condensation reactions with amines <1995JMC4508, 1996JMC4531> and variants are known, differing in either ketoester or amine components <1997T8307, 1998BMC1845, 1998T2619, 2001T6215>. α-Acyl-*N*-H-imines have been prepared in good yields (> 60%) by the reaction of various benzaldehydes with *N*-(*n*-octyl)-2,2,2-trifluoroacetimidoyl chloride <1995JFC247>. The treatment of substituted thiazolidines with DBU leads to ring cleavage, generating an α-acylimine (Scheme 33) <1999JOC7229>. Quenching α-metal imines with acid chlorides or chlorocarbonates gives α-acylimines in good yields <1997TL8903>. The same paper also describes the lithium–halogen exchange reaction of various N=C-halo compounds.



Scheme 33

α-Acylimines are readily reduced to the corresponding amine using a variety of reducing agents, for example sodium cyanoborohydride <1998BMC1845, 1998T2619, 2000CAR157, 2000TL663>, aqueous hydrochloric acid <1996JCS(P1)1833>, or hydrogen on palladium <1995JMC4508>. Aryl radicals readily add to the nitrogen atom of α-acylimines <2003JACS163>.

A novel method for the synthesis of imidazoles and oxazoles using aryl-substituted TosMIC reagents and imines (generated *in situ*) has been described (Scheme 34) <2000JOC1516>.

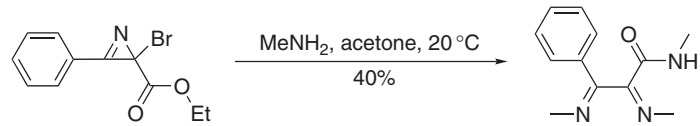


Scheme 34

3.10.3.8 Diimines

Diimines have been prepared using similar methods to those available for the formation of imines. For example, reaction of a 1,*n*-dicarbonyl compound with an amine <2000MI753, 2001SC2405, 2001JACS3229>. Similarly, tethered di- <1998ZOB637, 2003AX(C)m10> or triamines <2002AJC761> react with 2 or 3 equiv. of an aldehyde to produce di- or triimines. Diimines have frequently been prepared by the reduction of the corresponding dinitrile with DIBAL <2000JCS(P1)3578, 2000JOC1799>. The synthesis of 2,3-perfluoroalkyl- and perfluoroaryl-1,4-diazabutadiene (α-diimines) has been reported <1999TL8523>.

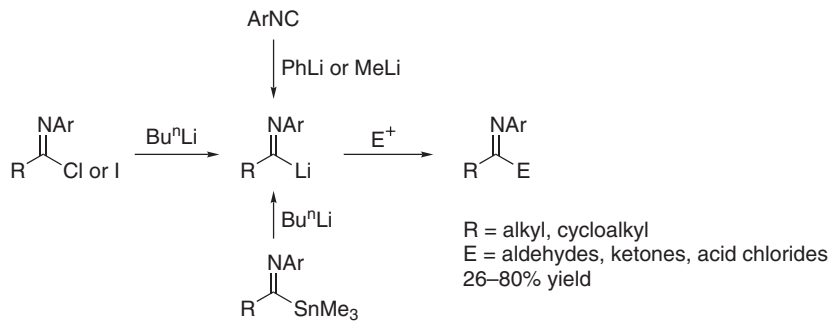
1,2-Diimines have been prepared by the ring opening of bromoazirines (Scheme 35) <2000TL7217>.



Scheme 35

3.10.3.9 *C*-Metal Derivatives of Imines

The reader is referred to COFGT (1995) for leading references for the preparation and uses of *C*-metal derivatives of imines. One paper reports three easy and high yielding methods for the preparation of *C*-lithiated imines: by tin–lithium exchange, by lithium–halogen exchange, and by addition to isonitriles <1998T12007>. The lithiated species could be trapped with a range of electrophiles in good yields (Scheme 36).



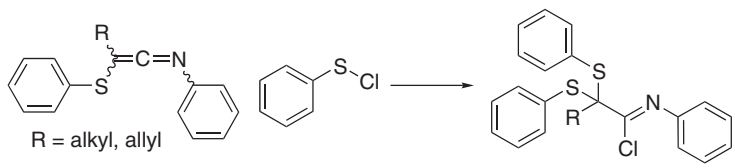
Scheme 36

A theoretical and experimental study of the deprotonation of *N*-isopropyldiphenylketenimine, and its subsequent trapping reactions with electrophiles has been described <1995T3767>.

The metallation and subsequent trapping reactions of (3-bromo-1-*t*-butyl-2-trimethylsilyl-propylidene)-trimethylsilylamine and related *N*-silylketimines have been reported <2000JCS(D)2301, 2001JCS(P1)1103>. Metallation of the 2-position of 1,3-diimines has been described <2000MI753>.

3.10.3.10 α-Sulfenylimines

The reader is directed to COFGT (1995) for general methods for the preparation of α-sulfenyl-imines. The condensation of a primary amine with an aldehyde remains the most popular method for the synthesis of these compounds <2000T5093>. α,α′-Disulfenyldiimines have also been prepared by this method, starting from ethane-1,2-diamine <1996BMC2399, 2000T5093>. The reaction of a 2-phenylsulfanyl alcohol with an amine under acidic dehydrating conditions (acetic acid/magnesium sulfate) gave α-sulfenylimines in good yields <1999TL3119>. Sulfenyl chlorides add to various sulfanyl-alkylidene amines to give α-disulfenylimines in good yields (Scheme 37) <1997PS397, 1999T5405>.



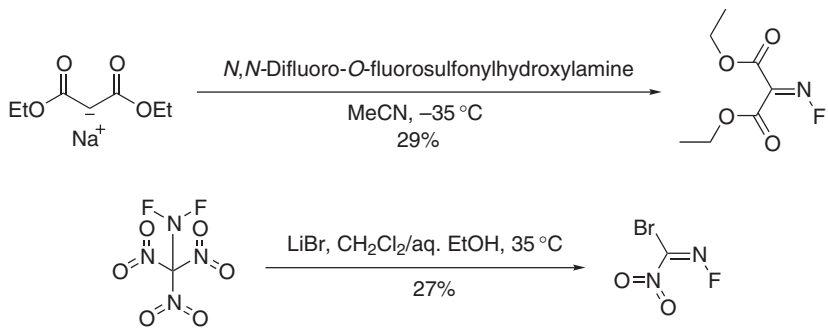
Scheme 37

α-Sulfenylimines may be reduced to the corresponding aminothiol using zinc bromide/sodium borohydride <2002JOC2692>.

α-Selenylimines have been prepared by the condensation of selenyl ketoesters with amines <2000TL663>.

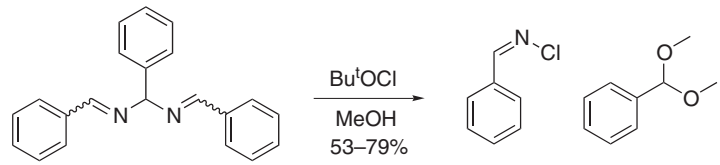
3.10.4 *N*-HALOIMINES

Although still a rare class of compounds, there have been new reports of the preparation of *N*-haloimines, including the first examples of *N*-fluoroimines. These were prepared by reaction of sodium diethylmalonate and *N*,*N*-difluoro-*O*-fluorosulfonylhydroxylamine in acetonitrile <1996DOK358> and by reaction of (difluoroamino)trinitromethane with lithium bromide <2001IZV706> (both illustrated in Scheme 38).



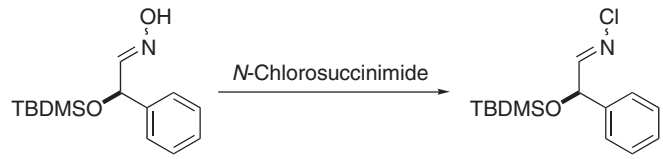
Scheme 38

Good yields (53–79%) of *N*-chloro-*C*-arylimines have been reported from the reaction of *N*,*N*′-disubstituted benzylidenediamines with Bu^{t}OCl (Scheme 39) <1996JOC4185>.



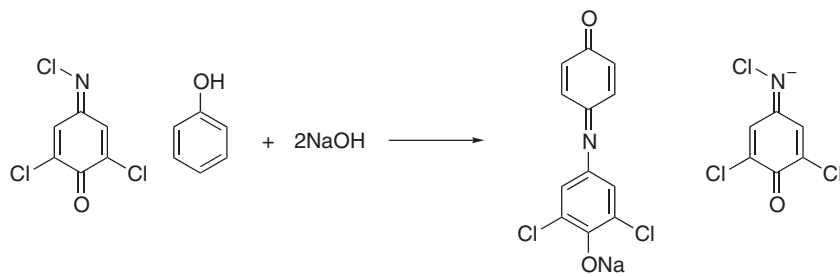
Scheme 39

N-Chloroketimines have been prepared by the reaction of two molecules of *N*,*N*-dichloroisopropylamine with potassium hydroxide <2001MI337>. *N*-Chloroketimines have also been prepared by reaction of chlorine with primary <1997MI1680, 2000MI1721> and secondary <1997MI1979> amines in water and a pH 7 phosphate buffer and also by the action of HOCl on *N*–*H* imines <1998MI29>. Treatment of aldoximes with *N*-chlorosuccinimide has also yielded *N*-chloroimines (Scheme 40) <2002SL1691>.



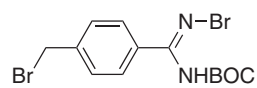
Scheme 40

The primary use for *N*-chloroimines continues to be in the Gibbs reaction—a colorimetric phenol assay and a comprehensive investigation of the mechanism has now been reported <1998JOC6530> and has shown that the *N*-chloroimine radical anion is the key intermediate (Scheme 41).



Scheme 41

An intriguing synthesis of *N*-bromoimines has been reported by accident. In attempting the NBS-mediated bromination of *p*-*N*-BOC-amidinotoluene, bromination occurred preferentially at the amidine imine nitrogen rather than at the benzylic position; bromination only occurred here on addition of a second equivalent of NBS to give **1** <1998BMC1531>. This did not affect the desired nucleophilic substitution occurring at the benzylic position, after which removal of the imine bromine atom was accomplished by washing with an aqueous $Na_2S_2O_3$ solution.



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3.10.5 IMINIUM ION SALTS

3.10.5.1 Iminium Ions

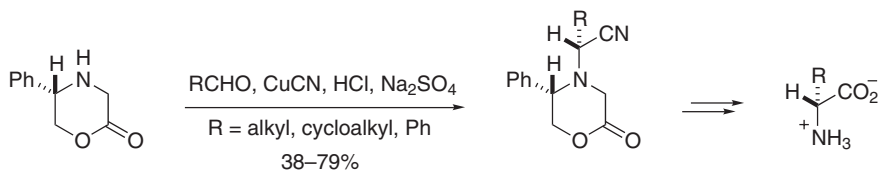
The chemistry of iminium ions continues to be of great interest. The principle methods for the preparation of iminium ions were described in the previous edition and continues to be the main methods for the synthesis of this class of compounds (COFGT (1995)). In addition, treatment of aminals and aminol ethers, derived from secondary alkylamines, with chlorosilanes gives good yields of iminium ions <1997T2941>. These underwent *in situ* reaction with electron-rich aromatic heterocycles to give good yields of mono-aminoalkylation products. Organometallic reagents add to iminium ions generated *in situ* from the treatment of cyclic *N*,*O*-acetals with Lewis acids <1997JOC8280>.

There have been several important physical studies performed on the properties and reactivity of iminium ions. Jencks has studied the lifetimes of a range of iminium cations, formed from the solvolysis of anilinoethers $ArN(CH_3)CH_2SR$, in aqueous solution <1995JACS4851>. The kinetic acidity of iminium ions and their deprotonation to generate azomethine ylides has been reported <2002T2627>. An application of the Exterior Frontier Orbital Extension Model (EFOE model) has been used to explain the origin of π-facial stereoselectivity in nucleophilic additions to imines and iminium ions <1999JOC5396>. The EFOE model was used successfully to describe the facial stereoselection in the addition to imines and iminium ions derived from cyclohexanone, tropinone, and adamantan-2-ones. The electrophilicities of various iminium ions and their rates of reaction with nucleophiles (such as in the Mannich and Vilsmeier–Haack reactions) have been reported <1997TL3503>. The hydride affinities of iminium ions (and also of arylcarbenium ions) in dimethyl sulfoxide and acetonitrile have been recorded <1998JOC4671>.

Amines, formed after hydrolysis of the corresponding iminium ion, are the ultimate product of the trapping of 3-trimethylsilyloxy-1,2-thiiranium ion (themselves formed by Lewis acid-induced rearrangement of 2,3-epoxy sulfides) by imines <1996T3609>.

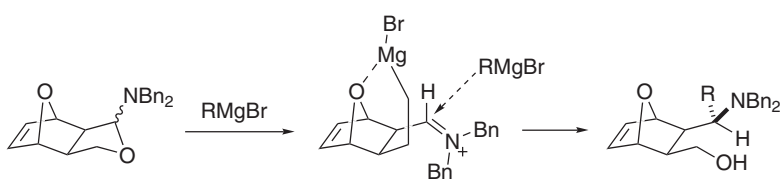
Factors influencing the stereochemical course of the reduction of cyclic iminium ions using sodium cyanoborohydride and sodium triacetoxyborohydride have been investigated, concluding that the conformation preferences of the iminium ion and the effective size of the reducing agent both play a role in determining reduction stereochemistry <1995T5757>.

Iminium ions derived from (*S*)-5-phenylmorpholin-2-one have been shown to undergo diastereoselective Strecker reactions in good yields and diastereoselectivities employing copper(I) cyanide and anhydrous hydrochloric acid. These adducts are useful since they readily undergo degradation to D-α-amino acids (Scheme 42) <2001JCS(P1)1581>.



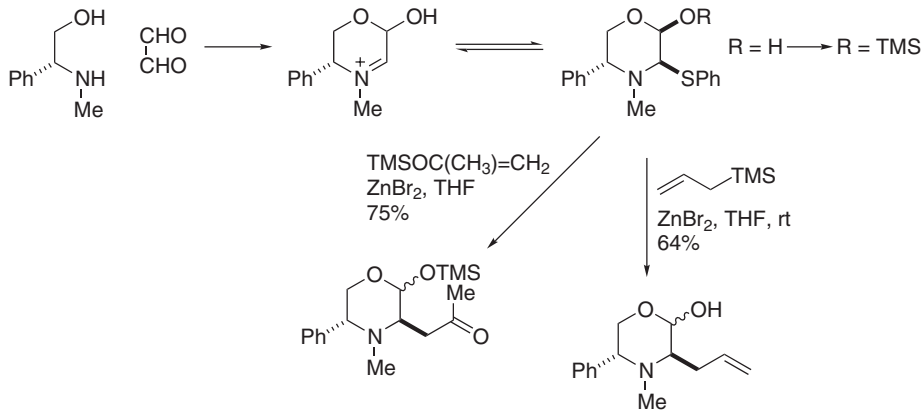
Scheme 42

Tin, aluminum, and zinc have all been shown to promote the Barbier-type allylation of iminium ions in aqueous media to generate homoallylic amines in excellent yields <2003TL667>. Good yields and excellent diastereoselectivities have been reported for the addition of Grignard reagents to masked imines and iminium ions (Scheme 43) <1996TL8729>. Cyanide has also been shown to be an effective nucleophile in the addition reactions to iminium ions, and this has been used in the total synthesis of clavepictine and analogs <2003MI2062>.



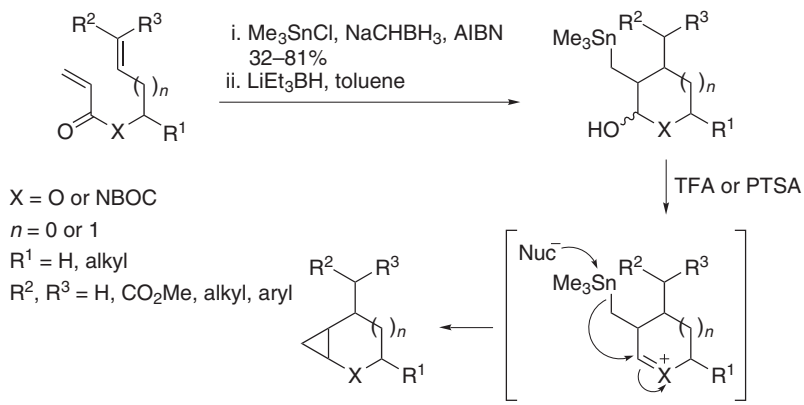
Scheme 43

The iminium ion formed from the condensation of glyoxal and *N*-methyl-(*R*)-phenylglycinol has been reversibly trapped as the aminothioether using thiophenol and shown to undergo zinc bromide-mediated addition of allyl- or allyloxysilanes in good yield (Scheme 44). The products could be hydrolyzed to unsaturated amino acids <1996T9079>.



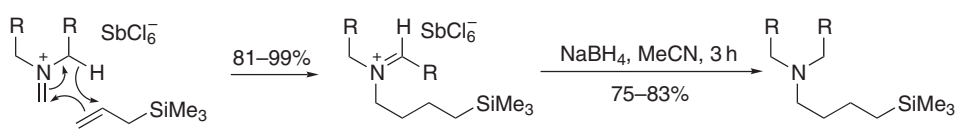
Scheme 44

Trimethylstannyl radicals add to acrylamide or acrylate in the presence of olefinic groups to give the corresponding lactams and lactones with excellent stereocontrol. Under acidic conditions, the products are readily converted to α-methanoheterocycles via the iminium or oxonium ion (Scheme 45) <1996TL8967>. The products may be thought of as rigid mimics of ω-amino acids.



Scheme 45

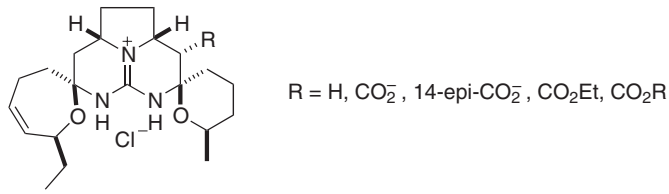
N,*N*-Dialkylmethyleneammonium hexachloroantimonates react with allyltrimethyl silane via inverse electron demand ene reactions, where the allyltriethyl silane acts as the enophile, to give alkylideneammonium ions, which are readily reduced to the tertiary amine (Scheme 46).



Scheme 46

An unusual [1,5] H-shift has been observed in the reaction of methyl acetoacetate to 2-nitrovinamidinium hexafluorophosphate salts, generating either aniline or phenols, depending on the alkylamine substituent <2002OL439>.

A unique class of iminium ion natural products—the crambescidin alkaloids—have been isolated and prepared synthetically by Overman (Scheme 47) <2004CC253, 2004BMC3445>.



Scheme 47

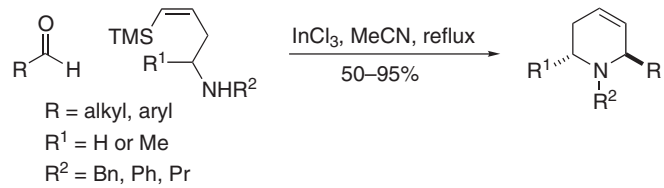
An aza-Wittig reaction has been used in the preparation of another cyclic iminium ion-containing natural product, Pinnatoxin <2003SL891>.

3.10.5.1.1 Iminium ion cyclizations

There are now several excellent reviews of the use of iminium ions in heterocyclic synthesis.

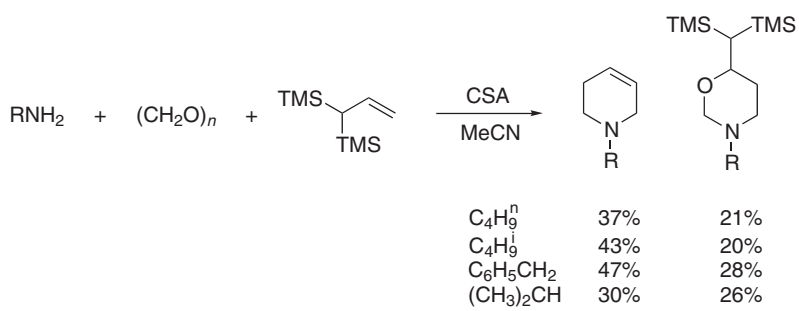
The intramolecular Diels–Alder reaction of iminium ions has been performed in highly polar media, such as 5 M lithium perchlorate–diethyl ether and water to give a range of carbocyclic arrays <1999JOC6041>.

The two major cyclization reactions described in the previous edition continue to attract more attention. In addition to the excellent work of Overman on iminium, ion–vinyl silane cyclizations reported previously, there have been three significant new contributions in the field. Lewis acid-mediated iminium ion–vinyl silane cyclizations have been reported employing indium trichloride to give exclusively 2,6-*trans*-1,2,3,6-tetrahydropyridines in excellent yields (Scheme 48) <2003JOC>.



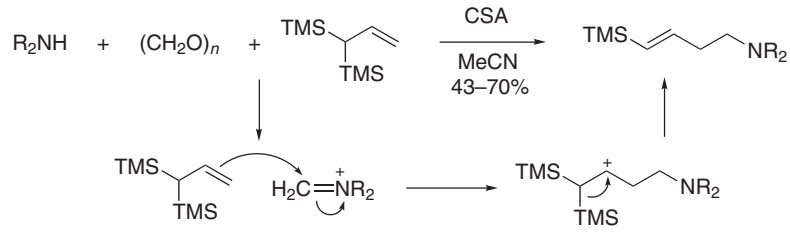
Scheme 48

3,3-Bis(trimethylsilyl)propene reacts with iminium ions, generated from primary amines by an aminomethylation–desilylation process and subsequent cyclization to yield *N*-alkyl-1,2,3,6-tetrahydropyridines (Scheme 49) <1999JOM34>.



Scheme 49

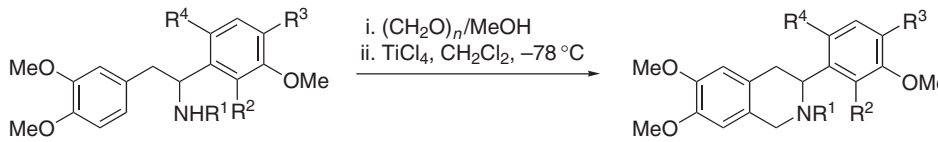
Identical reaction with the iminium ions generated from secondary amines was found to give exclusively (*E*)-β-aminovinyl silanes (Scheme 50) <2000JOM186>.



Scheme 50

Further, Tanner has published an experimental and quantum-mechanical investigation of the vinyl silane–iminium ion cyclization, in order to determine the probable reaction mechanism <2003OBC1041>. He concludes that cyclization via a silicon-stabilized β-carbocation is the most probable reaction pathway, in preference to an aza-Cope rearrangement for (*Z*)-vinyl silanes, but that the aza-Cope reaction does occur for (*E*)-vinyl silanes. A related ene reaction of alkynes has been employed in the stereoselective synthesis of allylamines <1997AG(E)143>.

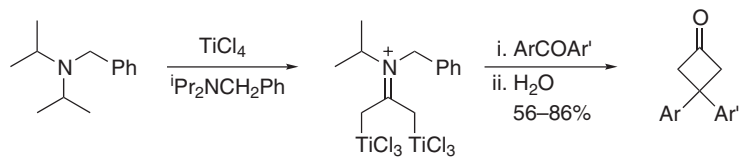
A titanium tetrachloride-promoted iminium ion cyclization is used to prepare 3-aryltetrahydroisoquinolines, important alkaloid building blocks, from *N*-methoxymethyl-*N*-1,2-diarylethylamines (Scheme 51) <1995T12159>.



Scheme 51

The vinylogous Mannich reaction has been used in several natural product syntheses <1999T8905, 1999JACS6990> and as a route to substituted nicotinonitriles <2003SL1959>. The Pictet–Spengler condensation has also continued to receive much attention for the synthesis of the β-carboline indole alkaloids <1995T4841>. Bailey employed a Pictet–Spengler reaction in the total synthesis of the indole alkaloid (−)-suaveoline <2000JCS(P1)3578>. Thioorthoesters have been employed in activated Pictet–Spengler cyclization reactions for the first time, for the synthesis of 1-thiosubstituted tetrahydroisoquinolines. The reaction proceeds via a sulfonyliminium ion <2003TL6137>. The stereoselectivity of the Pictet–Spengler cyclization in superacid media has been investigated <2003OL2078>.

The $TiCl_4$—R_3N couple is known to mediate aldol-type condensation reactions and has been extended to the reaction of iminium salts, generated *in situ*, and diaryl ketones to produce 3,3-diarylcyclobutanones (Scheme 52) <2001CC1728>.



Scheme 52

Rapoport has reported the total synthesis of (+) and (−)-ferruginine from L-glutamic acid via an iminium ion cyclization. It was found that iminium ions, generated by decarbonylation of *N*-benzyl-5-[1-(methoxycarbonyl)-4-oxopentyl]prolines underwent intramolecular cyclization to afford 2,4-disubstituted tropanes in good yield and with high stereospecificity. This methodology was applied to the natural product <1996JOC314>.

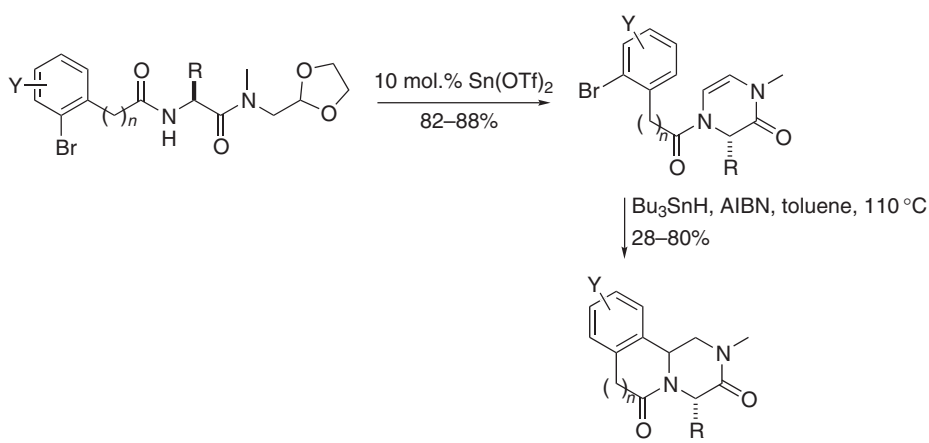
3.10.5.2 *N*-Acyliminium Ions

The chemistry of *N*-acyliminium cations has been reviewed <2000T3817>. A major review of the cyclization reactions of *N*-acyliminium ions has been published and the reader is directed, for a comprehensive coverage of the area <2004CRV1431>. The *bis*(homoallylic) stabilization of *N*-acyliminium ions and its reactions with nucleophiles has been reported <1998TL3341>.

The Mannich-type addition reactions of enol silanes to cyclic *N*-acyliminium ions has been investigated in the gas phase <2002JOC4652>. The reaction of nucleophiles with chiral *N*-acyliminium ions generated from *N*-[1-(phenylsulfonyl)alkyl]oxazolidin-2-ones has been reported <2000JOC8277, 2002JOC2989>. A silicon-induced Pummer/Mannich reaction sequence and cascade has been utilized to prepare various azabicyclic ring systems, including members of the protoberberine alkaloids <1998TL8585, 2000T10159>. Good asymmetric control in the Pictet–Spengler reaction has been achieved using *N*-protected amino acids as chiral auxiliaries <1996MI1566>. The stereocontrolled *N*-acyliminium ion cyclization of succinimide derivative of L-DOPA has been investigated and found to give 5,10b-trans pyrroloisoquinolones in moderate yields (34–36%) and excellent ee (>99%) <2001TL1511>.

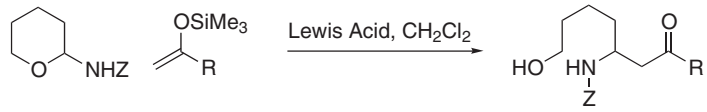
A *N*,*N*′-*bis*(*p*-methoxybenzyl)diketopiperazine asymmetric cation equivalent has been reported for the synthesis of homochiral α-amino acids <2002JCS(P1)2442>. 2,6-Bridged piperazine-3-ones have been prepared by a related methodology <2003JOC4486>.

The 6,5- and 7,5-fused bicyclic peptidomimetic lactams have been prepared by treatment of the hemiaminal, derived from pyroglutamate ring carbonyl in a serine- or homoserine-pyroglutamate dipeptide, with TFA to generate an *N*-acyliminium ion that was intramolecularly trapped by the side chain hydroxyl group <2001TL4943>. Novel amino acid derived heterocycles and peptidomimetic scaffolds have been prepared by the Lewis acid-mediated and radical bicyclization of peptide acetals <2002JOC3985>. Hiemstra has prepared β-aminoalcohols via a combination of *N*-acyliminium ion and Weinreb amide chemistry <2001JCS(P1)2909>. Oxazolo-, oxazino-, and oxazepinoisoindolinones have been prepared by the acid-mediated intramolecular cationic cyclization of *N*-acyliminium ions with an internal oxygen nucleophile <2002TL4747>. A one-pot method for the preparation of α-substituted nitrogen heterocycles (piperidines, pyrrolidines, and indolizidinones) from amino acids has been developed involving *N*-acyliminium ions generated by a radical decarboxylation–oxidation sequence (Scheme 53) <2000TL2899, 2000JOC4930>. A biocatalyic generation of starting materials followed by *N*-acyliminium ion-mediated C–C bond forming reaction has been used to prepare both enantiomerically pure forms of 4-hydroxypiperidines <2002JOC7869>.



Scheme 53

A systematic study of the Lewis acid-catalyzed ring-opening reactions of semi-cyclic *N*,*O*-acetals possessing an exocyclic nitrogen atom with silicon-based nucleophiles has been performed for the first time (Scheme 54) and the method applied to the total syntheses of (+)-isofebrifugine and (±)-sedacryptine <2001JACS12510>.



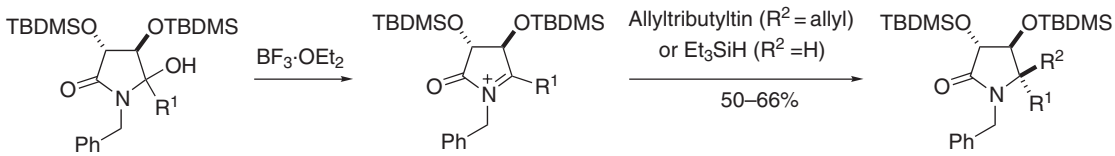
Lewis Acid = TMSOTf, $SnCl_4$, TfOH, $SnCl_4$–AgOTf
R = Ph, OMe, CH_2CH_2Ph, $OCH_2CH{=}CH_2$, OCH_2Ph
Z = CO_2Bn
Yield 31–100%

Scheme 54

A range of organometallic reagents added to *N*-acyliminium ions. Grignard-derived organocopper reagents added in high yield and stereoselectivity to chiral *N*-acyliminium ions formed from proline and 4-substituted prolines <1995JOC5011>. Copper(I) bromide promotes the coupling of alkynes with both *N*-acylimines and *N*-acyliminium ions in water <2002TL5731>. The combination of *N*-acyliminium ion chemistry to generate allene-containing lactams and oxazolidinones followed by the palladium(II)-catalyzed reaction with allyl halides is a rapid and efficient route to the pyrrolizinone and indolizinome skeletons <2001T5123>. The stereochemistry of the addition reaction of titanium enolates to six-membered *N*-acyliminium ions has been investigated <1999TL2891>. An *N*-acyliminium ion intermediate has been proposed in the Lewis acid-mediated addition of nucleophiles to imino glycals to give imino sugars <2003OBC2723>.

The stereoselectivity of the reactions of *N*-phthaloyl iminium ions has been described, along with the reactions of phthalimido-substituted radicals. In both cases, a simple model based on the minimization of allylic 1,3-strain may be invoked to explain the selectivities observed <1996TL2569>. The Lewis acid-promoted reaction of a ketone with an azido-alcohol generates imidate salts, the hydrolysis of which generates medium to large-ring lactams and lactones in excellent yields <1998SL1258>.

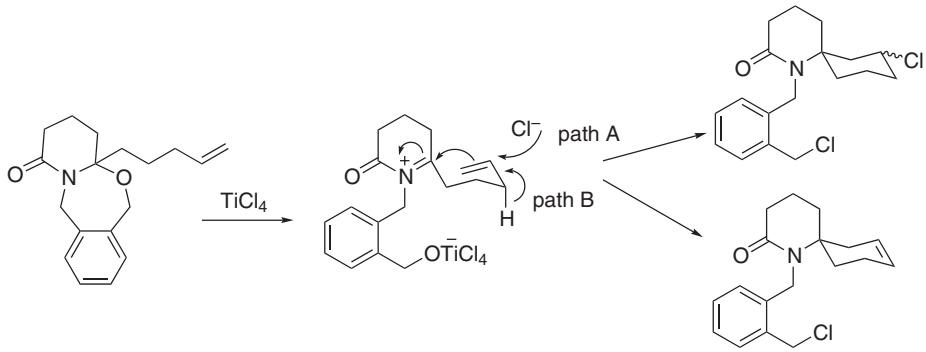
A range of 5,5-disubstituted pyrrolidinones have been prepared in moderate-to-good diastereoselectivities by the *cis*-addition of allyltributyltin and triethyl silane to the *N*-acyliminium ion prepared from the corresponding 5-hydroxylactam (Scheme 55) <2000TA753>. 5-Alkoxypyrroloxazolidin-3-ones have been prepared by a related nucleophilic addition reaction to bicyclic *N*-acyliminium ions <1997TL1415>. Spiro 2-pyrrolidin-5-ones have been obtained from *N*-substituted succinimides by TFA-promoted 5- or 6-*endo-trig* cyclization of *N*-acyliminium ions with a tethered aromatic π-nucleophile (Scheme 56) <2003T3369>. A range of fused nitrogen heterocycles based on the pyrido[2′,3′:3,4]pyrrolo[2,1-*a*] nucleus have been prepared by the same authors by heating pyridine-2,3-dicarboximides with polyphosphoric acid <2001JCS(P1)1446>.



Scheme 55

Cyclopentene-fused pyrroloisoquinolinone derivatives have been prepared by *N*-acyliminium ion cyclizations starting from 4,5-epoxylactams <2002SC2499>.

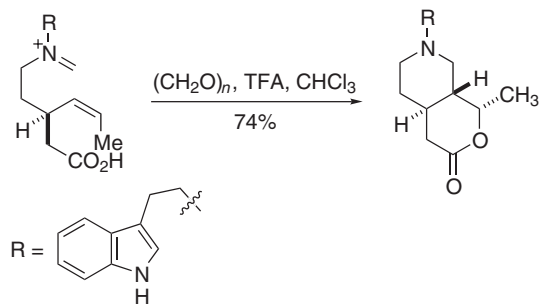
The chemistry of *N*-acyliminium ions has been successfully transferred to the solid support. Hiemstra has reported an acid stable/base labile carbamate linker for *N*-acyliminium ion reactions on solid support <1999TL6079>. The synthesis of homoallylic amines on solid supports via *N*-acyliminium ion reactions has been reported <1999TL1601>. The solid-phase synthesis of both piperidines <2002MI3133> and Δ^5-2-oxopiperazines <2002TL6293> via *N*-acyliminium ion chemistry proceed in high yields on solid supports. Solid-supported reagents often offer an easy



Scheme 56

method for handling reagents that would otherwise be unstable. For example, *N*-(α-methoxyalkyl)-amides have been prepared by solid-phase synthesis, when the solution phase would have been much more difficult <2001MI2318>; the method offers an easy method for handling unstable *N*-acyliminium ion precursors.

The reactions of *N*-acyliminium ions have been key in many natural product total syntheses and many different groups have been employed to terminate *N*-acyliminium ion cyclizations. Padwa has utilized a tandem Diels–Alder *N*-acyliminium ion cyclization reaction to build the erythrinane skeleton <1996JOC4888>. The same group have also performed a number of tandem cyclization reactions involving *N*-acyliminium ions. A tandem thionium/*N*-acyliminium ion cyclization cascade led them to a range of different heterocycles <1998JOC6778>, tandem dipolar cycloaddition–Mannich cyclization gave them tricyclic nitrogen heterocycles <1997JOC67>, and a tandem Pummerer–Mannich cyclization cascade of α-sulfinylamides gave them aza-heterocycles <2002JOC5928> and Jamtine <2003JOC929>. They have also trapped the *N*-acyliminium ions generated from isomünchnone cycloadducts, themselves formed by rhodium(II) perfluorobutyrate-catalyzed carbenoid formation and cyclization from 2-diazo-*N*-hept-6-enoylmalonamides <1999JOC556>. Guo has twice utilized *N*-acyliminium ion chemistry (propargyl silane addition and later a cyclization reaction) in the total synthesis of AG5473/5507 <2000TL5307>. Overman utilized a Mannich biscyclization in the total synthesis of (−)-ajmalicine (Scheme 57) <1995JACS9139>. Halide-terminated *N*-acyliminium ion-alkyne cyclizations have been used by Overman to prepare carbacephem antibiotics <1997JOC9210>.



Scheme 57

An allyl silane has been employed to terminate an acid-promoted *N*-acyliminium ion/spirocyclization in the synthesis of the marine alkaloid lepadiormine <2002JOC4337>. The addition of allyl silanes to *N*-acyliminium ions has also formed the basis of a versatile route to 5-alkylindolizidines, including (±)-indolizidine 167B <2001TL4617>. A novel iodide-promoted allene *N*-acyliminium ion cyclization has been employed in the total synthesis of *ent*-gelsedine <1997JOC8862, 2000JOC8317>. Furan-terminated *N*-acyliminium ion initiated cyclizations have been utilized in the synthesis of various alkaloids, including perhydrohistrionicotoxin <1998JOC6914> and the Lewis acid-promoted addition of siloxypyrroles with chiral imines has lead to the anti-influenza

compound A-315675 <2002JOC5445>. Bicyclic indolizidine and quinolizidine skeletons have been prepared via the intramolecular cyclization of alkynyltungsten compounds with *N*-acyliminium ions <2001JOC6193>.

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Biographical sketch

Adrian Dobbs was born in Bromley, Kent and studied at King's College London, obtaining a B.Sc. in 1992 and a Ph.D. in 1996, working under the guidance of Dr. Keith Jones. He then undertook postdoctoral research for two years with Professor Istvan Markó at the Université Catholique de Louvain, in Louvain-la-Neuve, Belgium, under a Royal Society Research Fellowship. On returning to the UK, he joined the process chemistry department of Glaxo SmithKline (Tonbridge, Kent), before taking up his first academic position at the Open University at the end of 1999. He moved to his current position as Lecturer in Organic Chemistry at the University of Exeter in 2001. His research interests encompass the development of new synthetic methodologies for the synthesis of complex heterocyclic systems and their application to the total synthesis of natural products.

Sharon Rossiter was born in London, studied at King's College London, where she obtained a B.Sc. in 1995 and her Ph.D. in 1999 under the supervision of Dr. Keith Jones. In 1998 she joined the Gray Cancer Institute in Northwood, Middlesex, and then moved to her current position as a Research Fellow at The Wolfson Institute for Biomedical Research, University College London, in 2002. Her research interests include heterocyclic chemistry, in particular transition-metal-mediated couplings, drug design and targeting, and the chemical biology of arginine-metabolizing enzymes.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 419–450

3.11 Imines and Their *N*-Substituted Derivatives: Oximes and Their *O*-R Substituted Analogs

S. ROSSITER
University College London, London, UK
and
A. P. DOBBS
University of Exeter, Exeter, UK

3.11.1 OXIMES AND THEIR DERIVATIVES

3.11.1.1 Oximes of Aldehydes and Ketones

There have been extensive reviews on the synthesis and reactions of oximes <1995COFGT(3)425> and the reader is directed to recent reviews <1997MI183, 2000JCS(P1)125, 2000OPP235>. Oximes and the related nitrones are useful intermediates as substrates for the Beckmann rearrangement, and for 1,3-dipolar cycloadditions <1998CRV863, 2001TCC1, 2002JCS(P1)2419>, for example, in the construction of carbohydrate mimics <2003CUOC585>. Aryloximes may be used as solid-phase ketone linkers <2003OL7>. The chemistry of thiophene and furan oximes, and of indole and isatin oximes, has also been recently reviewed <2001CHE141, 2003CHE3>.

3.11.1.1.1 Preparations of oximes from carbonyl compounds

Oximes are commonly prepared by condensing aldehydes and ketones with hydroxylamine or substituted analogs. These reactions do not always go to completion and reaction times can be long, and therefore there has been interest in more efficient catalysis of the reaction.

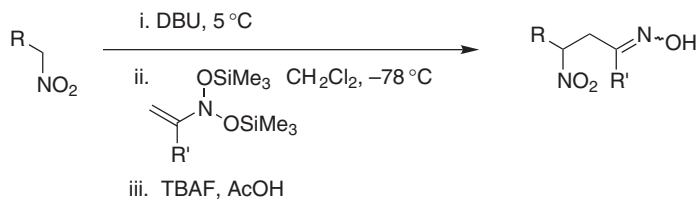
The yields of oximes from reaction of ketones with hydroxylamines can be improved by the use of perfluorinated carboxylic acids, which also act as phase-transfer catalysts <2002MI511>. Stereoselective synthesis of both the (*E*)- and (*Z*)-isomers of oximes has been reported. Reaction of an aldehyde or ketone with hydroxylamine hydrochloride at 90 °C using K_2CO_3 as catalyst gives exclusively the (*Z*)-isomer, whereas the use of $CuSO_4$ as catalyst gives exclusively the (*E*)-isomer <2001SL99>.

There have been recent moves toward greener chemistry methodology, such as solvent-free systems. Aromatic oximes can be prepared without solvent using NaOH <1999SC1697>, or TiO_2/SO_4^{2-} superacid catalyst <2001GC193>, by heating with calcium oxide <2000JCR(S)24> or by grinding with silica <1999SC1697>. Regioselective synthesis of *syn*-oximes can be achieved by grinding with 3 Å molecular sieves <2002JCR(S)20>, and aromatic aldoximes can also be prepared from the corresponding aldehyde and hydroxylamine by brief microwave irradiation with a few drops of methanol in the absence of catalyst <2001M403>. Aliphatic and aromatic aldehydes and ketones react in 47–99% yields when microwave irradiated with wet basic alumina <2001GC275>. Reaction with dry silica under microwave irradiation also gives improved yields <1999JCR(S)228>.

3.11.1.1.2 Preparations of oximes from noncarbonyl compounds

Reduction of nitro compounds has been the major route for synthesis of oximes other than from carbonyl compounds, and numerous methods are described in COFGT (1995).

Reduction of secondary nitronates with hexadimethyldisilane gives oximes in 40–73% yields <1999JOC2211>. Cross-coupling of *N*,*N*-bis(silyloxy)enamines with primary or secondary nitronates yields β-nitrooximes (Equation (1), Table 1) <1999S1767>. For secondary nitronates the reaction must be carried out in diethyl ether at 0 °C to avoid side reactions.



(1)

Table 1 Yields of β-nitrooximes from the cross-coupling of *N*,*N*-bis(silyloxy)enamines with nitronates

R	*R*′	*Yield* (%)
Et	Me	78
H	Me	64
CO_2Me	Me	64
CH_2CO_2Me	H	88
CO_2Me	$(CH_2)_2CO_2Me$	78

Coupling of nitronates with *N*-TMS azoles gives α-azolyloximes <2002HCA3489>.

α,β-Unsaturated nitroalkenes can be reduced with decaborane in the presence of DMSO to give the corresponding oxime in good yield <2003OBC1099>.

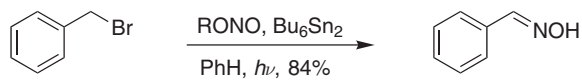
The electrochemical reduction of α-nitrobenzylic compounds produces oximes and hydroxylamines, although the oxime yield is improved when the phenyl ring contains electron-withdrawing groups <1995MI1877>.

Oxidation of amines to oximes is a reaction that has attracted attention in recent years, although selective oxidation and/or separation of the various oxidation products has limited the usefulness. Recently, a catalytic system using zeolites has been developed: tungsten silicate TS-1 and dilute H_2O_2 catalyze oxidation of benzylic and allylic amines to oximes in good yield <1995TL1903, 1995T11305>.

Activated alcohols can be converted directly into the oxime by manganese dioxide oxidation with Amberlyst 15-supported hydroxylamine <2002SL1287>.

Oximes may be synthesized from alkenes by cobalt(II) porphyrin-catalyzed reduction–nitrosation with *t*-butylnitrite <1998SL1270>. This reaction is applicable to styrenes, α,β-unsaturated carbonyl compounds, and $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds. The radical addition of tritylthionitrite to alkenes occurs under thermal or photochemical conditions to give the α-tritylthio-oximes <2001TL4377>.

Radical reaction of alkyl halides with nitrite esters and hexabutylditin gives oximes in good yield (Equation (2)), although this is not successful for secondary alkyl halides <1995TL323, 1997T16847>.

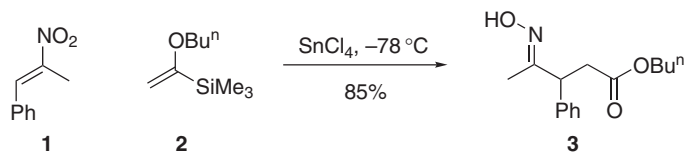


(2)

Radical reduction of peracetylated β-D-glucopyranosylnitromethane with tributyltin hydride leads to the oxime <2002M383>.

3.11.1.1.3 Miscellaneous methods for the preparation of oximes

The oxime **3**, and not the expected nitronate, was the product of the $SnCl_4$-mediated [4 + 2]-cycloaddition of nitroalkene **1** to vinyl ether **2** (Equation (3)) <1998JOC6167>.



1 **2** **3**

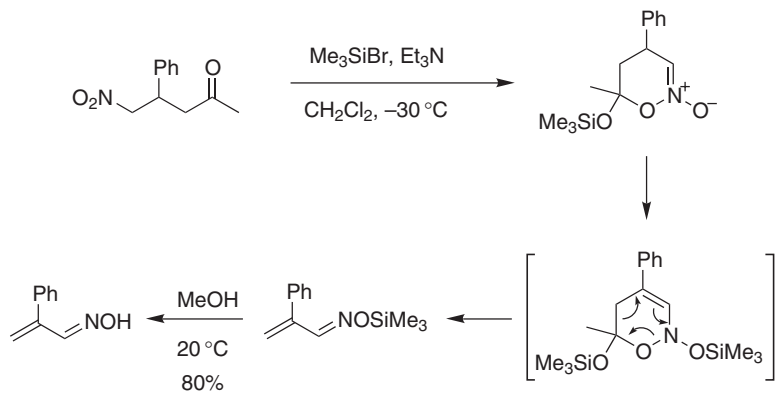
(3)

β-Ketoxime sulfones can act as soft nucleophiles for monoalkylation and then subsequently as electrophiles (via 1,4-elimination of the sulfinic acid) to give α,α-dialkylated oximes <1996T6903>.

3.11.1.1.4 α,β-Unsaturated oximes

Silylation of nitro compounds followed by ammonium fluoride desilylation gives β-functionalized α,β-unsaturated oximes <2002S635>.

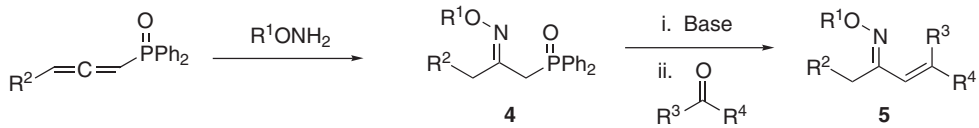
Silylation of the cyclic nitronate from 5-nitro-4-phenylpentan-2-one gives the TMS ether of 2-phenylpropenal oxime via the intermediate oxazine, which undergoes [4 + 2]-cyclofragmentation (Scheme 1) <2000EJO3229>.



Scheme 1

β-Oximophosphine oxides are simply prepared from hydroxylamines and phosphine oxide allenes, and act as intermediates for the synthesis of α,β-unsaturated oximes via treatment with base followed by a carbonyl compound (Scheme 2) (Table 2) <1996TL1289, 1998T599>.

α,β-Unsaturated oximes may be used to prepare primary allylamines via the phosphorylated azadiene <1998EJO1413>.



Scheme 2

Table 2 Synthesis of α,β-unsaturated oximes from β-oximophosphine oxides

R^1	R^2	R^3	R^4	*Yield* **4** (%)	*Yield* **5** (%)
H	H	H	*p*MeO–C_6H_4	80	79
H	H	H	$CH_3CH(CH_3)CH_2$	80	81
H	H	Ph	Ph	80	80
H	Me	H	*p*CH_3–C_6H_4	74	88
TBDMS	H	H	*p*CH_3–C_6H_4	84	80

3.11.1.1.5 Cyclic oximes

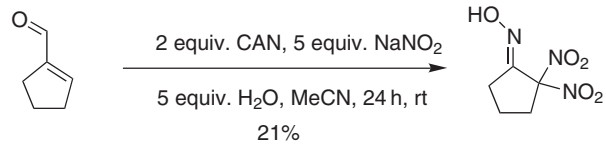
Cyclohexanone oxime has been prepared by reaction of cyclohexanone and ammonia with an oxidant (air or TBHP) in the presence of a bifunctional cobalt or manganese-based molecular sieve catalyst under solvent-free conditions <2001JA8153>.

Reaction of cyclic ketones on TS-1 (titanium silicate molecular sieves) with H_2O_2 and ammonia furnishes the oxime in ~20–30% yield <1996JCA570>. An improved catalyst for this reaction, a Ti-containing rigid hybrid mesoporous silsesquioxane, gives up to 90% yield of cyclohexanone oxime <2003CC470>.

Cyclohexanone oxime can also be obtained from the radical reaction of cyclohexyl iodide, isoamylnitrite, and hexabutylditin <1997T16847>.

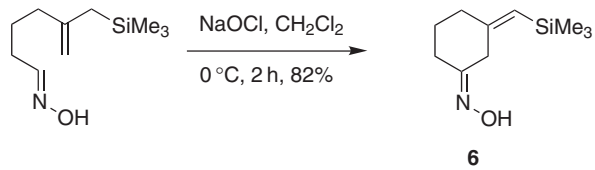
Reduction of cycloalkylnitronates with HMDS gives the oximes <1999JOC2211>.

Treatment of cyclopentene-1-carbaldehyde with ceric ammonium nitrate and sodium nitrite unexpectedly gives 2,2-dinitrocyclopentanone oxime (Equation (4)) <1998TL6617>.



(4)

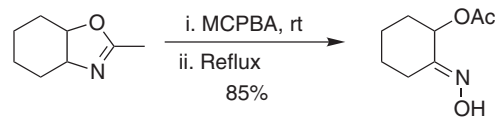
Oximes with a tethered allyltrimethylsilyl group can undergo a novel ene-like cycloisomerization to the cyclic oxime **6** (Equation (5)) <2002AG(E)1586>. The single geometric isomer shown is obtained, confirmed by NOE experiments.



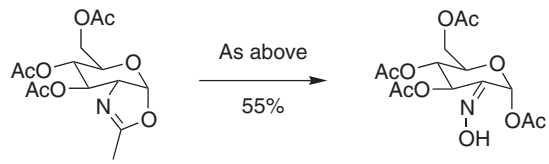
6

(5)

Cyclic α-acetoxyoximes are obtained on MCPBA oxidation of bicyclic oxazolines <2002TL347>, opening a route to novel saccharide derivatives (Equations (6) and (7)).



(6)

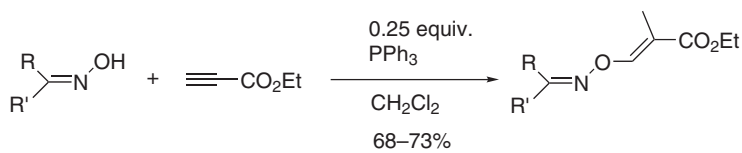


(7)

3.11.1.2 *O*-Carbon-substituted Oximes

Oxime ethers can be readily prepared from carbonyl compounds in high yields in a one-pot reaction with hydroxylamine, an alkyl halide, and potassium hydroxide in aqueous DMSO <2003SC543>.

O-Vinyloximes are generally prepared by direct reaction of the oxime with acetylene, although many are unstable and so their usefulness as synthetic intermediates is limited. The stable *O*-vinyldiaryl and *O*-vinyl(heteroaryl)ketoximes can be prepared from the parent oximes by heating with acetylene in KOH/DMSO under pressure <2002T10043>. Triphenylphosphine-catalyzed conjugate addition of oximes to ethyl propiolate selectively gives the (*E*)-*O*-vinyloxime (Equation (8)) <1997SC1449>.

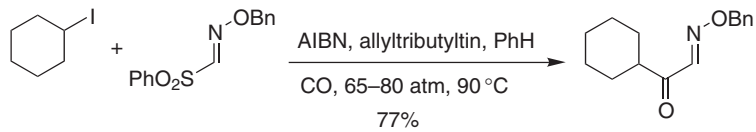


(8)

O-Methyloximes and *O*-benzyloximes can be prepared by oxidation of activated alcohols with manganese dioxide and methoxylamine hydrochloride or benzoxylamine hydrochloride, but preparation of *O*-allyl- and *O*-*t*-butyloximes requires the relevant hydroxylamine to be Amberlyst 15-supported <2002SL1287>.

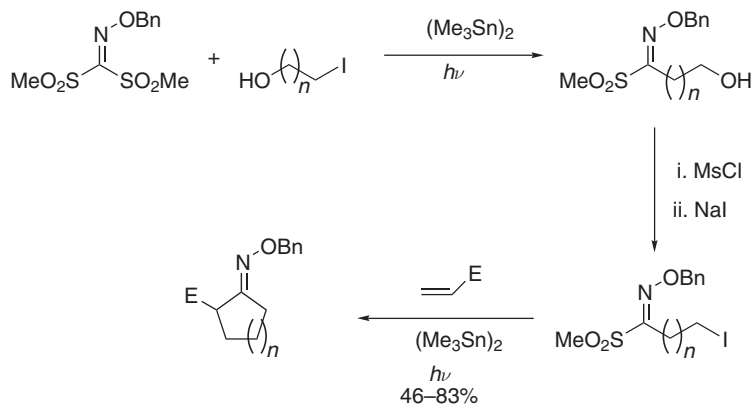
The previously mentioned synthesis of β-oximophosphine oxides (Scheme 2) is also applicable to the synthesis of *O*-methyloximes (where R^1 = Me). Alternatively, the *O*-TBDMS oxime can be *O*-alkylated by NaH/RX <1998T599>.

Vicinal mono- or di-acylated oxime ethers are obtained by multiple-component radical couplings between RX, carbon monoxide, and phenylsulfonyloxime benzyl ether (Equation (9)) <1999JA12190>.



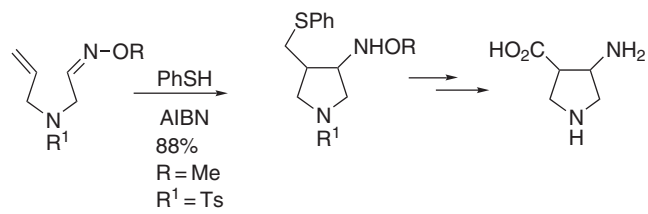
(9)

Cyclic oxime ethers are obtained from *O*-benzyl-bismethanesulfonyloxime ether by sequential radical acylation <2000SL1148> (Scheme 3).



Scheme 3

Radical additions to oxime ethers have been reviewed <2003YZ285, 2003OBC381>. Sulfanyl radical addition–cyclization of oxime ethers can be employed to synthesize cyclic β-amino acids (Scheme 4) <2002T4459>.



Scheme 4

3.11.1.3 Nitrones and Related Derivatives

Nitrones are extremely useful synthetic intermediates, and their use in 1,3-dipolar cycloadditions <1998CRV863> and their reactions with organometallics <2002CUOC695, 1998CRV1407> and nucleophiles <2000S759> have been reviewed. Efficient routes for the synthesis of nitrones have been discussed <2000OPP175>.

3.11.1.3.1 Acyclic nitrones

Nitrones are traditionally prepared from condensation of monosubstituted hydroxylamines with aldehydes and ketones <1995COFGT(3)425>.

Nitrones may also be prepared from disubstituted hydroxylamines by oxidation. Sodium hypochlorite <1999JOC7243>, *N*-*t*-butylbenzenesulfinimidoylchloride <2001MI58>, and manganese dioxide <2001TL6503> have recently been employed as less toxic oxidants than the mercuric oxide traditionally used for this transformation. Some enantioselectivity is observed in the oxidation of hydroxylamines with urea–hydrogen peroxide complex and Jacobsen's catalyst <1999TL1989>. *N*-Benzyl acyclic nitrones may be conveniently prepared by zinc chloride-catalyzed condensation of benzylhydroxylamine with aliphatic ketones <1995SC2275>. A green synthesis of α,*N*-diarylnitrones, by grinding an aryl aldehyde and phenylhydroxylamine with clay, is reported <1997SC4041>.

Reaction of aldoximes with α,β-unsaturated carbonyl compounds in the presence of zinc(II) iodide/boron trifluoride etherate generates the *N*-alkylated nitrones in high yields <2001TL6719>. Copper(II) triflate can also be used for this transformation <2002TL3891>. Moderate enantioselectivity can be achieved in this type of conjugate addition by using chiral Lewis acid catalysts <2002TL829>.

α,β-Unsaturated nitrone precursors to a series of 1,2-oxazin-6-ones were prepared by the photooxygenation of 2-methoxyfurans in the presence of acetaldehyde oxime <1999SL417>.

A novel synthesis of *O*-substituted nitrones has been achieved by the reaction of the anions of aliphatic nitro compounds with nitroso compounds <1996MI856>. A one-pot synthesis of functionalized nitrones by zinc-mediated reduction of nitroalkanes in the presence of aldehydes has been devised. The mild reaction conditions are compatible with α,β-unsaturated groups and sugars <2001SL1281>.

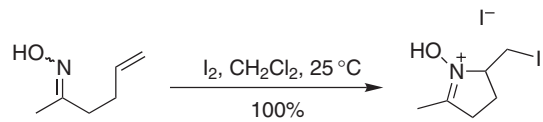
Nitrones are generated upon irradiation of imines in TiO_2/acetonitrile under oxygenated conditions <1998TL3547>.

Nitrones may be prepared by the oxidation of amines. The use of hydrogen peroxide as oxidant with a metal catalyst is well established. A phosphotungstate/ampiphilic polymer catalyst has been employed for this reaction <2002SL2031> and oxaziridines have been used as the oxidant <2000TL1583>. *p*-Toluenesulfonic peracid (TsOOH) can also oxidize amines to the corresponding nitrones <1996T5773>. Recently a system employing cumene hydroperoxide as the oxidant and a titanium alkoxide catalyst, which is protected from hydrolysis by the addition of a trialkanolamine ligand and molecular sieves, has been developed <2003TL49>.

α-Heteroatom-substituted nitrones have also been prepared <2002TL2445>. α-Amino nitrones have been used in the synthesis of amino acids <1998JCS(P1)955>.

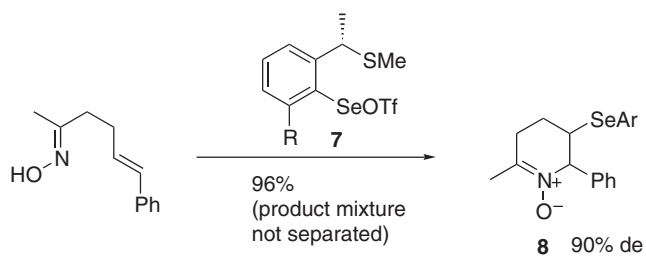
3.11.1.3.2 Cyclic nitrones

Grigg and co-workers have worked extensively on the formation of cyclic nitrones from oximes and oxime-nitrone-cycloaddition cascades <2000T10087, 2001T1119, 2001T7035>. Cyclization of γ- and δ-alkenyloximes with I_2 or ICl furnishes the cyclic nitrones or their dimeric salts (Equation (10)) <2001T1119>.



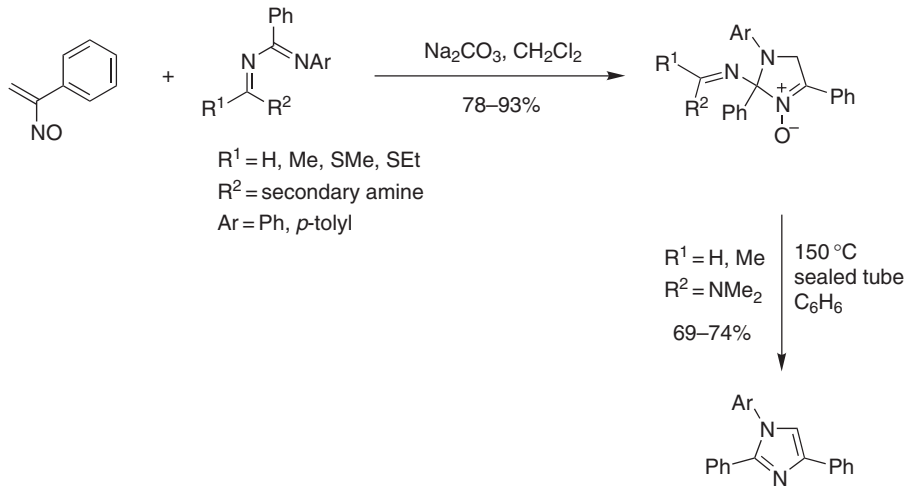
(10)

The regioselective selenocyclization of alkenyloximes to give the cyclic nitrones **8** is also effected by the selenylating agent **7** with good diastereoselectivity (Equation (11)). The diastereomeric ratios were determined by ^1H NMR spectroscopy <2001TA3297>.



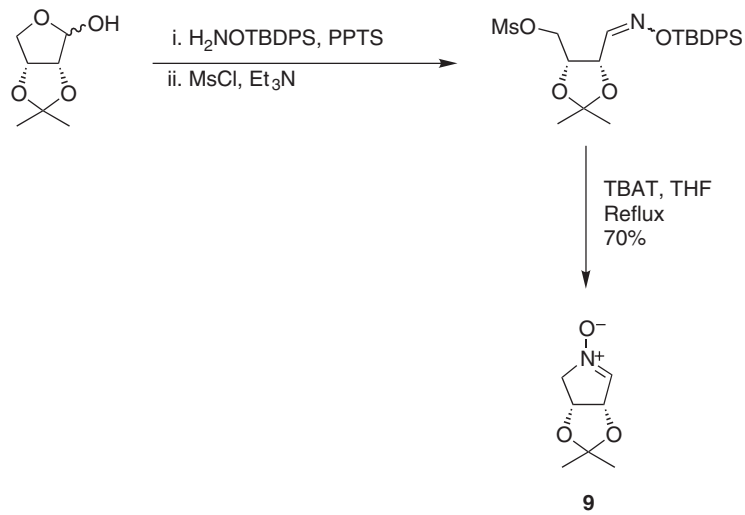
(11)

α-Nitrosostyrenes undergo regioselective [3 + 2]-cycloadditions with 1,3-diazabuta-1,3-dienes to give cyclic nitrones. For some examples, thermolysis of these nitrones gives imidazoles <1997JCS(P1)3065> (Scheme 5).



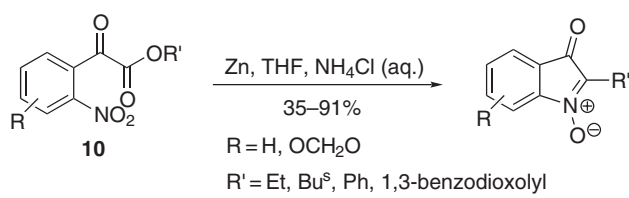
Scheme 5

Sugar-derived hemiacetals can be converted into *O*-TBDPS oximes by treatment with *O*-*t*-butyldiphenylsilylhydroxylamine. Mesylation of the terminal hydroxyl followed by desilylative cyclization with tetrabutylammonium triphenyldifluorosiliconate (TBAT) furnishes the cyclic nitrones **9** (Scheme 6) <2002SL1344>.



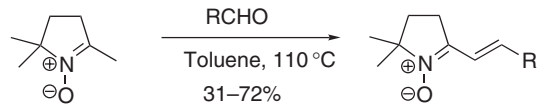
Scheme 6

2-Substituted-3*H*-indol-3-one-*N*-oxides can be obtained by the reductive cyclization of dione **10** (Equation (12)) <2001SL700>.



(12)

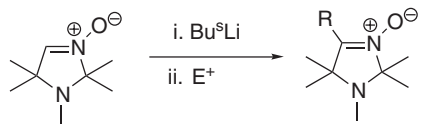
Cyclic nitrones, e.g., **11**, react with aldehydes in refluxing toluene to give the α,β-unsaturated nitrones **12** (Equation (13)) <2003S1367>.



11 **12**

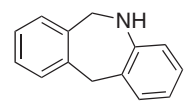
R = alkyl, aryl, alkenyl, CO_2Et (13)

Cyclic nitrones can undergo α-lithiation followed by electrophilic attack to give α-heteroatom-substituted cyclic nitrones (Equation (14)) <2002TL2445>.



R = HgCl, 55%; $SiMe_3$, 75%; $GeEt_2$, 75%; $SnBu_3$, 80%; $POPh_2$, 66%; Cl, 90% (14)

Azepine **13** can be safely oxidized to the cyclic nitrone on a large (60 mol.) scale using MCPBA <2002OPRD911> (Figure 1).

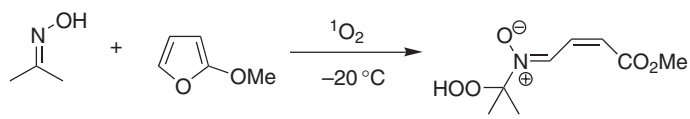


13

Figure 1

3.11.1.3.3 Miscellaneous nitrone derivatives

α-Hydroperoxynitrones may be obtained by the singlet oxygen oxidation of 2-methoxyfuran in the presence of an oxime (Equation (15)) <1996JOC8677>.

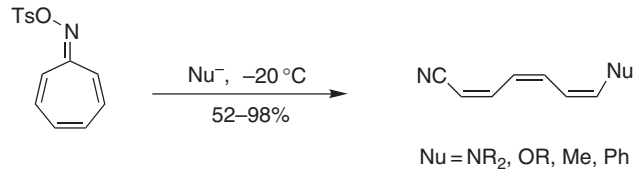


(15)

Lately, there has been an expansion in the use of enantiomerically pure nitrones in enantioselective syntheses. Carbohydrate-derived nitrones are an important tool for stereoselective cycloadditions, and their use has been reviewed <2002JCS(P1)2419>.

3.11.1.4 *O*-Chalcogen-substituted Oximes

Oxime sulfonates are useful intermediates for the synthesis of α-aminoketones. Oxime mesylates have been used for the conversion of indanones into 3,4-dihydroquinolin-2-ones <2003BMC2205> and 1,2,3,4-tetrahydroquinolines <2000TA4687>. Nucleophilic cleavage of tropone oxime tosylate generates the substituted (*Z*,*Z*,*Z*)-1,3,5-hexatriene carbonitriles (Equation (16)) <1995JA1258>.



(16)

The unusual oxaselenazole **14** is prepared by oxidative cyclization of the α-selenooxime <2002JOC499>. Reaction of α-methylcyclohexyloxime with selenium dioxide generates the cyclic selenooxime **15** <1995IJC(B)280> (Figure 2).

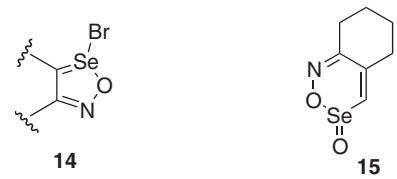
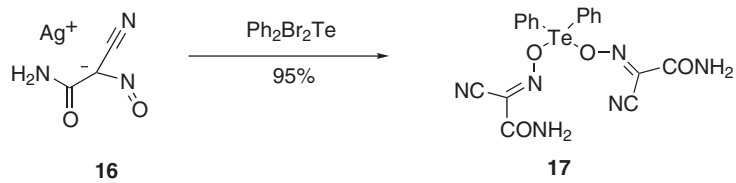


Figure 2 The unusual oxaselenazole **14** and cyclic selenooxime **15**.

The unusual bisoximo tellurium species **17** is prepared from Ph_2TeBr_2 and the silver complex **16** (Equation (17)) <1996ZN(B)832>.



(17)

3.11.1.5 *O*-Phosphorus and *O*-Arsenic-substituted Oximes

Novel oximoxy-tris-(dimethylamino)phosphonium salts undergo the Beckmann rearrangement in solution, and can be trapped to give a convenient synthesis of amidines <1999T1329>.

No further advances have occurred in the area of *O*–As oximes since the publication of COFGT (1995) (chapter 3.11.1.5).

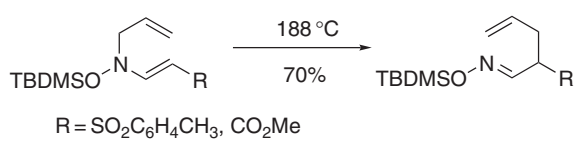
3.11.1.6 *O*-Silicon-substituted Oximes

Nitroalkyls react with TMSOTf to give the *O*-TMS oxime <2002S635>.

N,*N*-Bis(silyloxy)enamines, derived from silylnitronates, can generate α-silyloxy or α-ammonium *O*-silyloximes <2000JCS(P1)2926>.

O-TBDMS oximes can be α-homologated by reaction with LDA and an alkyl halide <1999T12275>.

N-Silyloxy-*N*-allylenamines undergo a 3-aza-Cope rearrangement to the oxime silyl ether, giving a mixture of *syn*- and *anti*-products (Equation (18)) <2002CC746>.



(18)

O-Silyloximes are also activated for hetero-Diels–Alder reactions to give pyridines <1997TL2211>.

3.11.2 *N*-HETEROATOM ANALOGS OF OXIMES

3.11.2.1 Sulfur Analogs

3.11.2.1.1 Sulfenimines

Sulfenimines are useful synthetic intermediates. Enantiomerically pure sulfenimines prepared from (+)-camphor <1999SC2645> can be used in asymmetric synthesis, e.g., the synthesis of amines via sulfenamides <1995SC1551> and α-amino acids via sulfenaminonitriles <1996SC63>.

1-Alkenesulfenimines are readily obtained by reaction of aldehydes or ketones with *N*,*N*-bis-TMS-1-alkenesulfenamides <1996T8387>.

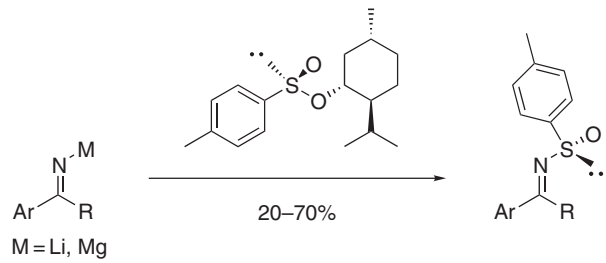
The thermal decomposition of (*E*)-3-azido-3-hexene-2,5-dione in the presence of *t*-butylthiol gives the sulfenimine as one major product. This is believed to be formed via a thio-Staudinger reaction <2003PS2169>.

The reaction between Grignard reagents prepared from allylic or propargylic halides and the *N*-phenylsulfenimine derived from the heptane-2,6-dione affords primary 1-alkenyl (or alkynyl)-3-methylcyclohex-2-enamines in good yields <1998SC3279>.

3.11.2.1.2 Sulfinimines

Chiral sulfinimines can be used in asymmetric synthesis, and preparation of sulfinimines in enantiomerically pure form has been of great interest. Sulfinimines have been used to synthesize a variety of important classes of compounds such as α- and β-amino acids <1998CSR13, 2000JOC8704, 2001TA1047>, 1,2-aminoalcohols <2001JOC8772>, aziridines <1996TA3407>, and β-hydroxy-α-aminophosphonates <2003JOC7249>.

Preparation of chiral sulfinimines via menthyl *p*-toluenesulfinate continues to be a popular method, and their subsequent use in synthesis has been reviewed (Equation (19)) <1997JOC2555>.



(19)

More recently, an improved synthesis of sulfinimines by the direct condensation of (*S*)-(+)-*p*-tolylsulfinamide with aldehydes and ketones has been developed <1999JOC1403>.

Preparation of *p*-tolylsulfinimines in >98% ee using a bornane-10,2-sultam as the chiral sulfinylating agent has been achieved <1997TL2825>.

Preparation of *t*-butylsulfinimines is achieved via the catalytic asymmetric oxidation of *t*-butyldisulfide <1998JA8011>, or by direct condensation of aldehydes and ketones with *t*-butylsulfinamide <1999JOC1278>. These *t*-butylsulfinimines have shown greater diastereoselectivity than the *p*-tosylsulfinyl derivatives <1996TA3407> and have been employed in the asymmetric synthesis of α,α-dibranched amines <1999JA268>.

Oxidation of (+)-camphor-derived sulfenimines with MCPBA gives the corresponding sulfinimines <1999SC2645>.

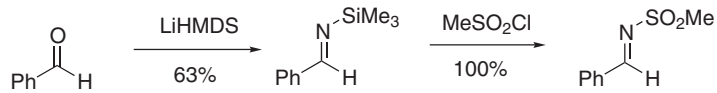
Masked oxo-sulfinimines are useful in the asymmetric synthesis of *cis*-proline and *cis*-pipecolic acids <2001OL759>.

3.11.2.1.3 Sulfonimines

Sulfonimines (*N*-sulfonylimines) have become useful synthons for a variety of reactions. Their preparation and uses have been reviewed <1997TCC131>. Sulfonimines are generally prepared from the oxime by reaction with a sulfonyl chloride or an *N*-sulfinyl sulfonamide. This can be

carried out in solvent-free conditions by microwave heating of the oxime with tosyl chloride, alumina, and pyridine <2001SC1803>. The Hudson reaction of oximes with appropriate sulfinyl chlorides generates *t*-butylsulfonyl- and trimethylsilylethanesulfonylimines <2001SL232>. These can be cleaved more easily than aryl- or methylsulfonylimines, giving greater synthetic versatility.

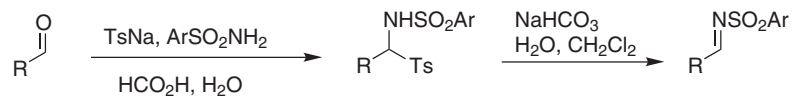
Sulfonimines may also be obtained from carbonyl compounds. Heating of aldehydes with a sulfonamide in the presence of TiO_2/SO_4^{2-} superacid gives *N*-sulfonylimines in 56–97% yields <2003JCR(S)591>. A solventless method employs microwave heating of aldehydes and sulfonamides with calcium carbonate and montmorillonite K10 clay <1999TL4951>. A one-pot synthesis from aldehydes and ketones via the silylimine has been reported. The (*E*)-imine is the only isomer obtained (Scheme 7) <1995JOC7366>.



Scheme 7

Condensation of diarylketones with *p*-toluenesulfonamide in the presence of $TiCl_4$ and $Ti(OPr^i)_4$ gives *N*-sulfonimines in moderate-to-good yields. Improved yields are obtained by using 0.6 equiv. of $TiCl_4$ and 2 equiv. of Et_3N <2001SC841>. Trifluoroacetic acid <2003TL1231>, tetraethyl orthosilicate, and titanium tetrachloride <2003SC341> have been used for the corresponding condensation of aryl aldehydes.

A two-step procedure for the synthesis of aliphatic and aromatic *N*-sulfonylaldimines avoids the use of Lewis acids <2000S75> (Scheme 8) (Table 3).

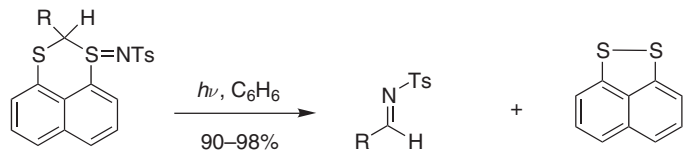


Scheme 8

Table 3 Synthesis of *N*-sulfonyl aldimines

R	*Ar*	*Yield* (%)
Bu^n	Ph	66
Cy	*p*-Tol	76
Ph	*p*-Tol	63
Pr^i	Ph	55

N-Sulfonylaldimines may be prepared by the photorearrangement of the 1,8-dithianaphthalene derivatives **18** (Equation (20)) <1995TL1075>.



(20)

18

N-Sulfonylaldimines can be reacted with trimethylsilyldiazomethane to give predominantly *cis*-*N*-sulfonylaziridines <2000TL9455, 2002JOC2335>, with formation of the *C*-methylated sulfonimine as a minor by-product <2000TL9455>. *N*-Tosylketimines are obtained by the palladium-catalyzed isomerization of *N*-tosylaziridines. The reaction takes place under mild reaction conditions, so that various functional groups are tolerated <2003OL4607>.

Base-mediated elimination of α-bromo-*N*-arylsulfonylglycine esters generates *N*-sulfonyliminoesters <2000JCS(P1)515>. These electron-deficient *N*-sulfonylimines can undergo either Diels–Alder cycloaddition, or α-substitution to give the α-amino acid derivative, and the various factors determining the product ratios have been investigated.

3.11.2.2 Phosphorus Analogs

Phosphinimines and arsinimines may be prepared from $PPh_3/AsPh_3$ under nitrene conditions, or from sulfonamides and $Ph_3As(OAc)_2$ <1999SC2301>.

N-Phosphinoylimines are highly electrophilic, and along with *N*-sulfonylimines have recently been used for stereoselective aldol reactions, aziridinations and allylations <1999PAC1033>. Reaction with allyl sulfonium ylide gives *trans*-aziridines at room temperature, or *cis*-aziridines at low temperature <1998CC747>. Asymmetric diethylzinc additions to *N*-phosphinoylimines have been explored <2001T1615, 2003JOC4322>. α-Trifluoromethyl-*N*-phosphinoylimines, useful intermediates in the synthesis of *N*-phosphinoyloxaziridines, are prepared by reaction of the oxime with chlorodiphenylphosphine at $-50\,^{\circ}C$ <2001TL101>.

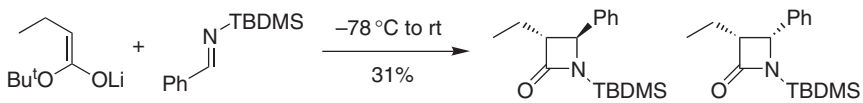
Reaction of diethylphosphoramidate with diethyl acetals of aromatic aldehydes at 120–160 °C gives *N*-(diethoxyphosphoryl)aldimines in 68–88% yield <1996T8789>.

3.11.2.3 Nitrogen Analogs

N-Nitrosoimines are used in the synthesis of heterocycles, and they have been reviewed as detailed in COFGT (1995). The *N*-nitroimine of camphor (obtained by reaction of the derived oxime with sodium nitrite) has been used to synthesize a number of diastereomerically pure *vic*-amino alcohols <2002TA1849>.

3.11.2.4 *N*-Silicon-substituted Imines

N-Silylimines are used as masked N—H imines, and their synthesis and uses have been discussed in COFGT (1995). Reaction of appropriate lithium amides with both enolizable and nonenolizable aldehydes gives the *N*-TIPS or *N*-TBDMS imines <1996SL657, 1997S886>. Exploration of the reactivity of these silylimines with ester enolates reveals that *N*-TBDMS imines give predominantly *trans*-TBDMS β-lactams, attributed to thermodynamic control in the ring-closure step (Equation (21)). This is in contrast to the known formation of *cis*-β-lactams by *N*-TMS imines. For *N*-TIPS imines, the ring-closure step is too slow to give products except in a few cases <1997S886>.

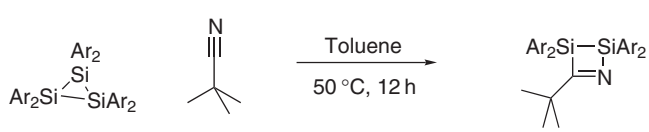


(21)

The mechanistic principles behind the stereocontrol of β-lactam formation in the reaction of silylimines and ketenes have been recently studied <2000JOC8458>.

N-TBDMS imines have been synthesized from nitrile by reduction with BH_3 and oxazaborolidines and used in amine synthesis<1998SC4067>. Modest-to-good enantioselectivity was observed. Allylboration of *N*-silylimines with allylboration reagents containing chiral *N*-sulfonylamino alcohol ligands yields homoallylic imines in up to 96% ee <1999JCS(P1)2011>.

The reaction of nitriles with cyclotrisilane gives *N*-silylimine products via the unstable azasilacyclopropene; for example, reaction with pivalonitrile gives the 1,2-disilaazetine **19** (Equation (22)) <1995TL8187>.



(22)

19

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Biographical sketch

Sharon Rossiter was born in London, studied at King's College London, where she obtained a B.Sc. in 1995 and her Ph.D. in 1999 under the supervision of Dr. Keith Jones. In 1998 she joined the Gray Cancer Institute in Northwood, Middlesex, and then moved to her current position as a Research Fellow at The Wolfson Institute for Biomedical Research, University College London, in 2002. Her research interests include heterocyclic chemistry, in particular transition-metal-mediated couplings, drug design and targeting, and the chemical biology of arginine-metabolizing enzymes.

Adrian Dobbs was born in Bromley, Kent and studied at King's College London, obtaining a B.Sc. in 1992 and a Ph.D. in 1996, working under the guidance of Dr. Keith Jones. He then undertook postdoctoral research for two years with Professor Istvan Markó at the Université Catholique de Louvain, in Louvain-la-Neuve, Belgium, under a Royal Society Research Fellowship. On returning to the UK, he joined the process chemistry department of Glaxo SmithKline (Tonbridge, Kent), before taking up his first academic position at the Open University at the end of 1999. He moved to his current position as Lecturer in Organic Chemistry at the University of Exeter in 2001. His research interests encompass the development of new synthetic methodologies for the synthesis of complex heterocyclic systems and their application to the total synthesis of natural products.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 451–467

3.12 Imines and Their *N*-Substituted Derivatives: Hydrazones and Other =*N*,*N*-Derivatives Including Diazo Compounds

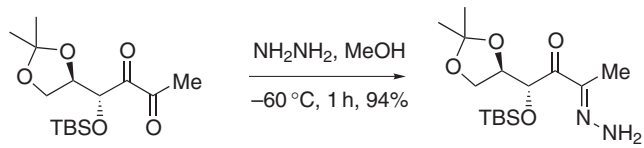
M. C. ELLIOTT
Cardiff University, Cardiff, UK

3.12.1 HYDRAZONES AND THEIR DERIVATIVES

This section covers the methods for hydrazone formation, and in some cases elaboration, reported since 1995. It seems unnecessary to list all examples of hydrazone formation reported during the period of coverage, so that emphasis will be placed on "unusual" examples. For examples prior to 1995, the reader is referred to the corresponding chapter in COFGT (1995) <1995COFGT(3)443>.

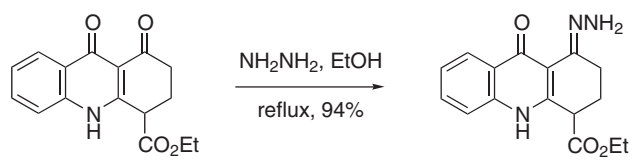
3.12.1.1 Hydrazones and Azines Derived from Hydrazine

Reaction of hydrazine and substituted hydrazines with carbonyl compounds remains the most popular method for the preparation of hydrazones, and works well for both aldehydes <1996TL4323, 2002JOC602> and ketones <1999TL3869, 2002JOC112, 2003TL1487>. In the case of compound **1**, hydrazone formation was regioselective at −60 °C to give **2** in extremely high yield (Equation (1)) <1998T6867>.



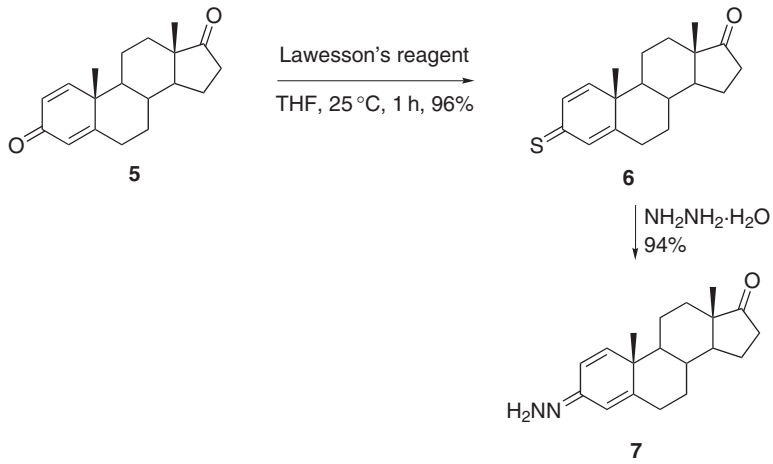
1 **2** (1)

Compound **3** provides a further example of regioselective hydrazone formation, forming **4** with complete selectivity (Equation (2)) <2002T175>.



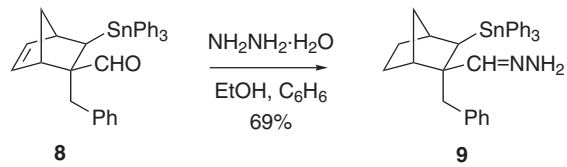
3 **4** (2)

In one instance, formation of a hydrazone from the less reactive of the two carbonyl groups has been accomplished in a two-step protocol. Reaction of steroid **5** with Lawesson's reagent gave thioketone **6**, which was then converted into the hydrazone **7** under standard conditions (Scheme 1) <1995S1245>.



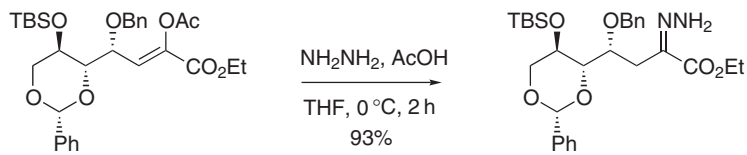
Scheme 1

Hydrazone-forming reactions are occasionally accompanied by unexpected side reactions. For instance, during the formation of a hydrazone from **8**, diimide generated during the reaction also reduced the double bond giving **9** (Equation (3)) <2001T10017>.



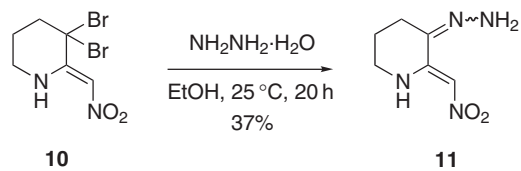
(3)

While carbonyl compounds are the most common substrates, a number of other compounds can be used as carbonyl equivalents in hydrazone formation. A minor variation on this approach uses enol acetates as substrates (Equation (4)) <2001T10271>.



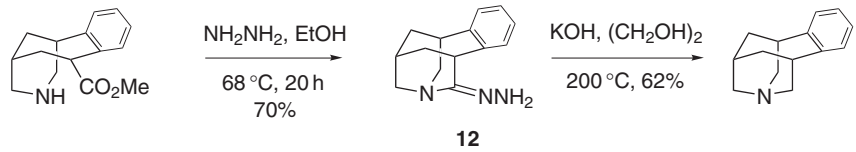
(4)

Dibromoalkane **10** provides a hydrazone **11** under similar conditions to those used for carbonyl substrates (Equation (5)) <2001TL1773>.



(5)

Amidine **12**, prepared as shown in Scheme 2, behaves more like a hydrazone due to the extremely twisted nature of the C—N single bond. In particular, it undergoes Wolff–Kishner reduction upon further treatment with hydrazine <2003JA3268>.



12

Scheme 2

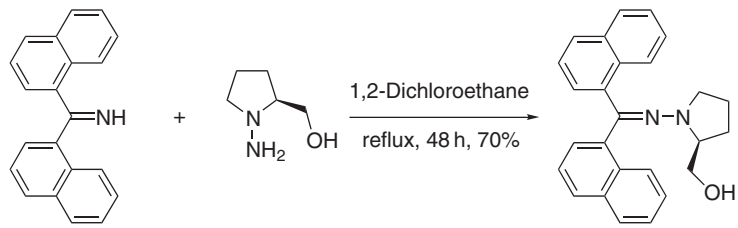
3.12.1.2 *N*-Substituted and *N*,*N*-Disubstituted Hydrazones

The reaction of a carbonyl compound with an *N*-substituted hydrazine is the most common method for the preparation of substituted hydrazones. The reaction is almost completely general, and so it is not necessary to list all examples of hydrazone formation reported between 1995 and 2003. Instead, this part of the discussion will focus on novel structures and new reaction conditions. Much of the recent work on functionalization of hydrazones deals with highly stereoselective reactions of SAMP and RAMP hydrazones. A brief overview of this work will be presented along with related work on other hydrazones. For a more comprehensive account of the use of (*S*)-1-amino-2-(methoxymethyl)-pyrrolidine/(*R*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP/RAMP) hydrazones in synthesis, the reader is referred to the excellent review by Enders and co-workers <2002T2253>.

3.12.1.2.1 Formation of the C=N bond

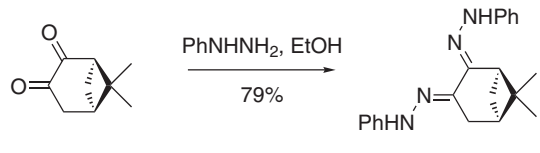
A range of *N*-substituted hydrazones and semicarbazones was prepared under solvent-free conditions by grinding the carbonyl compound, the hydrazine derivative, silica gel, and sodium hydroxide in a mortar <1999JCR(S)570>.

Hindered hydrazone **15** was best prepared by addition of hydrazine **14** to a refluxing solution of imine **13** in 1,2-dichloroethane. This order of addition gave a cleaner reaction than the more commonly used procedure (Equation (6)) <2000T8361>.

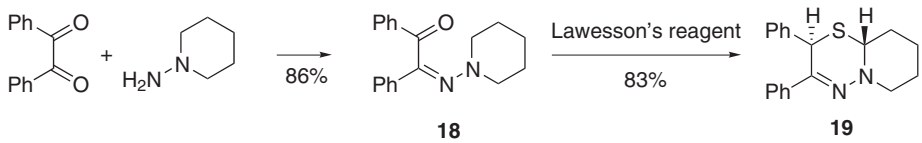


13 14 15 (6)

1,2-Diketones form mono- and bis-hydrazones readily. For instance, the novel chiral diketone **16** formed bis-hydrazone **17** under relatively standard conditions (Equation (7)) <2002TL5241>. Reaction of benzil with a single equivalent of a hydrazine gave hydrazones such as **18**. These compounds form thiadiazines **19** with the relative stereochemistry shown upon treatment with Lawesson's reagent (Scheme 3) <1998TA1531>. Hydrazones derived from α-keto esters are readily prepared simply by stirring the α-keto ester with the corresponding hydrazine at room temperature <1996T14673>.



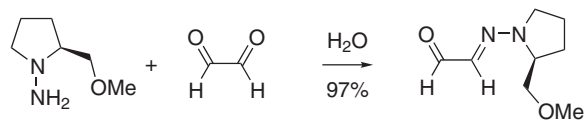
16 17 (7)



18 19

Scheme 3

The use of SAMP and RAMP hydrazones in asymmetric synthesis is discussed in more detail in subsequent sections. The mono-SAMP hydrazone **20** was prepared in a straightforward manner by the reaction of aqueous glyoxal with the SAMP hydrazine (Equation (8)). Unfortunately, 1,2-addition reactions to the aldehyde group proceeded with low diastereoselectivity <1999T1087>.



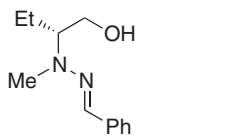
(8)

20

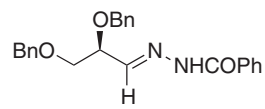
Other useful small chiral hydrazones have been prepared. For instance, addition of Grignard reagents to **21** allows the formation of diastereomerically pure secondary hydrazines <1998TA2181, 1999TA1579>. Direct addition to the C=N bond in **22** followed by deprotection and oxidative cleavage of the 1,2-diol provided α-hydrazinoacids <1997TA1605>.

The electrochemical properties of ferrocenes and related compounds are the subject of much contemporary research. In this context, compounds **23** <2003JOM(675)1> and **24** <2003OM153> have been prepared using conventional aldehyde–hydrazine condensation reactions.

One other area where hydrazones have made a significant impact is supramolecular chemistry. Lehn's group in Strasbourg has used hydrazones to impose rigidity and defined conformations on large molecules, as well as taking advantage of their metal-complexing ability. For example, compound **25** forms a 1.5 turn helix <2000CEJ4124>, while **26** forms a tetrameric array with cobalt or manganese salts <2003CC1338>. The (*E*)/(*Z*)-isomerization of hydrazones has also been used to reduce translational motion in rotaxanes, <1998S339> while Sanders and co-workers <2000OL1435> have prepared steroidal macrocyclic hydrazones, and demonstrated subtle conformational and thermodynamic effects.



21



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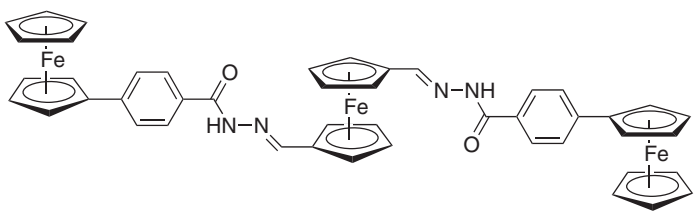
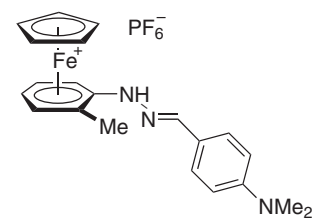
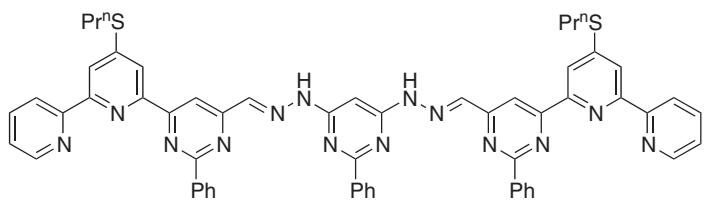


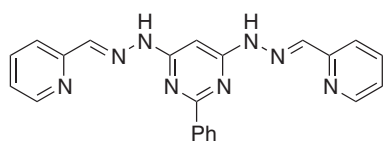
23



24

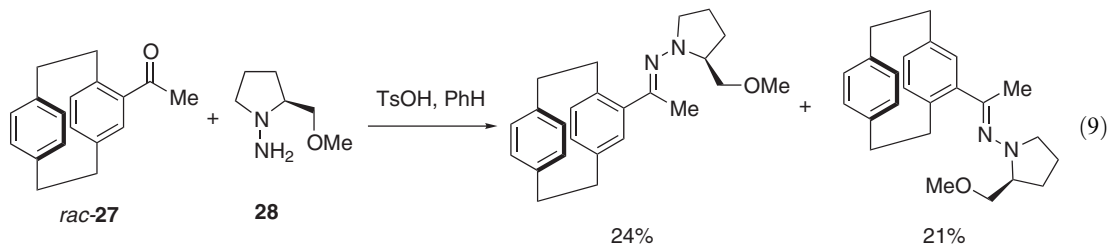


25



26

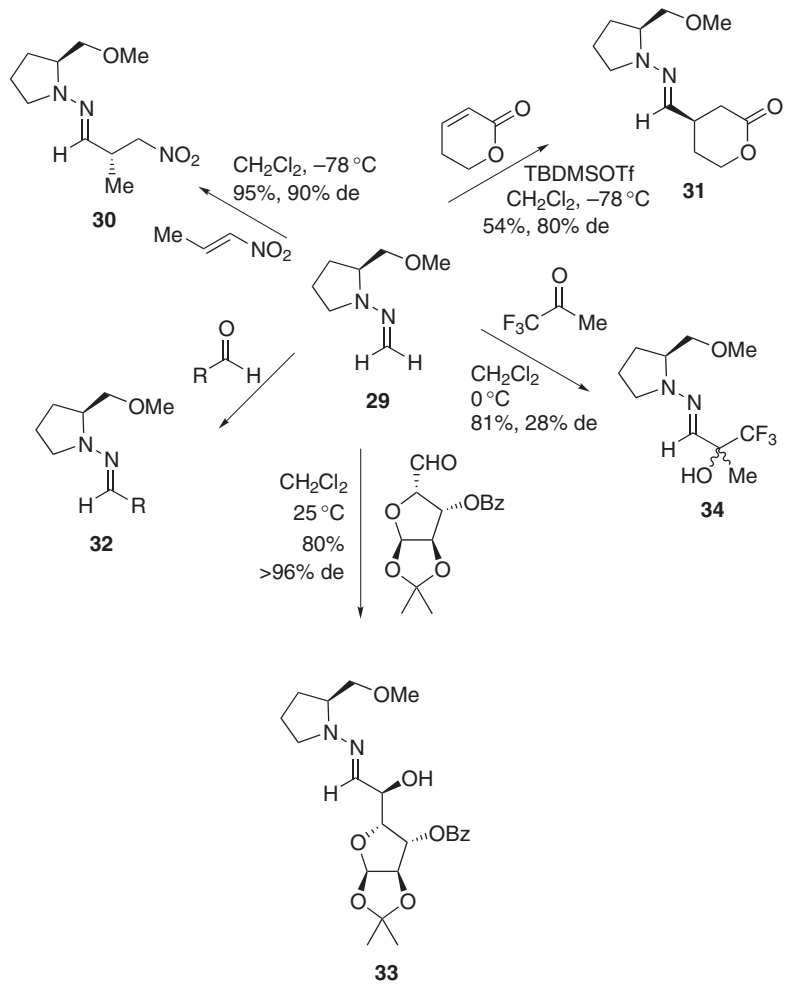
In the final example of hydrazone formation by imine bond formation, paracyclophane ketone **27** was successfully resolved as a result of hydrazone formation with the SAMP hydrazine **28** (Equation (9)) <2000TA4221>.



(9)

3.12.1.2.2 Functionalization of the hydrazone carbon

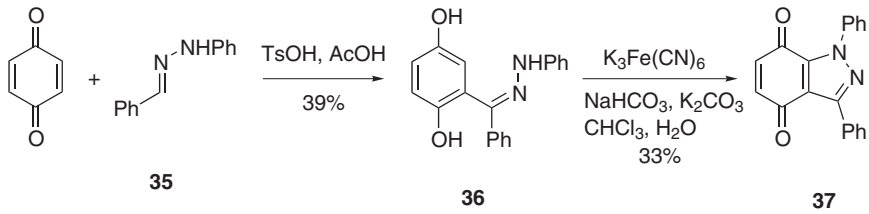
Formaldehyde hydrazones are nucleophilic at the hydrazone carbon, and undergo reaction with a wide range of electrophiles. Most of the examples reported between 1995 and 2003 use SAMP or RAMP hydrazones as chiral formyl anion equivalents. This aspect of SAMP/RAMP chemistry has recently been reviewed <1998EJO2051>, but selected results will be presented herein (Scheme 4).



Scheme 4

SAMP hydrazone **29** undergoes reaction with Michael acceptors such as nitroalkenes giving **30** <1996S48, 1996S627>. Reaction with unsaturated lactones gives, for example, **31** <1999CC701, 2000EJO893>. Reactions with other Michael acceptors have been reported <1999TA1145, 1999JOC6329, 2002CC498>. Reaction with simple aldehydes in the presence of most Lewis acids gave mainly products **32** derived from aldehyde exchange, although $ZnCl_2$ or Et_2AlCl did give rise to the formation of addition products <2001SL1158>. With more reactive aldehydes, such as α-alkoxyaldehydes, the expected adducts **33** were obtained without the need for catalysts <2001JOC5201>. With trifluoromethylketones, products such as **34** were obtained with modest diastereoselectivity. In this case, the diphenyl analog of SAMP proved more selective <1998AG(E)3428, 1999JOC8846>.

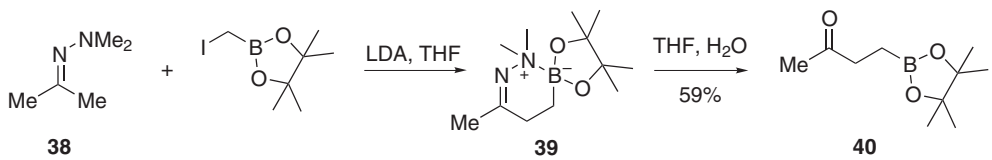
In other work, reaction of hydrazone **35** with benzoquinone gave the *C*-functionalized hydrazone **36**, which was subsequently oxidized to give the indazolequinone **37** (Scheme 5) <1997T15005>. However, analogous reactions with naphthoquinone gave the corresponding *N*-functionalized adducts <2000T5137>.



Scheme 5

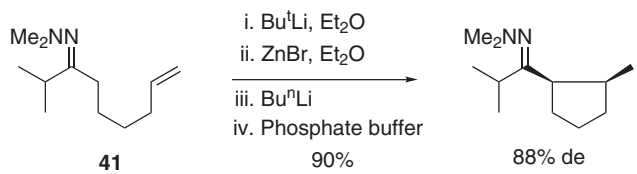
3.12.1.2.3 Functionalization of the α-position in hydrazones

Hydrazones are similar to carbonyl compounds, and undergo α-functionalization reactions in much the same way. For example, deprotonation of hydrazone **38** with lithium diisopropylamide (LDA) followed by electrophilic quench gave an intermediate, which was best represented as the "ate" complex **39**. This compound was not isolated, but instead was directly hydrolyzed to give the ketoboronate **40** (Scheme 6) <2000JCS(P1)3250>. These alkylation reactions are extremely general, and have also been carried out on a solid support <2002SL1931>.



Scheme 6

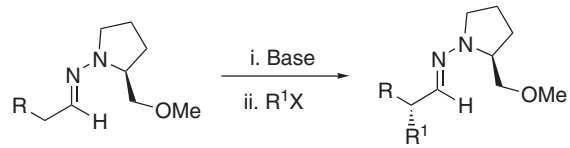
One novel application of this work is based on carbolithiation cyclization reactions of the corresponding zinc "enolate." Treatment of hydrazone **41** with *t*-butyllithium was followed by metal exchange with zinc bromide. This "enolate" underwent slow cyclization, but addition of a further equivalent of *n*-butyllithium promoted the reaction effectively (Equation (10)) <1998TL2157>.



(10)

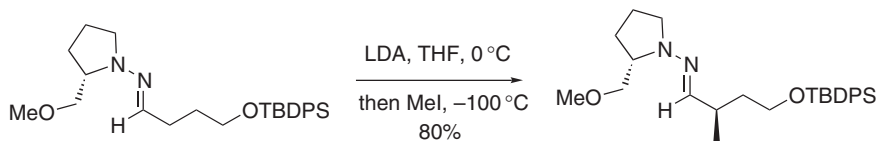
The SAMP and RAMP hydrazones, developed by Enders and co-workers, undergo highly stereoselective alkylation reactions (Equation (11)). In the case of aldehyde hydrazones there is only one possible site of alkylation. With ketone hydrazones, alkylation could take place on either side, and this aspect has been successfully exploited in novel desymmetrization reactions as

described later in this section. A significant factor in the extensive use of these reagents is the ready cleavage of SAMP and RAMP hydrazones either hydrolytically or oxidatively to regenerate the carbonyl compound, or oxidatively to give the corresponding nitrile <2000ACR157>.

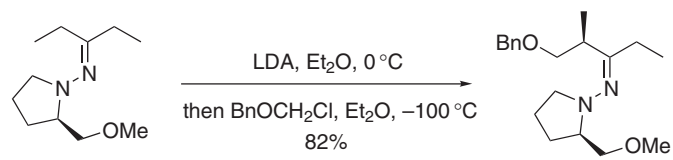


(11)

The versatility of the methodology is apparent in the synthesis of small chiral building blocks for use in total synthesis. For instance, the two reactions shown in Equations (12) and (13) were used in the Enders group's synthesis of callystatin A <2002OL1023, 2002CEJ4272>. These reactions are typical of the broad range of applications that the Enders group has reported <1998TL7823, 2000SL1745, 2000S1848, 2002TA587>.

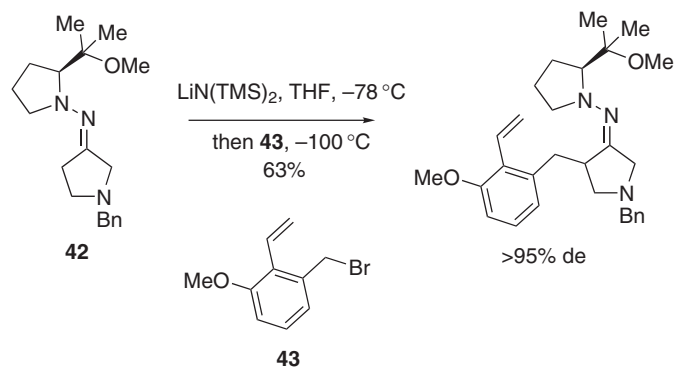


(12)



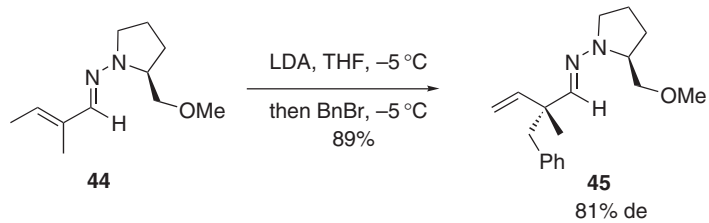
(13)

A modified hydrazone **42** proved superior for the regioselective and diastereoselective alkylation shown in Equation (14). The relative stereochemistry of the major isomer was not reported <2002SL1669>.



(14)

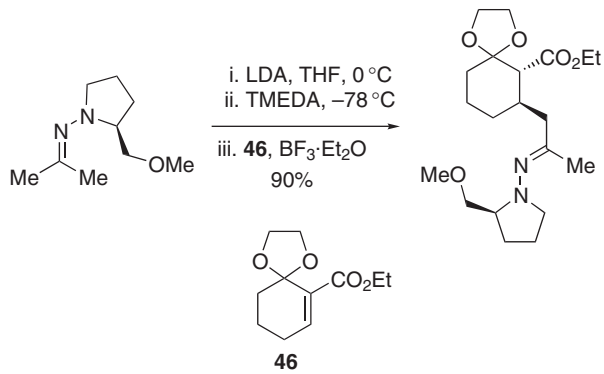
In the case of α,β-unsaturated SAMP hydrazone **44**, the deconjugated product **45** was obtained, forming a quaternary stereogenic center with impressive stereocontrol (Equation (15)) <1996SL645>.



(15)

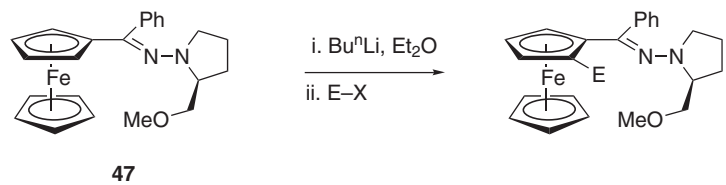
Although alkyl halides are more commonly used, other electrophiles work well, including tosylaziridines <2000EJO3337>. The hydrazones themselves may possess a range of functionality at the α-position, including heteroatoms such as nitrogen <1996S53>, sulfur <2002SL498>, and silicon <1997TA2787>.

While most reactions of SAMP and RAMP hydrazones form a new stereogenic center α- to the hydrazone, Michael addition of the hydrazone anion can lead to the creation of β- and γ-stereogenic centers, e.g., Equation (16) <1996S209>. The simultaneous formation of α- and β-stereogenic centers has also been reported using vinylphosphonates as Michael acceptors <1997T12961>. Not surprisingly, 1,2-addition to aldehydes is also efficient and stereoselective <1998CEJ311>.



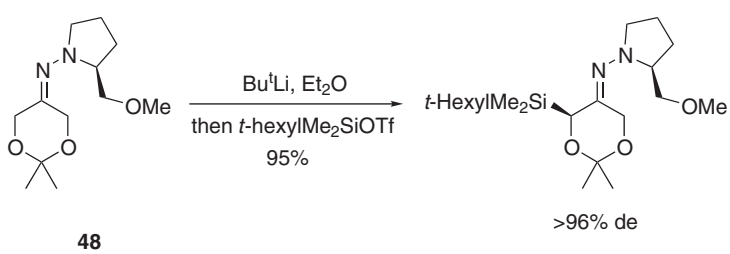
(16)

These reactions are not restricted to the use of carbon electrophiles. For example, ferrocenylhydrazone **47** underwent lithiation/electrophilic quench with carbon, silicon, phosphorus, and iodine electrophiles, all with excellent diastereoselectivity (Equation (17)) <1997SL1462, 2000EJO2839>. α-Silylation reactions of SAMP/RAMP hydrazones have been reviewed <2000SL1371>.



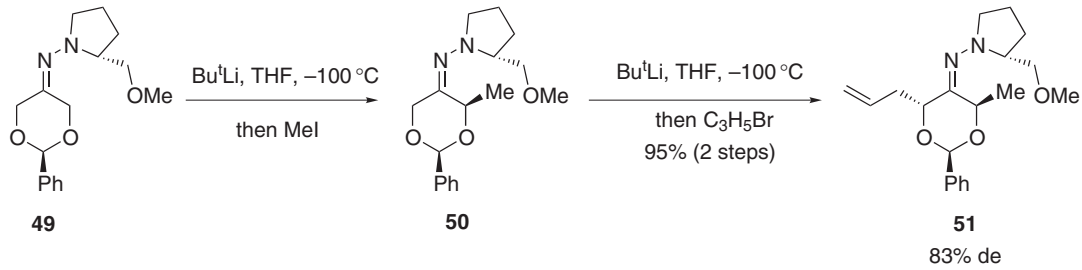
(17)

This preceding reaction is a desymmetrization of the ferrocene ring. Desymmetrization reactions using SAMP and RAMP hydrazones have been the subject of studies within the groups of Enders and others. Much of this work has focused on the desymmetrization of 1,3-dioxan-5-one hydrazones such as **48**. In the example shown in Equation (18), deprotonation and silylation occurred with almost complete stereocontrol <1996S1095>.



(18)

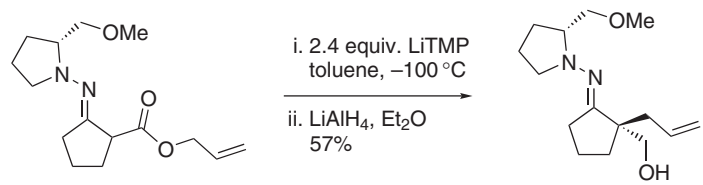
In the case of double alkylation of related hydrazone **49**, the first alkylation produces the equatorial isomer **50**. This is then followed by axial alkylation giving **51** (Scheme 7) <2001EJO3367>. There are a number of related examples, but generally the hydrazone is cleaved directly after alkylation without being isolated and characterized <1998EJO2839, 1998TA2611, 2002S1571, 2002S1775>. Quaternary stereogenic centers can also be formed extremely selectively using this method <2001S1406>.



49 **50** **51**
83% de

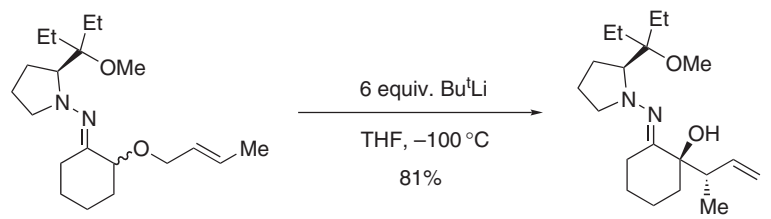
Scheme 7

Finally for this section, there are examples of intramolecular delivery of electrophiles by way of rearrangement reactions. Double deprotonation of **52** was followed by Carroll rearrangement to give **53** after reduction with lithium aluminum hydride, forming a quaternary stereogenic center with excellent stereocontrol (Equation (19)) <1996T5805>. The [2,3]-Wittig rearrangement proceeds in a similar fashion, although in this case the diethyl-substituted hydrazone **54** was used (Equation (20)) <1996S1438, 1995SL869, 1999S243>.



(19)

52 **53**
TMP = 2,2,6,6-tetramethylpiperidide >96% de

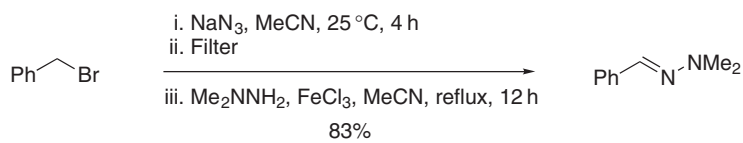


(20)

54
88% *anti*; >96% de

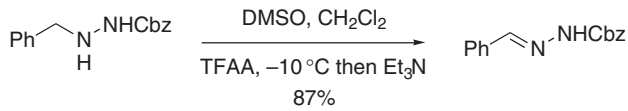
3.12.1.2.4 Miscellaneous methods

In a slightly unusual substitution reaction, Barrett and co-workers <2000JOC6268> have observed the oxidative substitution of azides by hydrazines. Concerned about the hazards associated with azides, an improved protocol was devised which does not require the isolation of these compounds. When alkyl bromides were used as substrates, it was found to be necessary to remove the sodium bromide formed in the first step by filtration before introduction of the hydrazine, although this manipulation was not necessary when tosylates were used as substrates (Equation (21)) <2000SL1673>.



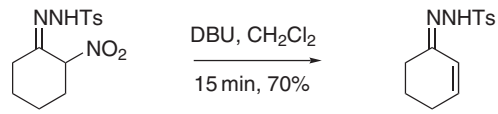
(21)

The oxidation of hydrazines to hydrazones is relatively uncommon, but occurs readily under Swern conditions for carbamate-protected hydrazines (Equation (22)) <2001TL1453>.



(22)

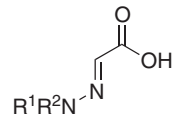
In the case shown below, hydrazone **55** was prepared by reaction of a ketone with tosylhydrazine. This was then followed by elimination of nitrous acid to give **56** (Equation (23)) <1995T4173>.



55 **56**

(23)

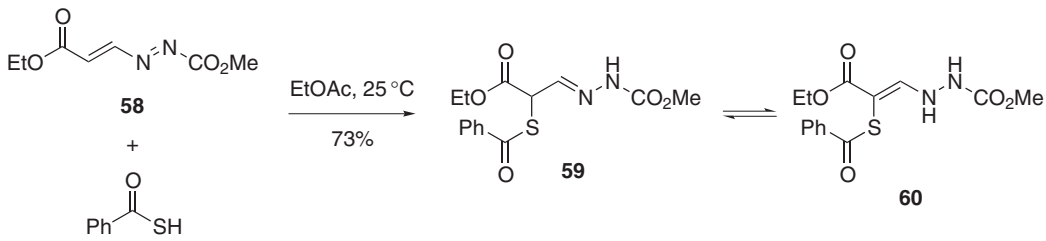
A range of carboxylic acids of general structure **57** have been prepared and used in coupling reactions to give the corresponding esters <2001JOC1233>.



57

3.12.1.3 Hydrazones from Azo Compounds

Conjugate addition of thiocarboxylic acids to unsaturated azo compounds **58** takes place β to the azo (and surprisingly α to the ester) to provide hydrazones such as **59**, which exist in a tautomeric equilibrium with the enamine form **60**. A less electron-withdrawing group on the azo-nitrogen favors the hydrazone tautomer exclusively (Scheme 8) <1996T1579>.



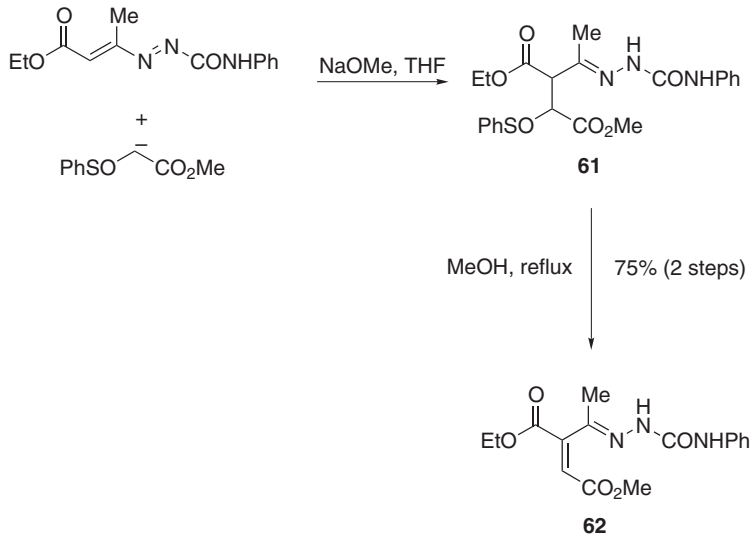
Scheme 8

An essentially identical reaction takes place with active methylene compounds. Upon heating in methanol, the adducts **61** can undergo elimination reactions giving conjugated hydrazones such as **62** (Scheme 9) <1998T7581>.

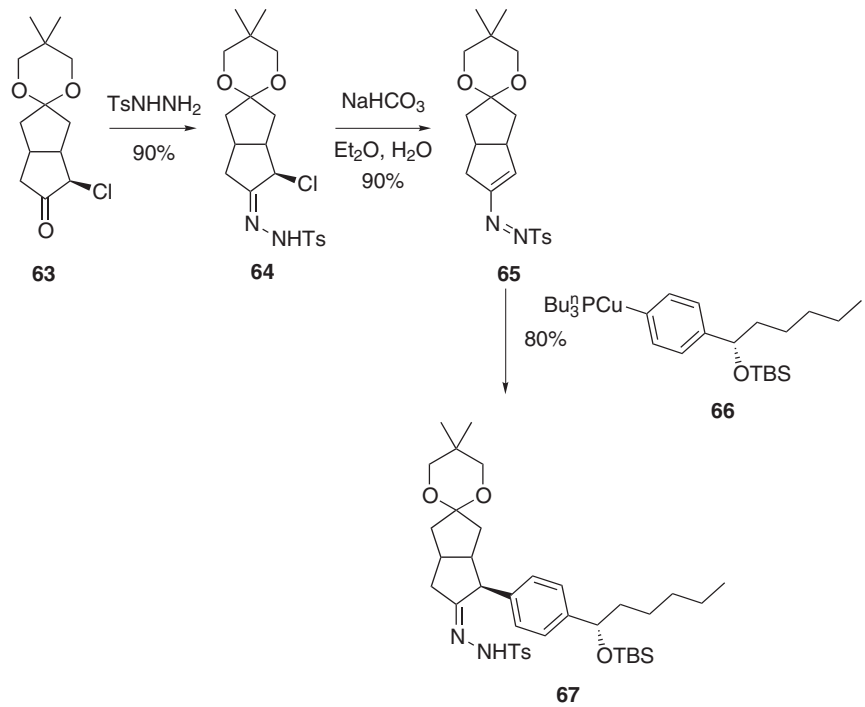
Further extensions to this work include the *in situ* formation of the conjugated azo-substrates from 2-chlorohydrazones, and conversion of the products into *N*-aminopyrrole derivatives <1999SL1367>.

A new approach to prostacyclin analogs makes use of hydrazone chemistry at two points. Single enantiomer ketone **63**, prepared by way of a chiral base-mediated desymmetrization, was converted into the tosylhydrazone **64** in the usual way. Elimination of HCl then gave the azo-ene **65**, which underwent conjugate addition of organocopper reagent **66** to finally give **67** (Scheme 10) <2002JA4321>.

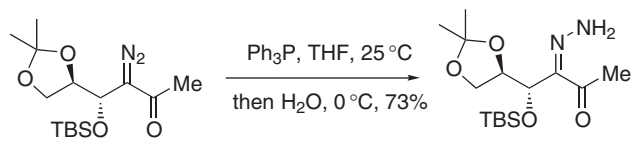
Reduction of diazo compounds to give hydrazones is much less common than the reverse reaction. However, treatment of diazo compounds with triphenylphosphine followed by hydrolysis does allow this useful transformation to be carried out under mild conditions (Equation (24)) <1998T6867>.



Scheme 9



Scheme 10



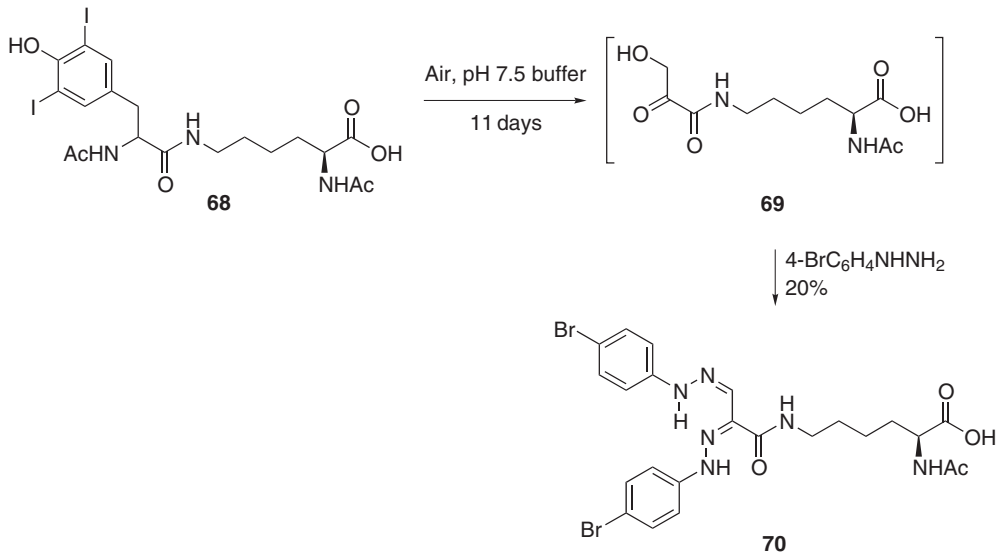
(24)

3.12.1.4 Semicarbazones

Mono- and bis-semicarbazones have been prepared from benzil, both in good yields (75–85%) <1998T11271>.

3.12.1.5 Osazones

Osazones, formed from 1,2-dicarbonyl and 2-hydroxycarbonyl compounds, have been widely used for characterization purposes. For example, aerobic oxidation of **68** followed by addition of excess 4-bromophenylhydrazine allowed isolation of osazone **70**, presumably formed from the intermediate hydroxypyruvate derivative **69** (Scheme 11) <1999TL9211>.



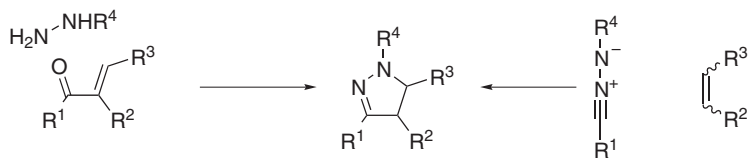
Scheme 11

3.12.1.6 Cyclic Hydrazone and Azine Derivatives

A range of cyclic hydrazones have been prepared, generally from hydrazine derivatives. As with the previous review, the present discussion will focus on those heterocycles, which have more in common with hydrazone chemistry.

3.12.1.6.1 2-Pyrazolines and 2-pyrazolin-5-ones

There are two general methods for the formation of 2-pyrazolines, namely condensation of an α,β-unsaturated ketone with a hydrazine and cycloaddition of a nitrilimine with an alkene (Scheme 12).

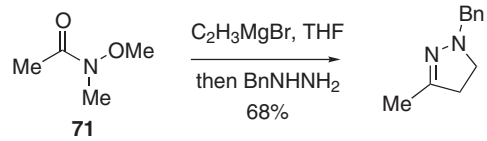


Scheme 12

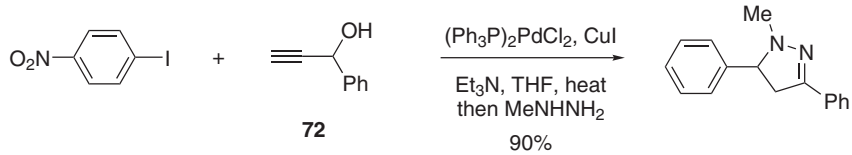
The former method is the most popular, and is extremely general. In most of the recently reported examples, R^1 and R^3 are aryl or heteroaryl groups, with $R^2 = H$ (i.e., chalcones) <1998T4085, 2000TL2713>. These reactions work well with substituted hydrazines <2000OL2833>. Introduction of substituents at R^2 is also possible, including electron-withdrawing groups such as phosphonates <2000JOC4326> and large heterocycles such as benzotriazole <2001JOC6787>.

A number of variations on this theme have been reported. These differ mainly in the method of preparation of the α,β-unsaturated ketone, and so will be mentioned only briefly. One-pot syntheses of 2-pyrazolines are shown in Equations (25) and (26), in which the α,β-unsaturated

ketones are prepared *in situ*. In Equation (25) this occurs by addition of vinyl magnesium bromide to Weinreb amide **71** <2001JOC3613>, while in Equation (26) a palladium-catalyzed cross-coupling with propargyl alcohol **72** was followed by isomerization <2000AG(E)1253>. In both cases, the actual pyrazoline formation was entirely conventional. An approach from the Ley group makes use of polymer-supported reagents in two steps prior to pyrazoline formation <1998JCS(P1)2235>.

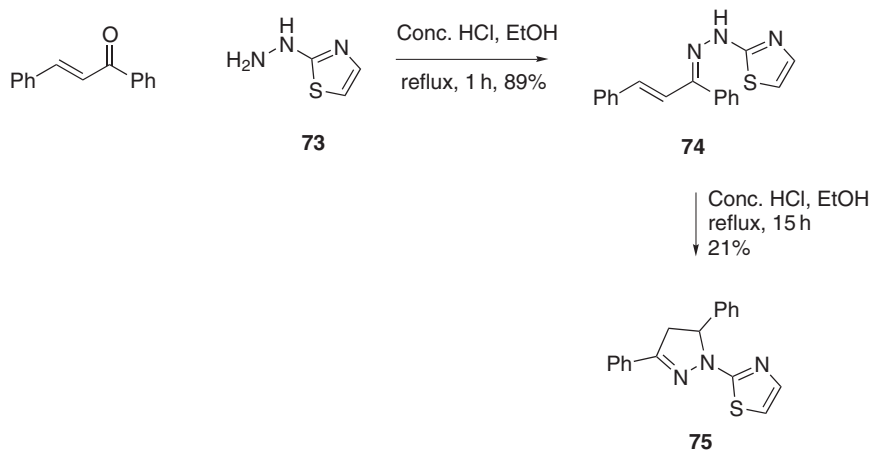


(25)



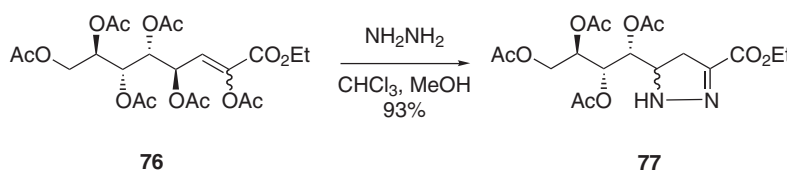
(26)

More complex hydrazines can also be used in this type of reaction. For example, use of **73** allowed isolation of the unsaturated imine **74**, which then underwent acid-catalyzed cyclization albeit in low yield, giving **75** (Scheme 13). The same product could be prepared in higher yield by the use of thiosemicarbazide to give a pyrazoline directly, followed by Hantzch thiazole synthesis <1999T5909>.



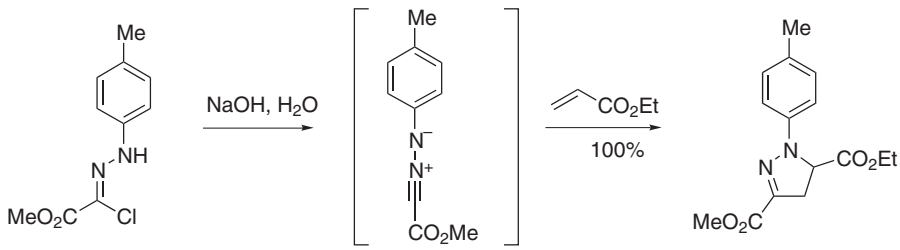
Scheme 13

In a mechanistically related reaction, treatment of enol acetate **76** gave pyrazoline **77** in high yield (Equation (27)) <1997T3325>.



(27)

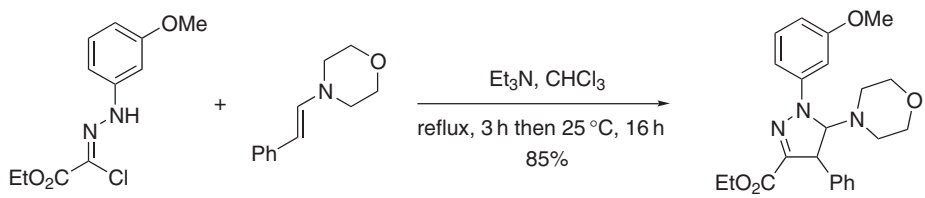
Nitrilimines **79** are prepared by elimination of HCl from hydrazonoyl chlorides **78**. Cycloaddition reactions in aqueous media work best with electron-deficient dipolarophiles to give the regiochemistry shown (Scheme 14) <2000JCS(P1)3742>.



78 **79**

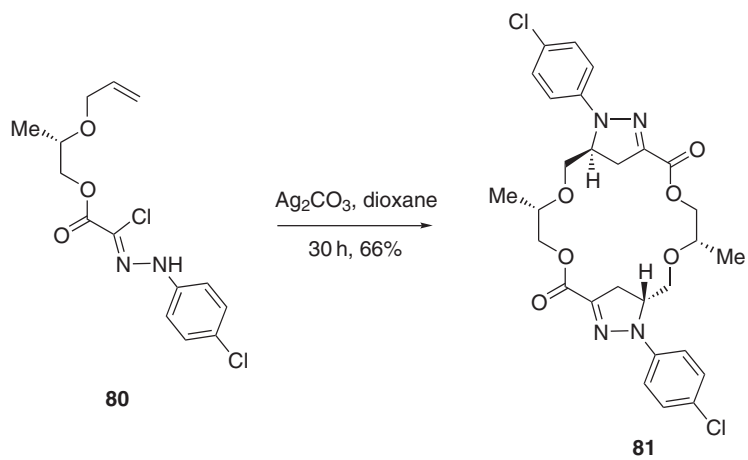
Scheme 14

Although in the previous case cycloaddition with dihydropyran was low yielding, similar *in situ* generated nitrilimines undergo cycloaddition with enamines in good yield (Equation (28)) <2001JCS(P1)2817>. This approach was extended to polymer-supported enamines to liberate, after elimination, the corresponding pyrazole. Cycloaddition to polymer-bound acrylates has also been reported <2002JCS(P1)2504>.



(28)

Treatment of hydrazonoyl chloride **80** with silver carbonate initiated a sequence of intermolecular and intramolecular nitrilimine cycloadditions giving macrocycle **81** (Equation (29)) <2000TA1975, 1998T2843>.

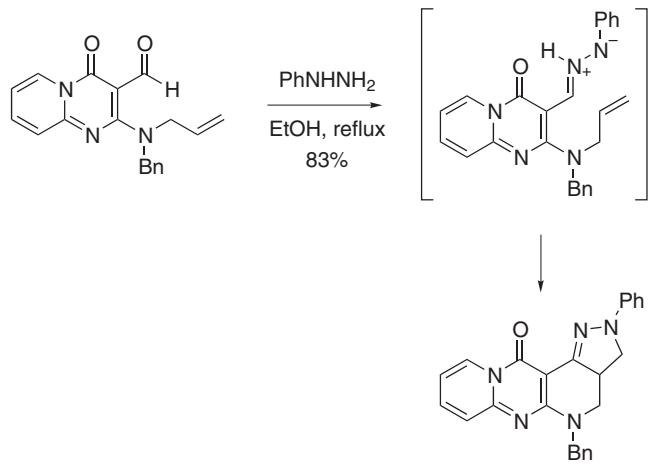


80 **81**

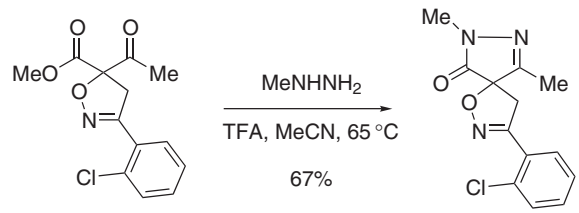
(29)

Azomethine imine cycloadditions give the corresponding pyrazolidines. These heterocycles are relatively unstable and in some cases the oxidized pyrazoline is obtained, even when the azomethine imine formation/cycloaddition is carried out under an inert atmosphere (Scheme 15) <1996T901>.

Finally for this section, the reaction of β-keto esters with hydrazines gives rise to the formation of pyrazolones <1999TA4211>. Again, this reaction is fairly general. Recently reported examples include the formation of a spirocyclic pyrazoline (Equation (30)) <2002JOC876>. Polymer-supported β-keto esters <1997BMCL1303, 2001EJO1631> and hydrazines <1999TL1341> have also been used in this transformation.



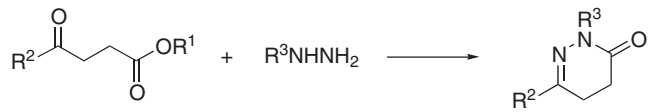
Scheme 15



(30)

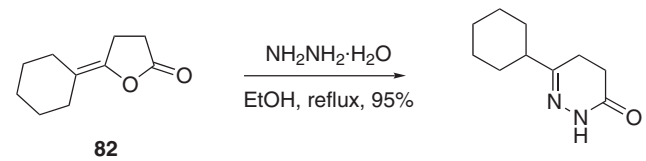
3.12.1.6.2 Tetrahydropyridazines

The most general route to 4,5-dihydropyridazine-3(2*H*)-ones involves reaction of a hydrazine with a γ-keto ester or γ-ketoacid (Equation (31)) <1996BMCL121, 2000HCA1599, 2001TL1305, 2001JMC2511, 2003TA529>. With substituted hydrazones, cyclization occurs such that the substituent is found on *N*-2 in the product. This reaction has also been carried out on a polymer support <2002JCS(P1)2234>.



(31)

A slight variation on this is shown in Equation (32), in which the lactone **82** is used as a γ-keto ester equivalent <1998T6553>.

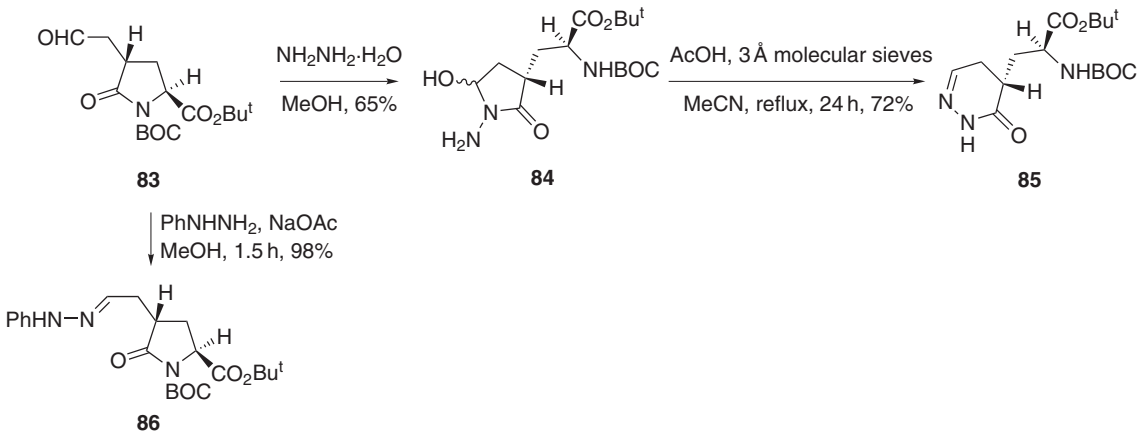


(32)

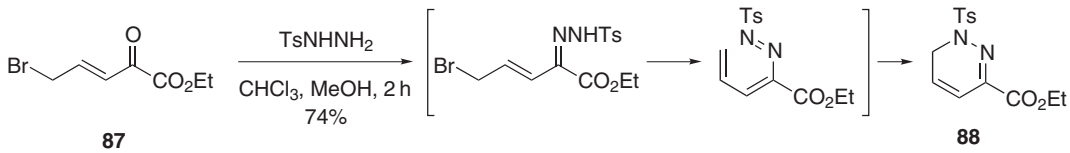
82

Young and co-workers <2002JCS(P1)613, 1999T7935, 2002TL3951, 2002JCS(P1)2459> have developed a ring-switching strategy based on pyroglutamate esters. Treatment of **83** with hydrazine resulted in lactam ring opening and re-cyclization to give **84**. Acid-catalyzed rearrangement then gave 85. However, the attempted use of phenylhydrazine in this sequence gave only the acyclic hydrazone **86** (Scheme 16).

Reaction of **87** with tosylhydrazine gives the cyclic hydrazone **88**. This is presumably a result of intermolecular hydrazone formation followed by elimination of HBr and electrocyclization (Scheme 17) <1996T14975>.

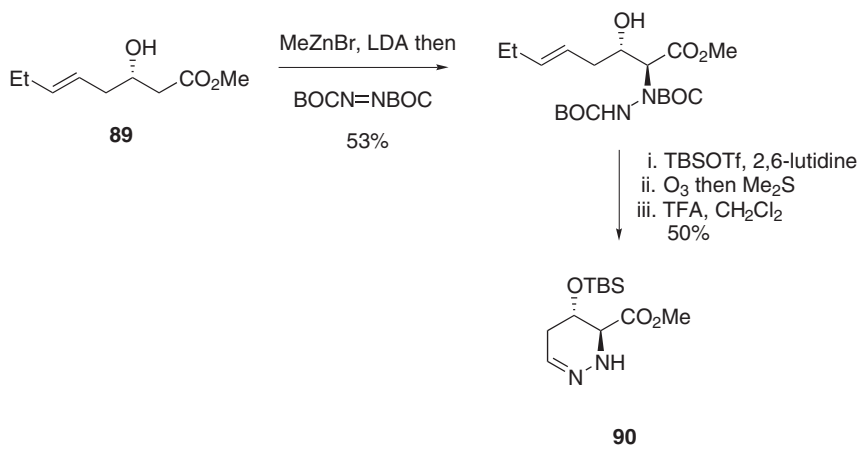


Scheme 16



Scheme 17

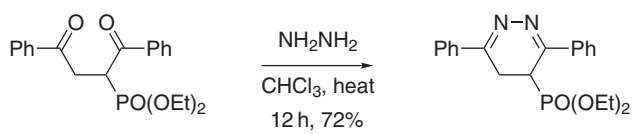
One final example is shown in Scheme 18. Electrophilic amination of **89** was followed by ozonolysis and acid-catalyzed cyclization to give **90**, the pyridazine component of luzopeptin A <1995TA1989>.



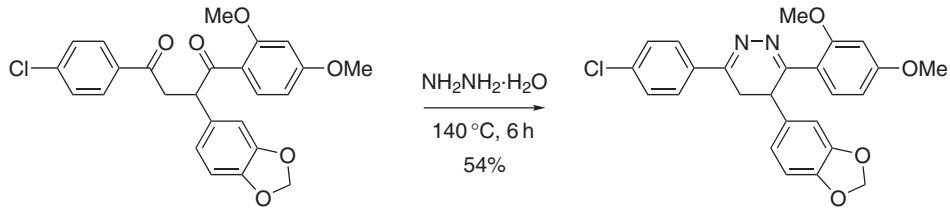
Scheme 18

3.12.1.6.3 Cyclic azines

Condensation of 1,4-dicarbonyl compounds with hydrazine gives rise to the formation of 4,5-dihydropyridazines. The reaction conditions shown in Equation (33) <1998PS(134)493> and Equation (34) <2000H(53)1129> are typical for this transformation.



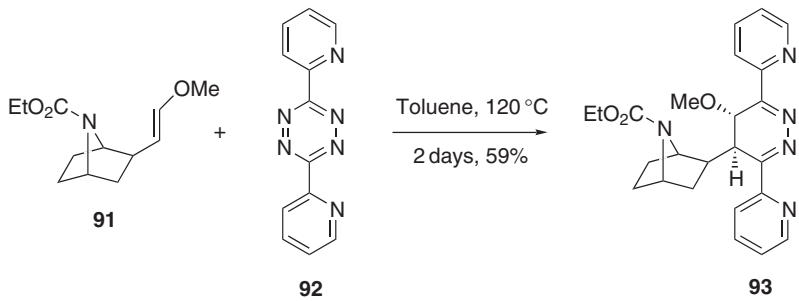
(33)



(34)

These heterocycles undergo ready oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the aromatic pyridazines <2002BMCL689>. The analogous seven-membered ring products are obtained by reaction with 1,5-dicarbonyls <2002TL143>.

An alternative method for the formation of 4,5-dihydropyridazines is shown in Equation (35). Hetero-Diels–Alder reaction of **91** with **92** followed by loss of nitrogen gave **93** as the major product, although some of the corresponding oxidized aromatic products were also isolated <2001JMC47>.



(35)

3.12.1.7 $R_2C{=}NX$ Functions (X = Li, Mg, B, Al, Si, P, Te, Ti)

Metal complexes featuring imine ligands are not described. Examples presented in this section will be restricted to those in which the imine nitrogen atom is bonded solely to a single heteroatom. In recent years there have been relatively few examples of this class of compounds reported, and so the ordering of this section has been modified slightly from the previous review <1995COFGT(3)443>. Where imines bonded to other elements are not mentioned, these compounds are either covered in Section 3.10.4 (*N*-haloimines), Section 3.11.1 (oximes), or Section 3.11.2.1 (sulfur analogs of oximes) or no examples were found.

3.12.1.7.1 Imines substituted with lithium

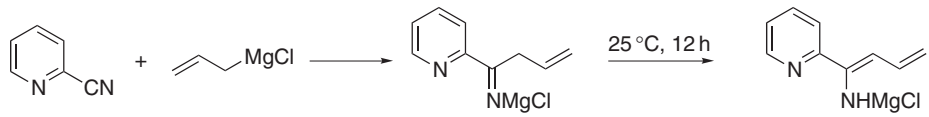
A range of compounds which can formally be classed as lithiated imines are involved in the reactions of $LiCHR_2$ reagents with nitriles lacking α-hydrogen atoms <2000JCS(D)2301>. These compounds are not generally isolated, although some have been characterized crystallographically <1998JCS(D)3431>. These species are versatile intermediates in the preparation of a range of other *N*-substituted imines found elsewhere in this section.

3.12.1.7.2 Imines substituted with magnesium

Magnesium imine **94** was isolated as a solid from the reaction of 2-cyanopyridine with allyl magnesium chloride. Whilst it could be characterized, 12 h at room temperature was sufficient for complete tautomerization to the conjugated enamine form **95** (Scheme 19) <1995JOC5284>.

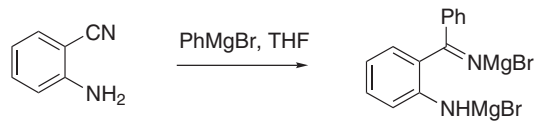
Copper(I) chloride was added to related reactions, and in these cases the magnesium imines were not isolated <1996JCS(P1)691>. The same reaction was used as the basis of a one-pot alkylation/reduction of nitriles to give secondary amines <2002TL8617>.

Reaction of anthranilonitrile **96** with phenyl magnesium bromide in tetrahydrofuran (THF) gave imine **97** (Equation (36)). This compound was not isolated, but is a synthetically useful dianion equivalent that was quenched with a range of reagents providing a selection of heterocyclic products <2003OBC367>.



94 **95**

Scheme 19

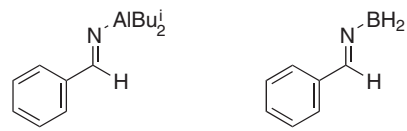


96 **97** (36)

There are no new examples of imines substituted with beryllium. Imines substituted with calcium, strontium, or barium have yet to be reported.

3.12.1.7.3 Imines substituted with boron or aluminum

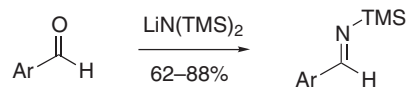
Imines substituted with boron and aluminum are rare. Compound **98** can be prepared by partial reduction of benzonitrile with diisobutylaluminum hydride <2000JA4217>. This compound and boron analog **99** were subjected to asymmetric reduction reactions <1995TA1507>.



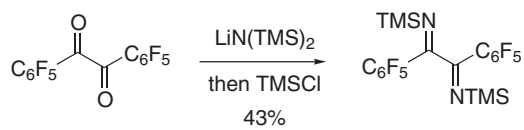
98 **99**

3.12.1.7.4 Imines substituted with silicon

Silyl groups can conveniently be used as protection for an imine nitrogen. However, the most convenient method for the preparation of trimethylsilylimines is the reaction of nonenolizable aldehydes with lithium hexamethyldisilazane. This reaction has been used to prepare a range of silylimines for use in reductive coupling reactions (Equation (37)) <1999JOC1958>. *N*-Silyl bisimines such as **100** are readily accessed by this method (Equation (38)) <1999TL8523, 1999HAC423>.

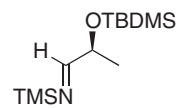


(37)



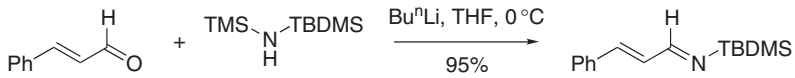
100 (38)

This reaction generally works best for nonenolizable aldehydes and ketones <1995JOC7366>. However, there are examples of enolizable silylimines prepared in this way, for instance compound **101** derived from lactic acid <1997JOC8911>. These compounds are generally not isolated, but can be used *in situ* in a range of reactions <1998JOC2824, 1998JCS(P1)2663>.



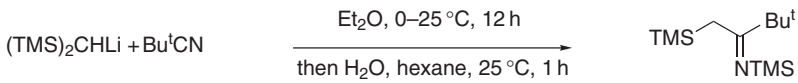
101

Silylimines bearing groups other than trimethylsilyl can be prepared from mixed bis-silylamines. For instance, reaction of cinnamaldehyde with the lithium amide derived from compound **102** gave imine **103** in extremely high yields (Equation (39)) <1997S886, 1998TL6257>.



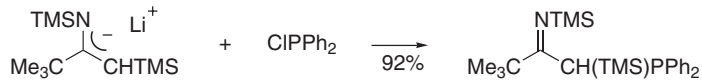
102 **103** (39)

Reaction of organolithium species **104** with pivalonitrile **105** gives silylated imine **106** via the intermediacy of a lithiated imine (Equation (40)) <1994CC2637>.



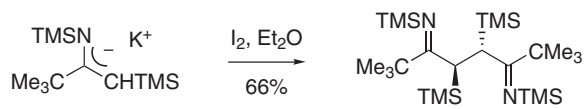
104 **105** **106** (40)

The reaction of silylimine **113** with phosphorus(III) chloride is described in the following section. Aza-allyl **107**, the precursor to **113**, undergoes reaction with chlorodiphenylphospane to give α-phosphonylsilylimine **108** (Equation (41)) <1997JOM(529)243, 1999JOM(580)386>.



107 **108** (41)

The potassium salt of the same aza-allyl underwent oxidative coupling to give *meso*-bisimine **109** in high yield (Equation (42)) <1997JOM(549)1>.

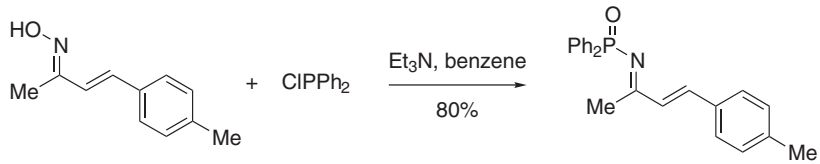


109 (42)

There are no new examples of imines bearing germanium, tin, or lead.

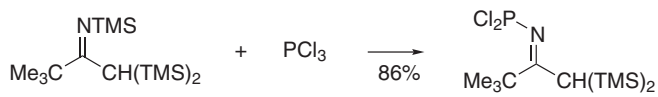
3.12.1.7.5 Imines substituted with phosphorus

Reaction of α,β-unsaturated imine **110** with chlorodiphenylphosphane **111** proceeded via initial *O*-phosphorylation followed by rearrangement to give **112** (Equation (43)) <1998EJO1413>. The same approach was used to prepare *N*-phosphonyltrifluoromethylimines <2001TL101>.



110 **111** **112** (43)

In a similar reaction, silylimine **113** gave **114** on treatment with phosphorus(III) chloride (Equation (44)) <1997JOM(529)243>.

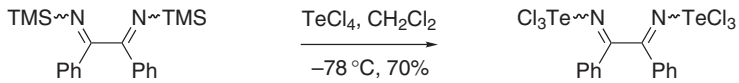


113 **114** (44)

There are no new examples of imines substituted with arsenic, antimony, or bismuth.

3.12.1.7.6 Imines substituted with tellurium

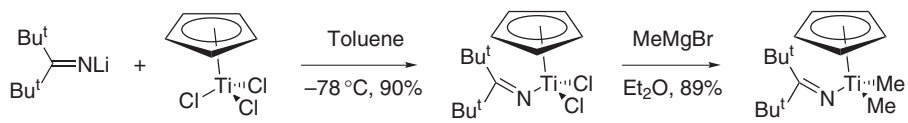
There is a single example of an imine substituted with tellurium. Reaction of bis-silylimine **115** with tellurium(IV) chloride gave compound **116** in good yield (Equation (45)) <1997JIC709>.



115 **116** (45)

3.12.1.7.7 Imines substituted with transition metals

Reaction of lithiated imines with cyclopentadienyltitanium trichloride **117** gave a range of compounds typified by structure **118**. The chloride ligands were then exchanged by reaction with methyl magnesium bromide (Scheme 20) <2000JA5499>.



117 **118**

Scheme 20

No other examples of imines bearing a transition metal on a neutral nitrogen atom were found.

3.12.2 DIAZO COMPOUNDS

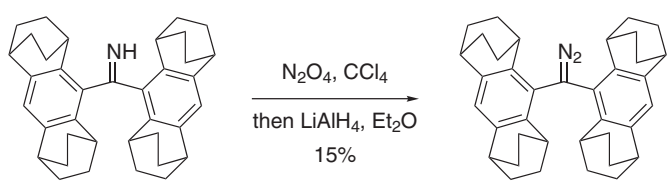
3.12.2.1 General Methods for the Preparation of Diazo Compounds

Methods for the preparation of diazo compounds can be broadly divided into three categories: (i) reaction of two different nitrogen-containing compounds to form a diazo compound; (ii) conversion of a functional group containing two nitrogen atoms into a diazo group; and (iii) diazo transfer from a donor compound to a suitable substrate. Additionally, there is a range of elaborations of existing diazo compounds, either at the diazo carbon or other positions, which are of general synthetic utility and are therefore covered in this review. COFGT (1995) should be consulted for examples prior to 1995 <1995COFGT(3)443>.

3.12.2.2 Alkyl and Aryl Diazo Compounds

3.12.2.2.1 Diazotization of amines

While there appear to be no reported examples of the diazotization of amines within the period covered by this review, imine **119** underwent a related reaction to give hindered diazo compound **120**, albeit in low yield (Equation (46)) <2000JOC8797>.



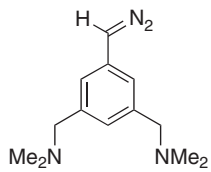
119 **120** (46)

3.12.2.2.2 Forster reaction of oximes

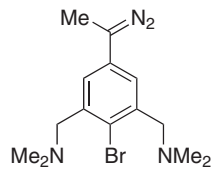
No new examples of this reaction class were found.

3.12.2.2.3 Dehydrogenation of hydrazones

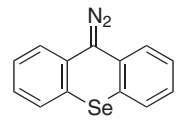
Two new diazo compounds **121** and **122** were generated by MnO_2 oxidation of the corresponding hydrazones. Due to their instability, these compounds were not isolated, but were used *in situ* for the cyclopropanation of [60]fullerene <1998TL6773>. Other oxidants are also effective in this reaction, and the formation of **123** in 84% yield demonstrates the tolerance of this reaction to other functionality. In this case, silver oxide proved superior to mercuric oxide <2000JCS(P2)725>. This approach is reasonably general for the formation of diaryl diazo compounds, and is particularly effective given the ready availability of the ketones <2002JA272>.



121

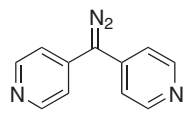


122

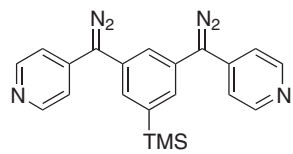


123

Diazopyridines **124** and **125** have been prepared by oxidation of the corresponding hydrazones with mercury(II) oxide/sodium hydroxide <1996AG(E)755, 1997JA8246, 1997CC1359>.

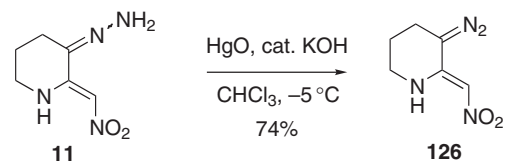


124



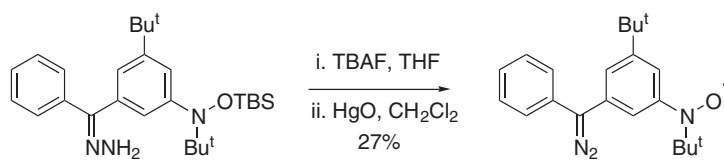
125

The slightly unusual heterocyclic diazo compound **126** was prepared by oxidation of hydrazone **11** (Equation (47)) <2001TL1773>.



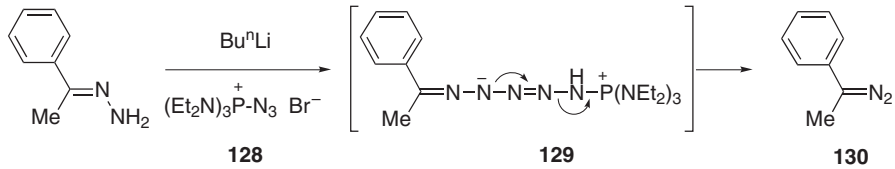
11 **126** (47)

Simultaneous oxidation of a hydrazone and oxime in the same molecule allowed access to stabilized radical **127**, which was subsequently used to investigate the interaction of the derived carbene with the radical (Equation (48)) <1998JCS(P2)1581>.



127 (48)

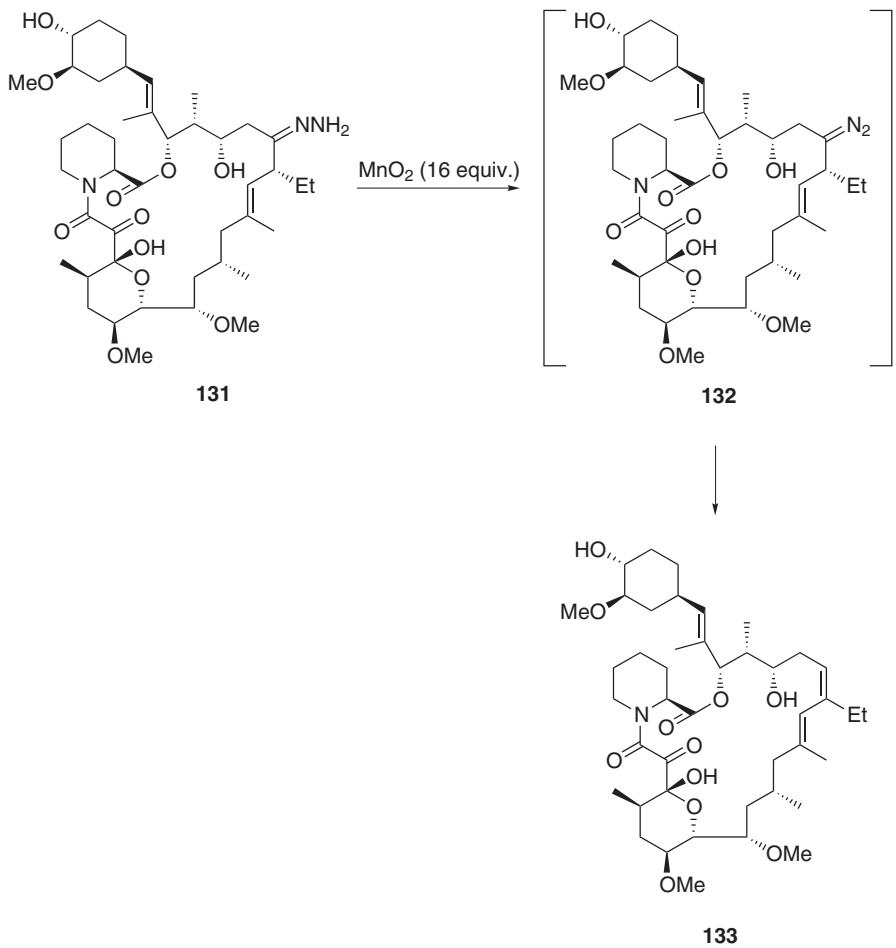
Although not an oxidation in the conventional sense, treatment of hydrazones with butyllithium followed by azidotris(diethylamino)phosphonium bromide **128** allows the formation of diazo compounds such as **130** via the intermediacy of **129** (Scheme 21) <2002TL8425>.



128 **129** **130**

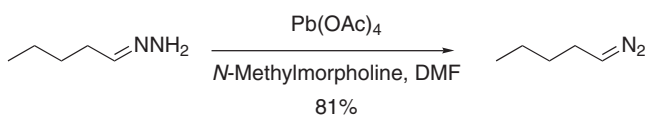
Scheme 21

Where there are no functional groups stabilizing the diazo compound, loss of nitrogen can be spontaneous. For instance, diazo compound **132**, formed by MnO_2 oxidation of **131**, was not isolated, but instead gave a mixture of products of which **133** was a major constituent (Scheme 22) <1999TL3869>. However, unstabilized diazo compounds can be isolated from the lead tetraacetate-mediated oxidation of hydrazones. Mixed solvent systems are occasionally superior, although dimethylformamide (DMF) is generally the solvent of choice (Equations (49) and (50)) <1995JOC4725>.

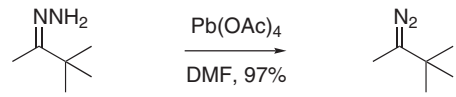


131 **132** **133**

Scheme 22

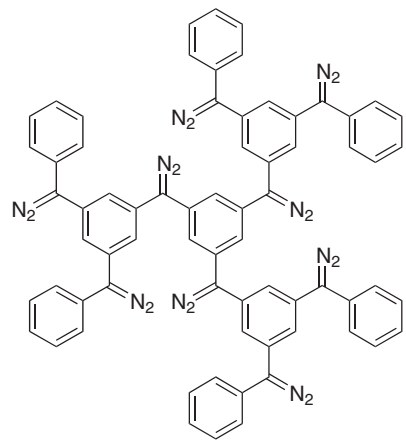


(49)



(50)

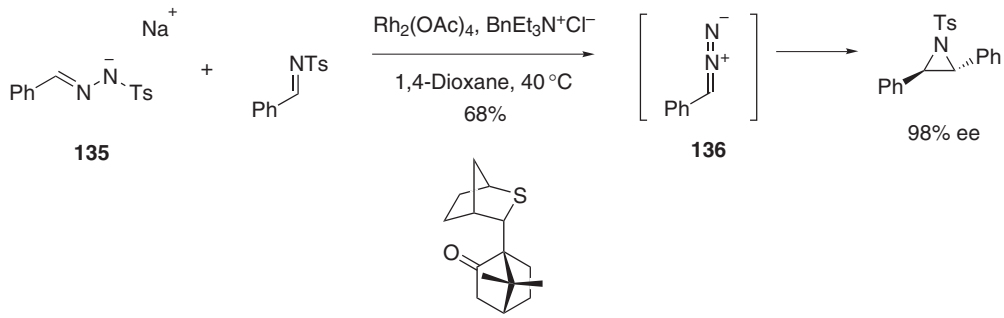
All these examples, while impressive and useful, pale in comparison to compound **134**, prepared in 11% yield by reaction of the corresponding nona-hydrazone with mercuric oxide <1995JA5550, 1996CEJ259>.



134

3.12.2.2.4 Bamford–Stevens reaction of tosylhydrazones

Recent work from Aggarwal and co-workers has shown that diazo compounds can be generated (and used) *in situ* by the Bamford–Stevens reaction of tosylhydrazone salts. For example, in the reaction of salt **135**, phenyldiazomethane **136** was formed and reacted further to give the aziridine with high enantiomeric excess (Scheme 23) <2001AG(E)1433, 2001OL2785>.

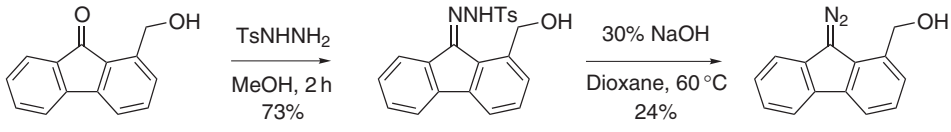


Scheme 23

Kirmse has extensively studied aryl carbene reactions, largely using diazo compounds as precursors. The formation of diazo compound **138** from ketone **137** is representative of this work (Scheme 24) <1998TL799, 1998TL6675, 1997T9935>.

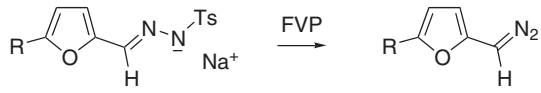
The same approach has been used by Lambert and Liu to prepare 1-phenyldiazopropane and 1-phenyldiazoethane in 43% and 20% yields, respectively. In this case, sodium methoxide in pyridine was used <1997T9989>.

Flash vacuum pyrolysis (FVP) of sodium salts of tosylhydrazones **139** and **140** (70–115 °C, 10^{-6} mbar) allowed diazo compounds **141** and **142** to be trapped at 30 K prior to photolysis (Equation (51)) <2001EJO269>.



137 **138**

Scheme 24

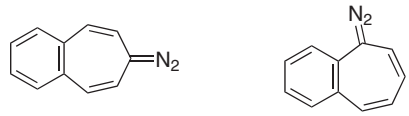


139, R = TMS
140, R = Me_3Sn

141, R = TMS
142, R = Me_3Sn

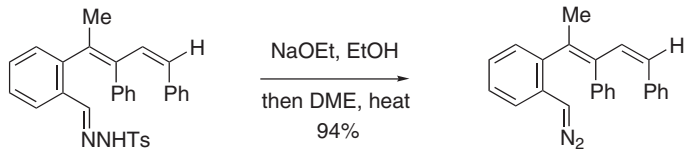
(51)

Diazo compounds **143** and **144** are difficult to prepare. A recent study has compared hydrazone oxidation and Bamford–Stevens as methods for accessing them. While it is fair to say that neither method is particularly good, hydrazone oxidation is preferable for the formation of **143**. However, compound **144** is better accessed by pyrolysis of the corresponding tosylhydrazone salt <2002JOC9031>.



143 **144**

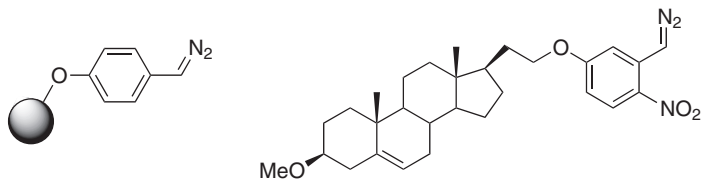
A range of substituted aryl diazomethanes was used in cycloaddition reactions giving a range of products. Of the diazo precursors used, only compound **145** was actually isolated (Equation (52)), compounds having different functionality on the double bonds undergoing spontaneous cycloaddition <2000JCS(P1)1139>.



145

(52)

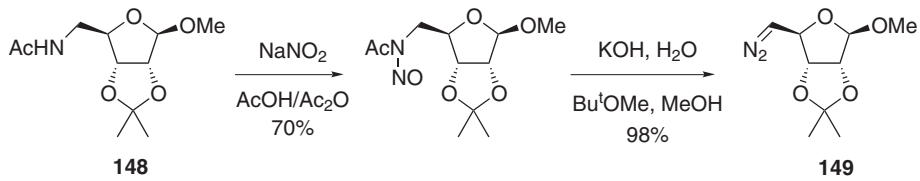
In other work, polymer-supported aryldiazomethane **146** <1998TL7803> and steroidal diazo compound **147** <2002T1685> were prepared in a similar fashion. In both cases, the diazo group was used as the basis for a linker to other functionality.



146 **147**

3.12.2.2.5 Cleavage of N-nitrosoamides

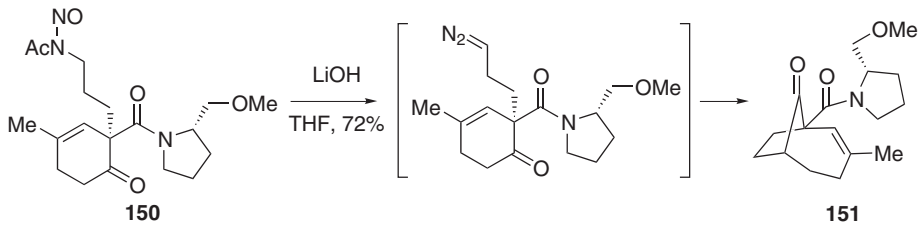
In studies directed toward the tunicamycin antibiotics, diazo compound **149** was prepared in a high-yielding two-step procedure from acetamide **148**. Thus, nitrozation of **148** with sodium nitrite was followed by treatment with potassium hydroxide in a mixed solvent system (Scheme 25) <1995T5491, 1996T4757>.



148 149

Scheme 25

In other instances, the diazo compounds formed by this method undergo further reaction. For example, treatment of **150** with lithium hydroxide in THF gave **151** in which the diazo carbon has undergone reaction with the ketone, followed by Wagner–Meerwein shift with concomitant loss of nitrogen (Scheme 26) <2002TL4711>.

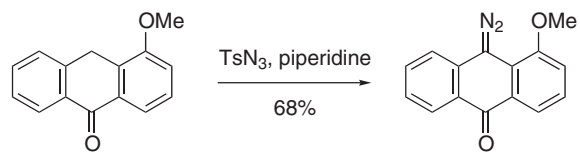


150 151

Scheme 26

3.12.2.2.6 Diazo group transfer

Diazo transfer is generally only applicable to compounds containing a methylene group between two electron-withdrawing groups. Recent work has revealed conditions in which only a single electron-withdrawing group is required (Section 3.12.2.3.7), but the examples of this reaction type in which no electron-withdrawing groups are present are extremely sparse. Compound **152**, in which the methylene group is vinylogous to the carbonyl group, undergoes efficient diazo transfer giving **153** (Equation (53)) <1998TL6675>. This example should be considered as the exception that proves the rule!

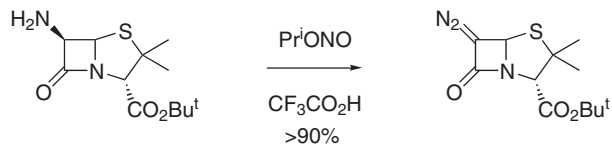


152 **153** (53)

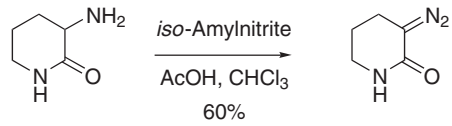
3.12.2.3 α-Diazo Carbonyl and β-Dicarbonyl Compounds

3.12.2.3.1 Diazotization of α-amino carbonyl compounds

Diazotization of *t*-butyl 6-aminopenicillanate was accomplished in greater than 90% yield using isopropylnitrite in the presence of an acid catalyst (Equation (54)) <1999JCR(S)270>. An essentially identical method was used by Buynak and co-workers <1998TL4945>, but in this case the diazo compound was not isolated. 3-Diazopiperidine-2-one was prepared in a similar manner (Equation (55)) <2002T3137>.



(54)

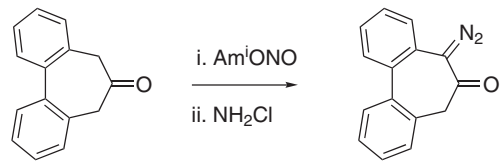


(55)

Although ethyl diazoacetate is readily available, it can also be generated *in situ* by diazotization of glycine ethylester hydrochloride to allow the rhodium(II)-catalyzed cyclopropanation of styrene under aqueous conditions <2002OL4531>.

3.12.2.3.2 Forster reaction of α-keto-oximes

2-Diazo-1-indanone was prepared by the Forster reaction of the corresponding oxime <2000TL1491>. This reaction was the method of choice for the preparation of mono diazo compound **155** from ketone **154** (Equation (56)). In contrast, diazo transfer gave the bis-diazo compound <1995JOC2344>.



154 **155**

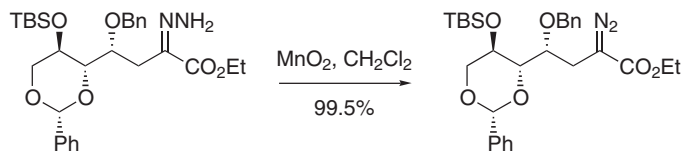
(56)

3.12.2.3.3 Direct nitrozation of carbonyl compounds

No new examples were found since the publication of COFGT (1995).

3.12.2.3.4 Dehydrogenation of α-carbonyl hydrazones

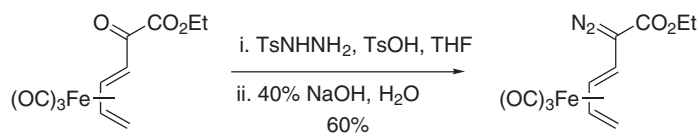
Preparation of diazocarbonyl compounds from the corresponding hydrazones is uncommon, mainly due to the use of diazo transfer as an alternative. However, in an analogous manner to aliphatic and aryldiazo compounds, MnO_2 oxidation provides ready access to the target compounds (Equation (57)) <2001T10271>.



(57)

3.12.2.3.5 Bamford–Stevens reaction of α-carbonyl tosyl hydrazones

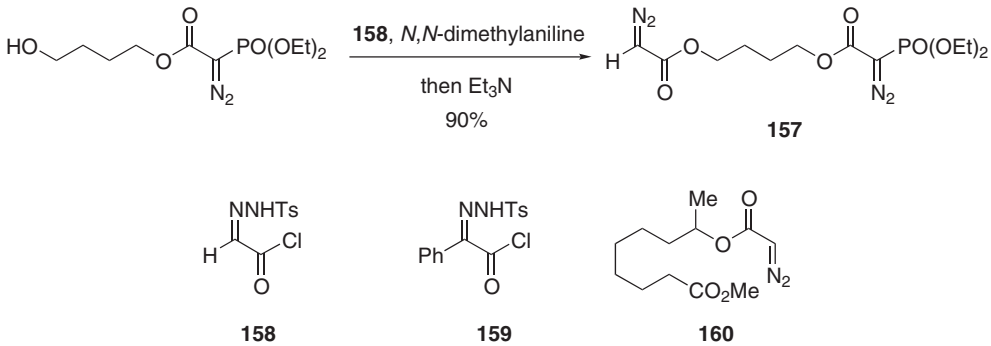
While it is seldom used, the reaction of 1,2-dicarbonyl compounds with sulfonylhydrazines followed by treatment with a base is an effective method for the preparation of diazocarbonyl compounds, for instance **156** (Equation (58)) <1995SL341>. If the stabilizing ester group is not present, the diazo compound is not isolated, but undergoes further reaction <2002SL2054>.



156

(58)

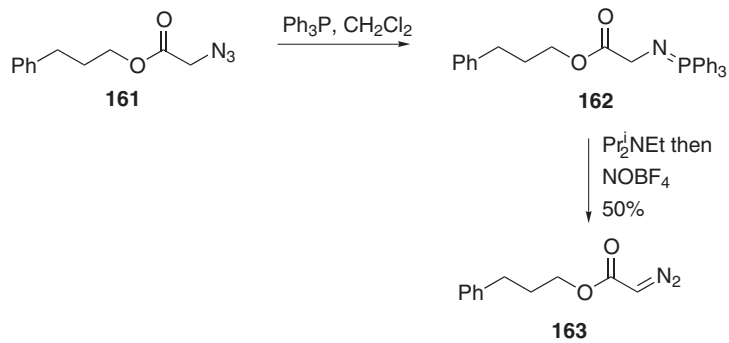
General methods for the introduction of diazo functionality are particularly attractive. Acid chlorides **158** and **159** have both been reported before. Diazo compounds such as **157** were liberated under mild conditions after esterification with either of these compounds in a one-pot procedure (Equation (59)) <1998T2257>. An essentially identical method was used for the preparation of **160** <2000OL1777>.



(59)

3.12.2.3.6 Cleavage of N-nitroso compounds

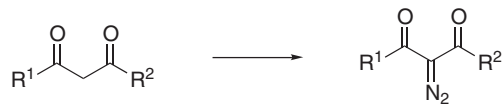
The formation of a P—O double bond has long been used as a driving force in organic chemistry. This method has been applied to the synthesis of diazo compounds as shown in Scheme 27. Treatment of azide **161** with triphenylphosphine gave the intermediate iminophosphorane **162**, which was then allowed to react with nitrosonium tetrafluoroborate in the presence of ethyldiisopropylamine to give diazo compound **163** in 50% yield <1998TL1129>.



Scheme 27

3.12.2.3.7 Diazo group transfer to carbonyl compounds

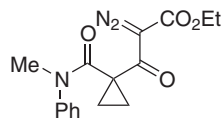
Diazo transfer to an active methylene group (Equation (60)) is without doubt the most popular method for the preparation of diazocarbonyl compounds, and works well for almost all cases where a methylene group is flanked by two carbonyl compounds. The metallocarbenes derived from these compounds have been the subject of numerous studies since the 1970s, and as a result, there are a wide range of reagents and conditions for effecting diazo group transfer. Sulfonyl azides are most commonly used in conjunction with a base, but the choice of reagent, base, and solvent is often a matter of personal preference. Efficient diazo group transfer occurs under a broad range of conditions, and selected examples will be presented in order to give representative coverage of the area.



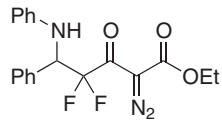
(60)

Tosyl azide is one of the more accessible reagents and has been used to prepare a wide variety of diazo compounds. These include 2-diazo-1,3-diketones <2000OL1357> and 2-diazo-3-ketoesters <2001TL6835, 2002HCA483>. These reactions are most commonly carried out in acetonitrile using triethylamine as base, although potassium carbonate <2001HCA1093> has also been used.

More complex diazo compounds, including **164** <2000JA8155> and **165**, <2003OL745> have also been prepared by the same general method. In the latter case, the β-keto ester substrate was treated with molecular sieves prior to diazo transfer due to its tendency to exist as the hydrate.

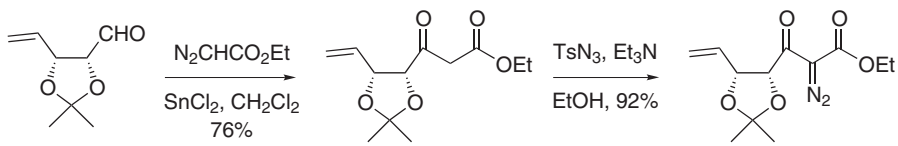


164



165

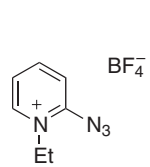
The tin(II) chloride-catalyzed reaction of ethyl diazoacetate with aldehydes provides efficient access to β-keto esters, so that the sequence shown in Scheme 28 is a particularly attractive approach to 2-diazo-3-ketoesters <2001TL7489>.



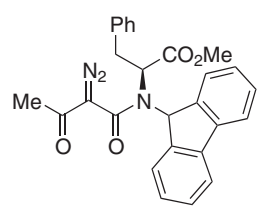
Scheme 28

Mesyl azide is also widely used as a diazo-transfer reagent, despite a higher risk of explosion <1997JOC2001, 2001JOC6323, 2002OL1419, 2001JOC944>. Safety is a major concern with azides and diazo compounds, so that a range of other azides is now widely used <1999OL667, 2001JOC1638, 2003JOC227>. A recent study has shown that polystyrene-supported benzenesulfonyl azide is comparable in reactivity to 4-carboxybenzenesulfonyl azide, and has the added advantage of ease of purification of the diazo product <2001JOC2509>. Dodecylbenzenesulfonyl azide has also been used in the synthesis of polymer-supported diazo compounds for use in heterocyclic synthesis <2001OL2173, 2002TL5407>.

2-Azido-1-ethylpyridinium tetrafluoroborate **166** is able to effect diazo transfer under particularly mild conditions, and was the reagent of choice in the preparation of **167** <1995T8829>.

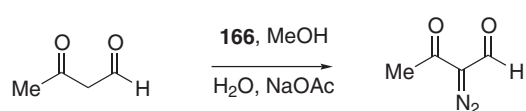


166



167

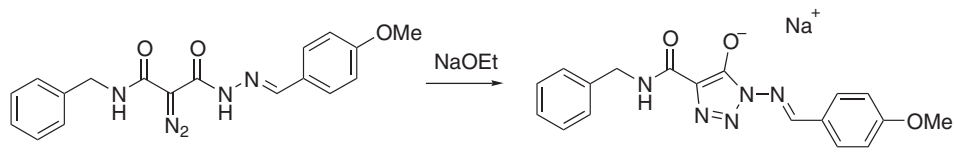
Diazoaldehydes are relatively difficult to prepare. The same diazo-transfer reagent **166** was used to prepare compound **168**, albeit in low yield. Under the conditions shown in Equation (61), minimal deformylation occurred <1994HCA2323>.



(61)

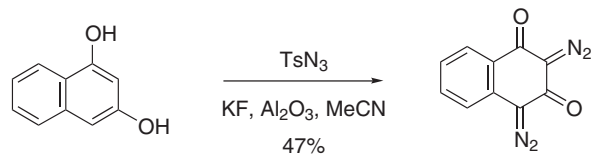
168

Not all diazocarbonyl compounds are stable, and diazohydrazide **169**, prepared by routine diazo transfer with tosyl azide, was not isolable. Instead, it cyclized exclusively via the hydrazide nitrogen to give **170** (Equation (62)) <2002JCS(P1)211>.



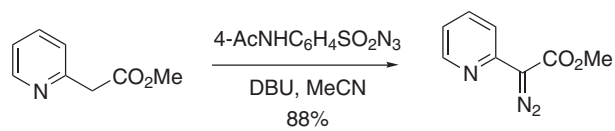
169 **170** (62)

Diazo-transfer reactions work well for cyclic 1,3-dicarbonyl compounds <1997TA699, 1999JOC3642, 1999T6577, 1999TL6603, 2000TL4795, 2000JCS(P1)2121>. A particularly unusual example is the double diazo transfer to naphthalene-1,3-diol **171**, which can be viewed as a completely enolized dicarbonyl (Equation (63)) <1998JA9088, 2000JOC6082>.



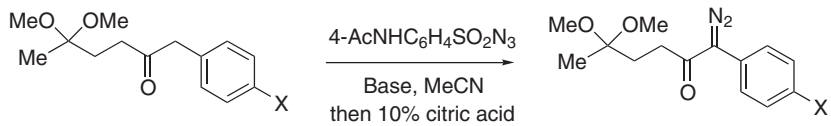
171 (63)

Although these reactions are most common when the methylene group is flanked by two strong electron-withdrawing groups, there are numerous reports of the combination of one good electron-withdrawing group and a group such as aryl or heteroaryl. Generally, a stronger base is required, and the combination of 4-acetamidobenzenesulfonyl azide and DBU is generally effective. For instance, diazo transfer to methyl 2-(2-pyridyl)acetate is efficient and high yielding under standard conditions (Equation (64)). A range of other aryl and heteroaryl derivatives were also reported <2001JOC6595>. Tosyl azide is also effective in this type of reaction <1999JA2875, 1999JA2883>.



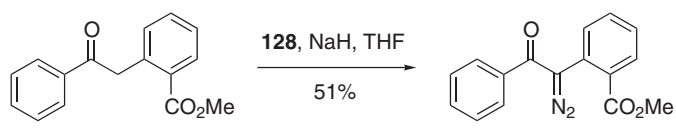
(64)

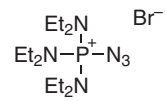
In the case of compound **173**, where the aromatic ring is more electron withdrawing, triethylamine was sufficient as base, while for **172** DBU was once again used (Equation (65)) <2002TL3927>. Some heterocycles are sufficiently activating to permit the use of triethylamine as base <1999TL397, 2000JOC3111>, although sodium ethoxide has also been used <1999T11537>.



172 (X = H), DBU as base
173 (X = NO_2), Et_3N as base (65)

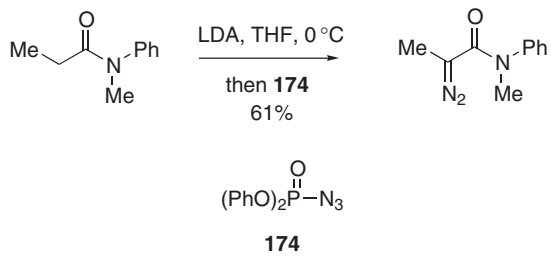
Azidotris(diethylamino)phosphonium bromide **128** has also been used for similar reactions, generally in THF solution and with sodium hydride as base (Equation (66)) <1999JOC4079>.





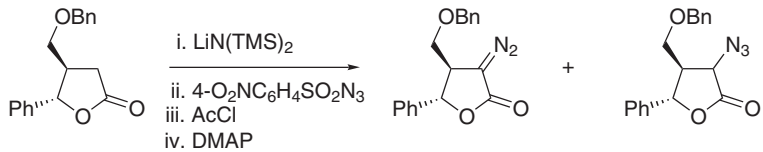
128 (66)

Examples of diazo transfer in which there is only a single electron-withdrawing group adjacent to the target methylene are rare. As might be expected, particularly strong bases are required, and in some cases less common diazo-transfer reagents such as **174** are used. The example shown in Equation (67) is moderately high yielding, although the corresponding *N*,*N*-dimethylamide gave none of the desired diazo compounds <1995HCA1983>.



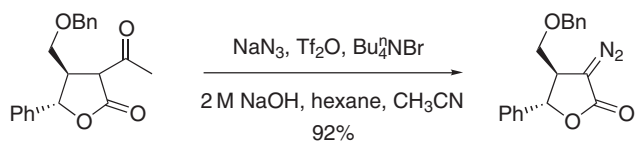
174 (67)

A relatively complex series of reactions was required to convert lactone **175** into diazo compound **176**. Deprotonation with LiHMDS was followed by treatment with a sulfonyl azide in the usual manner. This provided the lithium salt of an intermediate triazine, which was treated with acetylchloride followed by 4-dimethylaminopyridine (DMAP). Even so, a 1:1 mixture of diazo compound and azide **177** was obtained under these optimal conditions (Equation (68)) <1998CC1895, 2001JOC6719>.



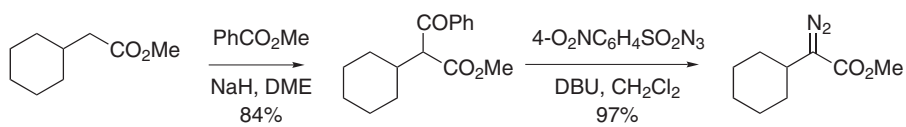
175 **176**, 51% **177**, 48% (68)

A common tactic for effecting diazo transfer to a position that is stabilized by only a single electron-withdrawing group is deacylative diazo transfer in which an additional stabilizing group is temporarily introduced. This group is then lost during the diazo-transfer reaction. An improved synthesis of compound **176** makes use of a modified version of this approach in which triflylazide is generated *in situ* (Equation (69)) <2002CC2042>.



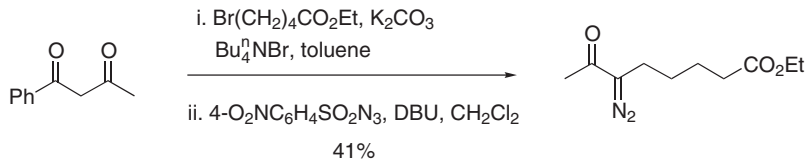
176 (69)

Taber and co-workers carried out much of the early work on this reaction. The benzoyl group is particularly effective, so that treatment of an ester enolate with methyl benzoate followed by standard diazo transfer is now a relatively general method (Scheme 29) <1995TL2587, 1995JOC1093, 1995JOC2283>.



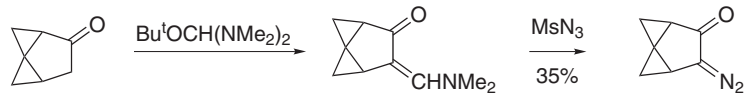
Scheme 29

These reactions are extremely versatile. For instance, in the example above the benzoyl group was temporarily introduced into a compound with the complete carbon skeleton of the product intact. Alternatively, straightforward alkylation of a 1,3-dicarbonyl compound is followed by diazo transfer to give similar products. The example shown in Equation (70) is taken from the work of Taber and Kanai <1999JOC7983>, although there are a number of other reports utilizing the same general approach <2000JOC5223, 1997SL189>.



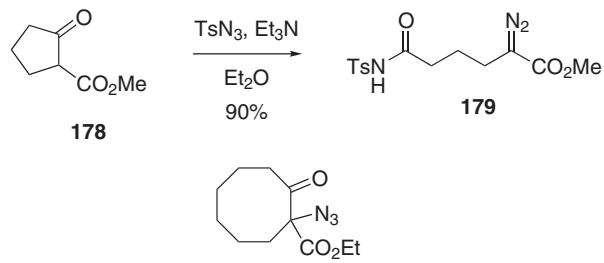
(70)

In addition to acetyl and benzoyl, the formyl group has been used to provide temporary activation <2000JOC3722, 2000HCA2617>. One slightly unusual example features the temporary introduction of an enamine (Scheme 30) <1996TL8285>.



Scheme 30

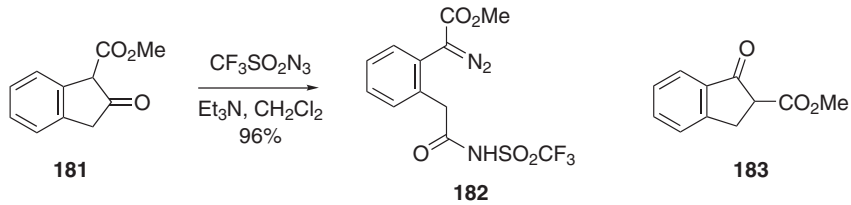
This general reaction type can be carried out on cyclic β-keto esters, in which the ketone is tethered to the alkyl group in the α-position. For example, treatment of compound **178** with tosyl azide in ether gave diazoester **179** in high yield (Equation (71)). While this pathway predominated for five- to seven-membered rings, the analogous cyclooctane gave azide **180** as the major isolated product (74% yield) <1997JCS(P1)457>.



178 **179** **180**

(71)

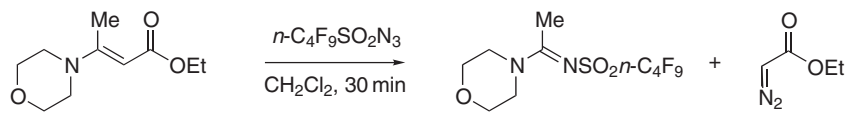
Benzo-fused β-keto esters give a range of products depending on ring size and position of fusion. For instance, while indanone **181** gave **182** in essentially quantitative yield, the diazo compound formed from isomeric indanone **183** was unstable under the reaction conditions, and gave only the products of carbene reaction. The corresponding tetralones gave different products again, while the homologous benzosuberone gave a small amount of diazo compound (Equation (72)) <1998JOC4679, 1999JOC5132>.



181 **182** **183**

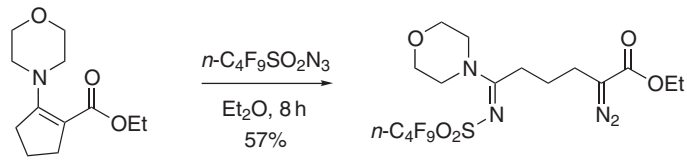
(72)

Fluorinated sulfonyl azides are particularly reactive, and react with β-keto ester enamines **184** to give amidines **185** and ethyldiazoacetate **186** (Equation (73)). In the case of compound **187**, an analogous reaction provided **188** in moderate yield (Equation (74)) <2000JFC(104)195>. Similar reactions also take place with cyclic β-keto esters in a manner reminiscent of the deacylative diazo-transfer reactions described above <2000JFC(105)25>.



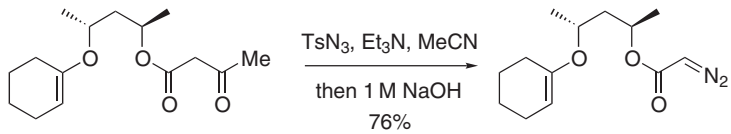
184 **185**, 81% **186**, 57%

(73)



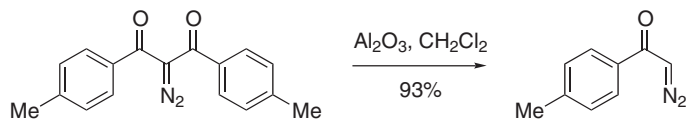
187 **188** (74)

It is possible to selectively deacylate a 2-diazo-3-ketoester to give a diazo compound stabilized by a single carbonyl group. For instance compound **189**, which was subsequently used to investigate the effect of the tether on stereoselective cyclopropanation reactions, was prepared as shown in Equation (75) <1997TA661, 2003TA881>.



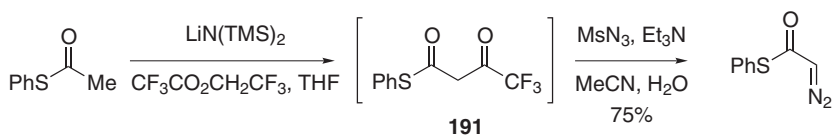
189 (75)

This reaction is mild and tolerates a range of functionality <2002TL9601>. Diaroyldiazomethanes such as **190** undergo smooth C—C bond cleavage upon treatment with Al_2O_3 in dichloromethane (Equation (76)) <1995S1248>.



190 (76)

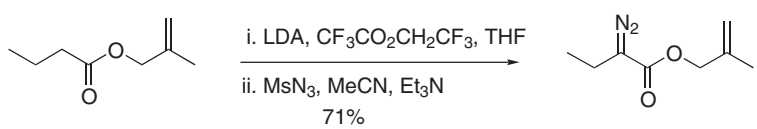
The trifluoroacetyl group is particularly easily cleaved, so that the method developed by Danheiser is a deacylative diazo transfer to a methylene (as opposed to methine) group. The intermediate 1,1,1-trifluoromethyl-2,4-dicarbonyl compound **191** is only briefly isolated before being subjected to diazo transfer (Scheme 31) <2000JOC4375>.



191

Scheme 31

This method, which provides an alternative to the Arndt–Eistert reaction, has been used to prepare a number of structurally complex diazo compounds <1997JCS(P1)2413, 2000JOC1899, 2001TL8965>. Further substitution at the diazo carbon is also possible (Equation (77)). In this case, the authors showed that although purification of the intermediate trifluoromethylketone is possible, the overall yield is lower <2000T9555>.

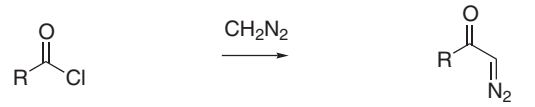


(77)

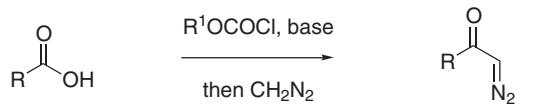
3.12.2.3.8 Substitution at the diazo carbon of α-diazocarbonyl compounds

The reaction of acid chlorides with diazomethane (the Arndt–Eistert reaction) to prepare α-diazoketones is relatively general, and is therefore one of the more effective methods for the formation of these compounds. The classical method of using acid chlorides as substrates

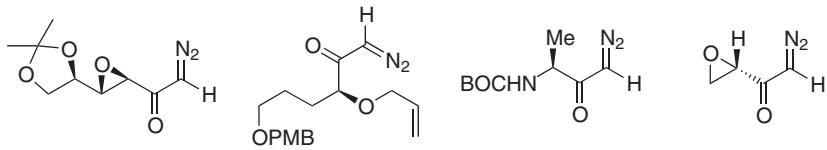
(Equation (78)) is being largely superceded by the use of mixed anhydrides (Equation (79)). In one instance it was noted that reaction of the acid chloride gave predominantly the methyl ester, while use of the mixed anhydride gave the required diazo compound in high yield <2000S395>. Diazo compounds prepared by the latter approach include **192** <1995T9699>, **193** <1996TL5605>, **194** <1998TL4239, 1998S837>, and **195** <2000OL2393>. Amino acid <1998JCS(P1)1919> and tartaric acid <2000S352> diazo compounds have also been prepared from the acid chlorides. The amino acid-derived diazoketones are particularly useful as substrates for the Wolff rearrangement to give β-amino acids <1997HCA1, 1998HCA187>. While diazomethane is most commonly used in such transformations, diazoethane also works, albeit when used in large excess <1996CC2595>.



(78)

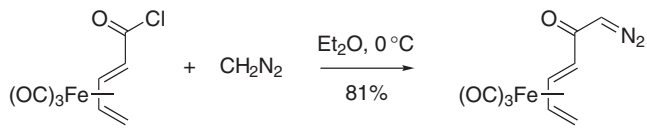


(79)



192, 64% **193**, 88% **194**, 93% **195**, 93%

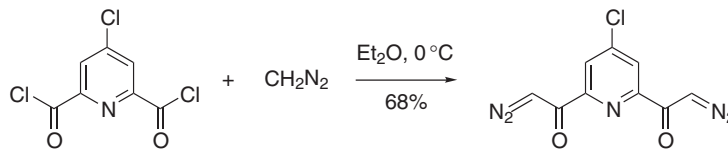
In other recent work, iron tricarbonyl complex **196** reacts smoothly under standard conditions to give the relatively stable diazo compound **197** (Equation (80)) <1995TL8213>.



196 **197**

(80)

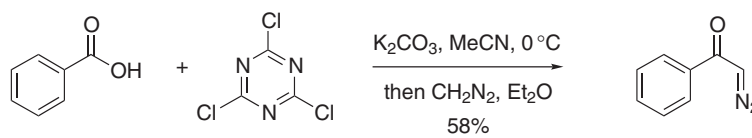
Bis-diazo compound **198** was prepared en route to the corresponding bismethylketone (Equation (81)) <2000T2043>. Other bis-diazo compounds have been prepared by this method <1995JOC2466>.



198

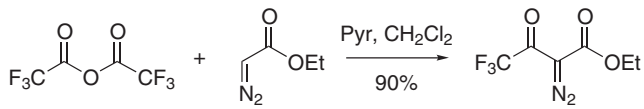
(81)

Cyanuric chloride is an effective activating agent for carboxylic acids prior to the addition of diazomethane (Equation (82)), although the formation of methyl esters is a significant competing reaction in some cases <2000TL9943>.



(82)

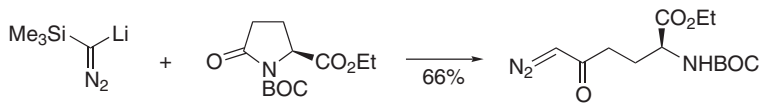
Two complementary methods have been used for the synthesis of trifluoromethylketone **199**. As a 2-diazo-1,3-dicarbonyl compound, diazo transfer is perhaps the most obvious approach, and is indeed successful. However, reaction of ethyl diazoacetate with trifluoroacetic anhydride (Equation (83)) provides a more than viable alternative <2000JFC(103)139>. Reaction of trifluoroacetic anhydride with diazomethane proceeds in a similar manner <1996CJC1348>.



(83)

199

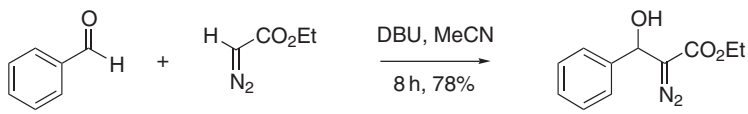
In a similar reaction, lithiotrimethylsilyl diazomethane is able to open pyroglutamate ester carbamates to give highly functionalized diazo compounds such as **200** (Equation (84)) <1998TL3243>.



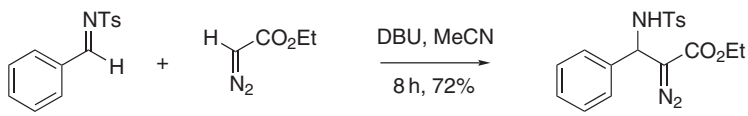
(84)

200

The hydrogen atom at a diazo carbon is acidic, particularly in the case of diazocarbonyl compounds. Historically a range of metallated derivatives (lithium, silver, mercury) have been used to effect further functionalization at this position. Recent work has shown that ethyl diazoacetate reacts with aldehydes <2002TL1285> and *N*-tosylimines <2003JOC893, 2002SL149, 2001OL2989> simply in the presence of DBU (Equations (85) and (86)).

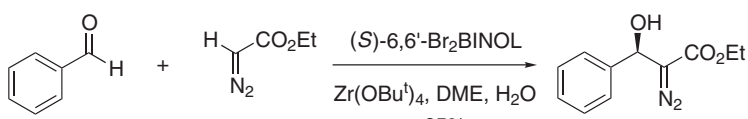


(85)



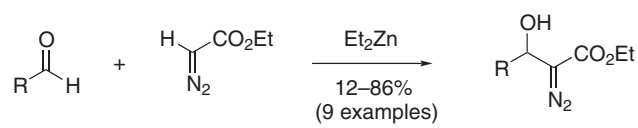
(86)

An asymmetric version of the former process has been reported, with enantioselectivities as high as 87% ee being obtained (Equation (87)) <2003OL1527>.



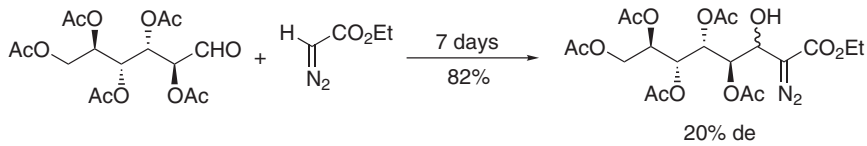
(87)

A range of metallated derivatives of diazo compounds have been used to enhance their carbanionic reactivity. For reactions of ethyl diazoacetate with aliphatic and aromatic aldehydes, the zinc derivative, prepared *in situ* by reaction with diethylzinc, is particularly effective (Equation (88)). This reaction is also chemoselective for aldehydes in the presence of ketones <1998S1039>.



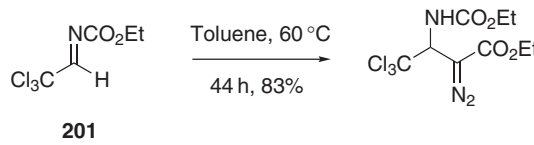
(88)

If one is prepared to accept lengthy reaction times, López-Herrera and co-workers <1997T3325, 1998T6867> have shown that these reactions proceed in the absence of solvent and catalyst (Equation (89)). However, more recent reports from the same group show that the use of diethylzinc is advantageous <2001T10271, 2001TL8801>.



(89)

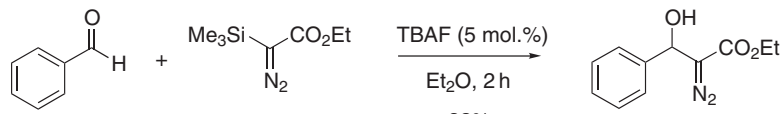
In the case of the particularly reactive imine **201**, direct reaction with ethyl diazoacetate occurs within a reasonable time and under mild conditions (Equation (90)) <1997CJC523>.



201

(90)

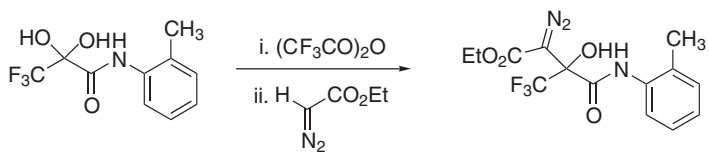
The use of fluoride to generate a carbanion from an organosilicon species is an attractive method given the mild conditions used. Since silylated diazo compounds are readily available (Section 3.12.2.5.6), treatment of **202** with 5 mol.% of tetra-*n*-butylammonium fluoride (TBAF) provided a high yield of the elaborated diazo compound **203** within 2 h (Equation (91)). The reaction is relatively general, working well for aromatic, heteroaromatic, aliphatic, and unsaturated aldehydes. However, it is less effective for ketones, even reactive ones such as ethyl pyruvate <1999TL5059>.



202 **203**

(91)

Addition of diazo compounds to reactive ketones can be accomplished by a number of methods. In the case of pyruvamide hydrate **204**, reaction with trifluoroacetic anhydride was followed by addition of ethyl diazoacetate to give **205** in good yield (Equation (92)) <1997SL797>.

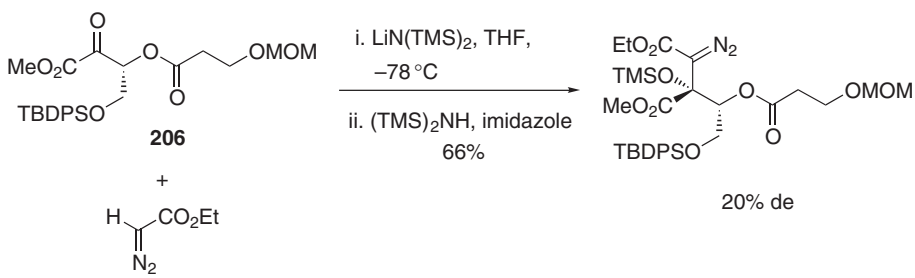


204 **205**

71%

(92)

Lithium hexamethyldisilazide was used as base in the addition of ethyl diazoacetate to **206** en route to zaragozic acid analogs (Equation (93)) <1998TL2371>.

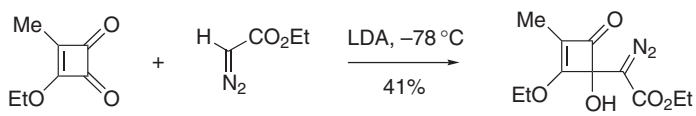


206

20% de

(93)

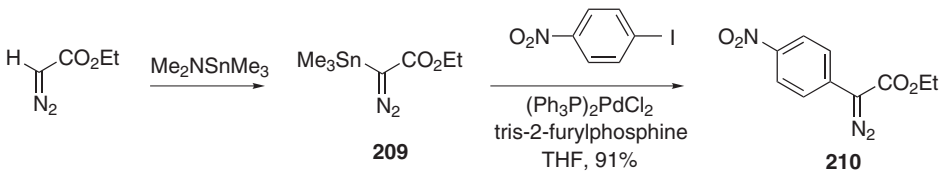
One further example of this reaction type features the reaction of ethyl diazoacetate with cyclobutenedione **207**. Despite the densely packed functionality in **208**, the compound was sufficiently stable to be purified by chromatography (Equation (94)) <1999JOC707>.



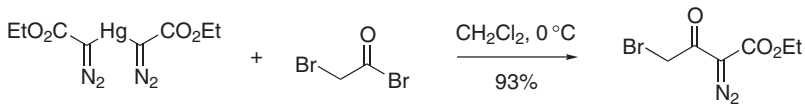
207 **208**

(94)

Given their propensity for transition metal-catalyzed decomposition, diazo compounds are unlikely candidates for palladium-catalyzed cross-coupling reactions. However, ethyltrimethylstannyldiazoacetate **209**, prepared *in situ*, undergoes cross-coupling with aryl halides to give **210** (Scheme 32). Coupling with acyl halides was more effective with the organomercury compound **211**, and proceeded in the absence of a catalyst (Equation (95)). An improved large-scale preparation of **211** was developed during the course of this work, and the synthetic scope of the products was demonstrated in a range of nucleophilic displacement reactions of **212** <1997T2371>.

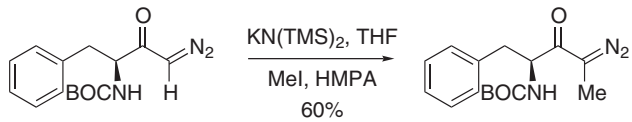


Scheme 32



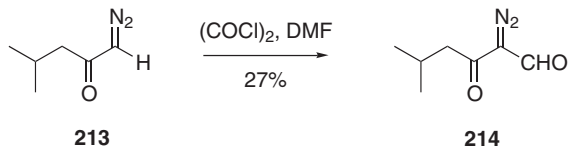
(95)

Alkylation at the diazo carbon is also possible, although the example shown in Equation (96) is the highest yielding of the four examples reported. The use of other alkyl halides was not mentioned, so that it is difficult to assess the general applicability of the method <2000OL2177>.



(96)

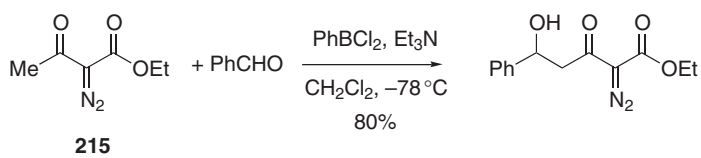
Finally for this section, a reinvestigation of earlier work has shown that the Vilsmeier formylation of diazo compounds is viable, with yields of over 15 examples being in the range 12–66%. For instance, reaction of diazoketone **213** gave aldehydes **214** (Equation (97)) <1997HCA960>.



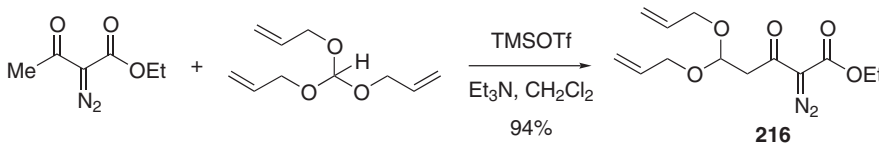
(97)

3.12.2.3.9 Substitution at other positions in α-diazocarbonyl compounds

α-Diazo-β-ketoesters are readily available by diazo-transfer reactions (Section 3.12.3.3.7). These compounds are ripe for further elaboration. Although diazo compounds can be decomposed by Lewis acids, Calter's group has described the aldol-type reaction of compounds such as **215** with aryl and alkyl aldehydes as shown in Equation (98) <1997TL3837>. Titanium(IV) chloride is equally effective as Lewis acid catalyst <1999JOC1415>. The related orthoester condensation provides acetal derivatives **216**, which are useful substrates for the formation and rearrangement of oxonium ylides (Equation (99)) <1998TL8813>.



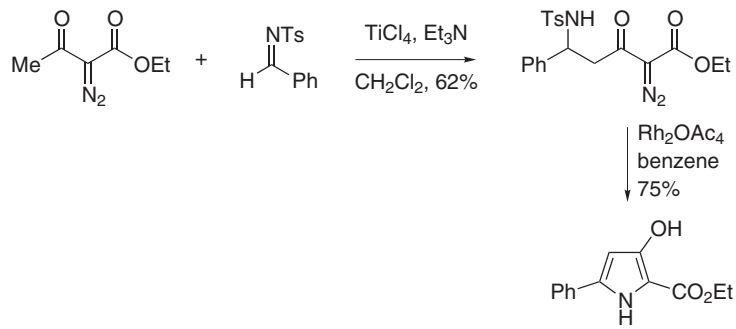
(98)



(99)

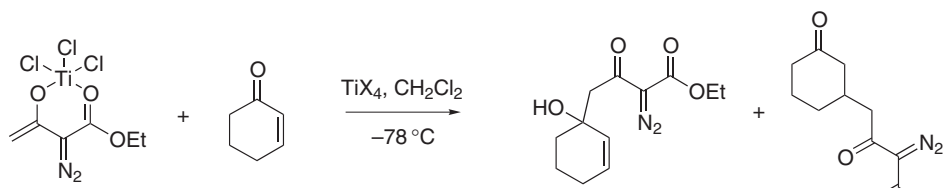
216

Reaction of the same diazo precursor with tosylimines allows, after diazo-decomposition, access to pyrrole derivatives (Scheme 33) <2002SL1913>.



Scheme 33

The titanium enolate **217** reacts smoothly with a range of cyclic and acyclic enones to give 1,2- and 1,4-addition products depending on the reaction conditions. For instance, with added titanium(IV) isopropoxide the 1,2-addition product **218** is favored, while with additional titanium(IV) chloride or tin(IV) chloride the 1,4-addition product **219** predominated (Equation (100)) <2002AG(E)2773>.

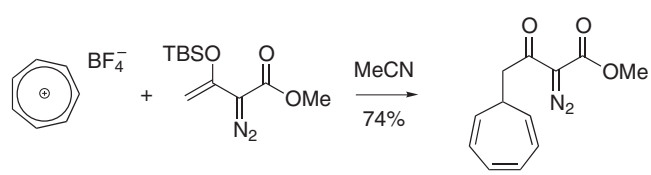


(100)

217 **218** **219**

X = OPr^i, **218**:**219** 99:1, 68%
X = Cl, **218**:**219** 1:99, 52%

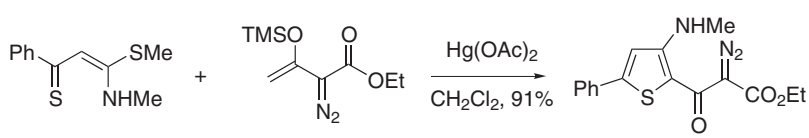
The silyl enol ether **220** can be isolated, and undergoes reaction with the tropylium cation to give cycloheptatriene derivative **221** (Equation (101)) <1997TL6993>.



(101)

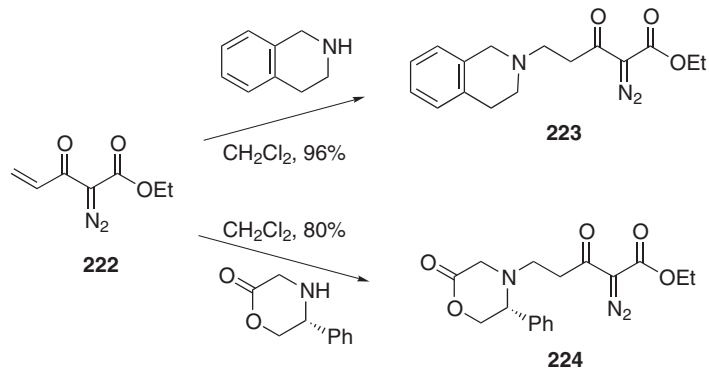
220 **221**

A particularly elaborate combination of these reaction types is shown in Equation (102) <2002OL873>.



(102)

Diazo compound **222** has been used as a Michael acceptor in reactions with amines, giving **223** <1998TL4159, 2001JOC2414> and **224** <2000TA3449, 2003TL2895> (Scheme 34). Both of these compounds were then used for the formation and rearrangement of ammonium ylides.

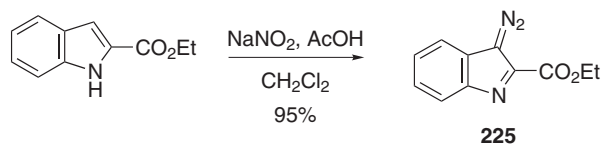


Scheme 34

3.12.2.4 α-Diazoimines, -amidines, -imidates, and -nitriles

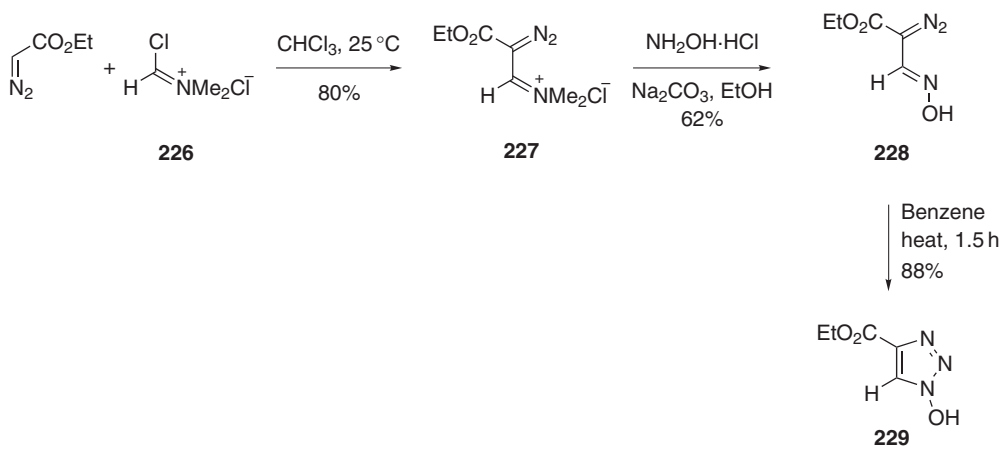
3.12.2.4.1 α-Diazoimines

α-Diazoimines have been seldom described in the chemical literature, as they exist in the more stable triazole tautomer. This requires the diazo and imine groups to adopt an *s-cis* conformation, so that diazoindole **225**, formed as shown in Equation (103), is stable and undergoes rhodium(II)-catalyzed O—H insertion reactions in the usual way <2000TL6905>.



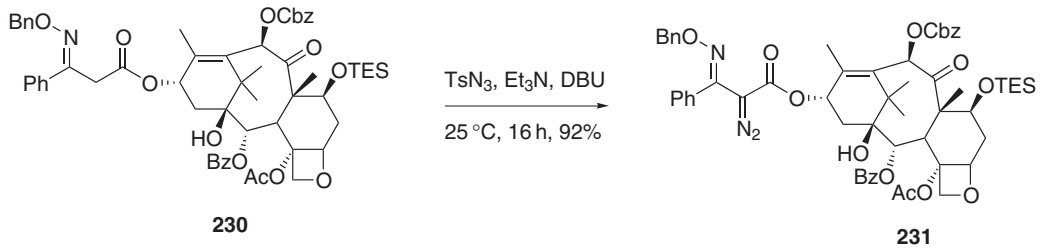
(103)

Reaction of ethyl diazoacetate with the Vilsmeier reagent **226** gave diazoiminium salt **227**, which was not fully characterized but instead was immediately treated with hydroxylamine hydrochloride to give diazooxime **228**. While this compound could be isolated and characterized, heating in benzene gave clean cyclization to the triazole **229** (Scheme 35) <1998T14233>.



Scheme 35

A further example of a diazooxime was prepared during studies on the modification of Taxol® side-chains. Diazo transfer to compound **230** provided the surprisingly stable diazooxime **231** in extremely high yield (Equation (104)) <2000TL243>.



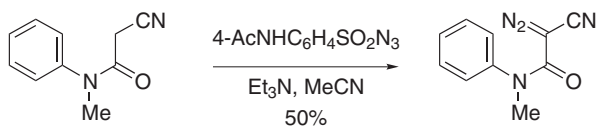
230 **231** (104)

3.12.2.4.2 α-Diazoamidines and -imidates

No new examples were found since the publication of COFGT (1995).

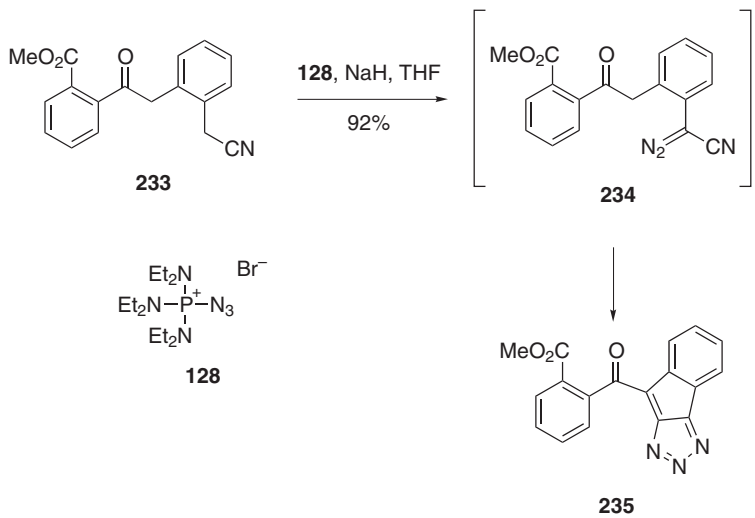
3.12.2.4.3 α-Diazonitriles

Diazonitriles have been seldom reported. However, they do not appear to be particularly unstable. Compound **232** was prepared under standard diazo-transfer conditions with 4-acetamidobenzenesulfonyl azide (Equation (105)) <1996T2489>.



232 (105)

Diazo transfer to **233** gave **234** rather than the expected α-diazocarbonyl compound. However, this compound was unstable, and upon standing at room temperature underwent an intramolecular aldol-type reaction followed by tautomerization to the triazole and aerobic oxidation to give **235** in high yield (Scheme 36) <1999JOC4079>.



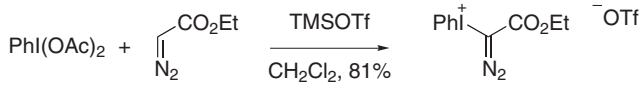
233 **234** **128** **235**

Scheme 36

3.12.2.5 Diazoalkanes Containing Heteroatoms at the Diazo Carbon

3.12.2.5.1 Diazoalkanes substituted with halogens

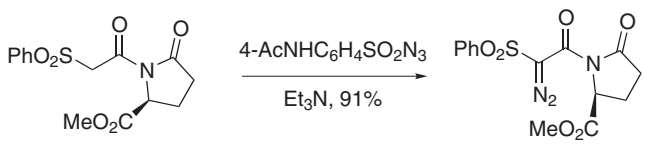
Diazo compounds bearing a halogen atom at the diazo carbon are particularly rare. However, reaction of ethyl diazoacetate with iodosylbenzene diacetate gave compound **236** in high yield (Equation (106)). This compound was subsequently used in a range of relatively uncommon nucleophilic substitution reactions at the diazo carbon <1994AG(E)1952>.



236 (106)

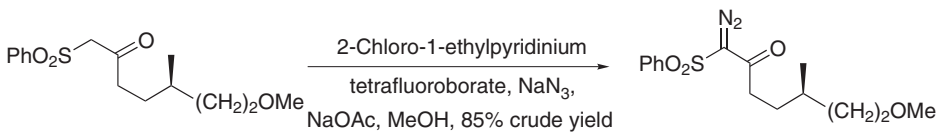
3.12.2.5.2 Diazoalkanes substituted with sulfur

The vast majority of compounds bearing a sulfur at the diazo carbon are sulfones analogous to 2-diazo-1,3-dicarbonyl compounds, and are generally prepared by diazo-transfer reactions in the usual way (e.g., Equation (107)) <1999OL83, 1999JOC8648>. These reaction conditions are typical for the formation of this class of diazo compounds <1999JCS(P1)593, 2000TL4773, 2001OL3539, 2002JOC6582>.



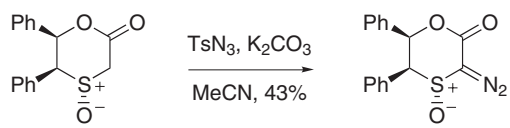
(107)

As an alternative, the diazo transfer can be carried out under neutral conditions using a combination of 2-chloro-1-ethylpyridinium tetrafluoroborate and sodium azide (Equation (108)) <1996T3879>.



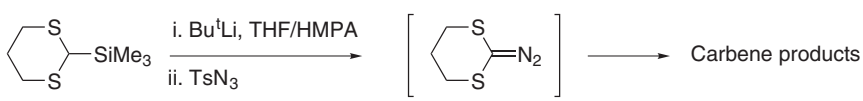
(108)

α-Diazosulfoxides are considerably less stable than α-diazosulfones, to the extent that diazo transfer to acyclic α-sulfinyl esters has thus far been unsuccessful. However, the corresponding lactones undergo diazo transfer in modest yield (Equation (109)) <1998TL2819, 2000EJO3329>.



(109)

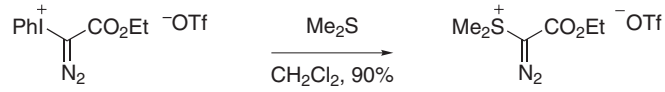
Diazo transfer to 2-trimethylsilyl-1,3-dithiane has been investigated. While the diazo compound **237** was not actually isolated, products of carbene-type reactions were obtained in a number of cases, pointing to the intermediacy of this compound (Scheme 37) <1995CC1999, 1997T9269>.



237

Scheme 37

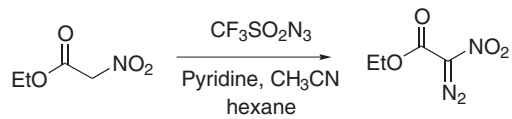
Introduction of sulfur into an existing diazo compound is possible by means of compound **236**. Reaction with dimethyl sulfide gave **238** in high yield (Equation (110)) <1994AG(E)1952>.



236 **238** (110)

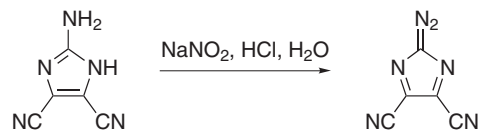
3.12.2.5.3 Diazoalkanes substituted with nitrogen

Triflylazide is effective for the diazo transfer to ethyl 2-nitroacetate **239**, where a number of other diazo-transfer reagents failed. A range of compounds related to **240** was also prepared, confirming the generality of the method (Equation (111)) <2000JOC9252, 2002HCA4468>.



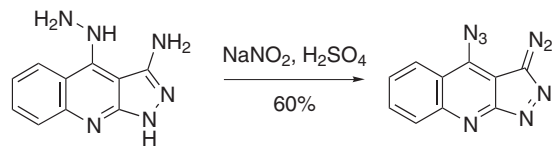
239 **240** (111)

2-Diazo-4,5-dicyanoimidazole **241** is a relatively unusual diazo compound, which was generated by diazotization of the corresponding amine (Equation (112)). This compound was not isolated, but its derived carbene was used directly in a reaction with [60]fullerene <2001TL6823>.



241 (112)

A further example of this reaction type is shown in Equation (113), in which the hydrazine also underwent diazotization <2000JCS(P1)3085>.

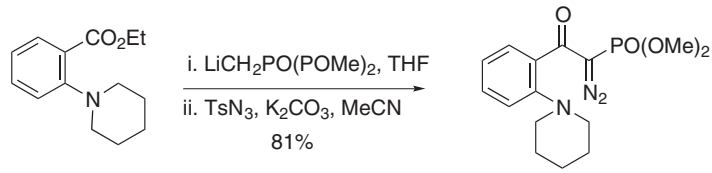


(113)

3.12.2.5.4 Diazoalkanes substituted with phosphorus

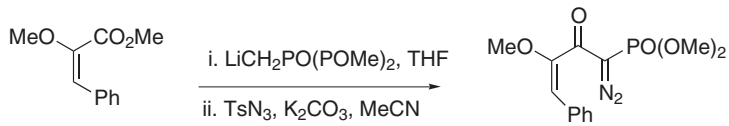
The phosphonate group significantly increases the acidity of hydrogen atoms on neighboring carbon atoms. In the context of diazo chemistry, they act in the same way as a carbonyl group, facilitating diazo-group transfer to active methylene groups. Diazophosphonates are generally more stable than diazocarbonyls such that diazocarbonyl groups can be decomposed chemoselectively in the presence of diazophosphonates under suitably mild conditions <1998T2257>.

Diazophosphonates such as **243** are readily prepared in two steps from carboxylic esters **242** by reaction with dimethyllithiomethylphosphonate followed by diazo transfer with a sulfonyl azide (Equation (114)) <1995TL7859, 1997T7557, 1998T6457>.



242 **243** (114)

An identical method was used for the preparation of compound **244**, in which the carbonyl group is conjugated with an enol ether (Equation (115)) <1996T6665, 1996T10455>.

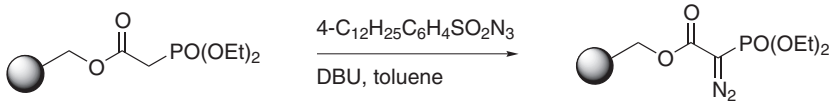


(115)

244

The same two-step process has been reported, starting with aliphatic esters <2001TL8455, 2002TL4131>. Sodium hydride has also been used as base in the diazo-transfer reaction <1997S356>.

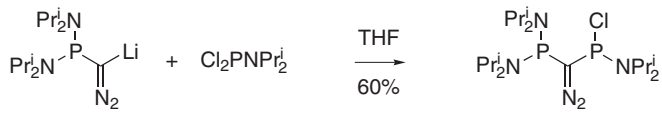
Polymer-supported diazophosphonate **245** has been prepared in a similar manner, using dodecylbenzenesulfonyl azide as diazo-transfer agent and DBU as base (Equation (116)) <2002CC210>.



(116)

245

Alternatively, electrophilic attack on a diazo carbon can be used to introduce phosphorus. For example, addition of dichlorophosphine **247** to lithiated diazomethane derivative **246** gave the crystalline diazo compound **248** in 60% yield (Equation (117)) <2000AG(E)3319>.

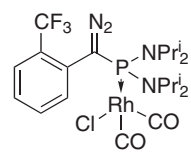


(117)

246 **247** **248**

Related compounds with only a single phosphorus atom have been prepared in a similar manner from aryldiazomethanes (Equation (118)) <2000SCI(288)834, 2003JA124>. Despite the fact that diazo compounds are readily decomposed by rhodium salts, complex **249** was isolated and even characterized crystallographically at a low temperature <2003OM1358>.

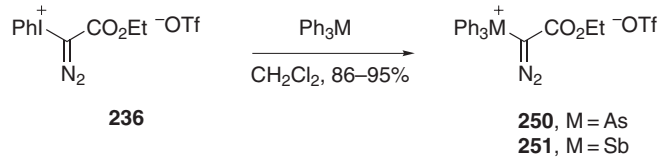
(118)



249

3.12.2.5.5 Diazoalkanes substituted with arsenic, antimony, or bismuth

Diazo compounds containing arsenic or antimony can be prepared by substitution reactions of compound **236**. In both cases, the salts **250** and **251** were obtained in high yields (Equation (119)) <1994AG(E)1952>. There have been no new reports of bismuth-containing diazo compounds.

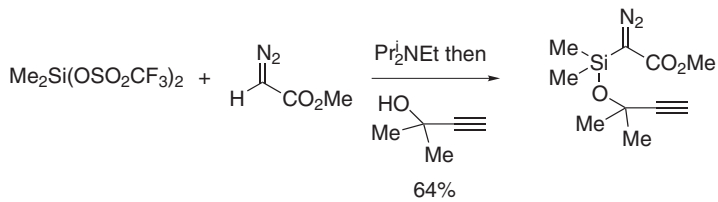


236 **250**, M = As; **251**, M = Sb (119)

3.12.2.5.6 *Diazoalkanes substituted with silicon, germanium, tin, or lead*

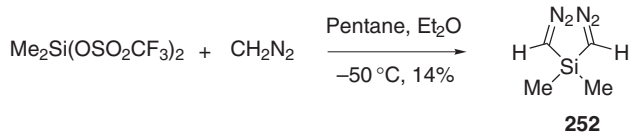
A range of silylated diazoketones has been prepared by reaction of the parent diazoketone with trialkylsilyltrifluoromethanesulfonates <1999CC1199, 1998TL6077, 2003TA1503, 2002OL2465, 1998JOC8380>.

The use of a silicon tether is a common tactic in organic synthesis. The sequential addition of a diazo compound and a propargyl alcohol to dimethylsilylbistrifluoromethanesulfonate is shown in Equation (120) <1999EJO1213>. The reaction is relatively general, with most types of alcohol being tolerated, as well as more bulky groups on silicon <1999EJO1939, 2000T4139, 2000CEJ1646>.



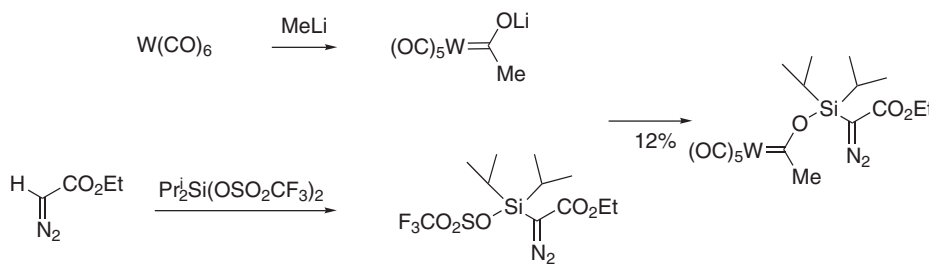
(120)

With an excess of diazomethane, the same precursor can give rise to the formation of silylbis-diazo compound **252**. This compound was purified by preparative gas chromatography (GC), and was stable at −78 °C but decomposed slowly at room temperature (Equation (121)) <1999OM2791>.



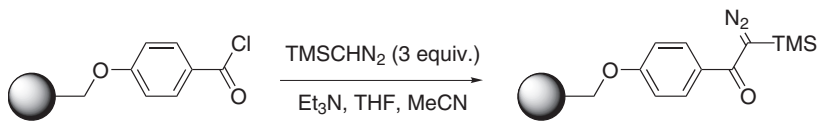
252 (121)

A further modification of this method allows the introduction of a Fischer carbene complex (Scheme 38), although this complex was unstable above 0 °C <2001JOM(617)339>.



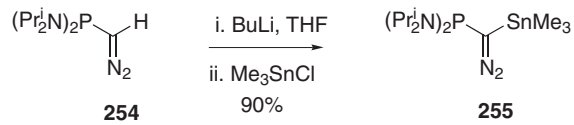
Scheme 38

As an alternative, reaction of trimethylsilyldiazomethane with acid chlorides can be used to provide polymer-supported α-silyldiazoketones such as **253** (Equation (122)) <2000T5353>.



253 (122)

The formation of stannylated diazo compounds by reaction of ethyl diazoacetate with (dimethylamino)trimethyltin was discussed in Section 3.12.2.3.8. Lithiation of bis(dimethylamino)phosphinodiazomethane **254** was followed by routine quench with trimethyltin chloride to give compound **255** in 90% yield (Equation (123)) <1995TL4231>.

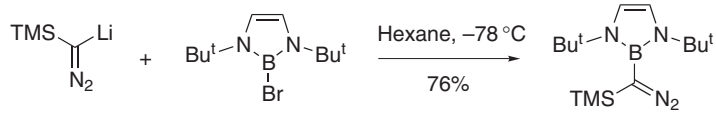


254 **255** (123)

There have been no new reports of germanium or lead-containing diazo compounds.

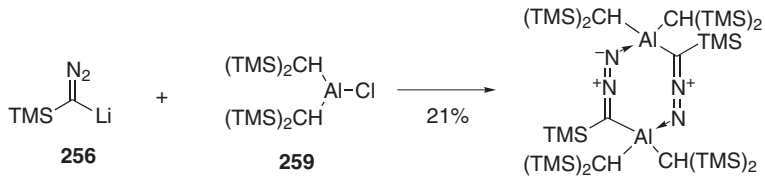
3.12.2.5.7 *Diazoalkanes substituted with boron, aluminum, or thallium*

Since many Lewis acids catalyze the decomposition of diazo compounds, it is hardly surprising that diazo compounds substituted with group 13 elements are rare. However, those that have been reported have been prepared by reaction of a metallated diazoalkane with a group 13 halide. For instance, reaction of lithiotrimethylsilyldiazomethane **256** with **257** gave compound **258**, which was sufficiently stable to be purified by vacuum distillation, prior to low-temperature recrystallization (Equation (124)) <2001OM5248>.



256 **257** **258** (124)

Reaction of lithiotrimethylsilyl diazomethane **256** with compound **259** gave a dimeric structure **260**, which was characterized crystallographically (Equation (125)) <1999EJI771>. However, with a phosphorus-containing diazo compound the analogous reaction gave a trimeric complex bound solely through the diazo nitrogen atom <1998AG(E)989>.



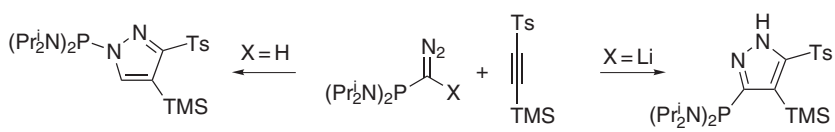
256 **259** **260** (125)

There have been no new reports of thallium-containing diazo compounds.

3.12.2.5.8 *Diazoalkanes substituted with lithium or sodium*

The lithiation of diazo compounds has become a routine practice in synthetic chemistry. The relatively stable organolithium species thus generated is rarely, if ever, isolated but undergoes reaction with a range of electrophiles as described in various sections of this review. Lithiation of diazo compounds has also been used to alter the outcome of their cycloaddition reactions, although the question of concerted (X = H) versus stepwise (X = Li) mechanisms has not been resolved (Scheme 39) <1999TL883>.

There have been no new reports of sodium-containing diazo compounds.



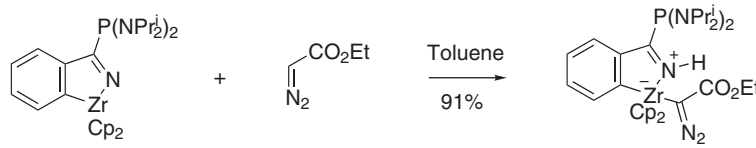
Scheme 39

3.12.2.5.9 Diazoalkanes substituted with magnesium

No new examples were found since the publication of COFGT (1995).

3.12.2.5.10 Diazoalkanes substituted with transition metals

Diazo compounds bonded to a transition metal at the diazo carbon itself are extremely rare. However, reaction of zirconacycle **261** gives rise to the zirconate complex **262** in extremely high yield (Equation (126)) <2000AG(E)4524>.



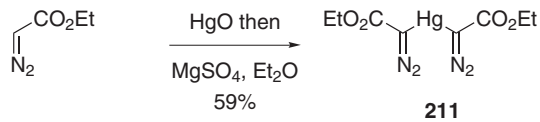
261 **262** (126)

3.12.2.5.11 Diazoalkanes substituted with silver

No new examples were found since the publication of COFGT (1995).

3.12.2.5.12 Diazoalkanes substituted with zinc, cadmium, or mercury

An improved large-scale preparation of bisdiazo-mercury compound **211** was developed during the course of studies into cross-coupling reactions of organometallic diazo compounds (Equation (127)) <1997T2371>. The cross-coupling reactions are described in Section 3.12.2.3.8.



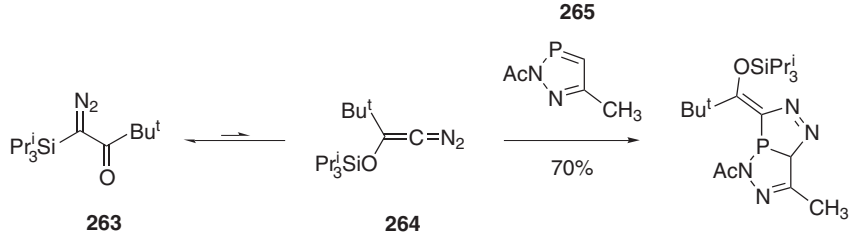
211 (127)

There have been no new reports of zinc- or cadmium-containing diazo compounds.

3.12.2.6 Unsaturated Diazoalkanes

3.12.2.6.1 Diazoalkylidenes

α-Silyl-α-diazoketones **263** exist in equilibrium with the alkylidenes **264**. While the latter compounds cannot be isolated, they can be trapped in 1,3-dipolar cycloaddition reactions with 1,2,3-diazaphospholes **265** (Scheme 40) <1999EJO2633>. Similar reactions also take place with acyclic phosphaalkenes <1996T10053> and with 1,2-thiaphospholes, although in the latter case loss of N_2 is followed by a further cycloaddition <2003EJO1894, 2000T35, 2001EJO1581>.

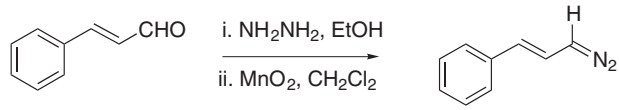


263 **264**

Scheme 40

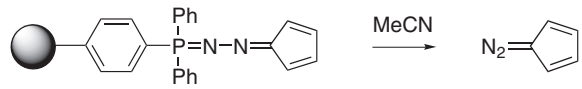
3.12.2.6.2 α,β-Unsaturated diazoalkanes

Styryldiazomethanes were readily prepared from the corresponding cinnamaldehydes via hydrazone formation and oxidation with activated MnO_2 (Equation (128)). Alternatively, the same compounds could be generated *in situ* from tosylhydrazone salts <2002JOC602>. The hydrazone oxidation method has been used by others <1995TL8745>.



(128)

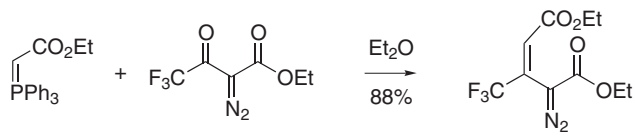
Diazocyclopentadiene forms a stable phosphazine adduct with triphenylphosphine. While this adduct dissociates in acetonitrile, its use as a diazocyclopentadiene equivalent in synthesis is hampered by the difficulty often encountered in removing triphenylphosphine from the reaction products. A new polymer-supported reagent **266** has been used to alleviate this problem (Equation (129)) <1999AG(E)1617>.



(129)

266

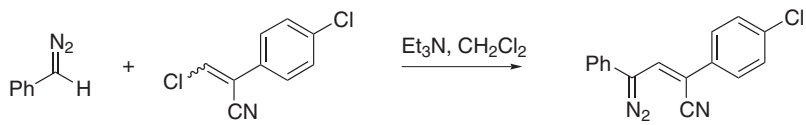
Since diazoketones are readily available, their olefination is an attractive strategy for the formation of unsaturated diazo compounds. The reactive ketone in **267** undergoes Wittig reaction with stabilized ylides to give compounds such as **268**, in this case solely as the (*E*)-isomer (Equation (130)) <1995S920, 2003OL745>.



(130)

267 **268**

Similar compounds have also been obtained by a vinylogous Arndt–Eistert-type reaction. Displacement of the chlorine in **269** with phenyldiazomethane gave compound **270** (Equation (131)). A range of reactions were carried out on this compound, but unfortunately the yield for its formation was not disclosed <2001JOC5395, 2003TL4339>.



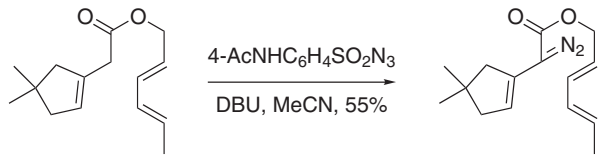
(131)

269 **270**

Diazoalkenes bearing electron-withdrawing groups can be prepared by diazo transfer in the usual way. Compounds **271** <1999OL219> and **272** <1999OL233> were prepared using 4-acetamidobenzenesulfonyl azide in this manner.

271 **272**

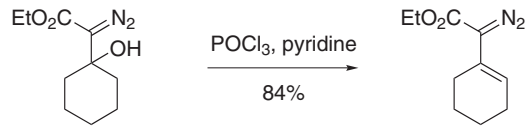
The added stabilization due to the aromatic ring is not actually needed for these reactions to be successful, although without it the yields are lower. For instance, diazo transfer to substrate **273** gave diazo compound **274** in 55% yield (Equation (132)) <1999JOC8501>.



(132)

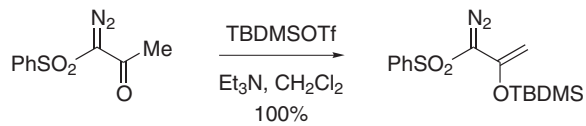
273 **274**

Elimination of alcohols adjacent to diazo groups has only rarely been reported. The example shown in Equation (133) uses relatively mild conditions to allow isolation of the diazo compound in high yield <1996JA1>.



(133)

Despite the vast array of diazocarbonyl compounds, their conversion into enol ethers is also uncommon. Compound **275**, prepared by diazo transfer under standard conditions, was quantitatively converted into enol ether **276** in a straightforward manner (Equation (134)) <1995JOC7529>.

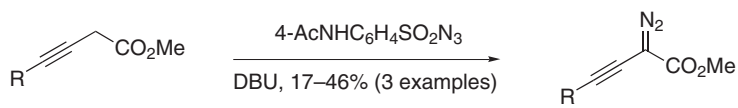


(134)

275 **276**

3.12.2.6.3 Diazoalkynes

Diazoalkynes **278** bearing an additional electron-withdrawing group have been prepared by diazo transfer to substrates of general structure **277**. The yields were only moderate over a small range of examples (Equation (135)) <2000TL8189>.



(135)

277 **278**

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Biographical sketch

Mark Elliott was born in Doncaster. He studied at Loughborough, where he obtained a B.Sc. in 1991 and a Ph.D. in 1994 working with Professor C. J. Moody on transition metal-catalyzed reactions of diazo compounds. This was followed by a two-year postdoctoral soujourn with Professor A. Pfaltz, initially in Basel under the auspices of a Royal Society European Exchange Fellowship, and later at the Max-Planck Institute in Mülheim. He returned to the UK in 1996 to take up his current position as Lecturer in Chemistry at Cardiff. His reseach interests include asymmetric heterocyclic chemistry, asymmetric catalysis, and natural product chemistry.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 469–523

3.13 Synthesis of P, As, Sb, and Bi Ylides ($R^1R^2R^3P{=}CR^4R^5$, etc.)

S. L. SCHWIKKARD
Kingston University, Kingston-upon-Thames, UK

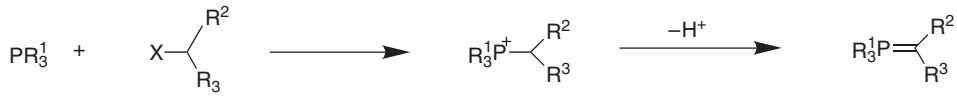
The research reviewed in this chapter reflects the advances in methods used to construct the C=X bond, where X can be P, As, Sb, or Bi. The majority of the work done has focused on phosphorus ylides and this is evident in the composition of the chapter.

The material reviewed in COFGT (1995) on the synthesis of phosphorus, arsenic, antimony, and bismuth ylides has briefly been summarized at the beginning of each section, but the details of the work and the references are not included. Since 1995, a number of general reviews on the topic have been published <B-1999MI001, 1996T1855, 1997RCR225, 2003TCC41> as well as a review on ylides with fluorine substituents on the phosphorus atom <2001SL1065>.

The main application of ylides is in the Wittig reaction in synthetic organic chemistry while they have also been used extensively as ligands in organometallic chemistry and catalysis.

3.13.1 PHOSPHORUS YLIDES FROM PHOSPHONIUM SALTS

By far the most commonly used method for the preparation of phosphorus ylides is the salt method. This involves the preparation of a phosphonium salt followed by a suitable transformation into the required ylide. This is most frequently done via deprotonation (Scheme 1), dehalogenation, or desilylaton of the phosphonium salt. The latest developments in each of these methods will be reviewed as well as some of the less frequently employed alternatives.



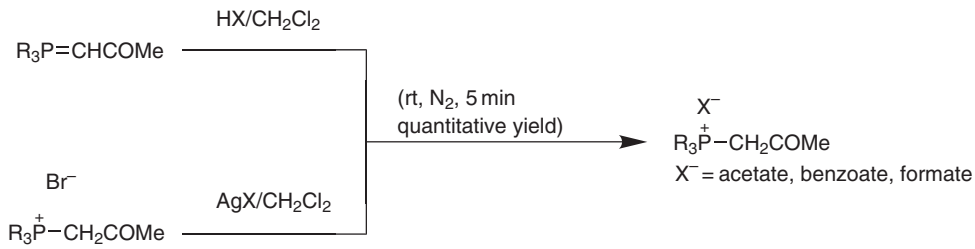
Scheme 1

3.13.1.1 Preparation of Phosphonium Salts

The simplest and subsequently the most frequently employed manner of preparation of phosphonium salts is via the quaternization of tertiary phosphines with alkyl halides. The tertiary phosphines can be trialkyl or triaryl, with triphenylphosphine often being used. It is easy to handle, crystalline, and air stable. While the trialkylphosphines are more nucleophilic than their aryl counterparts and as such produce ylides of increased nucleophilicity, they also tend to be more easily oxidized and carry the risk of competitive deprotonation at the α-position. Replacing the phenyl groups on the phosphorus by one, two, or three pyridyl or furyl groups affects the efficiency of the resulting ylide in the Wittig reaction, but with the right base the reaction proceeds as for triphenylphosphine <2000EJO2601, 2002EJO1143>.

The choice of available alkyl halides is extensive and the methodology has been used to produce a wide range of different phosphonium salts, containing alkyl, aryl, alkoxy, thioalkyl, carbalkoxy, carbamido, keto, cyano, halo, alkenyl, alkynyl, or silyl functionality. The halide reactivity tends to follow the expected pattern, I > Br > Cl.

In general, the purpose of making the phosphonium salt would be as a precursor to the ylide, which would then be used in a Wittig reaction to form the alkene. Hon and Lee <2000T7893> have shown that with the appropriate choice of counterion, it is possible to perform the Wittig reaction without first forming the ylide, that is directly from the phosphonium salt. The salts were prepared in two ways, either by the addition of a protic acid to the corresponding ylide or via the reaction of triphenylphosphonium bromides with silver salts (Scheme 2). The bromides and *p*-toluenesulfonates did not react with the aldehyde to form the Wittig products, whereas the acetates, benzoates, and formates reacted with excellent yields. It appeared that there was a correlation between the Bronsted basicity of the counterion and the reactivity. The more basic the counterion, the more reactive the salt.

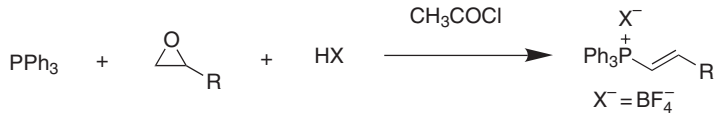


Scheme 2

The protonation of alkylphosphines with strong acids, HBF_4 or HOTf, allows for the formation of phosphonium salts with BF_4^- and OTf^- counterions <2003TL3467> with the added advantage that tetrafluoroboric acid stabilizes air-sensitive alkylphosphines. Methanesulfonic acid, in the presence of $Pd(PPh_3)_4$, allows for the formation of allylphosphonium salts from triphenylphosphine and the corresponding allene or alkyne. The counterion can then be exchanged, for example, with $LiPF_6$ or $NaClO_4$ <2000JA2387, 2001MI27>.

The quaternization of triphenylphosphine with alkyl halides is limited in application to those halides that are stable to work up. Certain benzyl- and thienylphosphonium salts cannot be prepared using this method, but have successfully been prepared by treating the appropriate benzyl or thienyl alcohol with triphenylphosphonium hydrobromide. The azeotropic removal of the water formed allows for almost quantitative yields in some cases <1996SC3091>.

Triphenylvinylphosphonium salts have been prepared by combining triphenylphosphine with an epoxide and an acid followed by acetyl or oxalyl chloride in a one-pot synthesis <2000MI548> (Equation (1)).



(1)

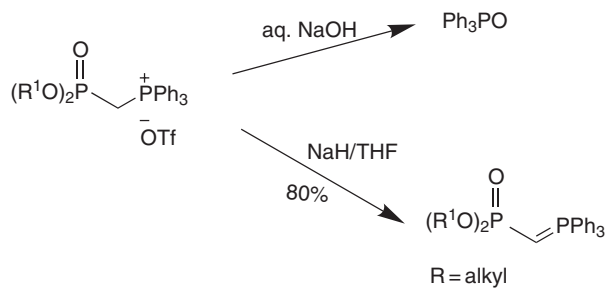
Aqueous base-soluble phosphonium salts have been prepared using substituted triphenylbenzylphosphonium salts bearing solubilizing groups (*p*-COOH and OH), which then allowed for the Wittig reaction to be done without organic solvent <1998TL7995>.

3.13.1.2 Deprotonations of Phosphonium Salts

Deprotonation of phosphonium salts to form ylides can be done using a wide range of bases and solvents, usually at or below room temperature. Common solvents include hexane, benzene, ether, THF, DMF, and DMSO. The only restriction would be that the solvent is inert to both the ylide and the base. Extensive research has gone into the factors to be considered when choosing an appropriate base for the deprotonation of phosphonium salts. Two of the most important things to be considered are the acidity of the phosphonium salt and the type of by-products that will be formed. The stabilized ylides (R = carbonyl, cyano, etc.) would be more acidic than the semistabilized ylides (R = aryl, alkenyl) followed by the nonstabilized ylides (R = alkyl, halo), and this would be reflected in the choice of base, ranging from ammonia to organolithium reagents. A more basic ylide can also be used and in this case the reaction is known as a transylidation. A table of bases that can be used for different solvents and phosphonium salts was reviewed in COFGT (1995) <1995COFGT(3)491>.

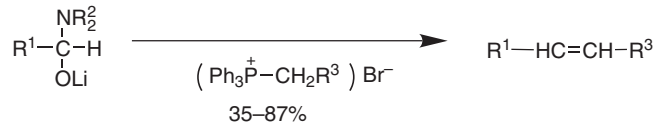
The importance of the correct choice of base has been demonstrated by Dieckbreder and co-workers <1996HAC281, 1996PS597, 2002HAC650> in their work on trifluoromethylated phosphines. While Schmidbaur and Zybill <1981CB3589> had demonstrated that the use of KH or *n*-BuLi to deprotonate fluorinated phosphonium salts resulted in the oligomerization of the methylene phosphoranes, Dieckbreder's work showed that the use of lithium bis(trimethylsilyl)amide or *N*-methyliminotris(diethylamino)phosphine imide resulted in the desired ylide being formed from the corresponding triflate salts.

Pinacolboratamethylenetriphenylphosphonium iodide was found to effectively produce alkenes when treated with either an aldehyde or a ketone in the presence of base. If the base used was a potassium alkoxide, 2 equiv. was necessary, while only 1 equiv. of lithium amide was needed <2002SC2575>. This preference for a particular base has also been demonstrated by Xu and co-workers <1996JOC7697> in their synthesis of α,β-unsaturated phosphonate esters. The treatment of the triflate salts with NaOH led to the formation of triphenylphosphonium oxide, while the use of NaH in THF resulted in the ylide (Scheme 3).



Scheme 3

The acylation of an organolithium reagent with a carbamide can be used in the preparation of aldehydes and ketones. The mineral acid used at the neutralization stage can be replaced by a phosphonium salt and this would allow for the preparation of an ylide and a carbonyl compound simultaneously, which could then undergo a Wittig reaction. Wang and co-workers <1999EJO3263> have shown that the reaction of lithium aminoalkoxides in the presence of phosphonium salts does indeed produce the expected alkenes (Equation (2)).



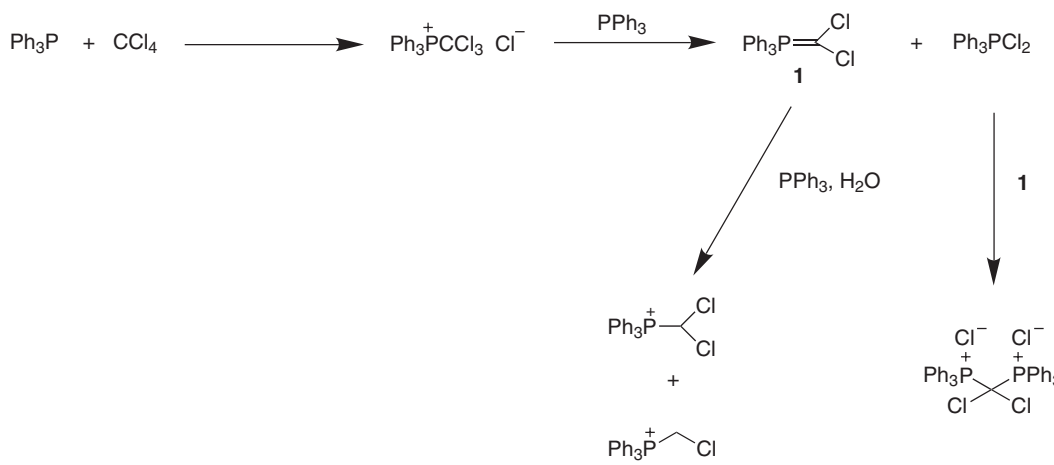
(2)

R^1 = aryl, alkyl, alkenyl; R^2 = alkyl; R^3 = aryl, alkyl, alkenyl

Phosphorus ylides have also been generated in the solid state via a ball-milling technique. Phosphorus salts were milled with K_2CO_3 as the base and the corresponding ylides were formed, in near quantitative yields <2002JA6244>. The use of perfluorinated ylides in perfluorinated solvents also allows for the easy separation of the phosphine oxide by-product of the Wittig reaction. The alkene formed can be extracted with diethyl ether while the perfluorinated by-products remain in the perfluorinated solvent <2001TL(41)5425>.

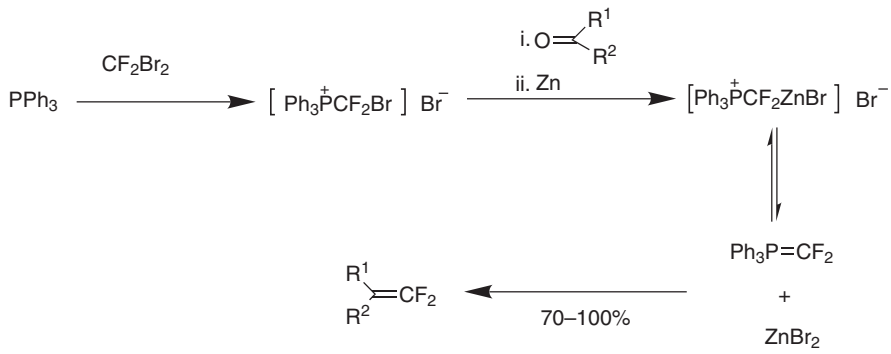
3.13.1.3 Dehalogenations of Phosphonium Salts

Another popular way to generate an ylide from a phosphonium salt is via dehalogenation, that is the abstraction of an α-halogen rather than an α-proton. If both are present, the reaction conditions can be manipulated by choice of halide and base <1995COFGT(3)491>. The preparation of haloylides can be achieved via the addition of triphenylphosphine to tetrahalomethanes, followed by dehalogenation of the salt. Careful control of the amount of water added influences the product range (Scheme 4).



Scheme 4

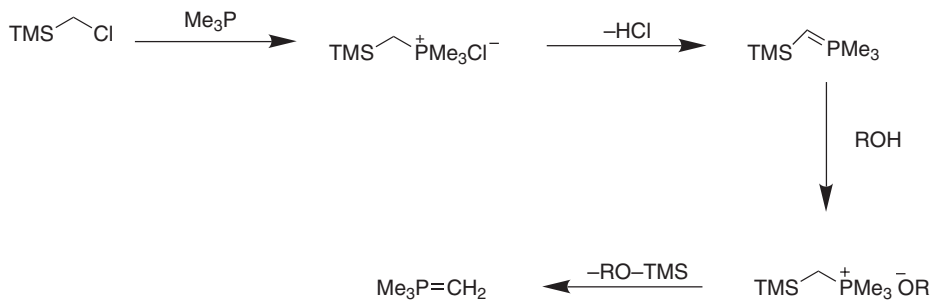
Fluorinated phosphorus ylides can be formed from the Zn metal dehalogenation of quaternary phosphonium salts (Scheme 5). The ylide formed is unstable, and unless the carbonyl complex is present in the reaction mixture upon formation of the ylide, the yield of alkene is low <2002JFC75>.



Scheme 5

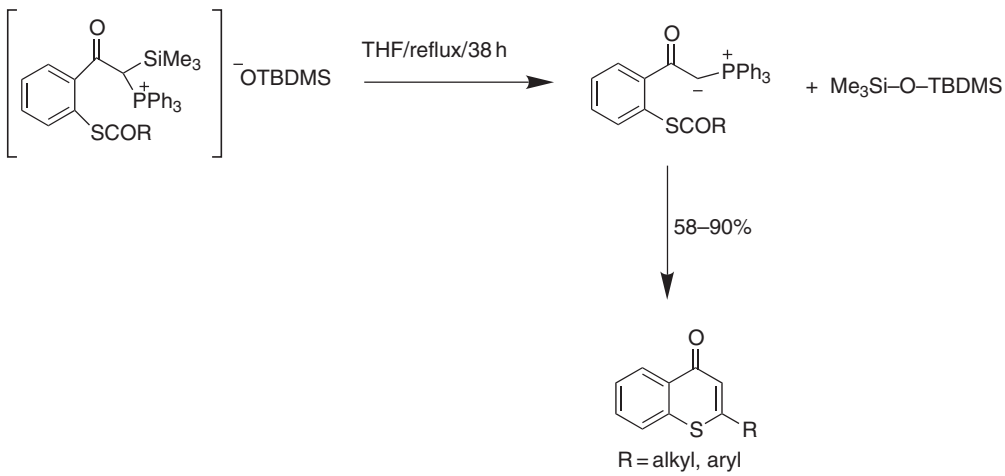
3.13.1.4 Desilylations of Phosphonium Salts

The desilylation of phosphonium salts usually entails the removal of a trimethylsilyl group and is a good way to make salt-free nonstabilized ylides (Scheme 6).



Scheme 6

The desilylation of phosphonium salts has found an application in the synthesis of thiochromones. The successful synthesis of a variety of these compounds has been achieved in good yields under relatively mild conditions <2001T9755> (Scheme 7).



Scheme 7 Reprinted with permission from *Tetrahedron*, Vol 57, No 48, 2001, pp 9755–9758, Kumar et al; "A New synthesis of . . .", Scheme 1

The loss of Me_3SiI from $(Me_3Si)_3C\text{-}P{=}N\text{-}(2,4,6\text{-}t\text{-}Bu_3C_6H_2)$ upon treatment with iodine resulted in the formation of the imino(methylene)phosphorane, $(Me_3Si)_2C{=}P(I){=}N\text{-}(2,4,6\text{-}t\text{-}Bu_3C_6H_2)$ <1998EJI83>.

3.13.1.5 Ylides from Vinylphosphonium Salts

An ylide can be formed from the nucleophilic attack at the β-position of a vinylphosphonium salt. This reaction allows for a number of possible competing side reactions, such as attack at the phosphorus. No further advances have been made in this area since the publication of chapter 3.13.1.5 in COFGT (1995) <1995COFGT(3)491>.

3.13.1.6 Ylides from Cyclopropylphosphonium Salts

Nucleophilic ring opening of a cyclopropylphosphonium salt can lead to the formation of an ylide. No further work has been done in this area since the publication of chapter 3.13.1.6 in COFGT (1995) <1995COFGT(3)491>.

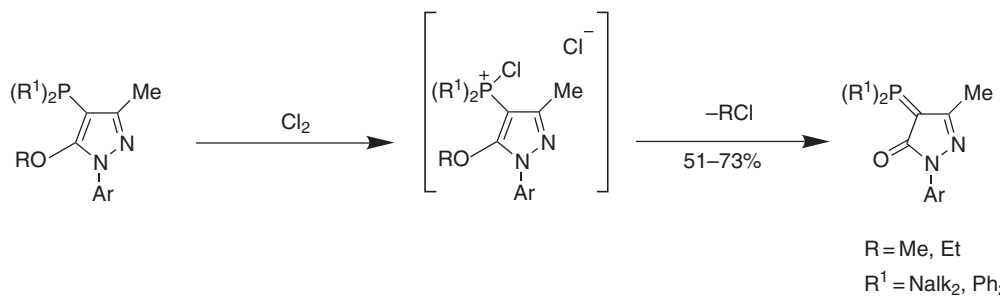
3.13.1.7 Ylides by the Electrolysis of Phosphonium Salts

A two-electron transfer process can result in the formation of an ylide. Jubault and co-workers <1995BSF850> used this in the formation of $(Me_2N)_3P{=}CF_2$ from the tetrafluoroborate $((Me_2N)_3P^+CF_2Br)BF_4^-$ in DMF. A carbon-felt cathode was used and a sacrificial magnesium anode.

The fact that phosphonium salts are usually colorless and their corresponding ylides are colored has led to investigation of these compounds for application in electrochromism <1996JCR(S)414>. It was found that the use of a mediator, such as benzophenone oxime phenyl ether, was necessary for the electroreductive abstraction of a proton to form the ylide and subsequently the reverse upon application of a positive potential.

3.13.1.8 Other Methods (Dealkylation)

Chlorination of 4-[chloro(diisopropylamino)phosphino]pyrazole and 5-alkoxybis(dialkylamino)- or diphenylphosphinopyrazoles leads to the formation of the unstable phosphonium chlorides, which undergo dealkylation to form the corresponding ylides <1998HAC41, 2003HAC452> (Scheme 8).



Scheme 8

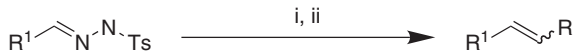
3.13.2 PHOSPHONIUM YLIDES FROM PHOSPHINES

3.13.2.1 Reactions with Carbenes

It is possible to form an ylide directly from the reaction of a carbene with a phosphine. Although it has not been used as often as the salt method, as the ways of producing carbenes have expanded, the method has found wider application and use. More recently, carbenes have been

used to produce ylides with phosphorus species other than phosphines and this work will also be reviewed here.

Substituents on the phosphorus atom of phosphorus ylides are generally limited to carbon- and nitrogen-containing groups. Aggarwal and co-workers <2003JA6034> have prepared phosphorus ylides with oxygen substituents on the phosphorus via carbene transfer to $P(OMe)_3$. A one-pot procedure in which both the carbene and the ylide are formed *in situ* has been optimized (Equation (3)). The reactivity and selectivity was found to differ substantially from ylides formed using triphenylphosphine in that this class of ylides gives particularly high (*E*)-selectivity in the Wittig reaction. Similarly the reaction of triethylphosphite with 1,1,3,3,3-pentafluoro-2-pentafluorophenylpropene oxide resulted in the formation of the ylide, $C_6F_5(CF_3)C{=}P(OEt)_3$ <1997HAC59>.



i. $KOBu^t$ (1.2 equiv.), toluene, 0 °C to rt
ii. RCHO (1 equiv.), ClFeTPP (catalyst), PTC, $P(OMe)_3$, 40 °C (3)

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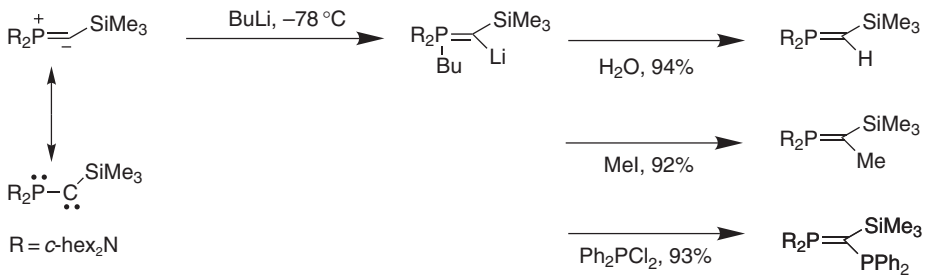
N-Heterocyclic carbenes have been used to form ylides with phosphalkynes <2000AG(E)2307> and with pentaphenylcyclopentaphosphane <1997CL143>. Gourri-Magnet and co-workers <1999AG(E)678> have used a stable phosphanyl(silyl)carbene together with 1 equiv. of BuLi to form the lithium phosphonium ylide. This is moisture sensitive and reacts easily with electrophiles at low temperature to give the corresponding ylides (Scheme 9).



Scheme 9

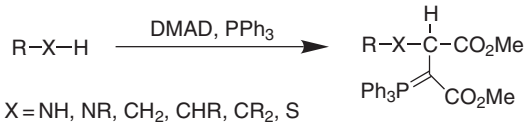
3.13.2.2 Via Azines

The thermal decomposition of phosphine azines can result in ylide formation. This method is not widely used and no further advances have been made since publication of chapter 3.13.2.2 in COFGT (1995) <1995COFGT(3)491>.

3.13.2.3 Reactions with Activated Multiple Bonds

The nucleophilic attack by a tertiary phosphine on an activated double bond can lead to the formation of a ylide. If the alkene is doubly activated, the process is relatively simple, as an adjacent ylide stabilizing group is available. More recently, a large amount of research has gone into the reaction between a tertiary phosphine and acetylenic esters such as dimethyl acetylenedicarboxylate (DMAD). This process leads to the formation of a reactive 1,3-dipolar intermediate, which can then be trapped by a protic reagent to form the ylide <2003T4785> (Equation (4)). The large range of protic reagents available has led to a large range of ylides being produced and as such the scope of this reaction is huge. Islami and co-workers <2002MI2244> produced phosphorus ylides in aqueous medium from triphenylphosphine, DMAD, and C—H acids such

as diethyl propane-1,3-dioate by using β-cyclodextrin to increase solubility of reagents in water. Tables 1 and 2 give some examples of work done using this method to form phosphorus ylides.



(4)

Table 1 Protic reagents used with activated multiple bonds to form ylides from phosphines

Phosphorus source	*Activated double bond*	*Protic reagent*	*Yield (%)*	*References*
PPh_3	DMAD	1-Methylparabanic acid,	80	<2003M445>
PPh_3	DMAD	diethyl *N*,*N*-(naphthalene-1,8-diyl)-dioxamate	90	<2002M1431>
PPh_3	DMAD, other acetylene esters (Bu^t, Et)	2-Aminobenzimidazole	94–97	<2001SC2639>
PPh_3	DMAD, other acetylene esters (Bu^t, Pr^i)	Pyrrole-2-carbaldehyde	70–75	<1999JCR(S)382>
PPh3	Bis(isobutyl) acetylene-dicarboxylate	Imidazole, benzimidazole, benzotriazole, carbazole	90–98	<1999JCR(S)216>
PPh_3	DMAD, other acetylene esters (Et)	2-Aminophenol, 1,2-phenylene diamine,	80–97	<2003T4993>
PPh_3	DMAD	aniline, 1-naphthylamine, *p*-toluidine, 4-bromoaniline, 4-nitroaniline, 4-acetylaniline, 2-aminopyridine, 2-amino-5-bromopyridine	>97	<2002T7213>
PPh_3	DMAD, other acetylene esters (Et, Pr^i)	2-Pyrrolylglyoxalate, *N*-benzyl-2-pyrrolylglyoxamate	Quantitative	<2001T5873>
PPh_3	DMAD	2-Acetylpyrrole, indole, ethyl 3-indolylglyoxalate	>95	<2002PS545>
PPh_3	DMAD, other acetylene esters (Bu^t, Et)	*N*-Isopropenyl benzimidazolone	>95	<2002PS1127>
PPh_3	DMAD, other acetylene esters (Bu^t, Et)	5,5-Dialkylhydantoin	86–95	<2002PS759>
PPh_3	DMAD, other acetylene esters (Bu^t, Et)	Arylsulfonamides	73–78	<2001PS(176)141>
PPh_3	DMAD	Arylamines	Low	<2001PS(174)223>
PPh_3	DMAD, other acetylene esters (Bu^t)	Imides		<2001PS(170)181>
PPh_3	DMAD, other acetylene esters (Bu^t, Et, Pr^i)	Acetanilide, 4-methylacetanilide, 2-cyanoacetanilide, 4-bromoacetanilide, 4-methoxyacetanilide, succinimide, malimide, phthalimide	90–96	<2002PS2599, 2002PS2547>
PPh_3	DMAD, other acetylene esters (Bu^t, Et)	Saccharin	86–98	<2002PS2537>
PPh_3	DMAD, other acetylene esters (Et)	2-Aminothiophenol	87–89	<2003T4785>

Table 1 (continued)

Phosphorus source	*Activated double bond*	*Protic reagent*	*Yield* (%)	*References*
PPh_3	DMAD, other acetylene esters (Et)	Thiophenol, 4-fluorothiophenol	64–95	<2003SC65>
PPh_3	DMAD, other acetylene esters (Et, Bu^t, Pr^i)	1-Methylimidazole-2-thiol	>96	<2003PS269>
PPh_3	DMAD	Ethyl 4-aryl-2,4-dioxobutanoates	78–87	<1998TL6343>
PPh_3	DMAD, other acetylene esters (Bu^t)	Nitromethane, acetylacetone, diethylmalonate		<2001PS(176)243>
PR_3 (R = Ph, Bu^n)	DMAD, other acetylene esters (Bu^t, Et)	Acetylacetone	95	<2003PS761>
PPh_3	DMAD, other acetylene esters (Bu^t, Et)	1,3-Diphenylpropane-1,3-dione	95	<1997PS229>
PPh_3	DMAD, other acetylene esters (Bu^t, Et)	Acetoacetanilide	87–92	<1999T11853>
PPh_3	DMAD, other acetylene esters (Bu^t, Et)	Methyl, benzyl, and allyl alcohols	63–70	<2000TL567>
PPh_3	DMAD, other acetylene esters (Et)	Dimethyl chloromalonate, diethyl bromomalonate	38–51	<1998TL1051>
PPh_3	DMAD, other acetylene esters (Bu^t, Et)	3-Chloropentane-2,4-dione	46–85	<1997TL4259>
PPh_3	DMAD, other acetylene esters (Et)	Dialkyl phthalimidomalonates, succinimidomalonate	85–95	<1998JCR(S)714>
PR_3 (R = cyclohexyl, cyclopentyl, Ar)	DMAD, other acetylene esters (Et)	C_{60}	23–91 94	<2003JOC3811, 1999JOC6664>
PPh_3	DMAD, other acetylene esters (Bu^t, Et, Pr^i)	3-Chloroindole-2-carboxaldehyde	85–99	<2002JCR(S)465>

Table 2 Products from activated double bonds and various phosphorus species

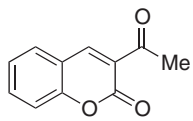
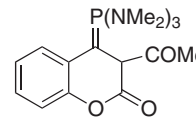
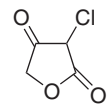
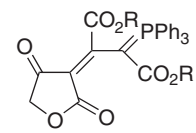
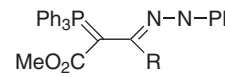
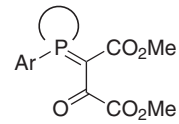
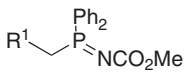
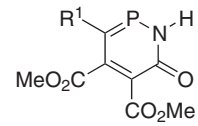
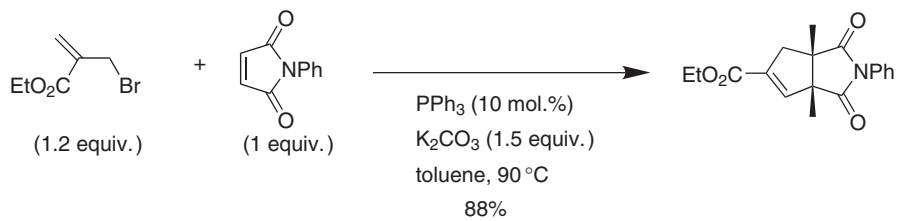
Phosphorus source	*Activated double bond*	*Protic reagent*	*Product*	*Yield* (%)	*References*
$P(NMe_2)_3$				68–72	<1999T14777>
PPh_3	DMAD, other acetylene esters (Et, Pr^i)			80–85	<2000T5221>
$Ph_3P{=}N$-NH-Ph	MeO_2CC-R (R=CO_2Me, Me, H)			70–80	<1999T14451>

Table 2 (continued)

Phosphorus source	*Activated double bond*	*Protic reagent*	*Product*	*Yield* (%)	*References*
P-Trialkylphenyl cyclic phosphine oxide 	DMAD			35–86	<2002T3721>
Phosphazenes  R^1 = Me, Pr^i, Et, allyl	DMAD			75–91	<2001T3075>

Du and co-workers <2003AG(E)1035> have succeeded in producing a catalytic Wittig reaction. An allylic bromide together with an activated double bond in the presence of K_2CO_3 and a catalytic amount of triphenylphosphine was used to form the alkene. An example of this reaction is shown in Equation (5).



(5)

Methylenediphosphines have been found to produce ylides upon treatment with hexafluoroacetone, thio-hexafluoroacetone, or $CF_3C{=}CHCN$ <2002PS1413>.

3.13.2.4 Reactions with Aziridines

Ring opening of aziridines with phosphines leads to β-amino ylides. No further advances have been made in this area since the publication of chapter 3.13.2.4 in COFGT (1995) <1995COFGT(3)491>.

3.13.2.5 Reactions with Arynes

Arynes will react with tertiary phosphines bearing an α-H to form ylides. No further work has been done in this area since the publication of chapter 3.13.2.5 in COFGT (1995) <1995COFGT(3)491>.

3.13.3 PHOSPHONIUM YLIDES FROM PHOSPHORANES

5(4*H*)-Oxazolones have been treated with either Ph_3PBr_2 or Bu_3PBr_2 in the presence of 2 equiv. of triethylamine in dichloromethane to produce the 4-phosphoranylidine-5(4*H*)-oxazolone ylides <1996M219>. Fluorinated phosphoranes upon treatment with 2 equiv. of various lithium amides have produced the *P*-fluorinated ylides <1998HAC659>.

3.13.4 PHOSPHONIUM YLIDES FROM OTHER PHOSPHONIUM YLIDES

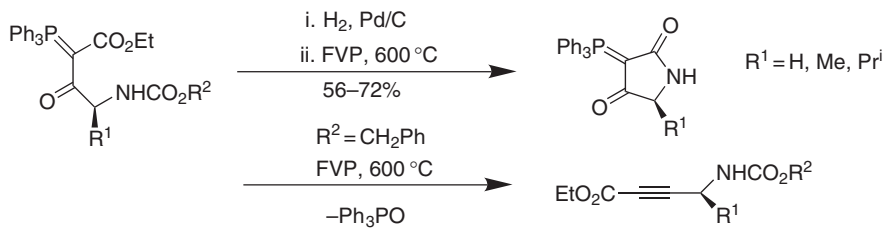
3.13.4.1 By Halogenation

A halogenating agent can be used to convert an ylide with an α-H into the corresponding halogenated derivative. This method avoids the possibility of base attack at the halogen, a complication when the salt method is used to produce α-haloylides <1995COFGT(3)491>.

It is also possible to substitute one halogen for another. This has been used in the synthesis of ylides that are fluorinated at the phosphorus atom. *P*-Chlorinated ylides were successfully converted to *P*-fluorinated ylides upon treatment with zinc or arsenic fluoride <1998HAC659>.

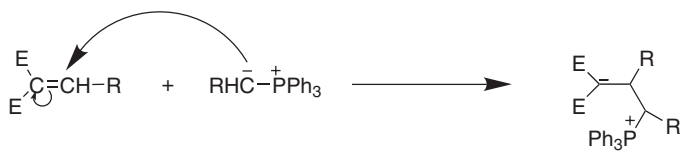
3.13.4.2 By Alkylations and Acylations

The alkylation or acylation of the nucleophilic ylidic carbon is a powerful way to extend the carbon skeleton of the original ylide. Aitken and co-workers <1998JCS(P1)3345, 1998JCS(P1)593, 1998JCS(P1)875, 1995JCS(P1)485, 2002JCS(P1)533, 1995JCS(P1)475> have used the acylation of ylides in the preparation of sulfinyl, sulfonyl, alkynoyl, α-aminoacyl, and phthalimidoacyl ylides for treatment by flash vacuum pyrolysis. A surprising result of the flash vacuum pyrolysis of (α-aminoacyl) (ethoxycarbonyl)ylides was that five-, six-, and seven-membered ring heterocyclic ylides were formed. If the amino group was protected (*N*-benzoxycarbonyl group), then the expected acetylenes were produced <2001TL(41)141> (Scheme 10).



Scheme 10

A large amount of research has focused on the reactions of phosphorus ylides with various unsaturated centers and the ylides formed from these interactions. The reaction takes the form of nucleophilic attack by the carbanionic center of the ylide, and the carbon skeleton of the ylide can be significantly extended in this manner <1997PS123, 2000HAC57, 1997T3649, 1998T9079, 1999HAC263, 1996T8835, 2003EJO840, 2003PS125, 2000PS(166)99, 1999JCS(P1)3049, 2002SL1417, 2000JCS(P1)1723> (Equation (6)).



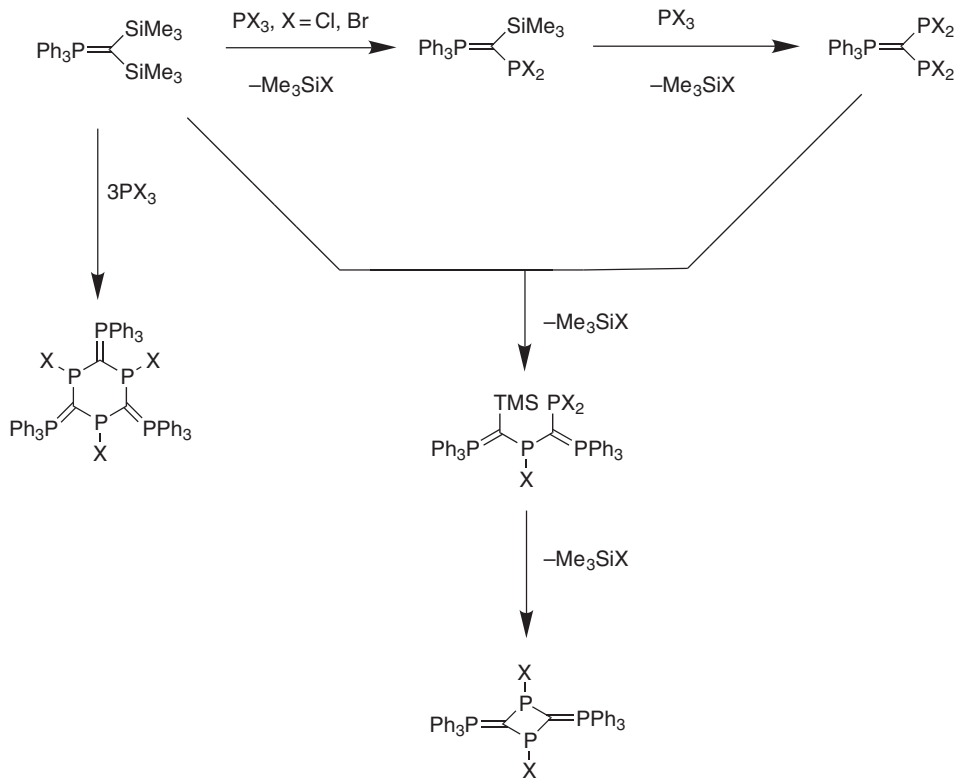
(6)

E = electron-withdrawing group, e.g., carbonyl, ester, cyano
R = alkyl, aryl

β-Oxidoylides have been generated from ethylene(triphenyl)phosphorane, various aldehydes, and BuLi <1995JCS(P1)1331>. This method has been used in the synthesis of 2-iodo-alk-2-enes by treating the β-oxidoylides formed with diiodoethane. The reaction of phosphonium ylides with epoxides has been found to produce betaines, which upon addition of BuLi produced a ylide with an extended carbon skeleton <2000PS(164)269>. Linear bisylides have been formed from the 2:1 interaction of phosphonium ylides with carbon suboxide. The nature of the product formed was influenced by the substituents on the carbon center of the ylide <1995ICA27>.

3.13.4.3 By Reaction with PX_3

The condensation of either phosphorus trichloride or phosphorus tribromide with triphenylphosphonium bis(trimethylsilyl)methylide results in the formation of a variety of linear and cyclic oligomers <1995AG(E)1853, 1997ZN(B)162, 1997CB(recueil)1519, 1997CB(recueil)89, 1997JOM87> (Scheme 11). The oligomer formed can be controlled by variation of experimental conditions such as solvent, reagent concentration, and temperature.



Scheme 11

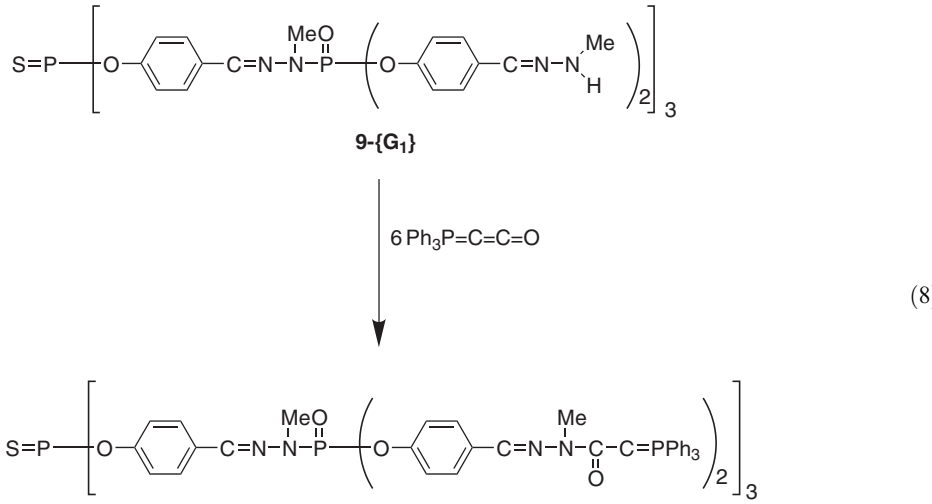
3.13.4.4 By "Phospha-Wittig" Reaction

The phospha-Wittig reaction is a process that takes a phospha-ylide and upon reaction with a carbonyl compound, gives a phospha-alkene. Shah and Protasiewicz <2000CCR181> have reviewed this reaction (Equation (7)).

(7)

3.13.4.5 Preparation of Ylide-terminated Dendrimers

A ylide-terminated dendrimer has been synthesized and successfully tested in a Wittig reaction with benzaldehyde and crotonaldehyde. The dendrimer was made from triphenylphosphoranylidene ethanone and 9-{G_1} at room temperature without the addition of base <1997JOC4834> (Equation (8)).



(8)

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3.13.5 PREPARATION OF As, Sb, AND Bi YLIDES

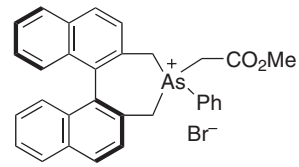
The methods used to prepare As, Sb, and Bi ylides are in general similar to those used to prepare phosphorus ylides. They have been prepared from their salts with the addition of a suitable base, though as the pK_a of these salts tend to be higher, a stronger base may be needed than for the phosphorus analog. They have been prepared via the reaction of arsines, stibines, or bismuthines with carbenes as well as by the reaction of the dihalopentacoordinate derivatives or tertiary oxides with active methylene compounds in the presence of triethylamine <1995COFGT(3)491>.

3.13.5.1 From Onium Salts

The work done by Hon and co-workers <2000T7893> (Section 3.13.1.1) on the effect of counterions on the Wittig reaction was extended to include arsonium salts. As with the phosphonium salts, these were prepared either via addition of a protic acid to the ylide or via the reaction of the triphenylarsonium bromide with silver salts.

Bismuthonium salts are harder to prepare than their phosphorus, arsenic, and antimony analogs due to the lower nucleophilicity of the lone pair in triphenylbismuthine. Matano <2000OM2258, 2001MI834> has investigated the various methods for preparation of these salts.

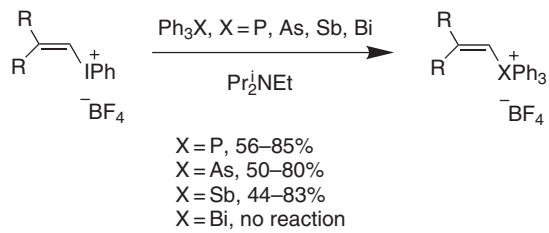
Asymmetric Wittig reactions have successfully been performed using chiral arsenic ylides <1997TA1979, 2001TL2541>. Dai and co-workers <2002TA2187> prepared the chiral arsine from (*S*)-(−)1,1′-bi-2-naphthol in three steps, and treatment of this arsine with methyl bromoacetate in xylene with the addition of microwave irradiation resulted in the formation of the bromide salt **2**. The stereochemistry of the Wittig product was affected by the nature of the counterion and as such by the base used to deprotonate the salt to form the ylide. Bu^nLi gave (*R*)-products while NaHMDS and KHMDS resulted in an inversion of this stereochemistry.



2

3.13.5.2 From Interactions with Carbenes

The treatment of 1-alkenyl(phenyl)iodonium tetrafluoroborates with base under mild conditions results in the formation of alkylidene carbenes. When these carbenes are formed in the presence of triphenylphosphine, triphenylarsine, or triphenylstibine, the 1-alkenyl(triphenyl)onium tetrafluoroborates are formed <1999JOC8563> (Equation (9)).



(9)

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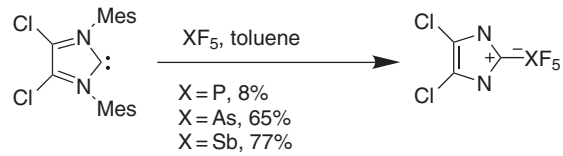
A reverse ylide (one in which the charge pattern of the ylide has been reversed) has been prepared from a heterocyclic carbene and $Sb(CF_3)_3$ <1999ZAAC1813>. A similar result was obtained from the reaction of a heterocyclic carbene with phosphorus, arsenic, and antimony pentafluorides <2000M251> (Equation (10)).



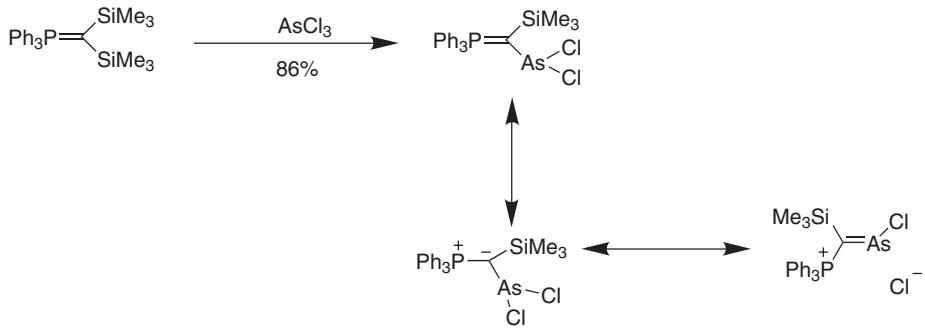
(10)

3.13.5.3 From Activated Multiple Bonds

The reaction of phosphines and phosphorus ylides with activated multiple bonds has been used extensively to modify the carbon skeleton of the ylide (Section 3.13.2.3). In a similar manner stabilized bismuth ylides have been prepared from iminotriaryl-λ^5-bismuthanes and dialkyl acetylenedicarboxylates <2000JOM89>. Stabilized arsonium ylides have been extended by reaction with methyl and ethyl propiolate <1998JCS(P1)1801>. This reaction is sensitive to solvent, with different isomeric products being formed when benzene or methanol was used. As with phosphorus ylides, arsenic ylides were found to react with carbon suboxide to form linear bisylides if a 2:1 ratio of ylide to carbon suboxide was used <1995ICA27>.

3.13.6 FORMATION OF MIXED YLIDES

The treatment of triphenylphosphonium trimethylsilyl ylides with $AsCl_3$ resulted in the formation of mixed phosphorus, asenic ylides <2000CEJ3531> (Scheme 12). Phosphonium–iodonium ylides have also been prepared as the salts with various counterions. These reagents combine, in one molecule, the synthetic potential of a phosphorus ylide and an iodonium salt <2002TL2359>.



Scheme 12

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Biographical sketch

Sianne Lindsay Schwikkard was born in South Africa and studied at the University of Natal, Durban, where she obtained her B.Sc. (hons.) in 1992, her M.Sc. in 1993, and her Ph.D. in 1998 under the supervision of Professor Dulcie Mulholland. She was awarded a National Research Foundation (South Africa) fellowship to carry out postdoctoral studies at Virginia Polytechnic and State University under Professor David Kingston. This was followed by a further postdoctoral fellowship from the Claude Harris Leon Foundation to carry out research at the Rand Afrikaans University under Professor Fanie van Heerden. Prior to relocating to the UK in 2002, she worked for Sastech Research and Development in Sasolburg, South Africa. Currently she is involved in postdoctoral research into the synthesis of various heterocycles at Kingston University in the laboratories of Professor Keith Jones.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 525–542

3.14
Doubly Bonded Metalloid Functions (Si, Ge, B)

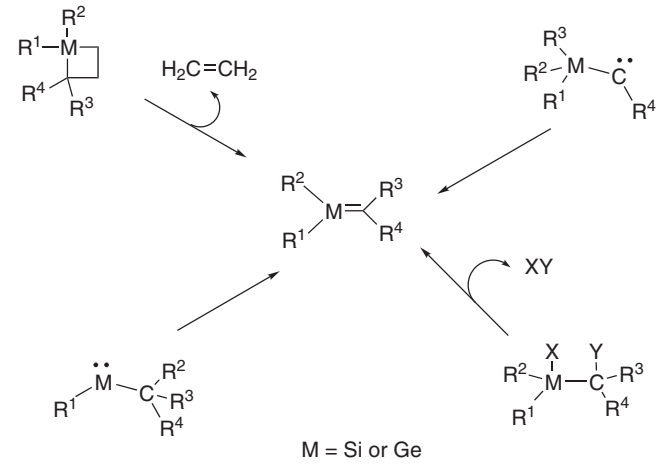
N. A. WILLIAMS
Kingston University, Kingston-upon-Thames, UK

3.14.1 GENERAL METHODS FOR THE PREPARATION OF THE C═METALLOID FUNCTIONS (Si, Ge, B)

Compounds that contain the Si═C or the Ge═C function are known as silenes and germenes, respectively. The synthesis of silenes and germenes has been reviewed previously <1995COFGT(3)501, 1998CCR(180)565, 1999AOC113, 2001ACR129, 2002POL467>. Non-heteroatom-containing methyleneboranes, which contain the B═C function, are very rare. In this chapter, only syntheses in which the carbon of the doubly bonded metalloid function is bonded to two nonheteroatom substituents are included. The prinicpal routes to R_2C═Si functions are: (i) thermally or photochemically induced [2 + 2]- or [2 + 4]-cycloreversion of silacycloalkanes; (ii) [1,2]-migration of α-silyl carbenes or silylene intermediates; and (iii) 1,2-elimination reactions, as shown in Scheme 1. Similar methods can be applied to the synthesis of germenes. A number of silenes and germenes have been identified as reactive intermediates; however, very few have been isolated. Yields and lifetimes are reported where they are available. A few examples of trapping reactions and rearrangement products are reported.

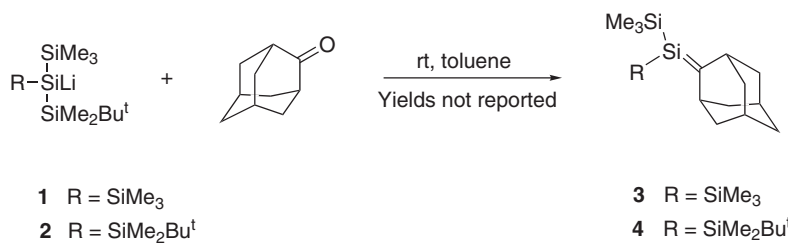
3.14.1.1 Doubly Bonded Silicon Functions

A range of silenes have been generated by sila-Peterson-type 1,2-elimination reactions, for example, the reaction of adamantanone with silyl anions **1** and **2** yielded the stable silenes **3** and **4** (Equation (1)) <1996JA12228>. Although **3** and **4** are stable for up to 6 months in solution at room temperature, isolated yields are not reported. Calculations indicate that the stability is due to the large steric congestion in the dimerization transition state. Compound **4** is the first silene with two nonheteroatoms attached to the carbene carbon to be structurally characterized by single-crystal X-ray diffraction. Related methods have been used to generate transient silene **5** from dibenzosuberenone (Equation (2)) <1996JOM(526)185> and a silatriafulvene **7** from a sterically congested cyclopropenone **6** (Scheme 2) <1997JA3405>. The silatriafulvene **7** was



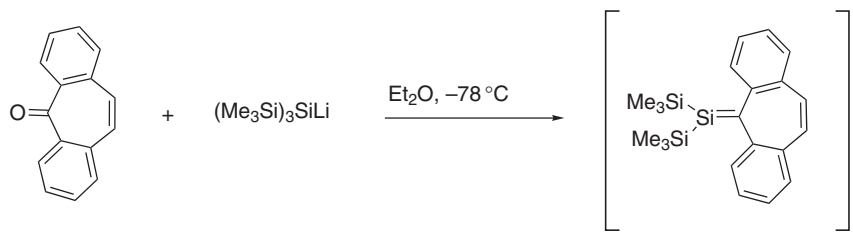
Scheme 1

trapped by reaction with 2,3-dimethyl-1,3-butadiene. The base-induced elimination of trimethyl silanol from **8** yields silene intermediate **9**, which rearranges to form **10** (Scheme 3) <1997JOM(544)49>. The stable dimesityl neopentyl silene **12** is synthesized in near quantitative yield via the elimination of LiF from **11** (Scheme 4) <1996JOM(514)59>. Treatment of 2,4,6-triisopropylbenzaldehyde with a silylmagnesium bromide **13** can also generate a transient silene **14** (Equation (3)) <1996JOM(510)181>.



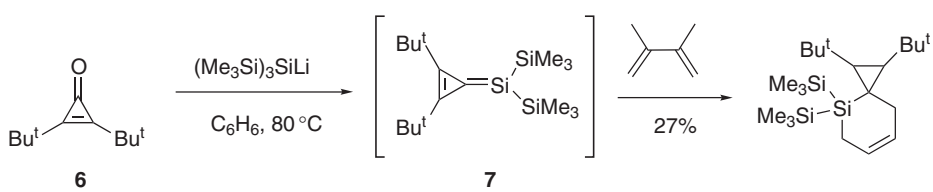
(1)

1 R = $SiMe_3$
2 R = $SiMe_2Bu^t$
3 R = $SiMe_3$
4 R = $SiMe_2Bu^t$



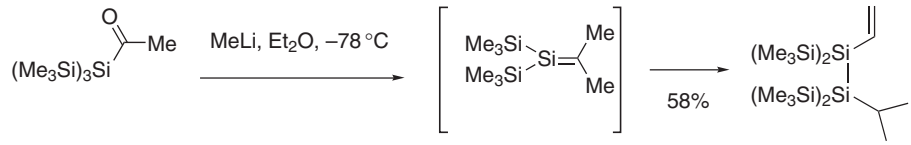
(2)

5



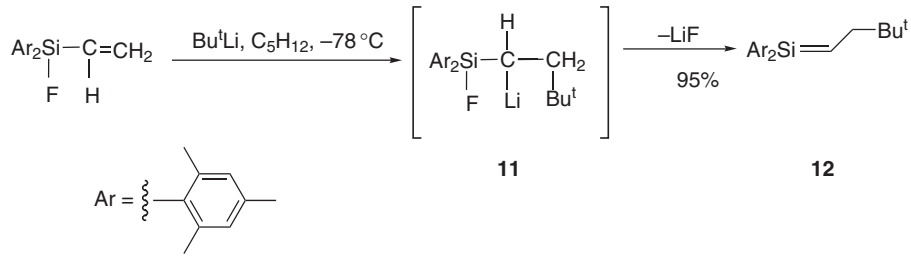
6 **7**

Scheme 2



8 **9** **10**

Scheme 3

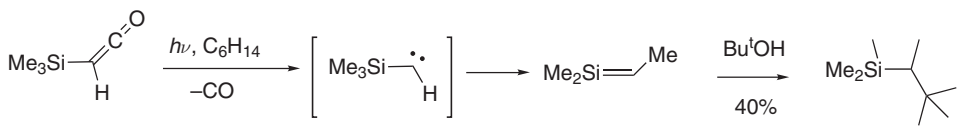


11 **12**

Scheme 4

13 **14** (3)

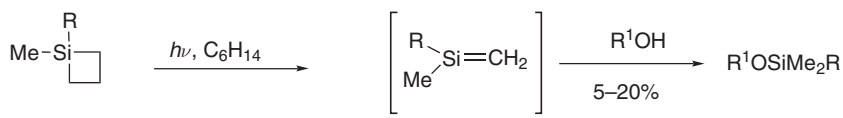
The photolysis of α-silyl diazo compounds is a well-established route to silenes, which proceeds via denitrogenation and a 1,2-migration. This method has been extended to α-silyl ketenes **15**, which generate transient silenes **16** via decarbonylation and a 1,2-methyl migration (Scheme 5) <1999JA4744>. The silene can be trapped with *t*-butanol to give **17**. A range of substituted 1-methyl silenes **19** have been generated by laser flash photolysis of the corresponding substituted 1-methyl silacyclobutanes **18** and subsequently trapped by alcohols (Scheme 6) <1998JA9504>.



15 **16** **17**

τ = 0.3 ns τ = 3 μs

Scheme 5

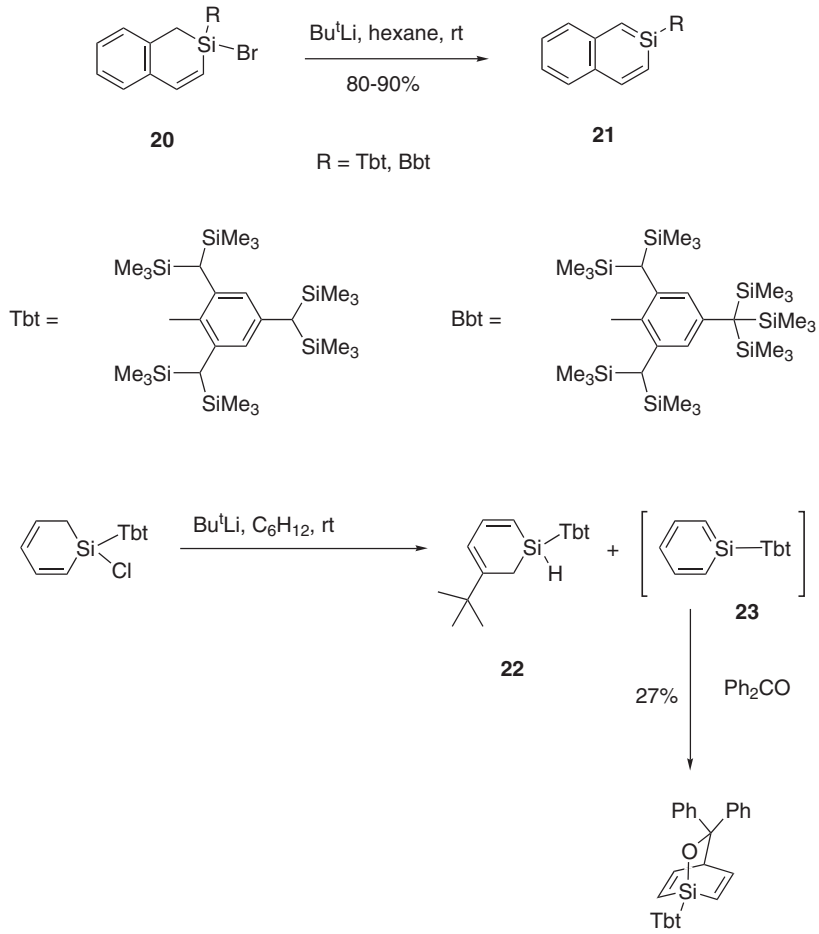


18 **19**

R = H, Me, Et, Bu^t, Ph, CH=CH$_2$, CCH, CH$_2$SiMe$_3$ R^1 = Et, Bu^t

Scheme 6

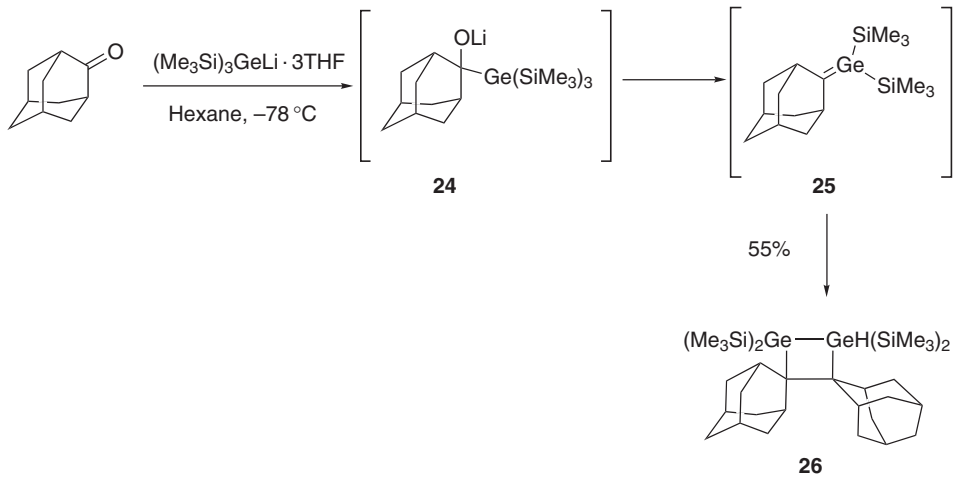
The first stable neutral silaromatic compound, a 2-silanaphthalene **21** with the extremely bulky protecting group 2,4,6-tris[bis(trimethylsilyl)methyl]-phenyl (Tbt), was prepared in 80% yield, by treatment of **20** with Bu^tLi (Equation (4)) <1997JA6951>. The structure was determined by X-ray crystallography. A further example with a 2,6-bis[bis(trimethylsilyl)methyl]-4-[tris(trimethylsilyl)methyl]phenyl (Bbt) steric protection group has also been prepared <1999JA11336>. The synthesis and characterization of the first stable silabenzene compound **23** bearing the Tbt protecting group, using a similar procedure, was reported in 2000. However, the silabenzene could not be separated from the side product **22**; however, it was trapped by reaction with benzophenone (Scheme 7) <2000AG(E)634>.



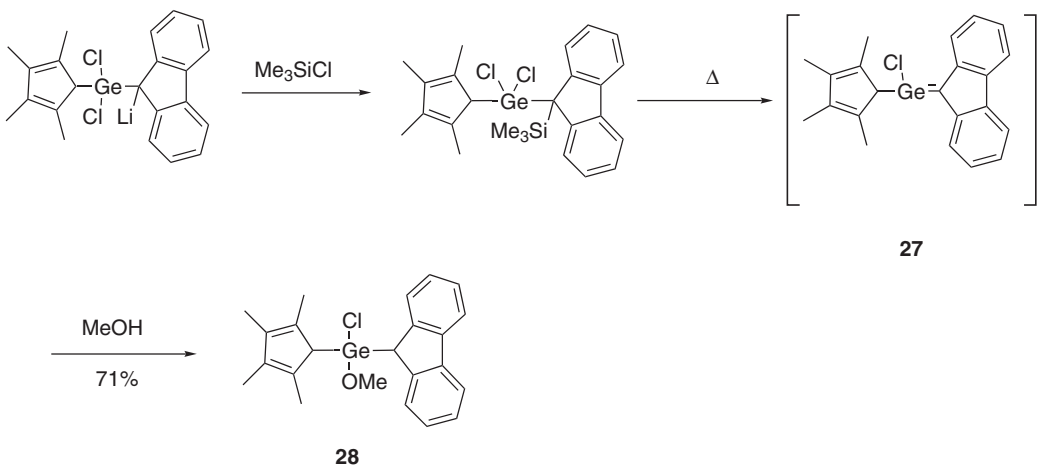
Scheme 7

3.14.1.2 Doubly Bonded Germanium Functions

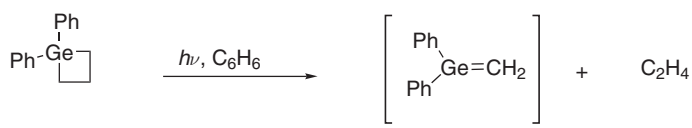
The reaction of adamantanone with $(Me_3Si)_3GeLi{\cdot}3THF$ generates a transient germene **25** via a Peterson-type elimination from intermediate **24** (Scheme 8) <1995CC1625>. In the absence of a trapping agent, it dimerizes in a head-to-head fashion to give **26**. A chlorogermene **27** has been produced by thermal dehalogenosilylation (Scheme 9) <1996JCS(D)893>. The bulky fluorenylidene and pentacyclopentadienyl groups were employed in an attempt to prevent oligomerization, but attempts to isolate the functionalized germene failed. It was trapped by reaction with methanol to give **28**. An alternative route to germenes **30** is the photo-induced [2 + 2]-cycloreversion of 1,1-diphenylgermetane **29** (Equation (5)) <1998JA1172>. The first stable germabenzene **32** has been synthesized in 98% yield by the dehydrohalogenation of the germacyclohexa-2, 4-diene **31** using lithium diisopropylamide (Equation (6)) <2002JA6914>.



Scheme 8



Scheme 9



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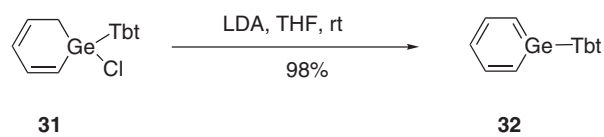

(6)

3.14.1.3 Doubly Bonded Boron Functions

No further advances have occurred in this area since the publication of chapter 3.14 in <1995COFGT(3)501>.

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Biographical sketch

Neil Williams studied at the University of Southampton, where he obtained a first class B.Sc. (Hons.) degree in Chemistry in 1989 and his Ph.D. in 1993, under the supervision of Professor J. Evans. He then spent two years at the National Institute of Materials and Chemical Research in Japan as a Royal Society/Japanese STA Fellow, working in the laboratory of Professor M. Tanaka. In 1995 he returned to the United Kingdom with a Royal Society Return Fellowship, which he took up at the University of Sussex, working with Professor Michael Lappert FRS. After a further period of postdoctoral work at the University of East Anglia and a temporary lecturership at the University of Central Lancashire, he took up his present position as a Senior Lecturer at Kingston University in 1999. His research interests lie in the field of organometallic chemistry and homogeneous catalysis.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 543–549

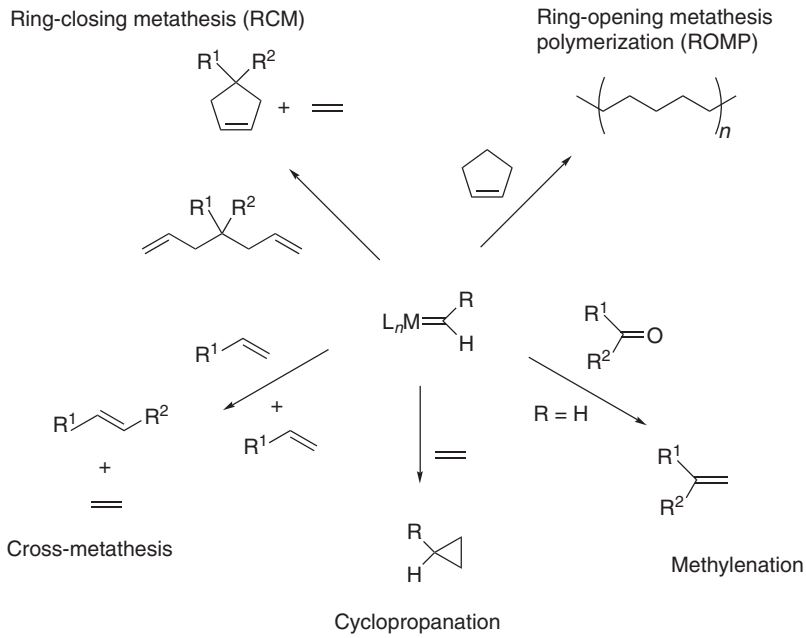
3.15
Doubly Bonded Metal Functions

N. A. WILLIAMS
Kingston University, Kingston-upon-Thames, UK

3.15.1 INTRODUCTION

Compounds that contain the double-bonded metal–carbon function are generally known as metal carbene complexes. These have traditionally been subdivided into two classes according to the nature of the carbene carbon substituents. The first class is Fischer-type carbene complexes where the carbene carbon is normally bonded to an electron-donating heteroatom. The heteroatom helps stabilize the electrophilic carbene carbon center. The second class of carbene complexes are the Schrock-type or alkylidene complexes. In these species the carbene carbon is bonded to H, alkyl, or aryl substituents. The electron-deficient carbene carbon is principally stabilized by the metal and its ancillary σ- and π-donor ligands.

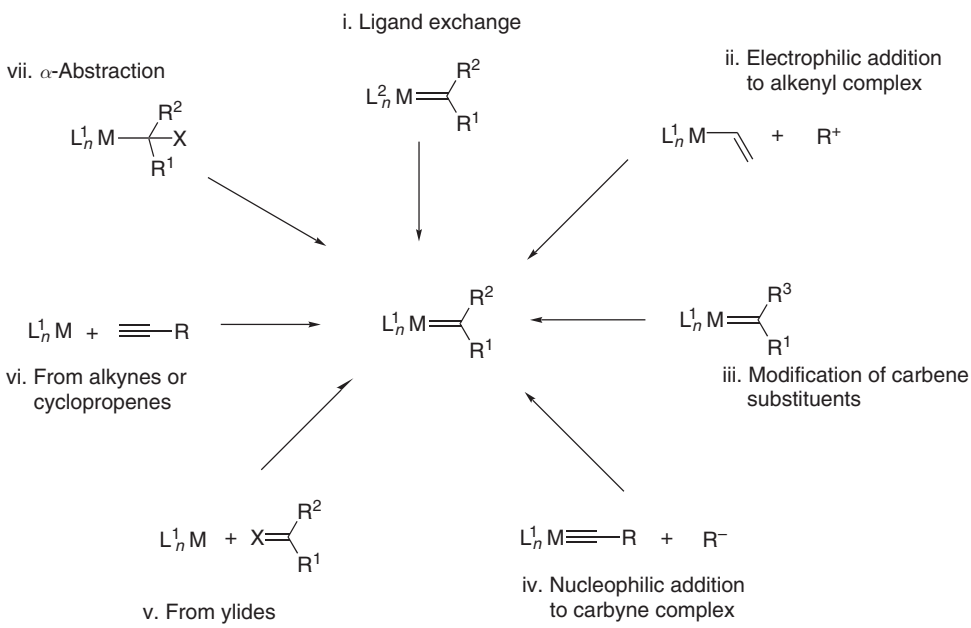
This chapter covers the methods of synthesis of nonheteroatom-stabilized carbene complexes, $L_nM{=}CR^1R^2$, which have appeared in the literature since the end of 1994. These complexes are used in a range of stoichiometric and catalytic reactions (Scheme 1). This chapter does not include vinylidene complexes, $L_nM{=}C{=}R$, or complexes with bridging alkylidene groups.



Scheme 1

3.15.2 GENERAL METHODS FOR THE PREPARATION OF THE C=METAL FUNCTION

Several reviews covering the early work on the synthesis of nonheteroatom-stabilized complexes are available <1991MI1, 1995COFTG(3)507>. Several recent reviews have appeared <2002CRV145, 1999CCR(181)177, 2000CCR(209)387, 2001CCR(214)215, 2002CCR(227)1>. A number of approaches to the synthesis of alkylidene complexes have been developed, as shown in Scheme 2: (i) ligand exchange; (ii) electrophilic addition to alkenyl complexes; (iii) modification of



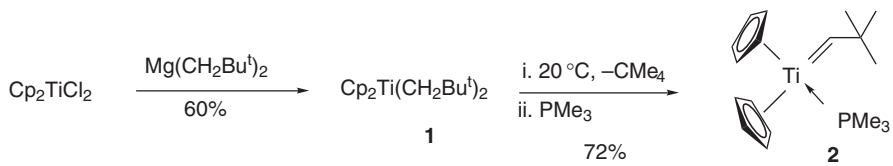
Scheme 2

carbene substituents in metal alkylidene complexes; (iv) nucleophilic addition to carbyne complexes; (v) use of organic ylides as carbene transfer agents; (vi) reaction of metal complexes with alkynes or cyclopropenes; and (vii) α-H-abstraction from an alkyl complex.

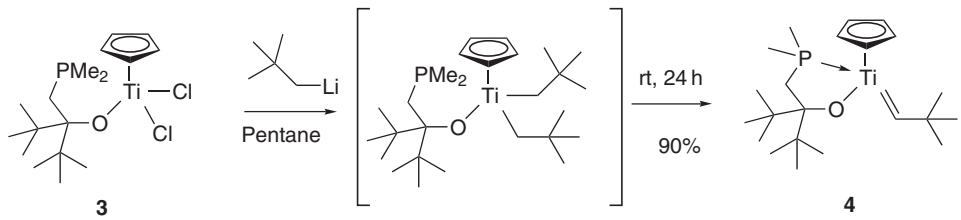
In this chapter, methods of preparation are organized according to the central metal atom. The emphasis is on the synthesis of the M=C function, but important examples of the synthesis of new alkylidene complexes by ligand exchange are also given. Representative examples of synthetic methods are given.

3.15.3 THE C=Ti FUNCTION

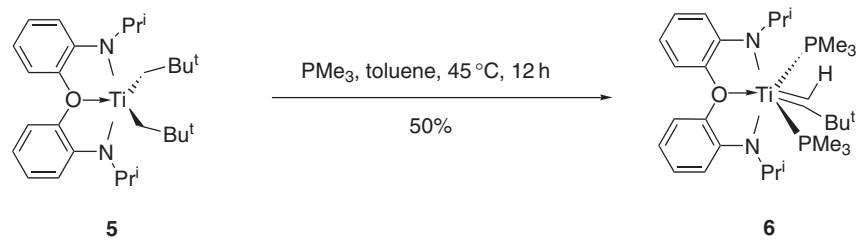
Thermal α-H-abstraction of bis(neopentyl)titanocene complexes **1**, followed by the trapping of the alkylidene intermediate with a trialkylphosphine, yields stable titanocene neopentylidene complexes **2** as shown in Scheme 3 <1995CC145>. Treatment of **3** with neopentyllithium generates a neopentylidene complex **4** via elimination of neopentane from a bis(neopentyl) titanium intermediate (Scheme 4) <1995OM1278>. Intramolecular coordination of the phosphino group of the (phenylphosphino)alkoxide ligand helps stabilize the complex. A neopentylidene complex **6**, containing the tridentate diamido ligand, $[(I\text{-}PrN\text{-}o\text{-}C_6H_4)_2O]^{2-}$, has been synthesized by using a similar strategy, starting from **5** (Equation (1)) <1999JA7822>. Amido-functionalized cyclopentadienyl titanium dialkyl complexes **7** also yield alkylidene complexes **8** after thermolysis and trapping with PMe_3 (Equation (2)). Neopentylidene and neophylidene complexes have been isolated <1997OM4245>.



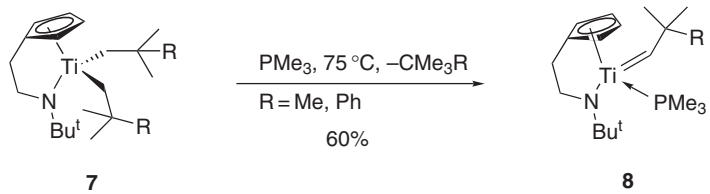
Scheme 3



Scheme 4

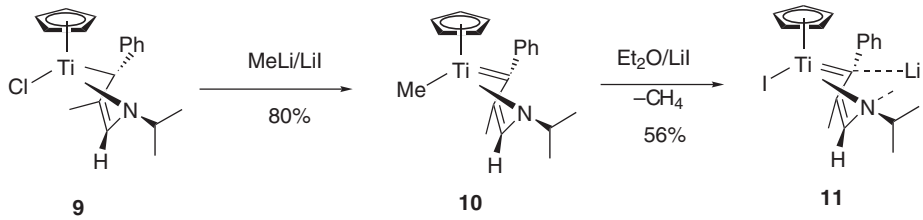


(1)



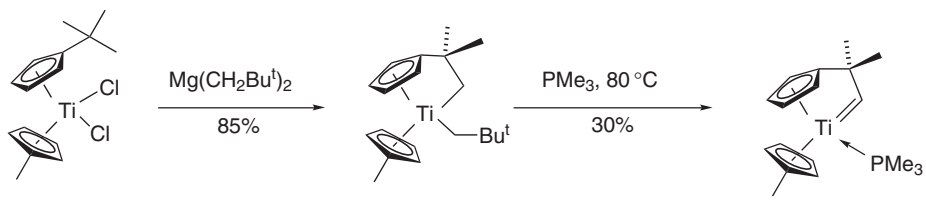
(2)

Treatment of 1-aza-1,3-diene titanium complexes **9** with methyllithium generates the methyl compound **10** that readily undergoes methane elimination to give a new titanocycloalkylidene complex **11** (Scheme 5) <1998AG(E)1857>. A titanocene neopentyl complex **12** with one cyclometallated *t*-butylcyclopentadienyl group yields an alkylidene complex **13** with a chelated alkylidene group, after losing neopentane by α-H-abstraction (Scheme 6) <2003ICA(345)27>.



9 **10** **11**

Scheme 5

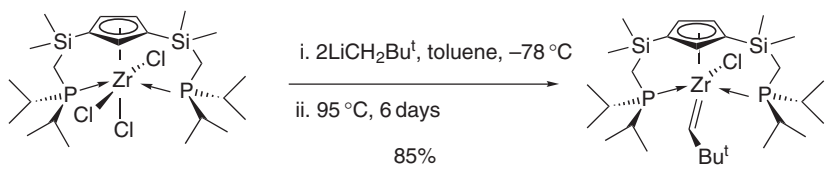


12 **13**

Scheme 6

3.15.4 THE C=Zr FUNCTION

Reaction of the zirconium complex **14** with 2 equiv. of neopentyllithium generates a mixture of mono-, bi-, and trisbenzyl zirconium complexes. Thermolysis of this mixture gives the neopentylidene complex **15** in 85% yield (Equation (3)) <1999JA2478>. Treatment of **14** with benzylpotassium followed by thermolysis at 95 °C for 6 days gives the butylidene complex.

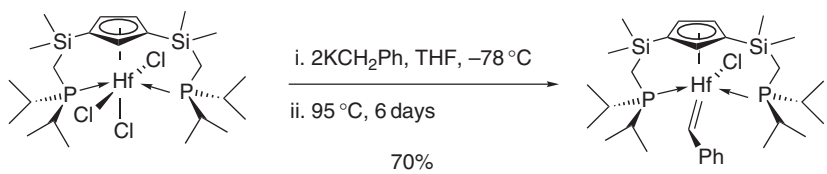


(3)

14 **15**

3.15.5 THE C=Hf FUNCTION

Reaction of the hafnium trichloride complex **16** with 2 equiv. of benzylpotassium gives a complex mixture of alkyl complexes, which after thermolysis at 95 °C for 6 days gives the first stable, structurally characterized hafnium alkylidene complex **17** (Equation (4)) <2001OM1608>. The benzylidene complex is thought to be formed via α-H-abstraction and elimination of toluene from a dibenzyl intermediate.

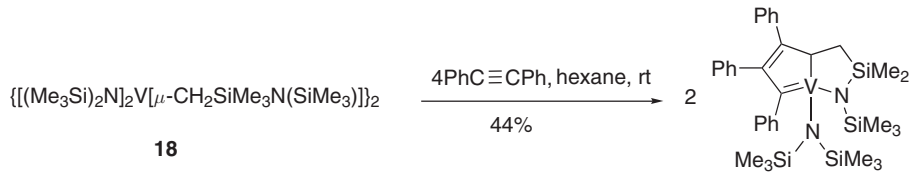


(4)

16 **17**

3.15.6 THE C=V FUNCTION

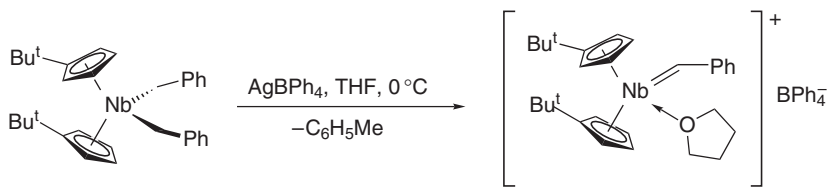
Treatment of **18** with an excess of diphenyl acetylene at room temperature generates 2 equiv. of the bicyclic carbene complex **19** in which two diphenyl acetylene units combine to form a tetraphenylvanadium cyclopentadiene ring (Equation (5)) <1997CC643>.



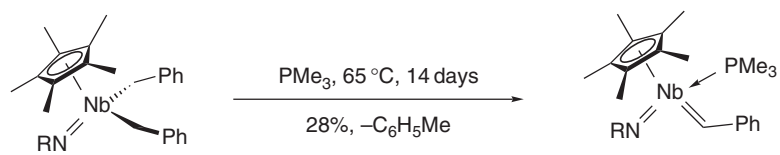
(5)

3.15.7 THE C=Nb FUNCTION

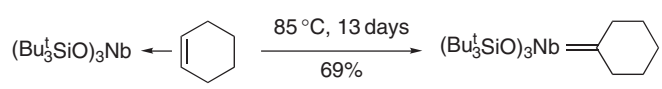
The first cationic niobium alkylidene complex was prepared by the oxidation of the dibenzyl compound **20** by $AgBPh_4$, subsequent α-elimination of toluene yields the benzylidene complex **21** (Equation (6)) <1995CC2421>. A cyclopentadienyl(imido) niobium complex bearing a benzylidene ligand **23** can be obtained as orange crystals in 28% yield from **22** (Equation (7)). The dibenzyl complex **22** is stable to thermolysis at temperatures above 100 °C, but the elimination of toluene is induced by the addition of PMe_3 and heating at 65 °C for 14 days <1998JCS(D)103>. Relatively rare cyclohexylidene **25** and butylidene **27** niobium complexes have been prepared via an alkene to alkylidene rearrangement, induced by the extended thermolysis of **24** (Equation (8)) and **26** (Equation (9)), respectively <2001AG(E)3629>. A range of nonheteroatom stabilized carbene complexes **29** have been prepared by the reaction of ketones and aldehydes with a Nb(III)=Nb(III) dimer bound to two [*p*-Bu^t-calix[4]-(O)] tetraanions **28** (Equation (10), Table 1) <1999JA8296>. The reaction proceeds via the metathesis of the Nb=Nb bond with the C=O bond, forming 1 equiv. of the alkylidene complex and 1 equiv. of the oxoniobium(V) complex **30**. The yields range from 40% to 80%.



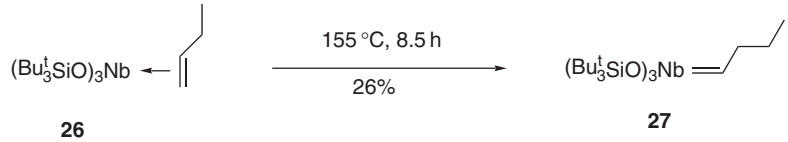
20 **21** (6)



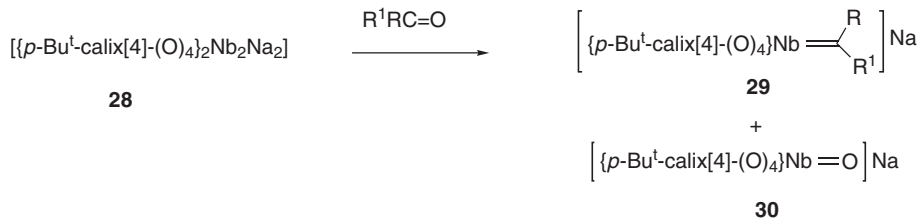
22 R = 2,6-Pr$^i_2$C$_6$H$_3$ **23** (7)



24 **25** (8)



26 **27** (9)



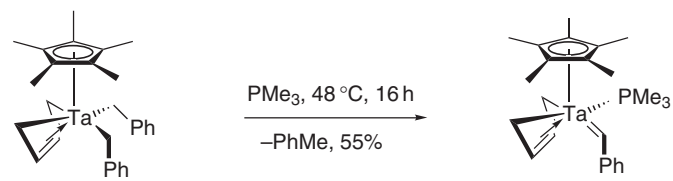
(10)

Table 1 Synthesis of **29**

R	R^1	**29** *Yield* (%)
Ph	Me	62
Ph	CH_2PH	40
Ph	Ph	74
Pr	H	<5

3.15.8 THE C=Ta FUNCTION

Tantalum has proved to be very successful at supporting nonheteroatom stabilized carbene ligands. Much of the recent work has been focused on preparing alkylidene complexes with different ancillary ligands. Complex **32** is prepared in 55% yield by thermolysis of the butadiene tantalum complex **31** at 48 °C for 16 h, in the presence of PMe_3 (Equation (11)) <1996OM2431>. In contrast, the related *o*-xylene complex **34** can be formed as dark red crystals in 17% yield by the thermolysis of **33** at 40 °C for 4 h without the addition of PMe_3 (Equation (12)) <1998OM4183>. Complex **35** containing the trimethylsilyl-substituted triamidoamine ligand reacts with 2 equiv. of benzylmagnesium chloride to afford **36** in 91% yield (Equation (13)) <1996JA3643>. The stable tantalum methylidene complex **38** containing the macrocylic bis(amido-phosphine) ligand is formed as an orange solid in 40% yield after photolysis of **37** ((Equation (14) <1999OM4059>. Benzamidinate tantalum carbene complexes **40** have been prepared by treating the dimethyl cation **39** with $Et_3P{=}CHSiMe_3$ (Scheme 7) <1997OM1111>. In all the above cases, the alkylidene is formed via α-H-abstraction.



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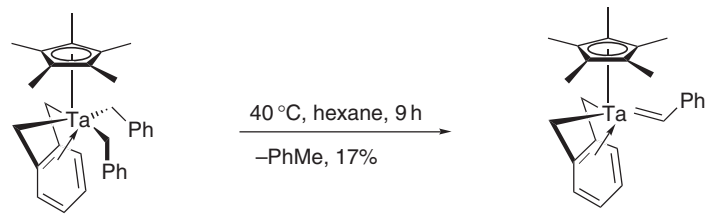

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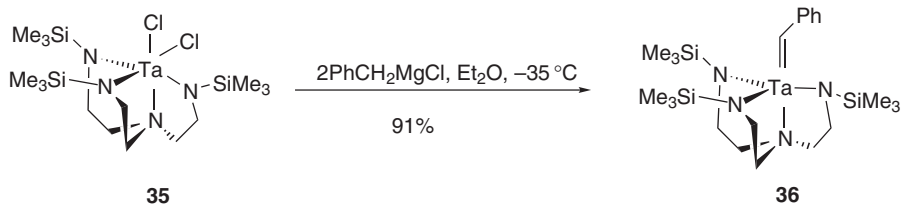

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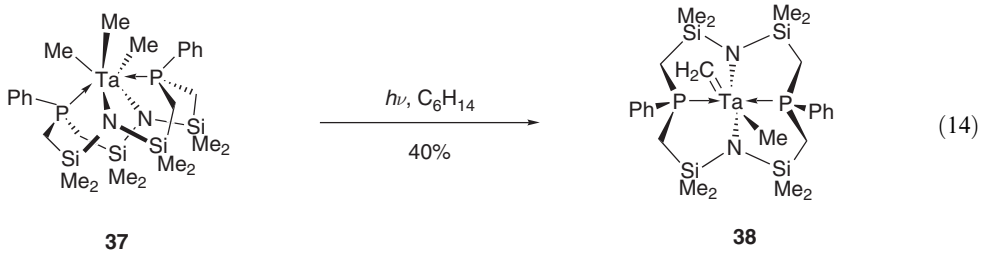
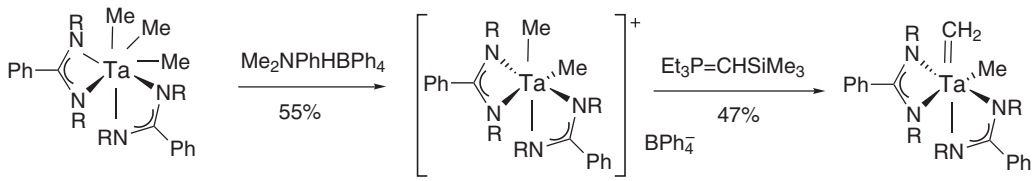


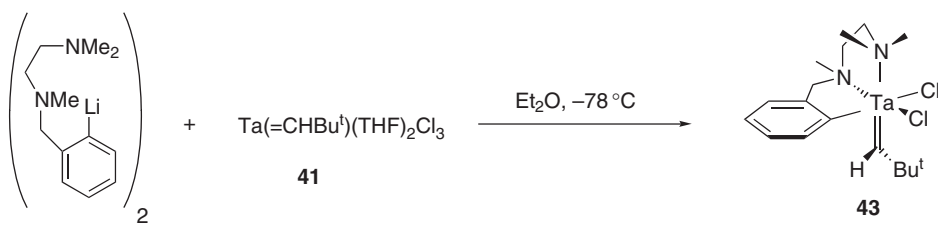
37 **38** (14)



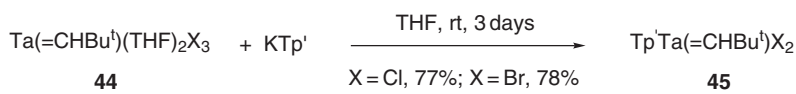
39 **40**

Scheme 7

Novel tantalum carbene complexes can be prepared by substituting the ancillary ligands of known tantalum carbene complexes. Treatment of **41** with the anionic aryldiamine ligand **42** produces a mixture of three diastereoisomers in an overall yield of 51%; the major diastereoisomer **43** is obtained after extraction with ether and recrystallization (Equation (15)) <1997OM1674>. Neopentylidene complexes **45** containing the tris(pyrazolyl)borate ligand have been prepared by ligand exchange with **44** (Equation (16)) <1996OM1904>.



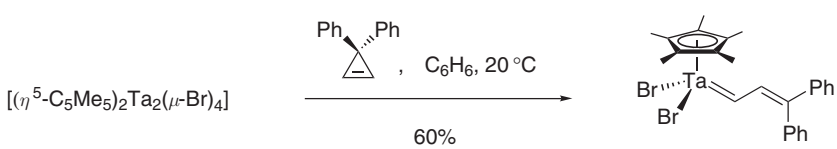
42 **41** **43** (15)



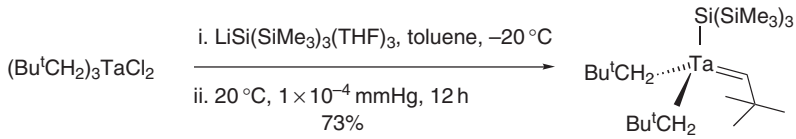
44 **45** (16)

Tp' = hydrotris(3,5-dimethylpyrazolyl)borate

A (phenylalkenyl)alkylidene complex **47** has been obtained from the ring opening of 3,3-diphenylcyclopropene by **46** (Equation (17)) <2003ICA(345)209>. In the reaction of **48** with 2 equiv. of $LiSi(SiMe_3)_3(THF)_3$, the neopentylidene complex **49** is formed due to the preferential elimination of the silane, $HSi(SiMe_3)_3$ (Equation (18)) <1996OM3520>. A novel cyclopentadienylidene complex **51** is formed in 15% yield after reaction of **50** with methyllithium (Equation (19)). A mechanism involving an intermolecular cyclopentadienyl transfer reaction and a C—H activation process is suggested <1997CC791>.

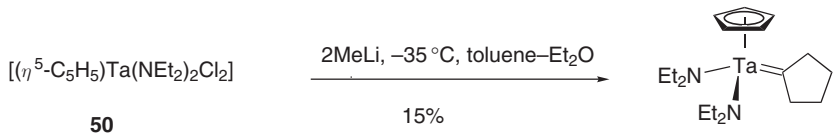


46 **47** (17)



(18)

48 **49**



(19)

50 **51**

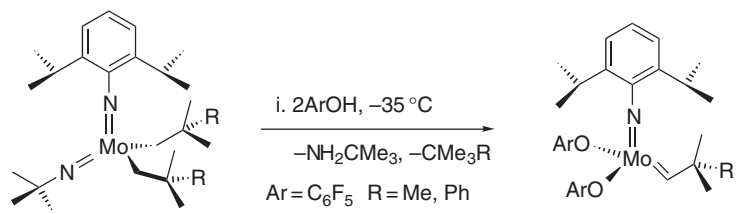
3.15.9 THE C=Cr FUNCTION

No further advances have occurred in this area since the publication of chapter 3.15 in <1995COFGT(3)507>.

3.15.10 THE C=Mo FUNCTION

Molybdenum alkylidene complexes are of great current interest because of their ability to catalyze alkene metathesis reactions. Particular attention has been paid to the synthesis of chiral molybdenum complexes for use as catalysts in enantioselective alkene metathesis.

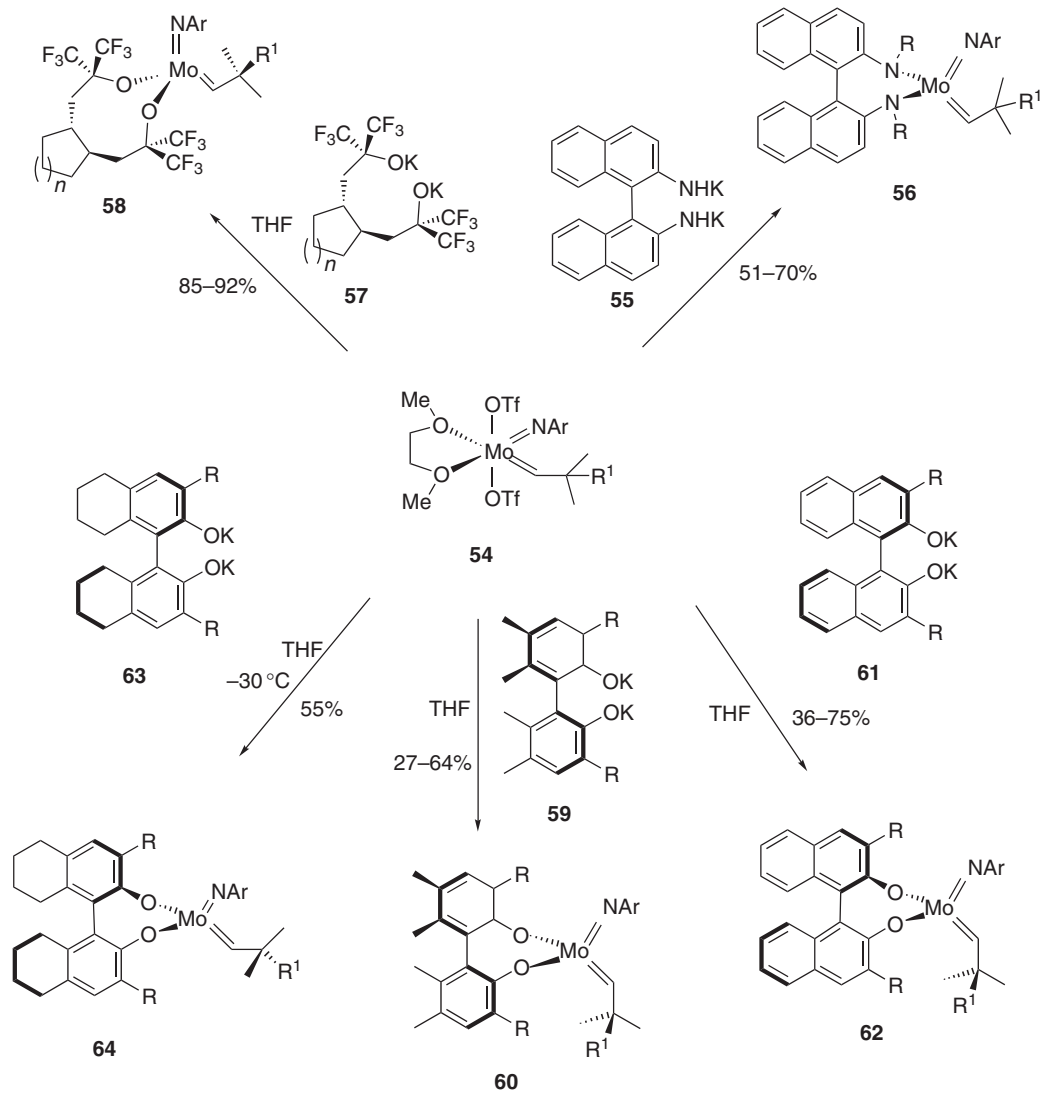
A number of new carbene complexes have been prepared by the introduction of alkoxide or imido ancillary ligands. Four coordinate carbene complexes **53** with pentafluorophenoxide ligands have been synthesized by treating a mixed imido molybdenum dialkyl precursor **52** with pentafluorophenol (Equation (20)). The reaction proceeds via protonation of the more basic imido ligand followed by α-H-abstraction and elimination of the alkane <1994CC2547>. A wide range of complexes have been generated from the known alkylidene complex **54** as shown in Scheme 8 and Table 2. The bis(amido-1,1′-binaphthyl)molylbdenum carbene complexes **56** are produced in 50–70% yields after the addition of the potassium salt **55** to **54** <2000OM925>.



(20)

52 **53**

Complex **58** (n = 1), prepared by Grubbs, <1996JA2499, 1996OM1865> was the first catalyst to show enantioselectivity in ring-closing metathesis. It was synthesized from the dilithium alkoxide **57** and molybdenum alkylidenebis(triflate) precursor **54** in pentane at −40 °C, in 85% yield. The complex is stable under nitrogen at −10 °C for several months. The cyclohexane analog **58**, n = 2, has also been synthesized <1998JOC824>. Enantiomerically pure biphenolate complexes **60** are obtained from the reaction of **54** with a dipotassium biphenolate **59** (Table 2) <1996MA6114, 1998JA4041, 2000OM3700>. These complexes are successful at controlling the stereochemistry of ring-opening metathesis polymerization <1996MA6114> and catalyzing asymmetric ring-closing metathesis to yield five-membered rings in large enantiomeric excess <1998JA4041>. Chiral molybdenum binaphtholate carbene complexes **62** have been synthesized from **61** by using a similar strategy <1999JA8251, 2001OM5658>. This class of complex catalyzes the asymmetric ring-closing metathesis of dienes and trienes to give six-membered rings. An easier to use and more generally applicable catalyst for asymmetric alkene metathesis is compound **64**, which has been prepared from octahydrobinaphtholate **63** <2001AG(E)1452>.

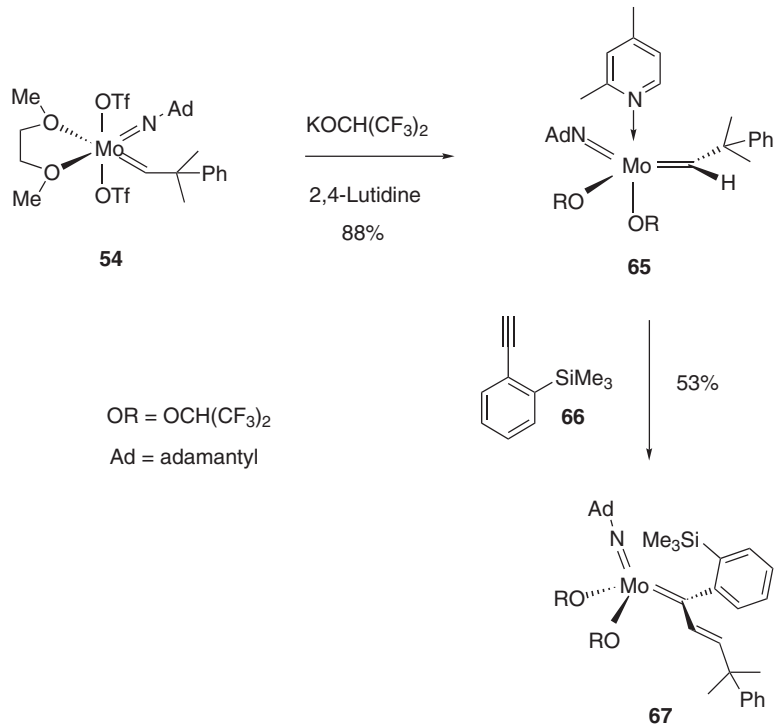


Scheme 8

Table 2 Chiral molybdenum alkylidene complexes derived from **54**

Compound	*R*	R^1	*Ar*	*Yield* (%)	*References*
56	Ts	Ph	2,6-$Pr^i_2C_6H_3$	68	<2000OM925>
	Ts	Ph	2-$CF_3C_6H_4$	70	
	Ts	Me	2-$CF_3C_6H_4$	65	
	Pr^i	Ph	2,6-$Pr^i_2C_6H_3$	60	
	SiMe3	Ph	2,6-$Pr^i_2C_6H_3$	51	
58	$n = 1$	Ph	2,6-$Pr^i_2C_6H_3$	85	<1996OM1865>
	$n = 2$	Ph	2,6-$Pr^i_2C_6H_3$	92	<1998JOC824>
60	Bu^t	Ph	2,6-$Me_2C_6H_3$	30	<2000OM3700>
	Bu^t	Ph	2,6-$Et_2C_6H_3$	27	
	Bu^t	Ph	2,6-$Pr^i_2C_6H_3$	64	
	Ad	Ph	2,6-$Pr^i_2C_6H_3$	34	
	Ad	Me	2-$CF_3C_6H_4$	43	
62	2,4,6-$Pr^iC_6H_2$	Ph	2,6-$Pr^i_2C_6H_3$	36	<1999JA8251>
	2,4,6-$Me_3C_6H_2$	Ph	2,6-$Pr^i_2C_6H_3$	75	<2001OM5658>
	C_6H_5	Ph	2,6-$Pr^i_2C_6H_3$		<2001OM5658>
64	Bu^t	Ph	2,6-$Pr^i_2C_6H_3$	55	<2001AG(E)1452>

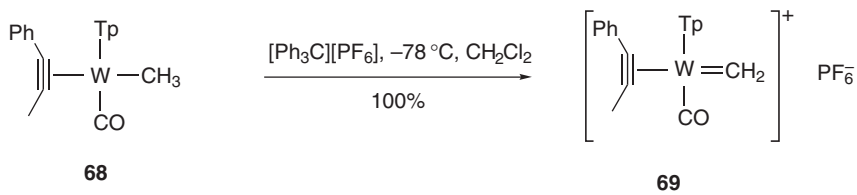
Addition of $KOCH(CF_3)_2$ to **54** in the presence of 2,4-lutidine generates the hexafluoroisopropoxide complex **65**. Compound **65** reacts with alkyne **66** to give alkylidene **67** via the opening of a metallocyclobutene intermediate (Scheme 9) <1996JA3883>.



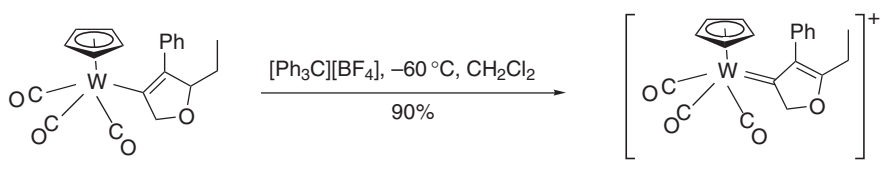
Scheme 9

3.15.11 THE C=W FUNCTION

Hydride abstraction has been extensively employed in the synthesis of tungsten carbene complexes. The cationic methylene complex **69** was obtained in quantitative yield from the methyl complex **68** using $[Ph_3C][PF_6]$ (Equation (21)) <1997OM4865>. The cationic alkylidene **70** is formed via a conjugate H-abstraction with $[Ph_3C][BF_4]$ at −60 °C (Equation (22)) <1996JA530>. The complex is thermally unstable.



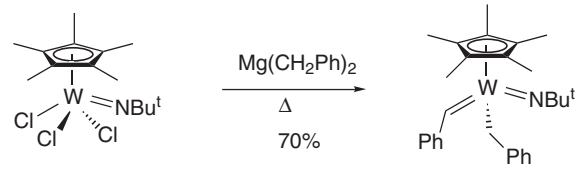
(21)



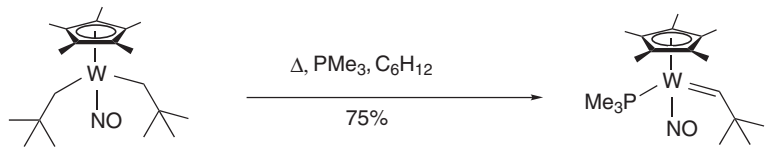
(22)

Cyclopentadienyl imido alkylidene tungsten complexes **72** have been accessed via H-abstraction of alkyl intermediates generated by treating **71** with Grignard reagents (see Equation (23) <1997OM5195, 1998JOM(564)277, 1999JOM(580)110>). Thermolysis in the presence of PMe_3

is required to achieve α-H-abstraction in (η-C_5Me_5)W(NO)(CH_2Bu^t) **73** and to isolate the alkylidene species **74** (Equation (24)) <1997JA5071>. Later work indicated that **74** exists in two isomeric forms <2001JA612>.

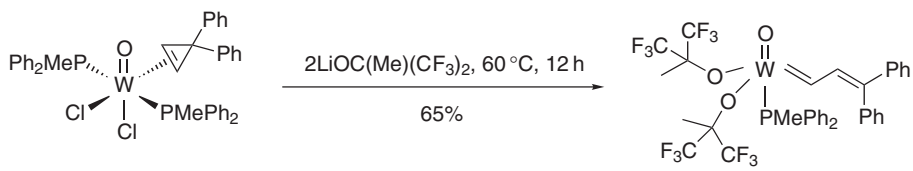


71 **72** (23)

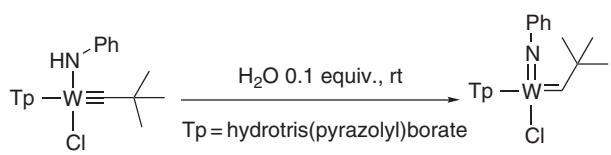


73 **74** (24)

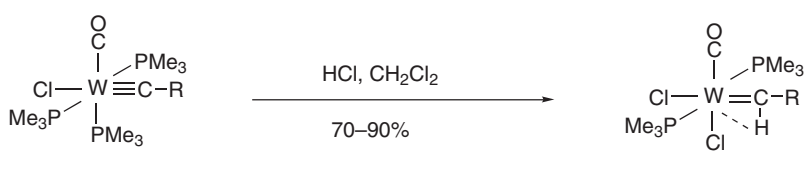
The diphenyl cyclopropene complex **75** can be converted into vinyl alkylidene complex **76** upon treatment with lithium hexafluoro-*t*-butoxide at room temperature, followed by the thermolysis at 60 °C for 2 h (Equation (25)) <1996OM577>. Tris(pyrazolyl)borate imido alkylidene complexes **78** are formed from the H_2O- or HCl-catalyzed tautomerization of amido alkylidyne complexes **77** (Equation (26)) <2003ICA(345)103>. The tautomerization involves proton transfer from the amido nitrogen to the alkylidyne carbon. The complexes were not isolated as the presence of water leads to some hydrolysis products. Protonation of alkylidyne carbonyltungsten complexes **79** with HCl has been employed in the synthesis of a range of alkylidene complexes **80** (Equation (27)) <1998ICA(279)7>. Protonation of calix[4]arene alkylidyne complexes **81** by using pyridine hydrochloride yields **82** (Equation (28)). The analogous *n*-butylidene complex **84** is obtained by a photochemically induced rearrangement of a metallocyclopentane **83** (Equation (29)) <1998JA823, 1999JA2784>.



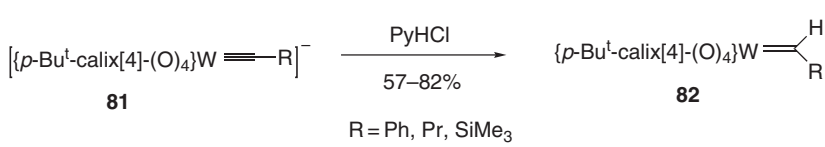
75 **76** (25)



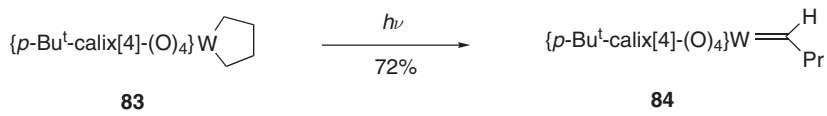
77 **78** (26)



79 **80** (27)



81 **82** (28)



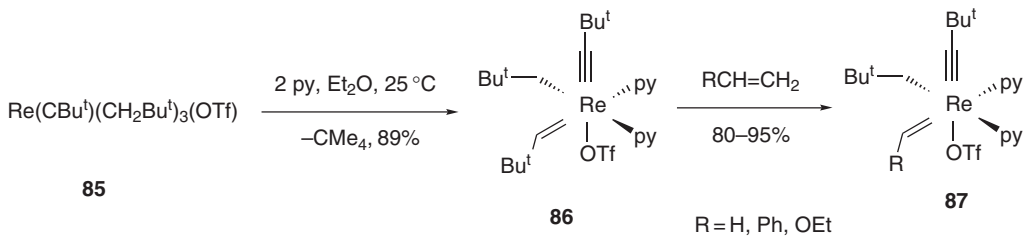
83 **84** (29)

3.15.12 THE C=Mn FUNCTION

No further advances have occurred in this area since the publication of chapter 3.15 in <1995COFGT(3)507>.

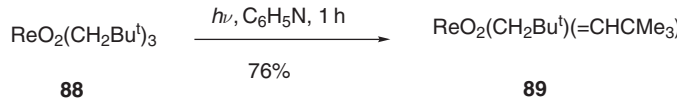
3.15.13 THE C=Re FUNCTION

The reaction of 2 equiv. of pyridine with **85** gives the novel alkyl alkylidene alkylidyne complex **86**. Derivatives **87** of compound **86** are accessible in 80–95% yields via alkene metathesis (Scheme 10) <1995OM1875>. Photolysis of $ReO_2(CH_2Bu^t)$ **88** in pyridine yields the butylidene complex **89** and neopentane (Equation (30)) <1996OM1023>. A cationic rhenium methylidene complex **91** was prepared by α-H-abstraction from **90** using $[Ph_3C][B(3,5\text{-}(CF_3)_2C_6H_3)_4]$ and isolated as a yellow solid in 80% yield (Equation (31)) <2000JOM(616)54>.

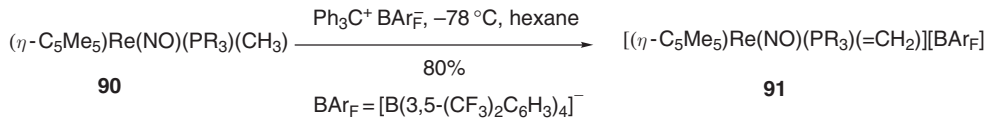


85 **86** **87**

Scheme 10



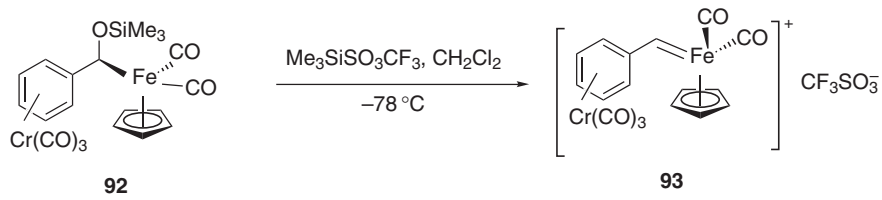
88 **89** (30)



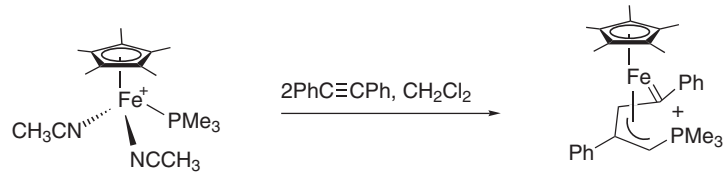
90 **91** (31)

3.15.14 THE C=Fe FUNCTION

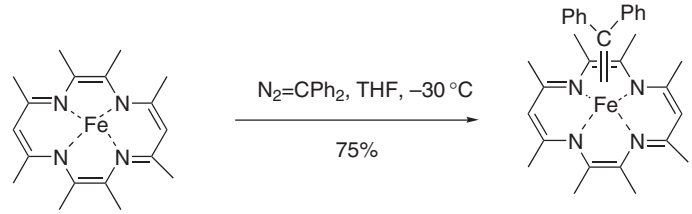
Chiral iron alkylidene complexes **93** are generated by the nucleophilic abstraction of the trimethylsiloxy group from precursor **92** (Equation (32)) <1998TA3971, 2002OM2596>. Treatment of **94** with ethynyl benzene yields the allyl carbene complex **95**. The reaction involves the coupling of two molecules of alkyne, followed by a migration of the phosphine (Equation (33)) <2002OM2578>. A macrocyclic iron carbene complex **97** can be prepared by reacting **96** with diphenyldiazomethane at −30 °C in THF (Equation (34)) <1999JOM(591)45>.



92 93 (32)



94 95 (33)

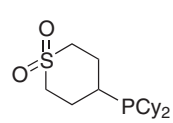
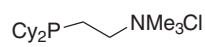


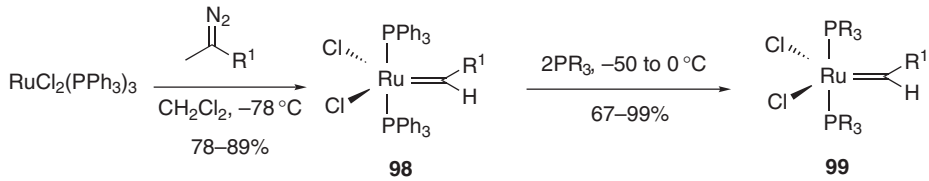
96 97 (34)

3.15.15 THE C═Ru FUNCTION

Ruthenium alkylidene complexes have been widely employed as catalysts for the alkene metathesis. The reaction of $RuCl_2(PPh_3)_3$ with alkyl- and aryldiazoalkanes gives alkylidene complexes **98** in good yields <1995AG(E)2039, 1996JA100>, subsequent phosphine exchange produces further derivatives **99**, including complexes soluble in protic media (Table 3, Scheme 11) <1996OM4317, 2000JA6601, 2002CC1070>. A variety of substituted alkylidene complexes **101** can be synthesized via cross-metathesis between **100** and a 10-fold excess of the appropriate alkene (Table 4 and Equation (35)) <1996JA100, 2002OM2153>. This method allows the introduction of a range of functional groups to the alkylidene moiety. Ethyldiazoacetate <1999OM1961> and dimethyldiazomalonate <1996CL1071> have also been successfully employed as carbene transfer agents in the synthesis of carbene complexes **102** (Equation (36)) and **103** (Equation (37)).

Table 3 Synthesis of ruthenium alkylidene complexes from diazoalkanes and phosphine exchange

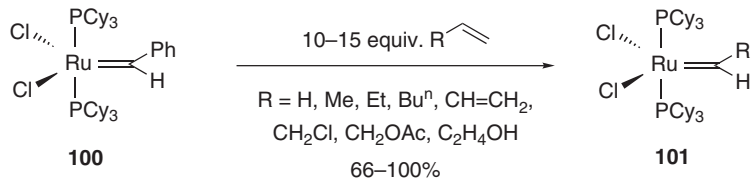
Compound	R^1	PR_3	*Yield* (%)	*References*
98	Me		78	<1996JA100>
	Et		81	<1996JA100>
	Ph		89	<1996JA100>
99	Ph	PCy_3	99	<1996JA100>
	Ph		73	<2002CC1070>
	Ph		67	<1996OM4317>



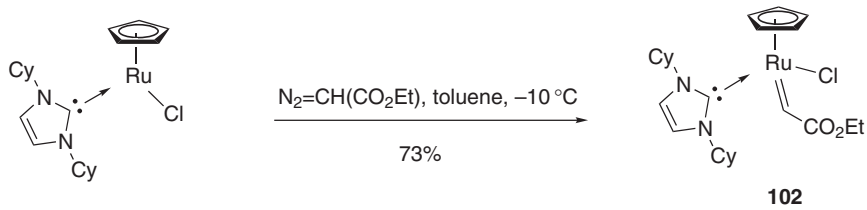
Scheme 11

Table 4 Synthesis of substituted ruthenium alkylidene complexes

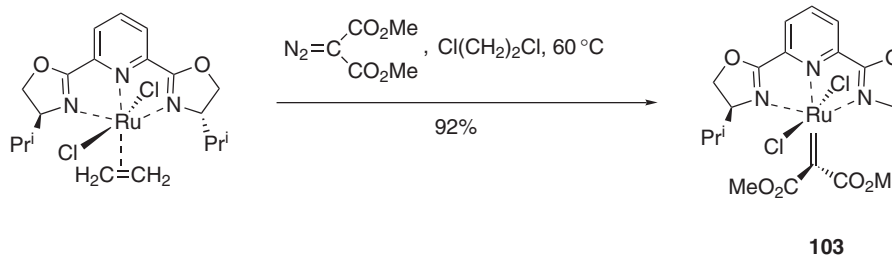
R	*Yield* (%)
$CH{=}CH_2$	95
CH_2Cl	80
C_2H_4OH	76
H	100
Me	98
Bu^n	95
OEt	66
SPh	87
N(carbazole)	77



(35)



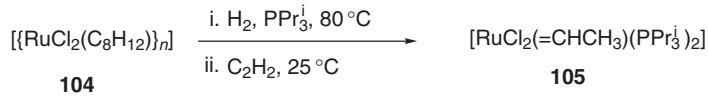
(36)



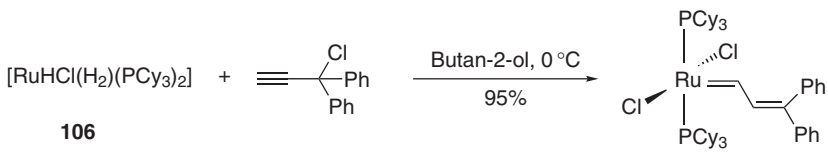
(37)

Werner has developed an alternative route to ruthenium alkylidene complexes starting from **104**; treatment with H_2 and triisopropyl phosphine, followed by the addition of ethyne, affords the ethylidene complex **105** (Equation (38)) <1996OM1960>. A very convenient one-pot procedure for the synthesis of vinyl alkylidene complexes involves the reaction of propargyl chlorides with the hydridochloride complex **106** to give **107** in high yields (Equation (39)) <1997OM3867,

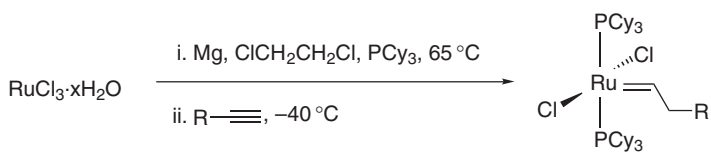
1997OM4001>. Werner has also reported an even more convenient one-pot procedure for the preparation of **108**, which starts from ruthenium trichloride and 1-alkynes (Equation (40)) <1998AG(E)1124>.



104 **105** (38)

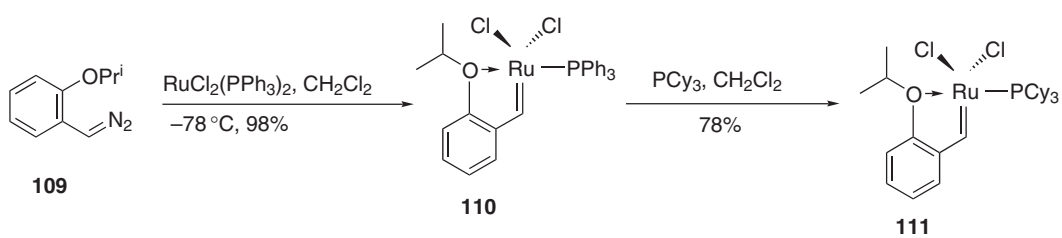


106 **107** (39)



108 (40)

Water- and oxygen-stable ruthenium complexes **110** and **111** with *O*-chelating benzylidene ligands are produced in high yields from alkoxyphenyldiazomethanes **109** (Scheme 12) <1999JA791>.



109 **110** **111**

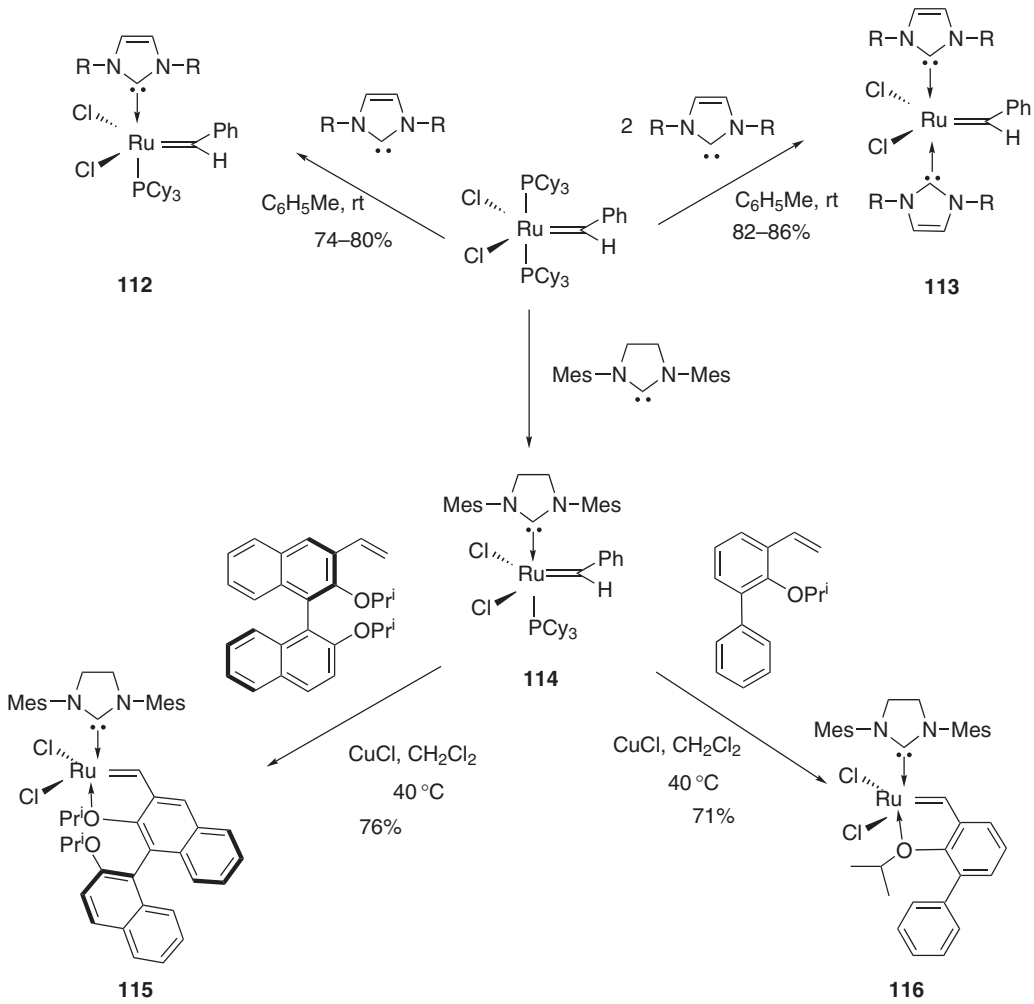
Scheme 12

An important new class of ruthenium alkylidene complexes have been prepared by substituting phosphine ligands with imidazol-2-ylidene ligands to give **112** or **113** <1999JA2674, 1998AG(E)2490, 1999TL2247, 1999JOM(582)382, 2000OM2055> or dihydroimidazol-2-ylidenes <1999OL953, 2000JA8168> to give **114** (Table 5, Scheme 13). Metathesis with alkenes produces further derivatives **115** and **116** <20002AG(E)794, 2002AG(E)2403, 2002AG(E)4038>. Alkylidene complexes **112** and

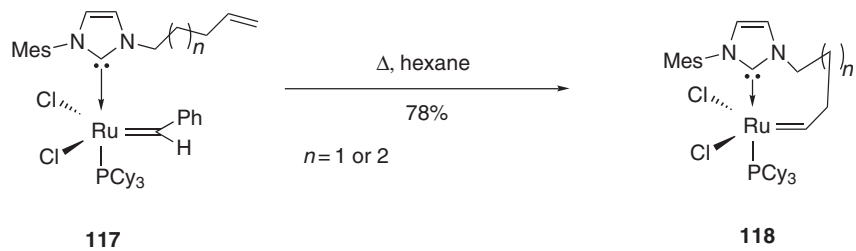
Table 5 Synthesis of *N*-heterocyclic carbene ruthenium alkylidene complexes

Compound	*R*	*Yield* (%)	*References*
112	Cyclohexyl	80	<1999JOM(582)362>
	2-Phenylethyl	74	<1999JOM(582)362>
	Mesityl	78	<1999JOM(582)362>
113	Pr^i	86	<1998AG(E)2490>
	Cyclohexyl	82	<1998AG(E)2490>
	2-Phenylethyl	83	<1998AG(E)2490>
114		80	<1999OL953>
115		76	<2002AG(E)794>
116		71	<2002AG(E)2403>

114 have demonstrated excellent activity toward ring-closing metathesis of alkenes. Complexes **117** have been shown to metathesize their own ligands to form metallacycles **118**, which link the imidazol-2-ylidene and the alkylidene unit (Equation (41)) <2001MI3236>.



Scheme 13

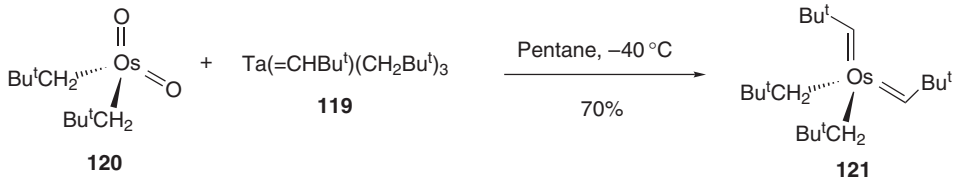


(41)

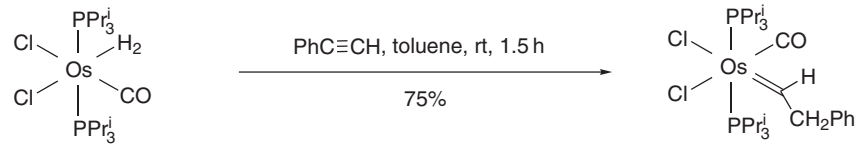
3.15.16 THE C═Os FUNCTION

The osmium carbene complex **121** is prepared via the transfer of a butylidene group from **119** to **120** in pentane at −40 °C (Equation (42)). The *anti*,*anti*-isomer is obtained in 38% yield <1995JA4802>. The reaction of the dihydrogen complex **122** with ethynyl benzene in toluene at room temperature gives the carbene complex **123** in 75% yield (Equation (43)) <1995JA7935>.

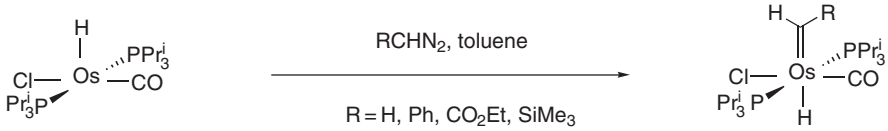
The reaction is thought to proceed via the protonation of an intermediate vinyl complex, formed by the insertion of the alkyne into a metal—hydride bond. The reaction of diazoalkanes with osmium hydride species **124** produces osmium hydridocarbene complexes **125** rather than the expected insertion products (Equation (44)) <1997OM2236>.



120 **119** **121** (42)



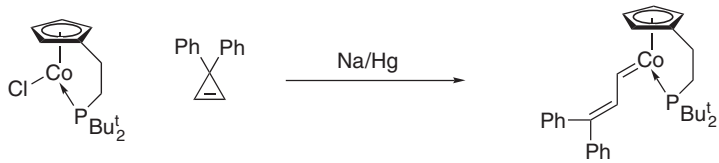
122 **123** (43)



124 **125** (44)

3.15.17 THE C=Co FUNCTION

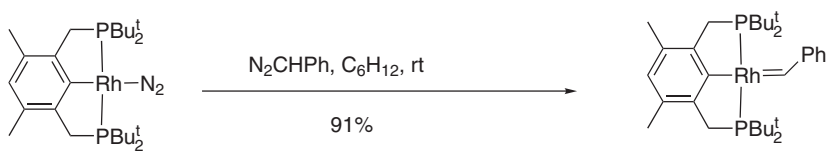
The cobalt alkylidene complex **127** is accessible through the reductive, ring opening of diphenyl cyclopropene in the presence of **126** (Equation (45)) <1998OM893>.



126 **127** (45)

3.15.18 THE C=Rh FUNCTION

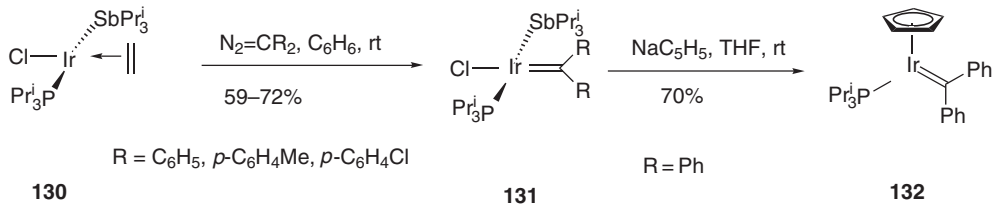
A thermally stable rhodium carbene complex **129** has been prepared in 91% yield by treating a dinitrogen complex **128** with 1 equiv. of phenyldiazomethane in cyclohexane (Equation (46)) <2000OM2061>.



128 **129** (46)

3.15.19 THE C=Ir FUNCTION

Reaction of the iridium complex **130** with 1 equiv. of diaryldiazomethane produced the stable carbene complexes **131** in 60–70% yield. Ligand substitution produced further derivatives **132** (Scheme 14) <2002OM2369>.



Scheme 14

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Biographical sketch

Neil A Williams studied at the University of Southampton, where he obtained a first class B.Sc. (Hons) degree in Chemistry in 1989 and his PhD. in 1993, under the supervision of Professor J. Evans. He then spent 2 years at the National Institute of Materials and Chemical Research in Japan as a Royal Society/Japanese STA Fellow, working in the laboratory of Professor M. Tanaka. In 1995 he returned to the United Kingdom with a Royal Society Return Fellowship, which he took up at the University of Sussex, working with Professor Michael Lappert FRS. After a further period of postdoctoral work at the University of East Anglia and a temporary lecturership at the University of Central Lancashire, he took up his present position as a Senior Lecturer at Kingston University in 1999. His research interests lie in the field of organometallic chemistry and homogeneous catalysis.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 551–571

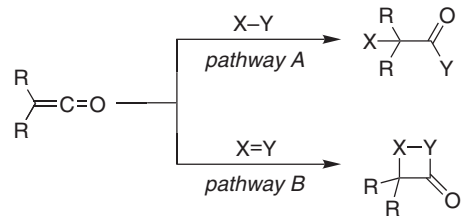
3.16
Ketenes, Their Cumulene Analogs and Their S, Se, and Te Analogs

C. M. TIMPERLEY
Dstl Porton Down, Salisbury, UK

3.16.1 KETENES

Ketenes have the general formula $R_2C{=}C{=}O$, where R can be a variety of substituents such as alkyl, aryl, acyl, hydrogen, halogen, and trialkylsilyl. Their study commenced in 1905 when Staudinger prepared diphenylketene for the first time <1905CB1735>. The value of such compounds was soon acknowledged and many synthetic uses have been developed. Ketenes are usually transient in nature, reacting with electrophiles, free radicals, and nucleophiles ("pathway A"). They are sensitive to moisture and oxygen, enter into cycloadditions and dimerize easily ("pathway B") (Scheme 1). Monoalkylketenes are less stable than dialkylketenes: methylketene dimerizes at room temperature in a few minutes, whereas dimethylketene dimerizes in about an hour.

Historical background and the methods of synthesizing ketenes appear in COFGT (1995). Developments in the synthesis and applications of ketenes during the period 1995–2004 are reviewed here. Ketene chemistry and, to a lesser extent, thioketene chemistry is a fertile area for research and continues to flourish. The generation of ketenes and their reactions are the subject of a book by Tidwell, which summarizes the literature up to 1995 <B-1995MI001>. Examples of the involvement of ketenes in polymer-assisted synthesis are numerous and have been collated <2003AG(E)2340>.

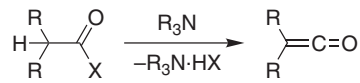


Scheme 1

An exciting area has been the use of ketenes in stereoselective transformations, new methods of which have been developed since 1960. Asymmetric synthesis using ketenes continues to be important and has been reviewed <2003T3545>. Throughout the text, schemes have been included to illustrate the diversity of ketene chemistry, with emphasis given to modern trends which include not only polymer-assisted and asymmetric synthesis, but also the inspired use of "old" techniques to generate bioactive substances (e.g., β-lactam antibiotics) and fluorinated products. The three major routes to ketenes are dehydrohalogenation of acid halides, dehalogenation of haloacyl halides, and Wolff rearrangement of α-diazocarbonyl compounds. A recent review of the latter, covering the literature of the last century <2002EJO2193>, has precluded a detailed coverage here. Other routes from carbonyl species (carboxylic acids, esters, anhydrides, amides, and ketones), derivatives of Meldrum's acid, alkynes, heterocyclic materials, and chromium carbene complexes, update entries in COFGT (1995), but often require specialized techniques (e.g., FVP) and are generally less useful for the synthesis of products in multigram quantities.

3.16.1.1 From Acyl Halides

Treatment of acyl halides with tertiary amines is one of the most versatile approaches to the preparation of ketenes (Equation (1)). The scope is broad and most acyl halides having a hydrogen atom enter into reaction, but if one of the R's is a hydrogen atom, only a ketene dimer is isolated. Although a variety of acyl halides can be used, the acyl chloride is chosen due to its good reactivity profile and ease of synthesis. The ketene is usually generated *in situ* and trapped immediately with a nucleophile, a free radical, or an unsaturated species already present in the reaction mixture. The rate of reaction must be faster than, or at least competitive with, the rate of ketene dimerization.



(1)

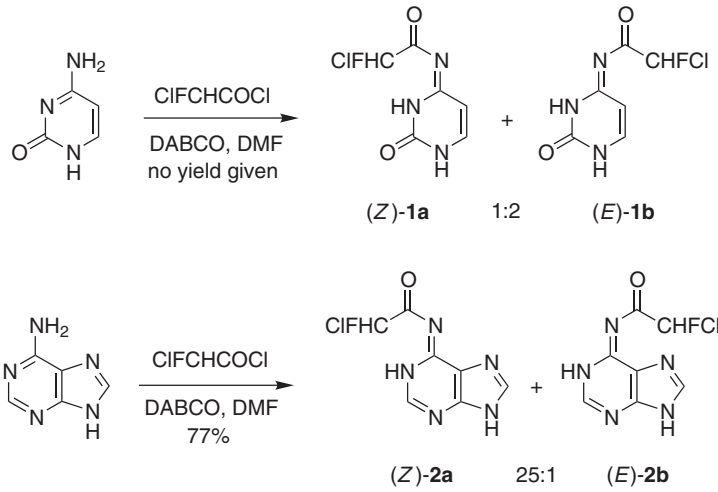
where X = F, Cl, Br, I

Reaction of chlorofluoroketene generated from chlorofluoroacetyl chloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) with nucleic acid components exemplifies this approach <1998CRT464>. Addition of the ketene occurred at the N^4-position of cytosine and at the N^6-position of adenine to yield diastereoisomers (**1a**–**1b**) and (**2a**–**2b**), respectively (Scheme 2). The products are useful for studying the toxicity of compounds that can be metabolized to ketenes in the body.

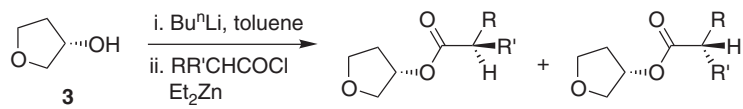
Conversion of an acyl chloride into a ketene and reaction with a chiral alcohol is one of the oldest stereoselective transformations <1963CB854, 1966CB151> and continues to be of interest to this day (Scheme 3). Reaction of the lithium salt of (*S*)-(+)-3-hydroxytetrahydrofuran **3** with ketenes produced diastereomeric esters (**4a**–**4b**) with high diastereoselectivity <2001TL5985>. This type of chemistry has also been transposed to a solid support. Supported alcohol **5**, when treated with an arylmethylketene, gives ester **6** which was saponified to generate the chiral acid **7** in excellent yield and good enantiomeric purity (ee >80%). The supported alcohol could be recycled without loss of efficacy <2001JOC5859>.

The most commonly used base for dehydrohalogenation is triethylamine <2001JOC5832>. Other tertiary amines such as *N*-methylmorpholine have been used successfully <1999JOC1065>. In cases where the starting material contains two acyl halide groups, treatment with 2 M equiv. of a tertiary amine can give rise to bisketenes (Scheme 4). For example, dehydrochlorination of bis(acyl chloride) **8** with 1,8-bis(dimethylamino)naphthalene and triethylamine led to immediate formation of an infrared band at 2115 cm^{-1} indicative of 1,2-bis(ketenyl)benzene **9** <2001RCB2130>. Addition of an excess of the stable radical tetramethylpiperidin-1-yloxyl (TEMPO, TO$^{\bullet}$) gave the tetraadduct **10** as a mixture

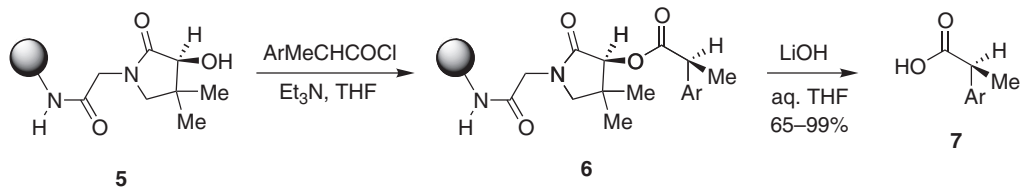
of isomers. The bisketene (*E*)-O═C═CH(CH═CH)CH═C═O has also been generated from suberyl chloride and trapped with TEMPO to give the 1,6-bis-addition product $TO_2C—CH_2(CH═CH)CH_2—CO_2T$ <2001OL4095>. Other examples of trapping ketenes with TEMPO have been reported <1999JA3939, 2001JOC5759, 2001JOC2611>. The chemistry of biseketenes, particularly those stabilized by silyl substituents, has been reviewed <1996CJC457>.



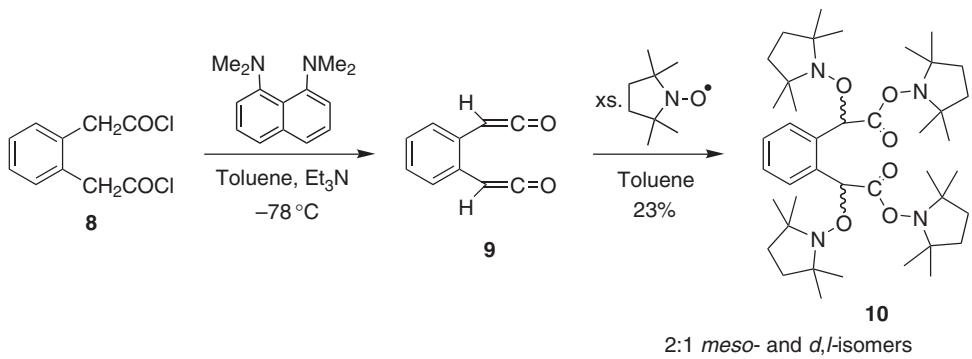
Scheme 2



R	*R'*	(*SS*)-**4a**	(*SR*)-**4b**	*Yield* (%)
Ph	Me	98	2	78
Ph	Et	94	6	72
Me	Br	90	10	80



Scheme 3



Scheme 4

Ketenes generated *in situ* from acid chlorides also react with various π-donors. The [2 + 2]-cycloaddition of the ketene with an imine to form a β-lactam is known as the Staudinger reaction and is of great importance in the construction of many antibiotics. It usually gives four-membered rings with *cis*-stereochemistry (Scheme 5) as illustrated by the conversion of benzodiazepine **11** into β-lactams (**12a**–**12c**) <2001HAC636>. Other examples of this transformation have been published <1997JHC823, 2001JHC561>. The use of imines attached to polymer supports to generate β-lactams in good yields with excellent *cis*-stereochemistry is possible. This strategy has permitted efficient asymmetric syntheses of β-lactams from chiral acid chlorides, an approach useful for establishing combinatorial libraries of potential antibiotics and enzyme inhibitors <2002TA905>.

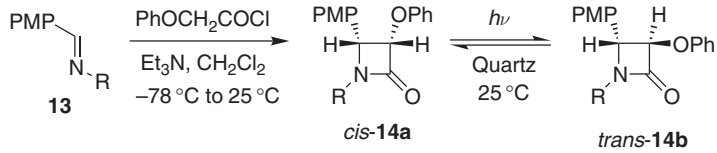
11	R = *o*-ClC_6H_4	18%	**12a**
	m-ClC_6H_4	40%	**12b**
	p-ClC_6H_4	32%	**12c**

Scheme 5

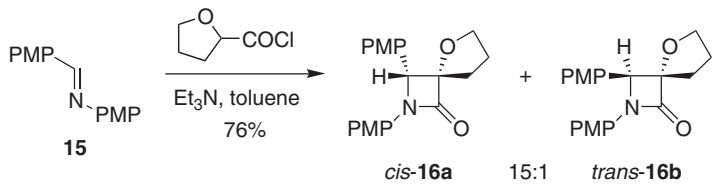
As the most important biologically active β-lactams contain a *trans*-2-azetidinone ring, routes to them often have to include an epimerization step. Base-induced isomerization through protonation then reprotonation at C-3 is commonly used, but the high concentration of a base and long reaction time required sometimes result in degradation <1995TL2555>. Photoisomerization is a milder option and reaction of imines **13** and various acid chlorides in the presence of triethylamine gave exclusively *cis*-β-lactams **14a** which on irradiation with a 125 W medium-pressure mercury lamp cleanly isomerized to the *trans*-isomers **14b** (Scheme 6). Eventually a photostationary state was attained, the degree and ease of isomerization depending on the substituent on the nitrogen atom <2001H511>. The *p*-methoxyphenyl (PMP) protecting group is easily removed by treatment with cerium ammonium nitrate in aqueous acetonitrile at room temperature. An imine **15** with two of these groups reacted with the unsymmetrical ketene generated from 2-tetrahydrofuroyl chloride to give a mixture of isomers (**16a**–**16b**). In this case, removal of the protecting group on nitrogen and sulfonation with pyridine–sulfur trioxide complex gave N-SO_3H derivatives which are interesting analogs of the antibiotic monobactam <2002JCS(P1)571>. Another example of this type of approach to β-lactams is the reaction of the chiral imine **17** derived from D-(+)-glucose with phenoxyketene which gave a single diastereoisomer **18** which could be processed to give a range of compounds of medicinal potential <2003T2309>. Other studies have progressed along similar lines <1998T11501, 1999TL8495, 1997CC233> and have produced useful products such as mammalian synthase inhibitors <2002BMC2641>.

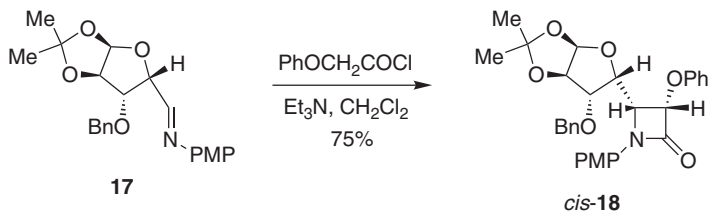
N,*N*-Dialkylhydrazones also give β-lactam derivatives after reaction with ketenes <2002AG(E)831>. Although the Staudinger reaction can proceed without catalysis, recent studies prove that nucleophilic catalysts can provide excellent levels of enantioselectivity <2003T3545>. Lectka and co-workers <2001OL2049, 2002OL627, 2002JA6626, 2003JOC5819> have demonstrated that cinchona alkaloid catalysts are useful for this purpose.

The Staudinger reaction can be used as the starting point for the synthesis of more elaborate antibiotics <2002OL749>. Treatment of acetylenic imine **19** with benzyloxyketene gave β-lactam **20** as a single diastereoisomer (Scheme 7). Ring opening with methyllithium gave ketone **21** which underwent Lacke reduction to give the single diastereoisomer **22**. Deprotection of the silyl group and exchange of the PMP group for the less basic carbobenzyloxy protecting group gave species **23** which cycloisomerized on photolysis in the presence of tungsten hexacarbonyl. The product **24** after hydroxylation of the double bond and deprotection is a structural component of vancomycin, an antibiotic generally considered to be the last line of defence for many severe bacterial infections.

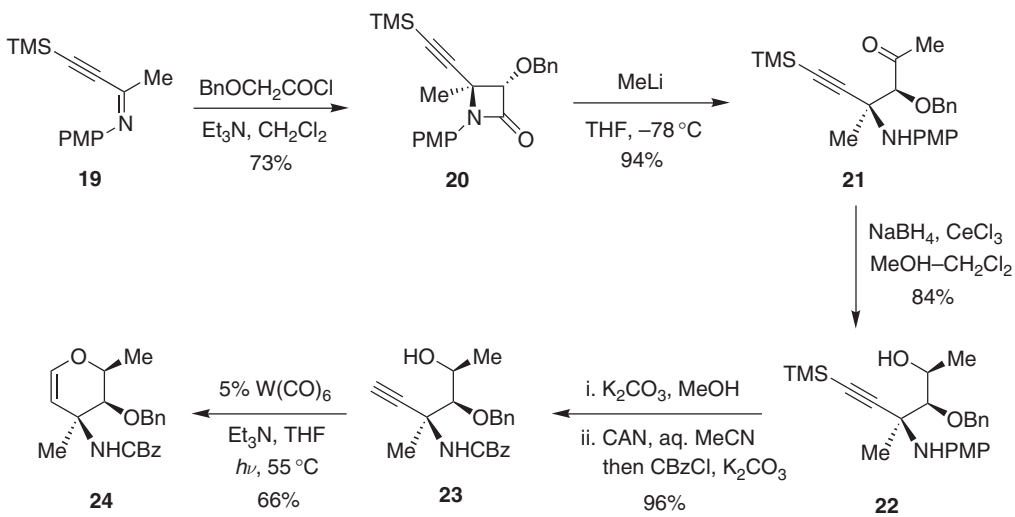


R	*Yield* (%)	*Irradiation time*	*cis-trans ratio*
Me	76	30 min	1:1
Bn	80	45 min	1:1
Allyl	68	150 min	6:1





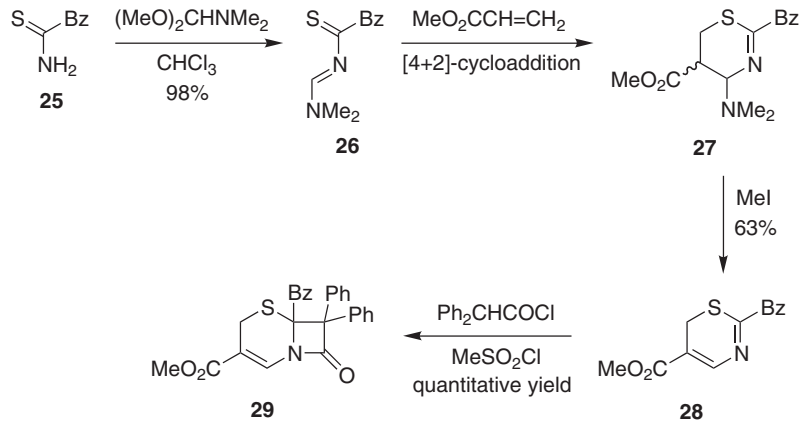
Scheme 6



Scheme 7

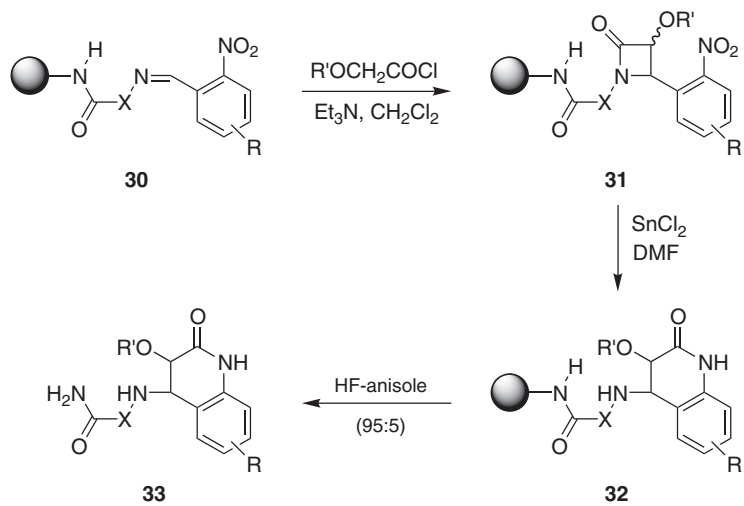
[2 + 2]-Cycloadditions can be used to make cephalosporins, another class of important antibiotics (Scheme 8). Condensation of benzoylthioformamide **25** with dimethyl formamide dimethyl acetal gave thia-azobutadiene **26** that participated in a Diels–Alder reaction to furnish heterocycle **27**. Elimination of dimethylamine gave precursor **28** which was transformed into the desired

cephem **29** by generating diphenylketene *in situ* and subsequent [2 + 2]-cycloaddition <1997PSS147>. Interestingly, a lower yield of the cephem was obtained when the intermediate was treated with a solution of diphenylketene in dichloromethane, illustrating the advantage of the *in situ* method.



Scheme 8

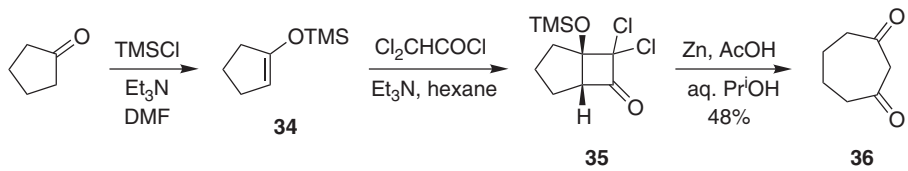
β-Lactams are not only interesting as final targets but are useful intermediates for the synthesis of other heterocycles (Scheme 9). Imines tethered to 4-methylbenzhydrylamine hydrochloride resin **30** reacted with alkoxyketenes to give β-lactams **31**. Treatment with tin(II) chloride resulted in ring expansion to give intermediates **32** which on deprotection gave dihydroquinolinones **33** in 68–100% yield and in greater than 85% purity <1997TL3349>.



X = arylene or alkanediyl; R = *O*-alkyl or halogen; R' = acetyl or aryl

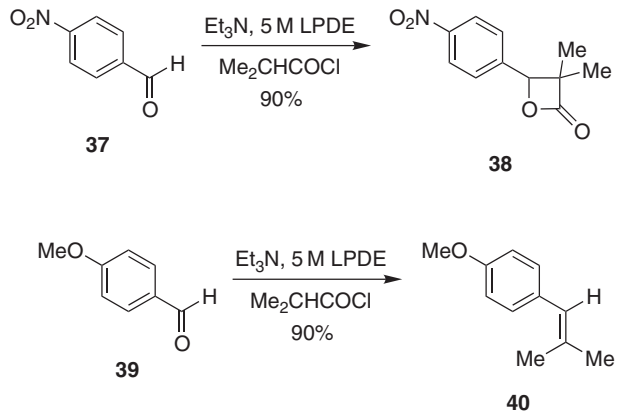
Scheme 9

Ketenes generated *in situ* from acid chlorides can be trapped with alkenyl or alkynyl compounds to give many useful derivatives arising from [2 + 2]-cycloaddition. An ingenious three-step synthesis of cycloheptane-1,3-dione in multikilogram quantities starts with cycloaddition of the silyl enol ether **34** with dichloroketene (Scheme 10) <1998OPRD379>. The cycloadduct **35** is treated with zinc dust and acetic acid to give the target compound **36** in an overall yield of 80%.



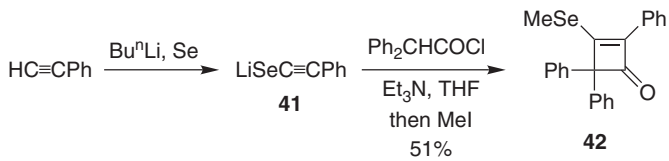
Scheme 10

The generation of ketenes and trapping with aromatic aldehydes can occur through two pathways depending on the substituents on the benzene ring and their influence on the electronic properties of the CHO group, as illustrated by the reaction of dimethylketene with 4-substituted benzaldehydes in the presence of triethylamine and lithium perchlorate-diethyl ether (LPDE) <1996TL7143>. With an electron-withdrawing group as in 4-nitrobenzaldehyde **37**, cycloaddition occurs to give the expected 2-oxetanone **38** (Scheme 11). However, with an electron-donating group as in 4-methoxybenzaldehyde **39**, the reaction goes further, the 2-oxetanone decarboxylating to yield the alkene **40**.



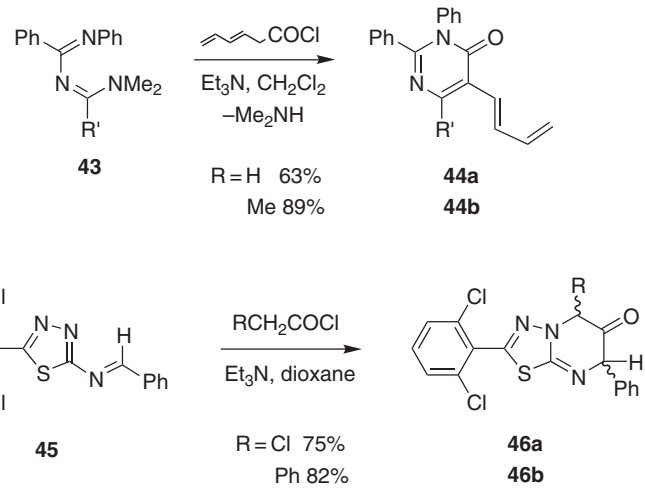
Scheme 11

[2 + 2]-Cycloadditions not only occur for substrates with double bonds, but also take place with reagents with triple bonds such as acetylenic species. The first reaction of a ketene with an alkyneselenolate was reported recently <2002SL805>. Lithiated selenoalkyne **41** reacted with diphenylketene to give cyclobutenone **42** in modest yield (Scheme 12).



Scheme 12

When the substrate has diene character, the ketene may enter into a [4 + 2]-cycloaddition of the Diels–Alder type (Scheme 13), two examples of which include the conversion of 1,3-diazabut-1,3-diene **43** to pyrimidones (**44a**–**44b**) <2002JCS(P1)774> and 1,3,4-thiadiazole **45** to thiadiazolo[3,2-*a*]pyrimidin-6-ones (**46a**–**46b**) <1999JCR(S)36>. It has also been shown that chiral 2-alkenyloxazolines and 2-alkenylthiazolines react with diphenylketene generated *in situ* to give hetero-Diels–Alder adducts with complete diastereocontrol <1999SL1379>.



Scheme 13

The introduction of fluorine into organic molecules often results in dramatic modification of their chemical and physical properties as well as their biological activity. The search for practical methods for obtaining fluorinated compounds has been an area of intense activity in the 1990s and has been extended to the synthesis of fluoroketenes and their transformations. These include addition reactions with nucleophiles under various conditions and cycloaddition reactions with unsaturated compounds such as dialkylcyanamides, enamines, and vinyl ethers (Scheme 14). For example, dehydrohalogenation of hexadecanoyl chloride **47** with pyridine in the presence of trifluoroacetic anhydride gave ketene **48** which after hydrolysis gave the trifluoromethyl ketone **49** or after treatment with nitrous acid, the alkyl nitrile **50**. The latter constitutes a method to shorten an alkyl chain by a methylene unit <1995T2573>. Ketene **48** was also used to construct trifluoromethylated heterocycles <1995T2585>. Cycloaddition occurred with dimethylcyanamide to give heterocycle **51** and 1-morpholino-1-cyclohexene to give cycloadduct **52** in addition to amide **53**. Similarly, 1-(3,4-dihydro-2-naphthyl) pyrrolidine gave cycloadduct **54** and ethyl vinyl ether the pyrone **55** which eliminated ethanol yielding product **56**.

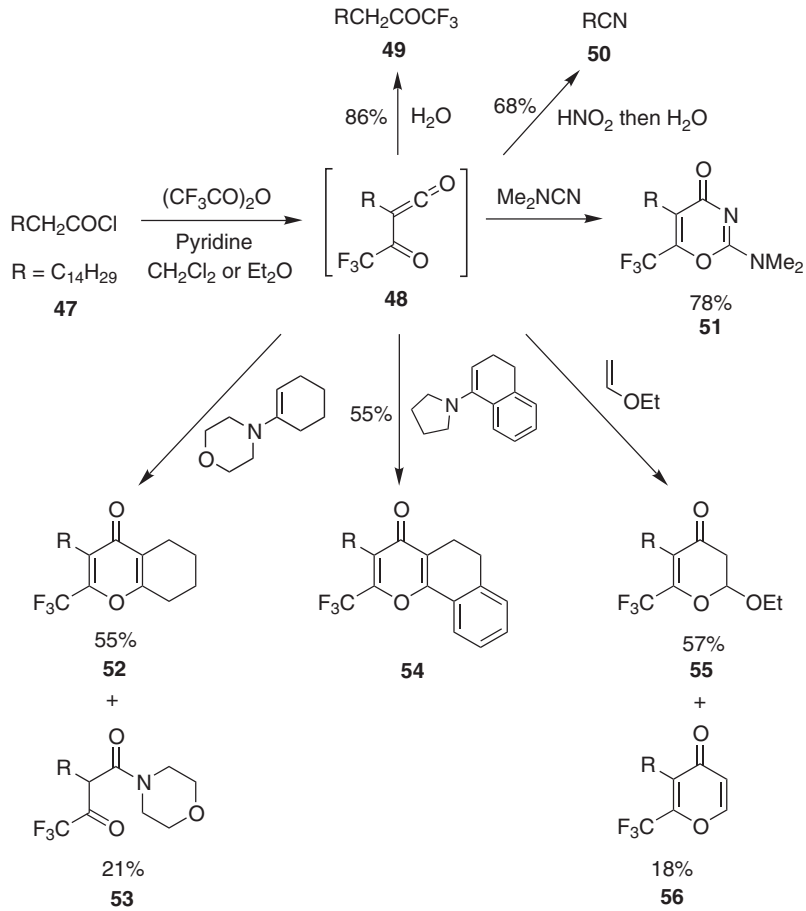
Ketenes generated *in situ* from acyl chlorides and dry potassium carbonate in dichloromethane can be treated with allylamines to give Claisen rearrangement products <1995JOC3773>. A typical outcome is shown in Scheme 15. Under such conditions, in the presence of trimethylaluminum, compound **57** was converted into a mixture of *syn*- and *anti*-products **58a** and **58b**.

Ketenes generated from acyl chlorides also react with stabilized Wittig reagents. This is a well-known and efficient method for the generation of allenes. Recent trends in such research involve the use of Wittig reagents attached to a rigid framework or polymer support (Scheme 16). Treatment of phosphorus ylide **59** with ketenes led to asymmetric induction and selective synthesis of allenes (**60a–60b**) with axial chirality corresponding to the (*S*)-configuration <2003TL6409>. Similarly, treatment of a Wittig reagent on a soluble support **61** with ketenes gave allenes **62** which reacted with amines to give enamines **63** <1999JCO458>. Other examples of the synthesis of chiral allenes from ketenes appear elsewhere <2002S579>.

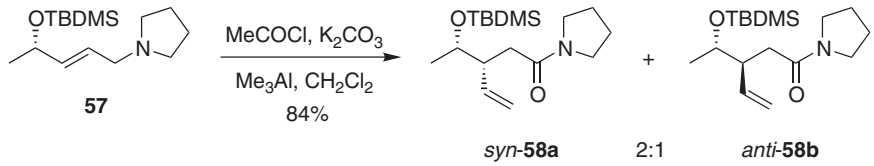
Besides chemical methods, physical methods such as laser irradiation can be used to generate haloketenes from α-halogenated acetyl chlorides (Scheme 17). Irradiation of fluoroacetyl chloride **64** in a static cell gave the short-lived molecule fluoroketene **65** whose IR spectrum was recorded and compared to spectra obtained from other haloketenes prepared similarly <2002JCP5252>.

3.16.1.2 From 2-Haloacyl Halides

The first ketene to be discovered, diphenylketene, was made by dehalogenating chlorodiphenylacetyl chloride $Ph_2CClC(O)Cl$ with zinc <1905CB1735>. Organozinc reagents, zinc–copper couples, or



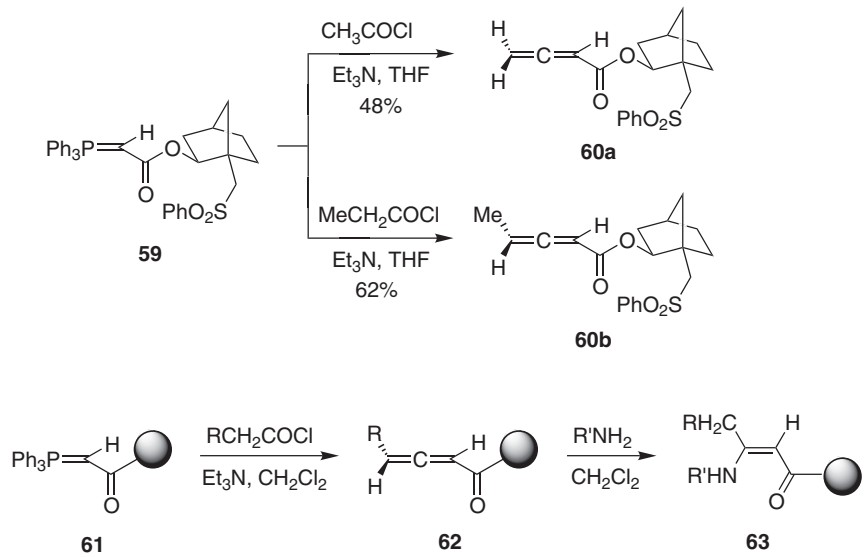
Scheme 14



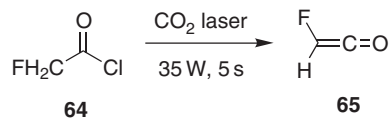
Scheme 15

standard dehalogenating reagents such as triphenylphosphine can also be used (Equation (2)). The reaction generally gives good results when the two R groups are alkyl or aryl, but not when either one is a hydrogen atom.

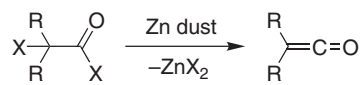
Zinc dust has been used to generate ketenes for addition across the termini of 1,5-dienes <1995T3435> and for trapping experiments with bis-silylalkynes (Scheme 18). Reaction of alkyne **66** with dichloroketene gave cycloadduct **67** which on exposure to silver(II) trifluoroacetate gave squaric acid derivative **68** <1996JOC6227>. Thermolysis of this gave bisketene **69**, one of a family of bis-silyl 1,2-bisketenes that have been studied extensively <1995PAC777, 1995CJC1818, 1997JOC18, 1997JA12125, 1998JOC8636>. The bis(trimethylsilyl) analog of species **69** has been prepared from the corresponding four-membered precursor <1995JCS(P2)847>. Other derivatives of squaric acid, such as methylsquarate, have been used as precursors to enyne-ketenes that can be used to make substituted 1,4-benzoquinones via radical cyclization <1996CRV207, 1997JOC8841>.



Scheme 16



Scheme 17



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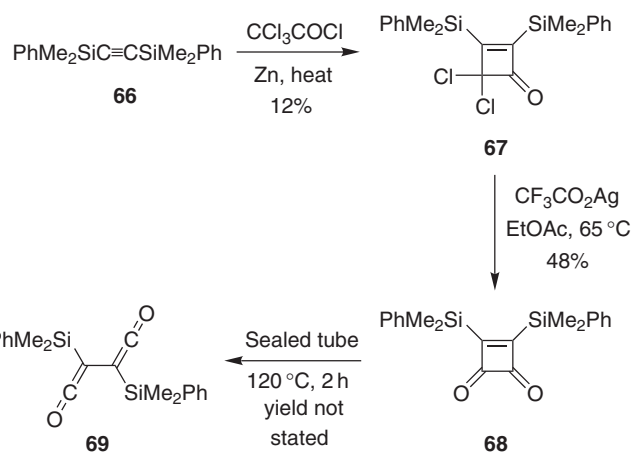
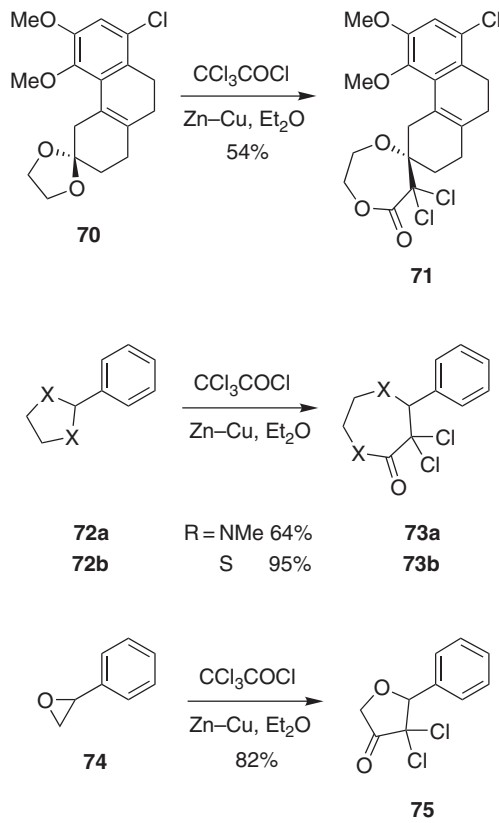


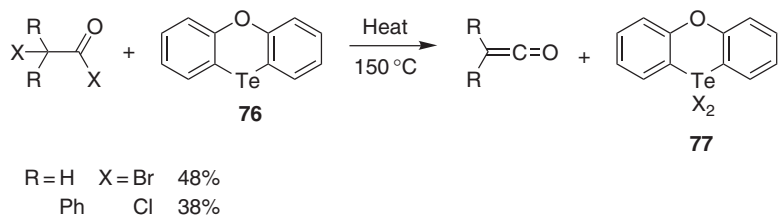
Scheme 18

A zinc–copper couple has been employed for the synthesis of dichloroketene which can be inserted into various ring systems (Scheme 19). Thus, morphine derivative **70** could be converted into dichlorodioxepanone **71**, compounds (**72a–72b**) into heptacycles (**73a–73b**), and styrene oxide **74** into γ-butyrolactone **75** <1998S653>. A zinc–copper couple has also been used in the Staudinger reaction to construct β-lactams from ketenes derived from 2-haloacyl chlorides <1995CC1735>.



Scheme 19

Reagents capable of abstracting two halogen atoms from 2-haloacyl halides and undergoing valency expansion offer a less-explored option for making ketenes (Scheme 20). Heating 2-haloacyl bromides or -chlorides with phenoxatellurine **76** gave ketenes which could be trapped with aniline; dichlorophenoxatellurine **77** was the by-product <1997MI-143>.

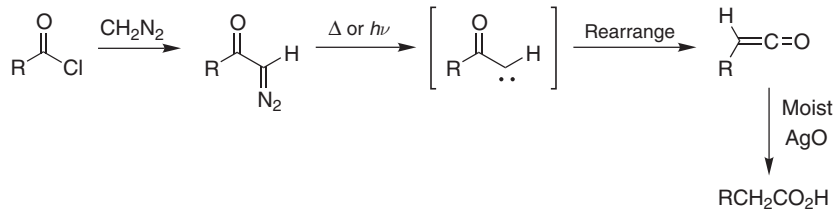


Scheme 20

3.16.1.3 From α-Diazocarbonyl Compounds

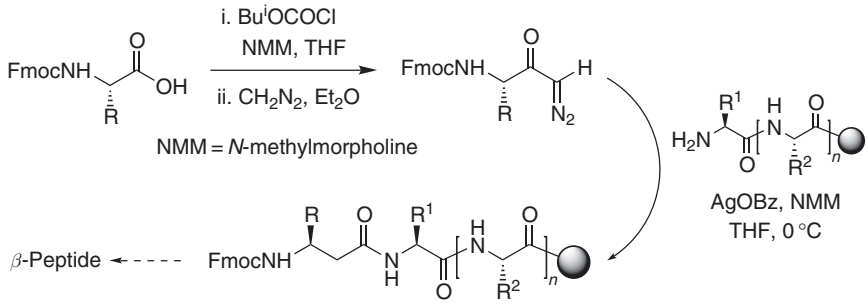
In the Arndt–Eistert synthesis an acyl halide is converted into a carboxylic acid with an extra carbon atom by treatment with diazomethane (Equation (3)). The diazoketone formed rearranges on exposure to moist silver oxide or silver benzoate and triethylamine. If an alcohol is used instead of water, the ester is isolated. Similarly, ammonia gives the amide. The rearrangement of a diazoketone to ketene is called the Wolff rearrangement. Other catalysts are sometimes used (e.g., colloidal platinum or copper) but occasionally the diazoketone is simply heated or photolyzed in the presence of water, an alcohol, or ammonia without catalyst. Photolysis often gives better results than silver catalysis. The R group may be alkyl or aryl and may contain many functional groups including unsaturation but not groups acidic enough to react with CH_2N_2 or diazoketones. Sometimes the reaction is performed with other diazoalkanes $R'CHN_2$ to give acids of

general formula $RR'CHCO_2H$. Developments in the Wolff rearrangement over the last century up to 2002 have been reviewed by Kirmse <2002EJO2193> and will not be duplicated here. Only very recent examples are discussed to illustrate the scope of this particular transformation. Diastereoselective construction of small building blocks through [2 + 2]-cycloadditions involving ketenes, including Arndt–Eistert chemistry, has also been reviewed <1996MI-2463>.



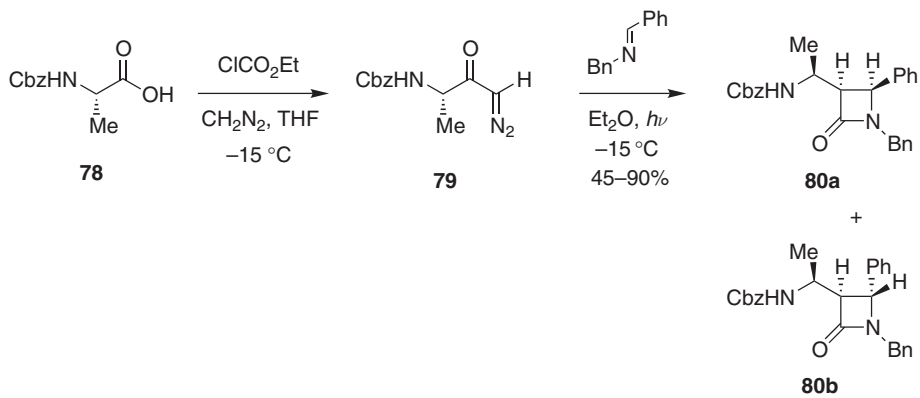
(3)

Arndt–Eistert homologation has been used to make an enantiopure β-amino acids which when incorporated into peptides (so-called β-peptides) impart unusual properties, such as a number of very stable secondary structures <1997HCA173>. β-Peptides can be prepared by standard coupling methods from β-amino acids. Alternatively, an *N*-protected amino acid can be converted into the diazocarbonyl species, then treated with a *C*-protected peptide on a solid support (Wang resin or 2-chlorotrityl resin) in the presence of silver benzoate <1997TL6145, 1998HCA187>. Several β-amino acids can be incorporated into a peptide this way (Scheme 21).



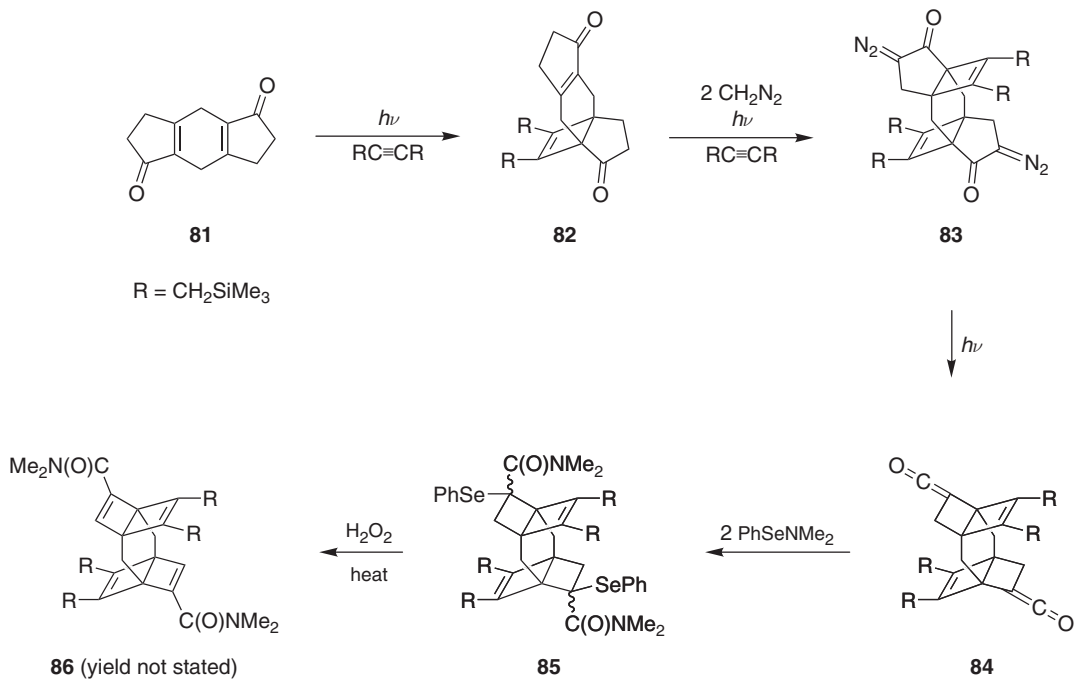
Scheme 21

The Wolff rearrangement can also be used to make β-lactams (Scheme 22). Thus, treatment of *N*-protected alanine **78** with ethyl chloroformate then diazomethane furnished diazoketone **79**. Irradiation of this in the presence of *N*-benzylphenylimine gave two of the four possible diastereoisomers (**80a–80b**). Reactions with other amino acid derivatives showed that the diastereoselectivity was predominantly influenced by the bulkiness of the amino acid <1997JOC5873>. The transformation of diazoketones derived from α-amino acids to ketenes that, in turn, combined with imines to afford β-lactams, has been realized under the action of microwave irradiation <2001OL1849>.



Scheme 22

An ingenious route to kinetically stabilized [1.1]paracyclophanes has been developed that relies on photochemical generation of a ketene intermediate (Scheme 23). Irradiation of a mixture of bisketone **81** and a silylated alkyne gave tetracycle **82** that progressed through pentacycle **83** to the bisketene **84**. Treatment of this with a selenylamine gave the selenated carboxamide **85**, which after oxidation and elimination gave the target compound **86**, which could be converted into the [1.1]paracyclophane on irradiation with a high-pressure mercury lamp <1998AG(E)817>.



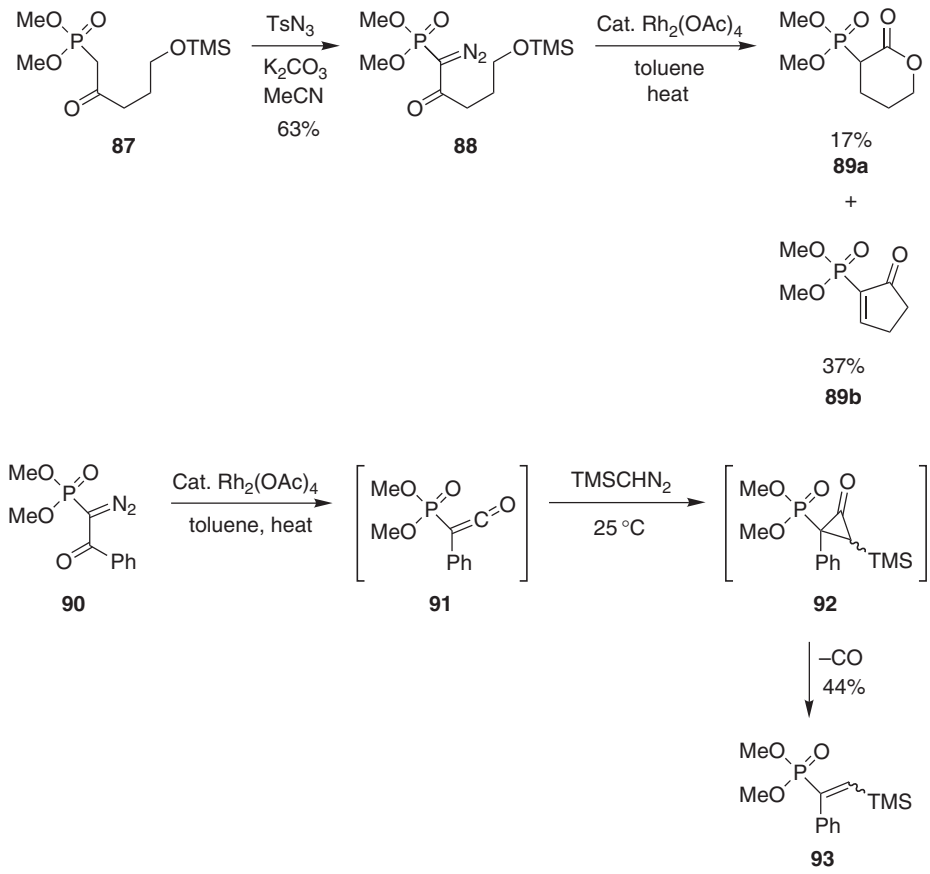
81 **82** **83** **84** **85** **86** (yield not stated)

Scheme 23

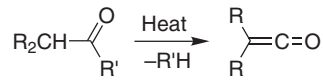
Some recent publications describe the synthesis of several interesting dimethylalkylphosphonates via diazoketone intermediates (Scheme 24). Diazotization of phosphonate **87** with tosylazide in the presence of potassium carbonate gave diazo-species **88**. Slow addition of this to rhodium(II) acetate catalyst in refluxing toluene led to rapid evolution of nitrogen. Aqueous work-up gave phosphoryl lactone **89a** and cyclopentanone **89b**. The former resulted from initial Wolff rearrangement of the intermediate metallocene (—C═N_2 → —C═RhL_n) to the ketene, followed by cyclization due to the attack of the oxygen atom. Hydrolysis during aqueous work-up resulted in loss of the silyl group. Other interesting phosphonylated lactones were prepared using the same methodology <2001TL8455>. Rhodium-catalyzed Wolff rearrangement of diazo-compound **90** gave ketene **91** which under the action of trimethylsilyldiazomethane gave the presumed cyclopropanone **92** which, after loss of carbon monoxide, gave the silylated styrene **93** in modest yield <1999TL847>. Diazomethane instead of trimethylsilyldiazomethane, and the phenyl sulfonyl group instead of the phosphonate group, were tolerated under these conditions and led to the expected products.

3.16.1.4 From Other Carbonyl Species

Ketenes can be made from a variety of carbonyl-containing species. These include carboxylic acids, esters, anhydrides, amides, and ketones (Equation (4)). Various examples where these types of starting material have been used to prepare ketenes are now discussed. Earlier literature is covered in the corresponding chapter in COFGT (1995).



Scheme 24

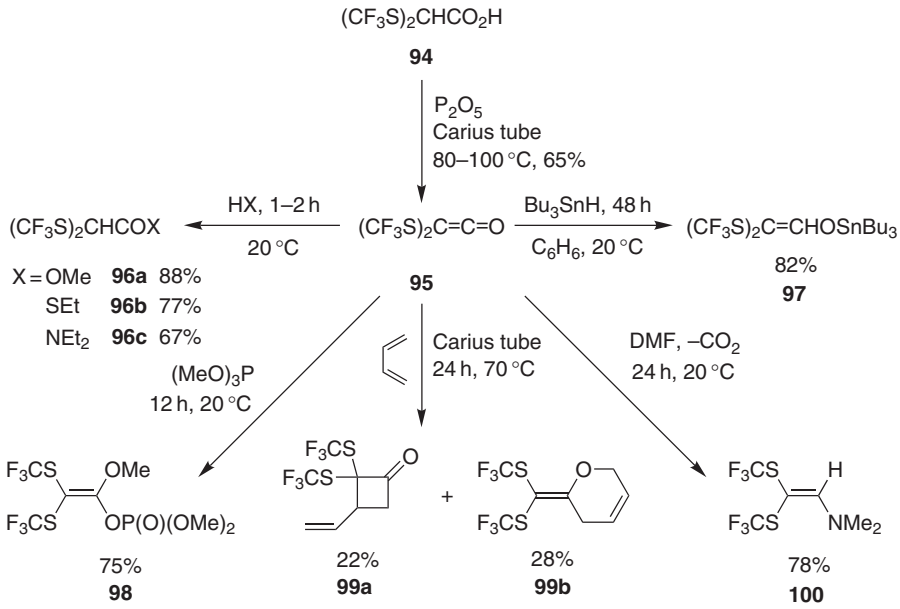


where R' = OH, OR, OC(O)R, NR_2, alkyl (4)

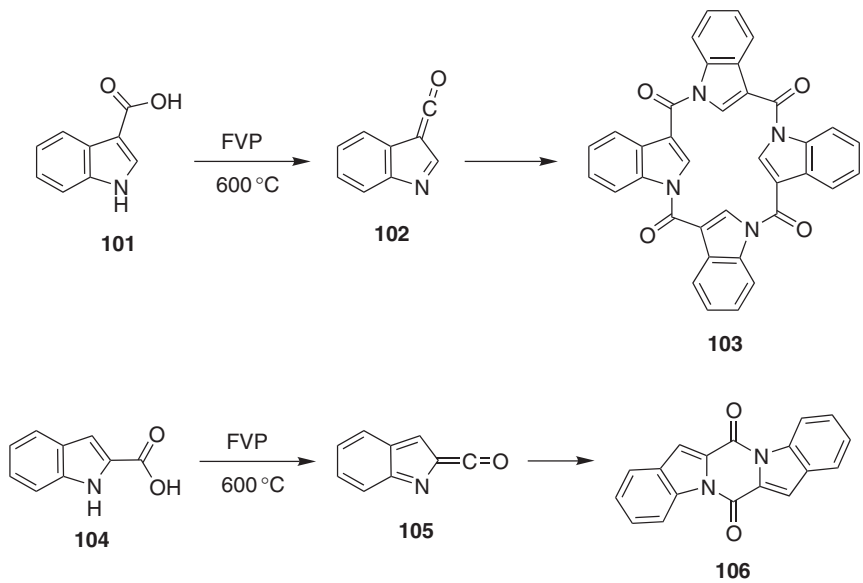
3.16.1.4.1 From acids

Ketenes can be made by dehydration of carboxylic acids or their esters with dehydrating agents such as phosphorus pentoxide <1995MI-529>. Heating acetic acid derivative **94** with phosphorus pentoxide in a sealed tube gave bis(trifluoromethylthio)ketene **95** as a distillable liquid (Scheme 25) <1989JFC329>. Its chemistry, like that of other fluorinated ketenes <1967FCR107>, is fascinating and allows construction of rare molecules. It adds to alcohols, thiols, and amines to give carboxylic acid derivatives (**96a–96c**), to tributyltin hydride to give stannyl product **97**, and to trimethylphosphate to give phosphonate **98** <1998JFC9>. It undergoes [2 + 2]- and [2 + 4]-addition to butadiene, giving adducts **99a** and **99b** in equal amounts, and reacts with dimethylformamide to give enamine **100**.

Heating carboxylic acids can sometimes results in dehydration and ketene formation (Scheme 26). FVP of indole carboxylic acids produces ketenes that self-assemble to give curious heterocyclic compounds <1996JA3852>. The 2-carboxylic acid **101** dehydrates to give ketene **102**, four molecules of which in an argon matrix at 12 K spontaneously react to yield tetramer **103**. This compound has also been made by Wolff rearrangement and was isolated and fully characterized <1995TL3913>. Thermolysis of the 3-carboxylic acid **104** gave small amounts of ketene **105** which dimerized to give the propeller-shaped heterocycle **106** <1996JOC8125, 1997PAC847>.



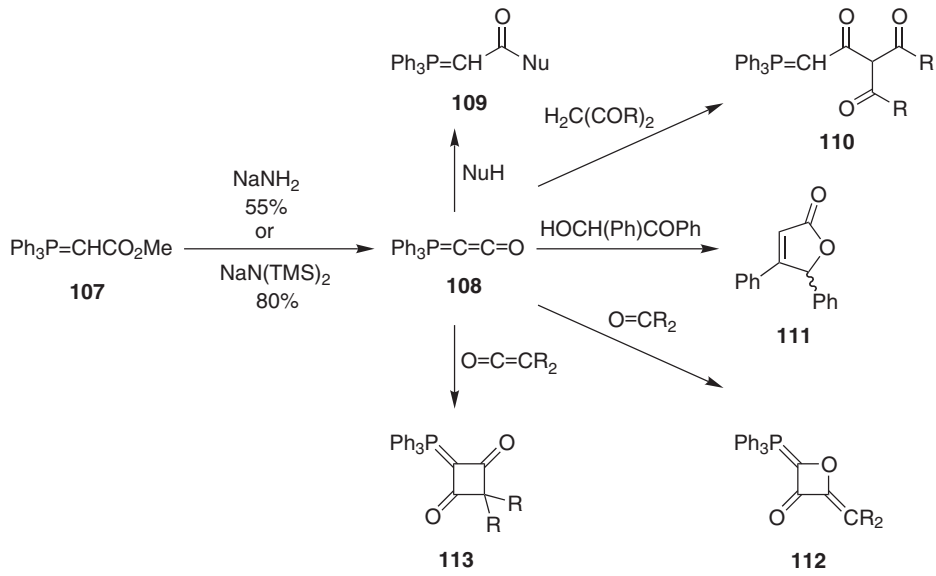
Scheme 25



Scheme 26

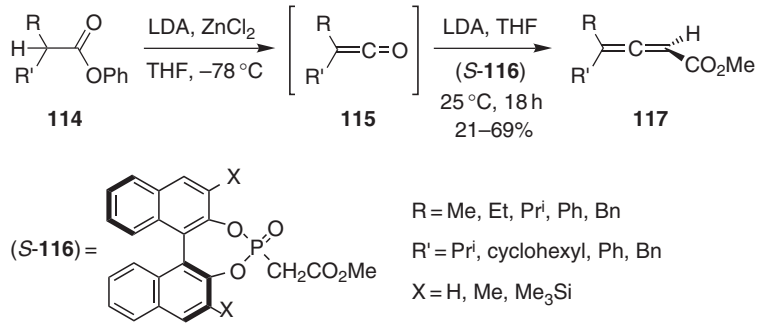
3.16.1.4.2 From esters

Esters of carboxylic acids on treatment with strong bases can give ketenes through formal loss of an alcohol, and such a reaction has been used for the synthesis of ketenylidenetriphenylphosphorane (Scheme 27) <2003CCR15>. Treatment of methyl ester **107** with sodamide or its bis(trimethylsilyl) derivative gave stable species **108** as a white solid (m.p. 172 °C). Its reactivity differs from that of typical ketenes due to the presence of the phosphorus grouping. It combines with protic nucleophiles (alcohols, thiols, and amines) and with 1,3-dicarbonyl compounds to give ylides **109** and **110**, respectively. Acid reagents H–Y, in which the Y group can react intramolecularly with the ylide moiety after addition to the carbonyl group, produce heterocycles such as **111**. Carbonyl compounds such as ketones and ketenes undergo [2 + 2]-cycloaddition with the central double bond to give four-membered rings such as **112** and **113**.



Scheme 27

Base treatment of α,α-disubstituted phenylacetates **114** also gives ketenes **115** which undergo Horner–Wadsworth–Emmons reactions with chiral phosphorus reagents (*S*-**116**) to give optically active allenes **117** (Scheme 28). The enantiomeric excesses were generally high (up to 89%) <2001TA669>.



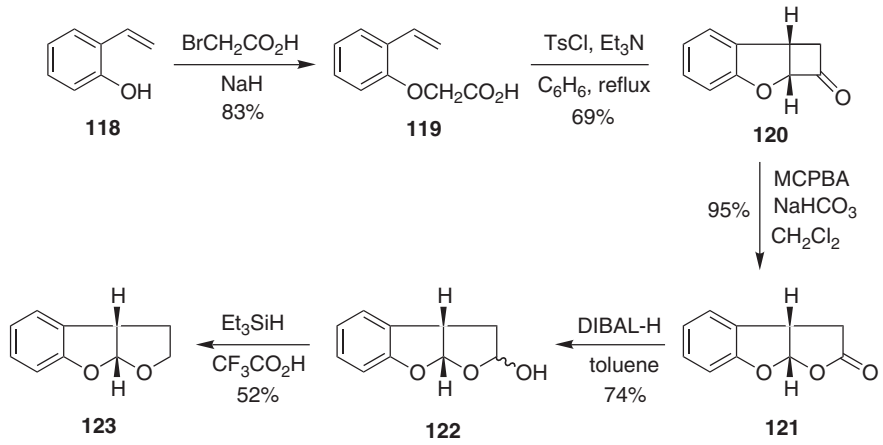
Scheme 28

3.16.1.4.3 From anhydrides

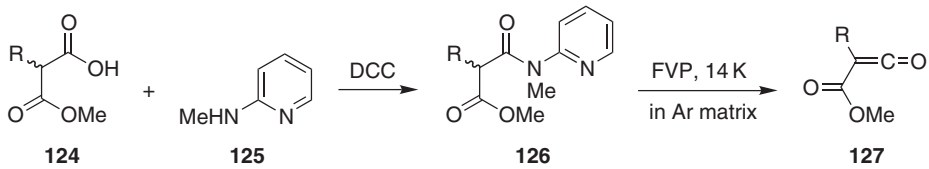
Symmetrical or mixed anhydrides can be cleaved to provide ketenes (Scheme 29). In the example shown, 2-alkenylphenol **118** was alkylated with bromoacetic acid to give acid **119**. Treatment of this gave the tosylate which, in the presence of triethylamine, gave the ketene which underwent spontaneous [2 + 2]-cycloaddition to give cyclobutanone **120**. Baeyer–Villiger oxidation to species **121**, reduction to alcohol **122**, and dehydration gave target compound **123**, a structural motif found in a large number of natural products, including the toxic fungal metabolite aflatoxin B_1 <2001SC141>.

3.16.1.4.4 From amides

Amides can eliminate amines on heating and generate ketenes (Scheme 30). Condensation of methyl malonate and derivatives **124** with 2-methylaminopyridine **125** with the aid of dicyclohexylcarbodiimide (DCC) gave malonylamides **126**, a convenient source of methoxycarbonylketenes **127**.



Scheme 29

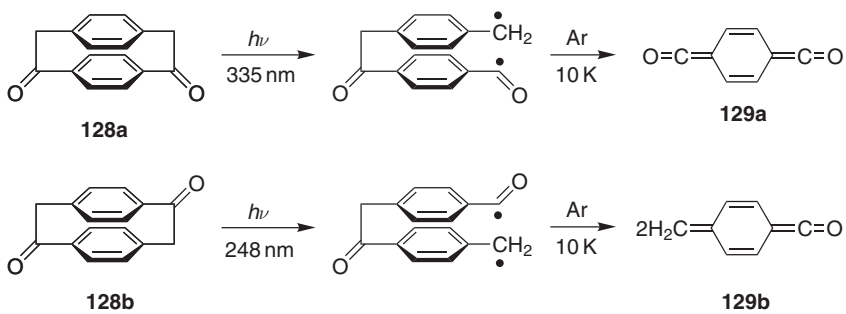


Scheme 30

This methodology has advantages over other ketene-producing reactions in that the starting materials are stable and nonhygroscopic; the reactions occur under relatively mild conditions and the spectral purity of the ketenes obtained is excellent <1998ACS654>.

3.16.1.5 From Ketones

Certain cyclic ketones can be transformed into ketenes (Scheme 31). For example, irradiation of [2.2]paracyclophane diones (**128a**–**128b**) resulted in ring scission to give diradical intermediates that collapsed to ketenes (**129a**–**129b**) <1996PAC353, 1995LA1643>.

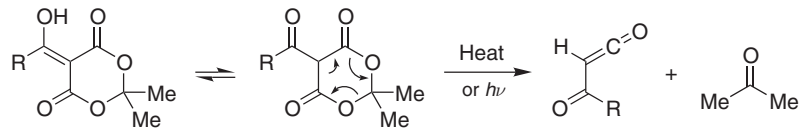


Scheme 31

3.16.1.6 From Derivatives of Meldrum's Acid

Conjugated ketenes such as acylketenes (α-oxoketenes), vinylketenes, and bisketenes are currently of major interest in synthetic and theoretical studies. Among several methods of generating acylketenes, cycloreversion of 4*H*-1,3-dioxin-4-ones is most attractive because the reaction can be conducted under neutral conditions either thermally or photochemically (Equation (5)).

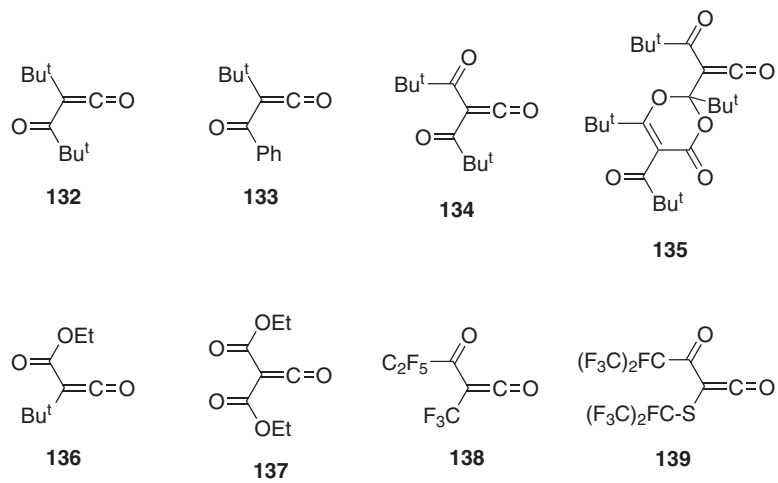
Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) reacts with aliphatic acyl chlorides in the presence of pyridine to give acyltautomers (**130a–130b**). These compounds are excellent sources of acylketenes **131** and have gained in popularity <1978JOC2087, 1994S1219>. In agreement with computational results, acyclic acylketenes can normally exist as a mixture of two conformers: *s-E* (carbonyls opposed) and *s-Z* (carbonyls adjacent). If substituted by bulky substituents, the former predominates.



130a **130b** **131**

s-(*E*)-Conformer (5)

Acylketenes are highly reactive and cannot normally be isolated or observed under ordinary conditions. They can be stabilized sterically (by groups such as *t*-butyl) and electronically (by electron-withdrawing substituents such as fluorinated groups). A few have been isolated as pure compounds: e.g., structures (**132–139**) (Figure (1)). The chemistry of stabilized ketenes has been reviewed <2001CCA815, 1994S1219>. The ability of acylketenes to react with nucleophiles to give 1,3-dicarbonyl compounds has been widely exploited <1997TL6689>.



132 **133** **134** **135**

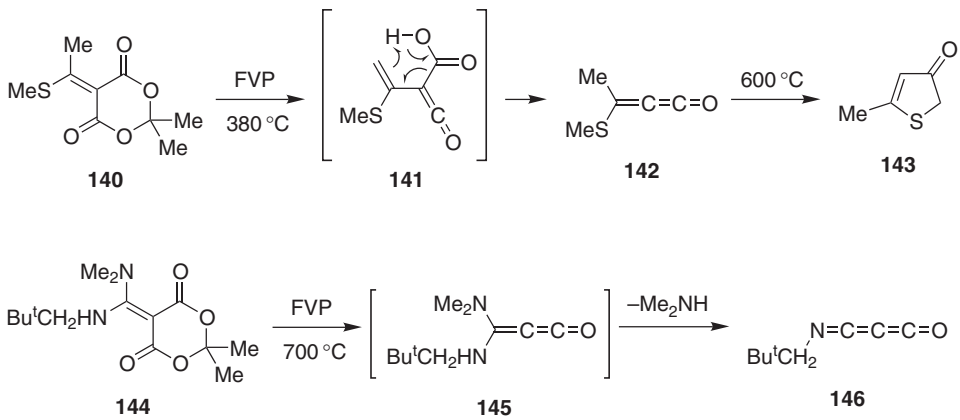
136 **137** **138** **139**

Figure 1

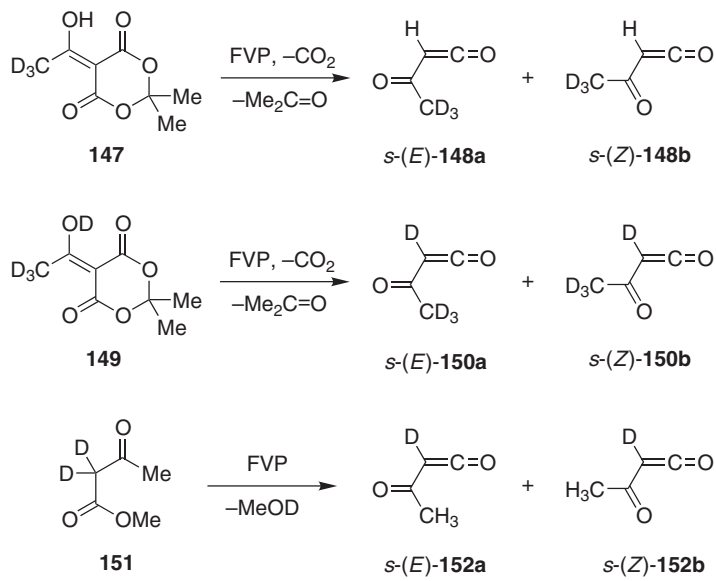
Derivatives of Meldrum's acid have been used to prepare some otherwise inaccessible ketenes using the technique of FVP. Derivative **140** followed two decomposition pathways (Scheme 32). Elimination of acetone and carbon dioxide gave ketene **141**, which at higher temperature rearranged to ketene **142** that cyclized to the thiophene derivative **143** <1998JCS(P2)493>. Similarly, thermolysis of derivative **144** gave intermediate **145** which lost dimethylamine to give (neopentyl)iminopropadienone **146** as a distillable yellow oil that was stable at room temperature. (Mesityl)- and (2-*t*-butylphenyl)iminopropandienones were also isolated and reactions with nucleophiles explored <2002JOC2619>. (2-Pyridyl)iminopropandienone has been made by FVP of the corresponding pyridopyrimidinone <2001JCS(P2)602>.

Matrix isolation infrared spectroscopy at cryogenic temperatures allows ketenes to be generated and studied in an inert gas matrix. The absence of rotational absorptions allows not only the detection of a particular species in a mixture but also the possibility of distinguishing between individual conformers. These can be deuterated to aid interpretation of the spectra <1996JPC3917>. FVP of deuterio-derivatives **147** and **149** between 450 and 650 °C allowed isolation of ketenes (**148a–148b**) and (**150a–150b**) in an argon matrix at 15 K (Scheme 33). The ratio of *s-E* to *s-Z* conformers was equal and did not alter at different temperatures. Acyclic precursor **151** could similarly be converted into an equal mixture of deuterated conformers (**152a–152b**). The perprotio analog of acetyl Meldrum's acid **149** also gave, after FVP at 300–800 °C

and isolation in an argon matrix at 14 K, an equal mixture of both conformers <1995JOC1686>. Chloroformylketene conformers have been generated by thermolysis of malonyl dichloride at 50 °C and isolated in rare gas matrices <1996JPS7034>. Trifluoroacetylketene has also been made in a similar way <1999JA8345>. The use of malonates to prepare ketenes for cyclocondensation reactions has been demonstrated <2001MI-338>.



Scheme 32



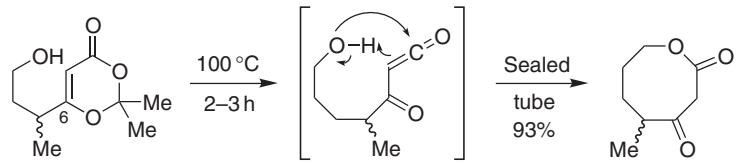
Scheme 33

A two-step synthesis of 6-substituted 1,3-dioxin-4-ones, such as compound **153**, from "diketene-acetone adduct" allows, after heating, the construction of eight-membered oxacycles which are common structural motifs in marine natural products (Scheme 34). Compound **153** on warming in a sealed tube gave a ketene **154** that cyclized to give ring system **155** in good yield <1996RCI781>.

3.16.1.7 From Alkynes

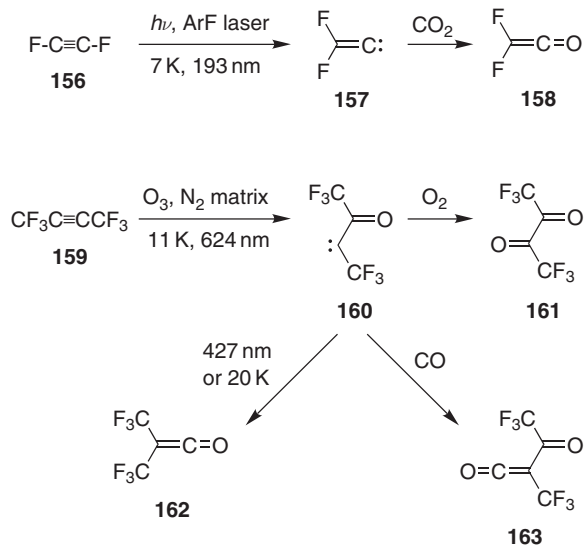
The low temperature and lack of diffusion in a rigid frozen matrix enhance the kinetic stability of reactive molecules. Carbene intermediates, which cannot be otherwise isolated due to their high reactivity, can be identified by spectroscopy (e.g., IR, ESR, and FTIR) and reacted with reagents introduced into the matrix (Scheme 35). Irradiation of difluoroacetylene **156** gave singlet carbene

difluorovinylidene **157** which on matrix isolation and exposure to carbon dioxide gave difluoroketene **158** <1998CEJ1611>. Light-induced ozonolysis of hexafluorobutyne **159** in a nitrogen matrix allowed isolation and characterization of carbene **160** which oxidized readily to dione **161** but on laser irradiation or warming, rearranged to bis(trifluoromethyl)ketene **162**. When carbon monoxide was present, acylketene **163** could be isolated <2000JA9078>. Matrix isolation and laser flash photolysis, where short-lived intermediates are generated using pulsed lasers and observed using time-resolved spectroscopy, are specialist techniques of limited use in synthesis.



153 **154** **155**

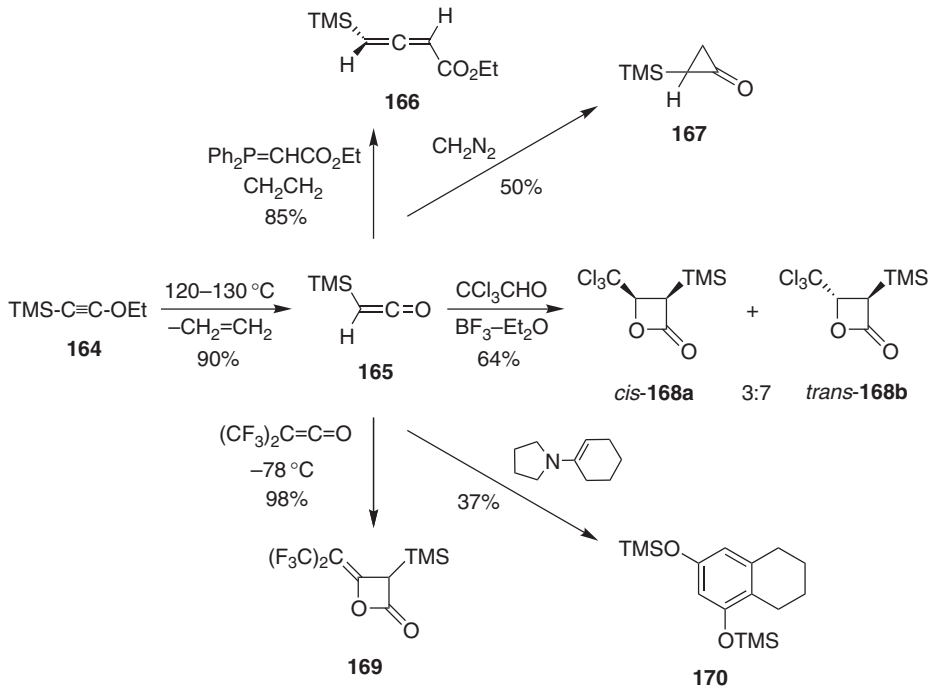
Scheme 34



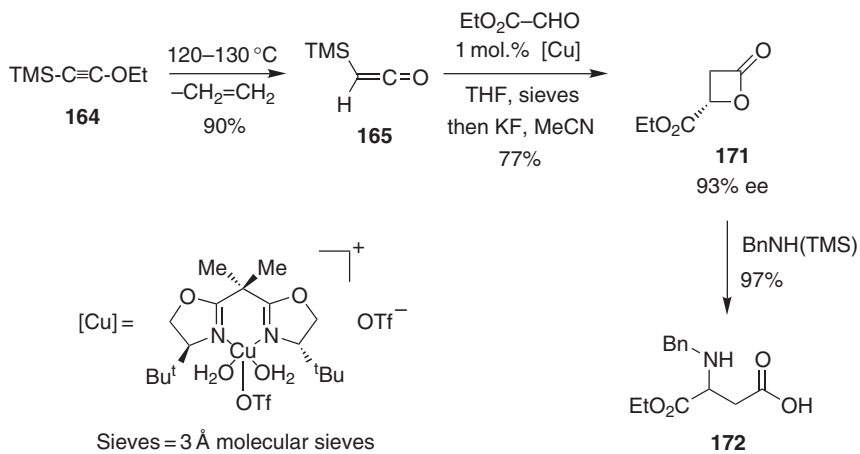
Scheme 35

While the first ketene, diphenylketene, was discovered in 1905, the first silylketene awaited discovery for another sixty years: pyrolysis of ethoxy(trimethylsilyl)ethyne **164** gave trimethylsilylketene **165** with loss of ethene (Scheme 36) <1965DOK357>. Since then, many different silylketenes have been prepared by various approaches and have been involved in a large number of reactions. Silylketenes are remarkably stable compared to most other ketenes. They do not easily dimerize and can therefore be stored for a protracted period of time; ketene **165** has been used successfully after storage at −20 °C for over a year <1998JCS(P1)2105>. It reacts with phosphorus ylides to give the Wittig olefination product (e.g., allenic ester **166**) <1974JOC3607> and with diazomethane to give cyclopropanone **167** <1978ZOB131>. It undergoes [2 + 2]-cycloaddition with carbonyl compounds. Thus, it is added to chloral to give a mixture of diastereoisomers (**168a**–**168b**) <1978ZOB1363> and with bis(trifluoromethyl)ketene to give cycloadduct **169** <1983ZOB2068>. Trimethylsilylketene undergoes a formal [2 + 2 + 2]-cycloaddition with enamines to give a resorcinol-type silyl ether **170** <1994SL1005>.

Trimethylsilylketene **165** can also be used in the asymmetric construction of four-membered heterocycles <2001OL3125>. Treatment with ethylglyoxylate in the presence of symmetric bis(oxazoline) copper(II) complexes results in an enantioselective [2 + 2]-cycloaddition (Scheme 37). After deprotection, cycloadduct **171** was isolated in high yield and enantiomeric excess. Reaction with *N*-benzyl-*N*-(trimethylsilyl)amine gave the *N*-protected aspartic acid **172** in excellent yield.



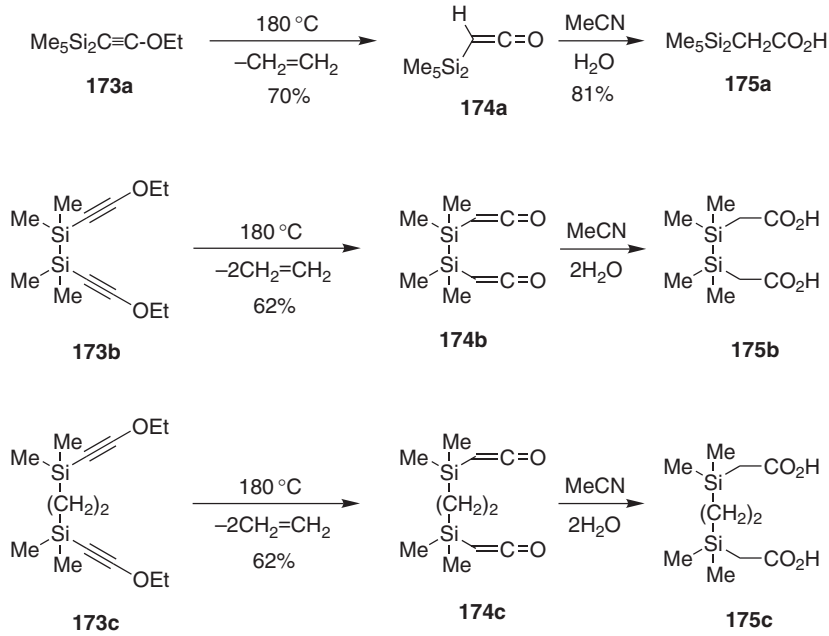
Scheme 36



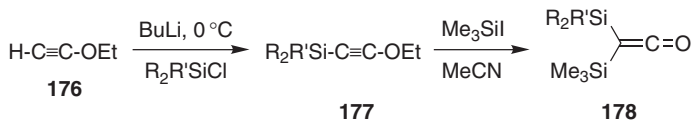
Scheme 37

Thermolysis of other silylethoxyalkynes furnishes ketenes that can be used to make various interesting materials (Scheme 38). Lithium ethoxyacetylide reacted with chloropentamethyl disilane, 1,2-dichlorotetramethyl disilane, or 1,2-bis(chlorodimethylsilyl)ethane to give silylalkynes (**173a**–**173c**) which lost ethene on heating to give ketenes (**174a**–**174c**). Hydrolysis gave the silicon-containing acids (**175a**–**175c**) <1997OM78>.

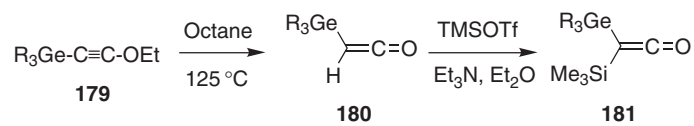
Ethoxyethyne **176** has been used to prepare silyl species (**177a**–**177e**) (Scheme 39). These on treatment with iodotrimethyl silane in acetonitrile give unsymmetrical silylketenes (**178a**–**178e**) <2001RCB1088>. Similarly, thermolysis of germylethoxyalkynes (**179a**–**179b**) gave ketenes (**180a**–**180b**) which could be converted into stable germylsilylketenes (**181a**–**181b**) on treatment with trimethylsilyl triflate and triethylamine <2001RCB1093>. Also, germylethoxyethyne **182** reacted with bromotrimethylgermane to give the bis(germyl)ketene **183**, a stable liquid <2001RCB1088>.



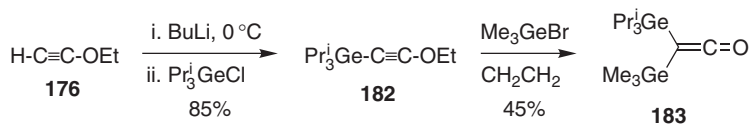
Scheme 38



	R	*R′*	*Yield* (%)	*Yield* (%)
a	Me	Bu^t	74	82
b	Ph	Bu^t	93	47
c	Pr^i	Pr^i	81	37
d	Ph	Me	80	7
e	Ph	Ph	58	26

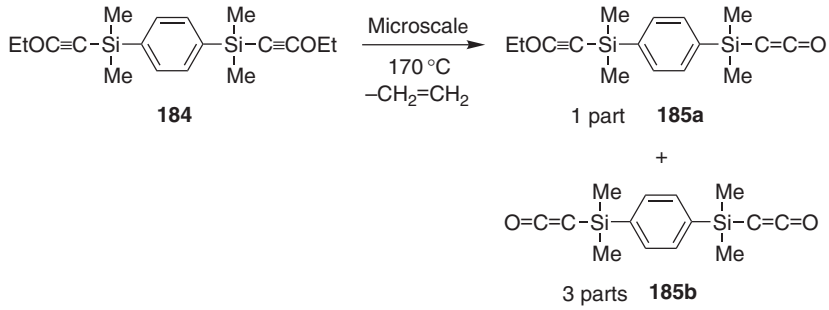


	R	*Yield* (%)	*Yield* (%)
a	Me	68	81
b	Pr^i	53	23



Scheme 39

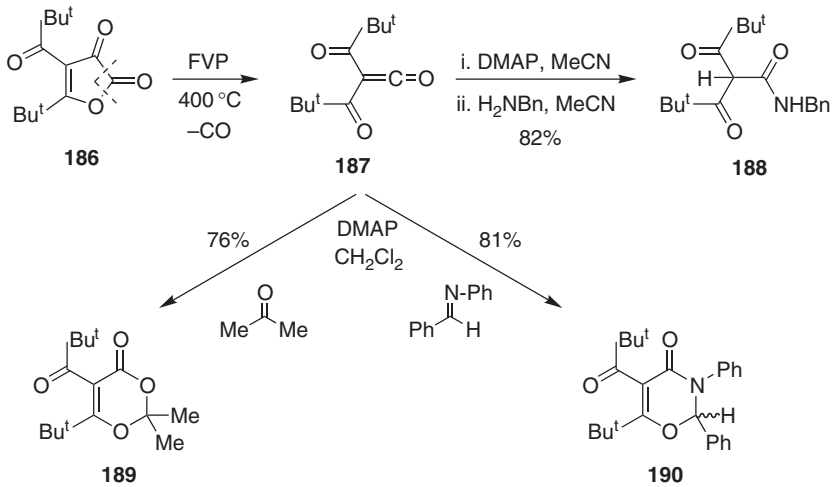
Bis(silyl)alkynes with a hydrocarbon bridge can be used to prepare bisketenes on a small scale (Scheme 40). For instance, thermolysis of bis(silyl)alkyne **184** in a GC oven gave a mixture of mono- and bis(silyl)ketenes **185a** and **185b**, respectively <1996JOC6227>.



Scheme 40

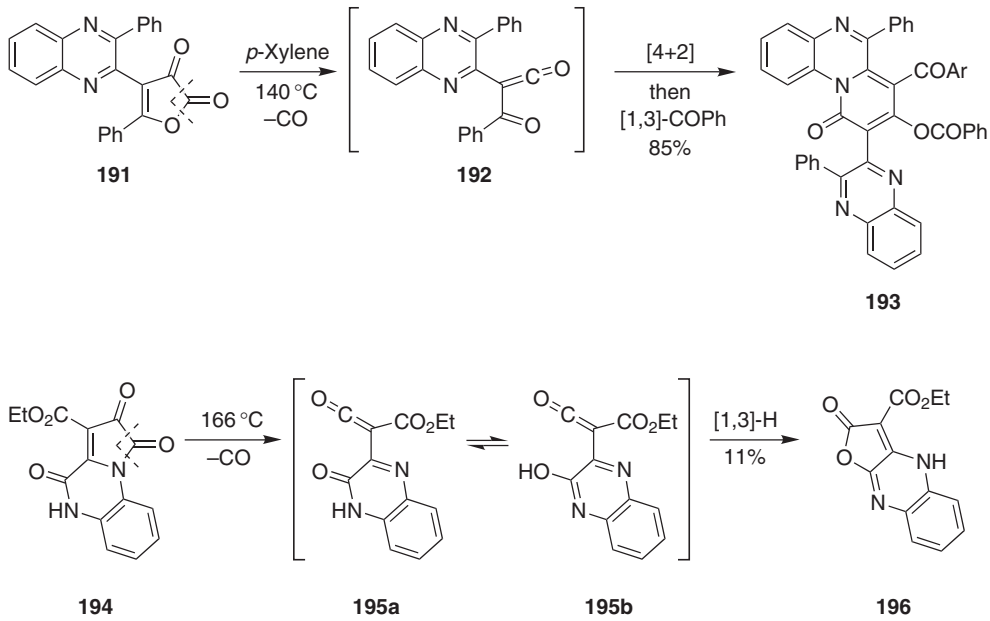
3.16.1.8 From Heterocyclic Materials

The formation of ketenes by flash vacuum pyrolysis of five-membered heterocycles has been reviewed <2001EJO2209>. Most work in this area involves the thermal cleavage of furandiones <1997H1047> such as furan-2,3-dione **186** which gives dipivaloylketene **187** in nearly quantitative yield (Scheme 41). Treatment with 4-(dimethylamino)pyridine (DMAP) gives a zwitterion that reacts readily with primary amines and alcohols to afford amides (e.g., product **188**) and esters. The salt serves as an excellent oxadiene system in [4 + 2]-cycloaddition reactions with C=O, C=N, and C=S dienophiles. For example, it reacted with acetone and benzylideneaniline to give, respectively, the 1,3-dioxin-4-one **189** and 1,3-oxazin-4-one **190** in high yield <2001EJO1315>.



Scheme 41

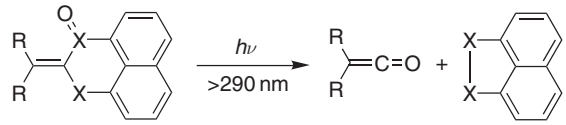
Analogous chemistry occurs with furandione derivatives with aromatic side chains and can be applied to the preparation of polycyclic systems (Scheme 42). Thus, decarbonylation of precursor **191** gave ketene **192** which most likely underwent [4 + 2]-cyclodimerization followed by [1,3]-migration of the benzoyl group. Heterocycle **193** was obtained in good yield <2002RCB850>. The same type of chemistry was observed for related furandiones <2003RJO103>. Decarbonylation of compound **194** on heating for 15–20 min in Dowtherm A (a eutectic mixture of biphenyl and diphenyl ether) gave ketene **195a** <2001RCB1317>. Tautomerization of the amide to the hydroxyimine **195b** presumably enabled cyclization. A 1,3-proton transfer to the *N*-atom gave heterocycle **196** in low yield. FVP of triazoles can also lead to the formation of ketenes through expulsion of nitrogen <1998JOC5779>.



191 **192** **193** **194** **195a** **195b** **196**

Scheme 42

One unusual method of ketene preparation involves irradiation of ketene dithio- (or seleno) ketene derivatives (Scheme 43). Thus, photolysis of naphthalene derivatives **197** resulted in elimination of the ketene and formation of the disulfide or diselenide **198**. Ketenes produced this way were trapped *in situ* with alcohols or amines <1999TL5211>.

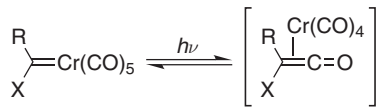


197 R = Me, Et or Ph; X = S or Se 71–81% **198**

Scheme 43

3.16.1.9 From Chromium Carbene Complexes

Irradiation of chromium carbene complexes is thought to give rise to transient chromium–ketene complexes (Equation (6)). These revert to the carbene complexes if they are not trapped <1997T4105>. The utility of chromium carbene complexes in the synthesis of polymer-supported peptides <2003AG(E)2340> and asymmetric materials <2003T3545> has been reviewed.

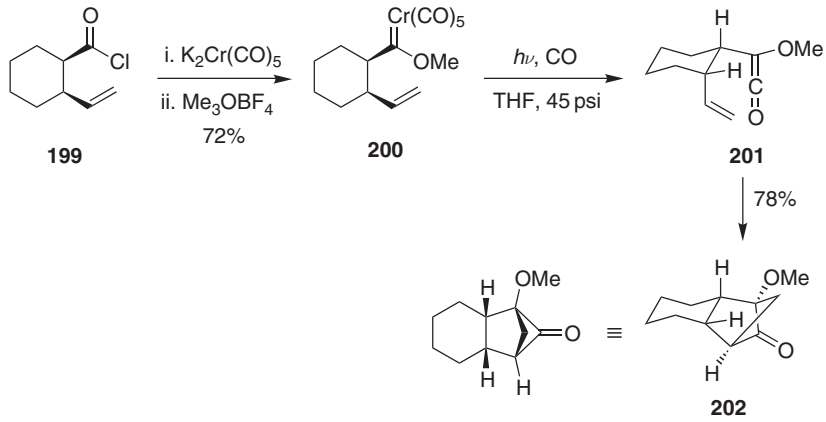


(6)

Their use as substrates in pericyclic reactions is an important method for synthesizing naturally occurring compounds. Reaction of *cis*-acid chloride **199** with potassium pentacarbonylchromium then trimethyloxonium tetrafluoroborate gave carbene complex **200** which, on photolysis in the presence of carbon monoxide, gave species **201** which underwent [2 + 2]-cycloaddition between the olefin and ketene moieties (Scheme 44). Cyclobutanone **202** was isolated as a single diastereoisomer in good yield <1996JA7873>.

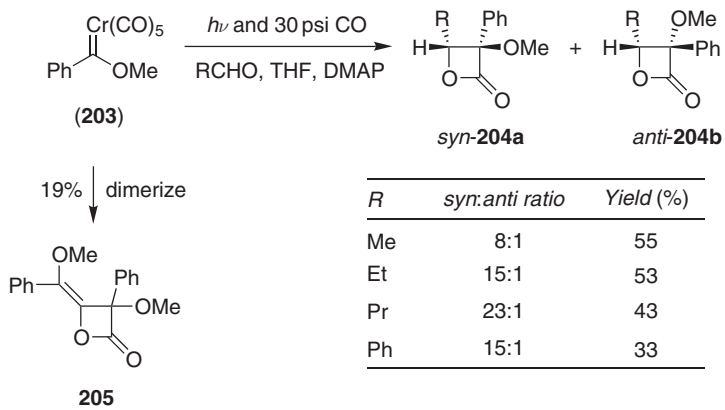
Chromium complexes can also be used for stereoselective formation of β-lactones, which are subunits in many natural products. For example, photolysis of the phenylmethoxycarbene complex **203** with various aldehydes in the presence of 4-(dimethylamino)pyridine (DMAP) and

carbon monoxide gave β-lactones in modest yield (Scheme 45). They were obtained as mixtures of *syn*- and *anti*-isomers, **204a** and **204b** respectively, with the *syn*-isomers predominant <2003JOC6056>. Diastereoselectivity was maximal for butyraldehyde; the reaction did not proceed with electron-deficient aldehydes such as bromal. Dimerization of the chromium-bound ketene to give olefin **205** as a single isomer occurred in the absence of an aldehyde.



199 **200** **201** **202**

Scheme 44

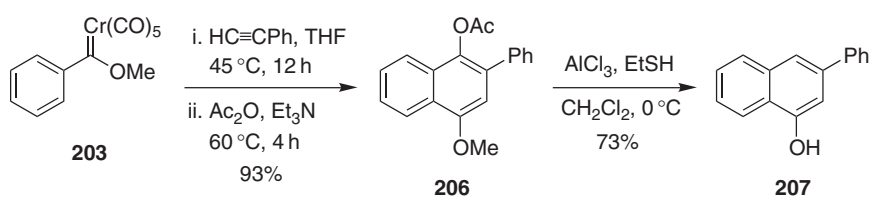


(**203**) *syn*-**204a** *anti*-**204b** **205**

R	*syn*:*anti* ratio	*Yield* (%)
Me	8:1	55
Et	15:1	53
Pr	23:1	43
Ph	15:1	33

Scheme 45

Chromium carbene complex **203** has also been shown to undergo benzannulation when treated with phenylethyne and then acetic anhydride and triethylamine <1996JA3392>. The acylated naphthol **206** was obtained in excellent yield (Scheme 46). Treatment with aluminum chloride and ethanethiol not only cleaved the methyl ether, as anticipated, but also reduced the acetoxyl group, yielding the surprise product **207**. Similar aromatic species were prepared following this discovery. Ketenes generated by photolysis of chromium alkoxycarbene complexes in certain cases undergo intramolecular Friedel–Crafts acylation <1998JOC1462>.

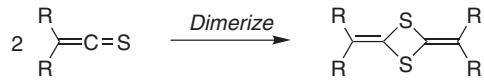


203 **206** **207**

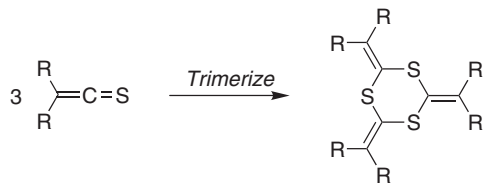
Scheme 46

3.16.2 THIOKETENES

Thioketenes are less stable than the corresponding ketenes partly because π-orbital overlap between carbon and sulfur is less efficient than that with oxygen. Their use in synthesis is compounded further by their tendency to form dimers **208** and trimers **209** (Equations (7) and (8)). The stability of thioketenes depends on the substituents: thioketene $H_2C{=}C{=}S$ dimerizes above $-200\,^{\circ}C$ yet di-*t*-butylthioketene is stable at room temperature. Electronic factors also play an important role with electron-withdrawing groups (e.g., silicon, phosphorus, and fluoroalkyl substituents) enhancing stability.



208 (7)



209 (8)

In general, the synthesis of thioketenes is difficult and requires the use of special techniques such as FVP, matrix generation, and characterization at low temperature. Thioketenes are generally prepared *in situ* for most synthetic purposes. The literature of the 1990s contains few additions to the repertoire of methods of making thioketenes. For a review of methods prior to 1995, the interested reader should consult the relevant chapter in COFGT (1995).

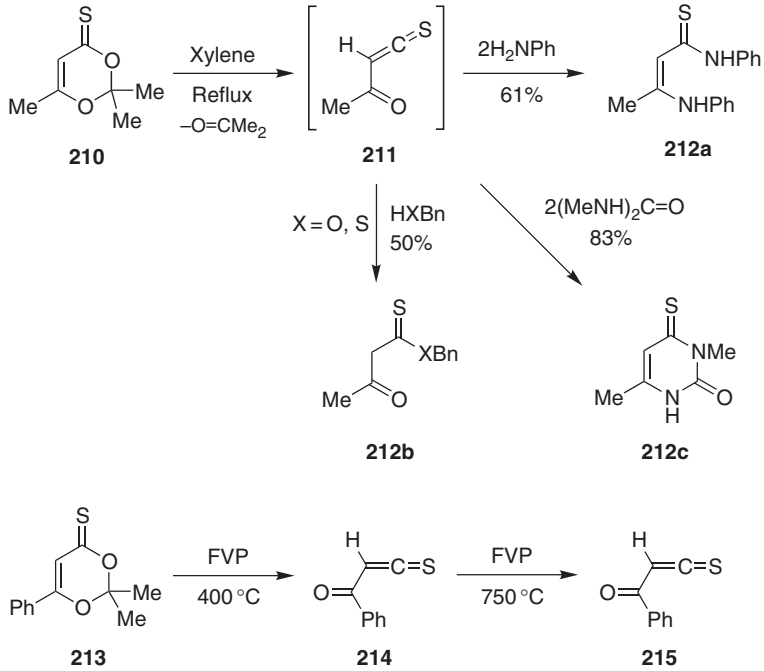
Modifications of natural β-lactams, such as β-thiolactams, are a promising synthetic target from the medicinal standpoint but the use of thioketenes in the Staudinger reaction is limited to sterically hindered thioketenes. More reactive ketenes, such as *t*-butyl(chloro)thioketene, tend to give 2:1 cycloadducts with azomethines or thioimidates <1988T1827>. The easiest way to β-thiolactams is probably through thionation of the corresponding β-lactams, made by [2 + 2]-addition of a ketene and imine, using Lawesson's reagent <1997PSS349>.

3.16.2.1 From Derivatives of Meldrum's Acid

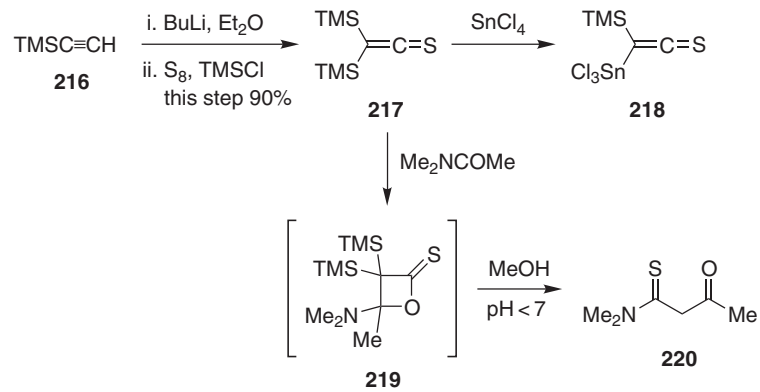
Thione derivatives of Meldrum's acid undergo similar chemistry to the nonsulfur derivatives (see Section 3.16.1.6) and yield thioketenes when heated (Scheme 47). Thermolysis of 4*H*-1,3-dioxine-4-thione **210** gave thioketene **211** which reacted with two molar equivalents of aniline to produce enaminothioamide **212a**. Benzyl alcohol or benzylthiol gave species of structure **212b** and an excess of acetone, thiouracil derivative **212c** <1996CC775>. Phenyl-substituted thione **213** under harsher FVP conditions yielded thioketene **214** which at higher temperature underwent a 1,3-aryl shift to give thioacylketene **215** <2000JOC2706>. These are unstable and cyclize to 3-aryl-thiet-2-ones.

3.16.2.2 From Alkynes

Alkynylsilyl sulfides are thioketene equivalents and can be used to generate β-thiolactams from thioimidates. Yields are variable and competing side reactions can result in ring enlargement <1994AG(E)439>. Trimethylsilylethyne **216** can be converted into bis(trimethylsilyl)thioketene **217** in excellent yield by lithiation, sulfurization, and treatment with chlorotrimethyl silane (Scheme 48). The thioketene can be treated with tin(IV) chloride to give the stannylated thioketene **218** <1976CC1008> or with secondary amides such as *N*,*N*-diethylacetamide to give intermediates of type **219** which give 3-oxothioamides such as **220** on acid work-up <1996CC1621>.



Scheme 47



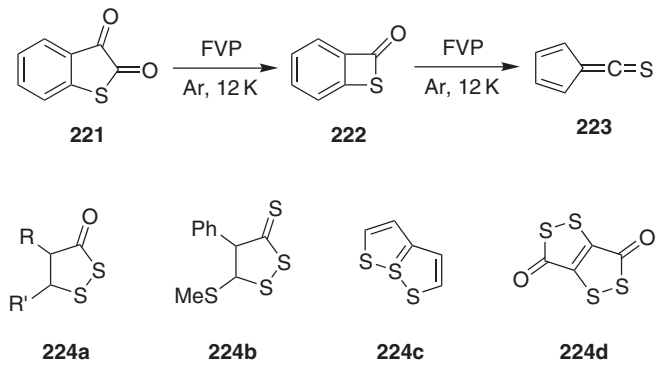
Scheme 48

3.16.2.3 From Heterocyclic Materials

Thiophenediones, like furandiones (see Section 3.16.1.8), lose carbon monoxide when heated and can provide thioketenes (Scheme 49). Thermolysis of 2,3-dihydrobenzothiophene-2,3-dione **221** resulted in extrusion of carbon monoxide and gave benzothietan-2-one **222** and then thioketene **223** <2001JCS(P2)2047>. Thermolysis of heterocycles (**224a–224d**) gives thioketenes in addition to products of formula C_nS which are of interest as they are present in the outer-space <1997PSS399>. 1,3-Dithiole-3-thiones also produce thioketenes when heated <1997JCS(P2)173>.

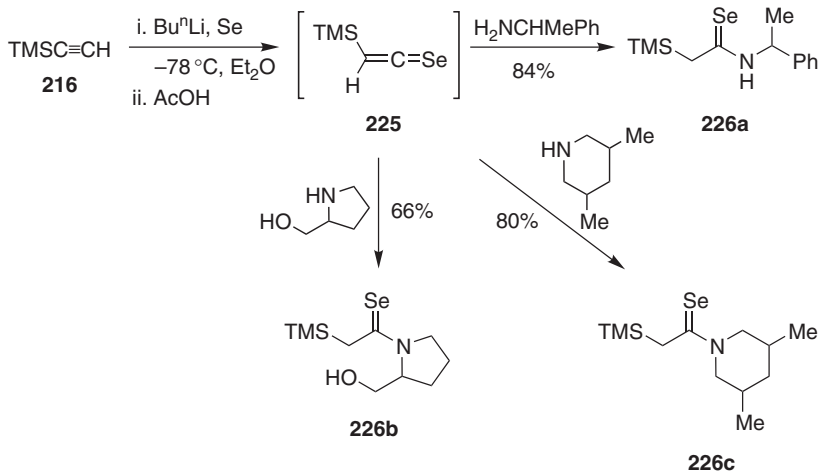
3.16.3 SELENOKETENES

Very few selenoketenes have been reported and methods of obtaining this curious class have paralleled those used to make thioketenes. Routes to some selenoketenes are summarized in COFGT (1995) and are not repeated here. The use of lithium alkyneselenoates has gained in



Scheme 49

popularity (Scheme 50). Lithiation of trimethylsilylethyne **216** and sulfurization gave a thiolate which on acification gave thioketene **225**. This could be trapped by primary or secondary amines to give a variety of selenoamides (**226a**–**226c**) <1996SL865>.



Scheme 50

3.16.4 TELLUROKETENES

A search of Chemical Abstracts Service failed to reference any example of a telluroketene $R_2C{=}C{=}Te$. Whether it is possible to prepare such compounds is a matter for speculation and presents a challenge to synthetic chemists. If they can be prepared, then their use as intermediates is likely to be very limited.

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Biographical sketch

Chris Timperley was born in Cheshire UK. He was awarded a B.Sc. by the University of Sheffield in 1991 and a Ph.D. in 1995 by the University of Newcastle-upon-Tyne. He then joined Chemical and Biological Defence Establishment, Porton Down (now the Defence Science and Technology Laboratory, Dstl). His scientific interests include all aspects of synthesis, especially the synthesis of organic fluorine and phosphorus compounds.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 573–604

3.17 Ketenimines and Their P, As, Sb, and Bi Analogs

R. A. AITKEN
University of St. Andrews, St. Andrews, UK

3.17.1 KETENIMINES AND THEIR DERIVATIVES ($R_2C{=}C{=}NH(R)$, etc.)

3.17.1.1 Introduction

This section covers advances in the synthesis of compounds containing the C=C=N functional group since the publication of chapter 3.17.1 in <1995COFGT(3)555>. As before, these are categorized according to whether the ketenimine atoms come from modification of precursors already containing the CCN triad or by combination of CC + N or C + CN fragments.

3.17.1.2 Ketenimines from Precursors Containing the CCN Triad

3.17.1.2.1 By elimination reactions

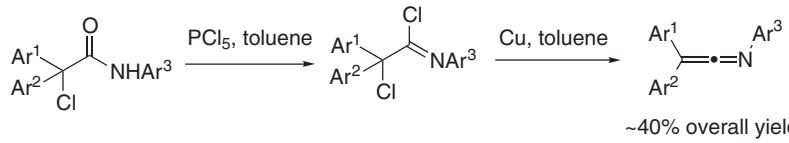
This is one of the main methods available for formation of ketenimines but since the publication of chapter 3.17.1.2.1 in <1995COFGT(3)555> there have only been a few significant developments. These are described here according to the starting material and reagents involved.

(i) Dehydration of secondary amides with dihalotriphenyl phosphoranes

The yield of $Bu^t(Br)C{=}C{=}NBu^t$ formed from $Bu^tCH_2C(O)NHBu^t$ has been increased from 40% to 61% by using 3 equiv. of Ph_3PBr_2 with Et_3N <1995LA2171>. Ketenimines bearing bulky pentamethylphenyl groups, $(C_6Me_5)_2C{=}C{=}NR$, have been prepared by reaction of $(C_6Me_5)_2CH{-}C(O)NHR$ with Ph_3PBr_2 for R = Me (68%) and R = Pr^i (21%) <1997JCS(P2)1175>.

(ii) Dechlorination of α-chloroimidoyl chlorides

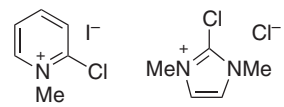
Both the formation and dechlorination of α-chloroimidoyl chlorides, which were previously conducted using benzene as solvent, may be successfully carried out in the safer substitute toluene to give a range of triaryl ketenimines (Equation (1)) <1993T6285>.



(1)

(iii) Eliminations from thioamides

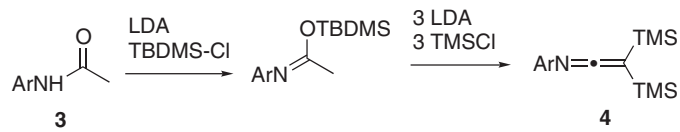
A new method of converting thioamides, $R^1R^2CH{-}C(S)NHR^3$, into the corresponding ketenimines, $R^1R^2C{=}C{=}NR^3$, involves treatment with a heterocyclic haloiminium salt such as **1** or **2** followed by triethylamine to give the products in 30–94% yield <2000S517>.



1 **2**

(iv) Miscellaneous eliminations

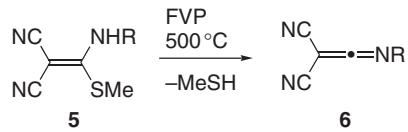
Sequential deprotonation and silylation of the *N*-aryl acetamides **3** results not only in ketenimine formation but also in further silylation to give the products **4** (Equation (2), Ar = Ph (38%), 2-pyridyl (65%)) <2001CEJ573>. The dicyanoketenimines **6**, which are not isolable at room temperature but can be trapped in an inert gas matrix at low temperature, have been generated by FVP of the precursors **5** at 500 °C (Equation (3), R = Me, Et, Ph) <2002JOC1084>.



3 **4**

Ar = Ph 38%
Ar = 2-pyridyl 65%

(2)



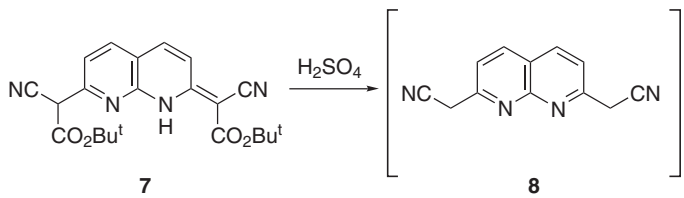
5 6 (3)

3.17.1.2.2 From alkane nitriles, their α-anions, or their α-radicals

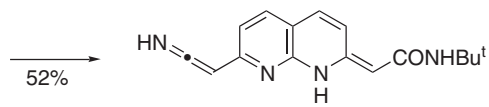
There have been several developments in this area since the publication of chapter 3.17.1.2.3 in <1995COFGT(3)555>.

(i) Tautomerism and sigmatropic rearrangement of alkane nitriles

Removal of the *t*-butoxycarbonyl protecting groups from compound **7** in 70% sulfuric acid is accompanied both by a Ritter reaction and nitrile-ketenimine tautomerism of the intermediate **8** to afford ketenimine **9** in 52% yield (Equation (4)) <1994PJC459>.

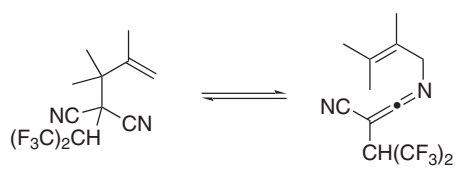


7 8 (4)



9

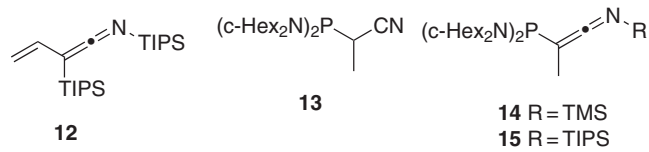
The dinitrile **10** is isolable in pure form but when it is dissolved in $CDCl_3$ it equilibrates with the ketenimine form **11** resulting from a [3,3]-sigmatropic rearrangement (Equation (5)). The authors speculate that this unusual process may be driven by relief of steric strain associated with the hexasubstituted ethane moiety present in **10** <1994TL3281>.



10 11 (5)

(ii) Reaction of α-deprotonated alkane nitriles with electrophiles

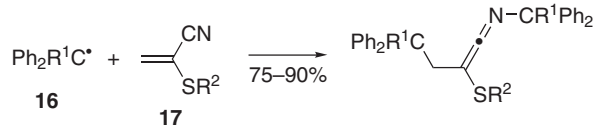
The product **12**, previously prepared by treatment of vinyl acetonitrile, $CH_2{=}CHCH_2CN$, with LDA and TIPSCl, has now been prepared in ^{13}C-labeled form from the labeled nitrile <1996RTC431> and the same product can also be formed starting from the isomeric crotononitrile, MeCH=CHCN <2002EJO2094>. Treatment of compound **13** with LDA and an appropriate silyl chloride has been used to gain access to the first phosphine-substituted ketenimines **14** and **15** <2002CEJ5305>.



12 **13** **14** R = TMS **15** R = TIPS

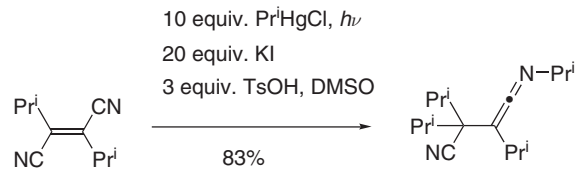
(iii) Conjugate addition to α,β-unsaturated nitriles

Stabilized diphenylmethyl radicals **16** undergo addition to α-alkylthioacrylonitriles **17** to give the ketenimine products (Equation (6)) <1993CB1179>, and the formation of a similar adduct **19** from the substituted fumaronitrile **18** upon photolysis with isopropylmercuric chloride is also thought to be a radical reaction (Equation (7)) <1995JA5967>.



16 **17** (6)

Eight examples
R^1 = Bu^t, TMS, $GeMe_3$, $SnMe_3$, CO_2Me
R^2 = Me, Pr^i, Bu^t



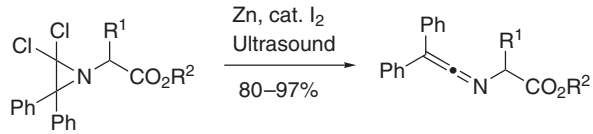
18 **19** (7)

3.17.1.2.3 By cleavage of heterocyclic compounds

Since the publication of chapter 3.17.1.2.4 in <1995COFGT(3)555>, there have been a large number of new developments in this area. These are considered here according to the starting ring system.

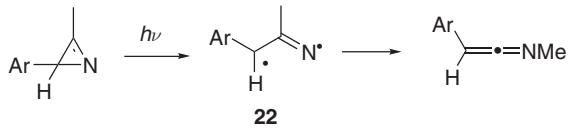
(i) Cleavage of aziridines and azirines

Treatment of the amino acid-derived 2,2-dichloroaziridines **20** with zinc and a catalytic amount of iodine under conditions of ultrasonication affords the ketenimine products **21** in 80–97% yield (Equation (8)) <1997SL929>.



20 **21** (8)

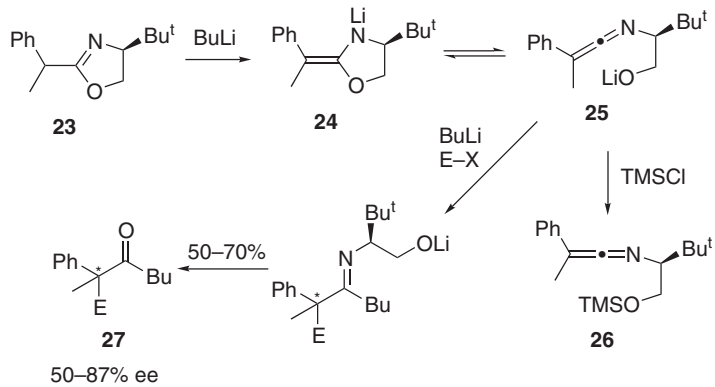
The mechanism of the rearrangement of 2*H*-azirines to give ketenimines upon photolysis (Equation (9)) has been examined by low-temperature matrix isolation/IR methods and the diradical **22** has been identified as an intermediate for both Ar = 4-nitrophenyl <2001CC1036> and Ar = 1-naphthyl <2002CPL(359)267>.



22 (9)

(ii) Cleavage of oxazolines

The ring cleavage observed upon lithiation of achiral oxazolines has been extended to chiral oxazolines <1999TL4765>. Thus, for example, treatment of oxazoline **23** with BuLi gives the derivative **24**, which exists predominantly in the ketenimine form **25**. This may be trapped, for example, with TMSCl to give **26**, but more usefully it can react with a second equivalent of BuLi followed by an electrophile to afford, upon work-up chiral ketones such as **27** in 50–70% yield and 50–87% ee (Scheme 1).



23 **24** **25**

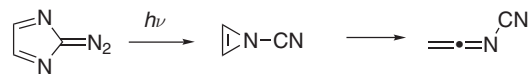
27 **26**

50–87% ee

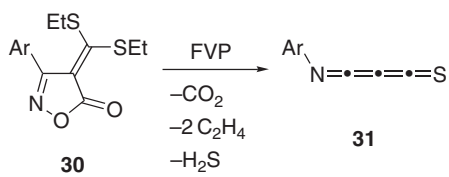
Scheme 1

(iii) Cleavage of other five-membered rings containing two heteroatoms

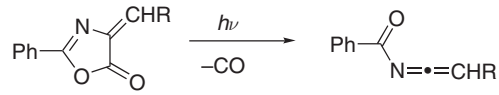
Low-temperature matrix irradiation of the diazoimidazole **28** results in extrusion of nitrogen and rearrangement via the *N*-cyanoazirine to produce *N*-cyanoketenimine **29** detected spectroscopically (Equation (10)) <1999CEJ1590>. Under FVP conditions, the isoxazolinones **30** undergo a series of extrusion processes to afford the iminopropadienethiones **31** detected by matrix IR spectroscopy and also chemical trapping (Equation (11)) <2001JOC1827>. The extrusion of CO from oxazolinones **32**, previously achieved using FVP, also occurs on photolysis to give *N*-benzoylketenimines **33** detected by NMR spectroscopy and trapped by addition of alcohols or water (Equation (12)) <1996TL4019>. Treatment of the oxazolinone **34** with triphenylphosphine followed by water gives the zwitterionic intermediate **35**, which undergoes loss of CO_2 and HCl when reacted with triethylamine to afford the phosphoranylideneketenimine **36** in 88% yield (Equation (13)) <1994RJGC1552>.



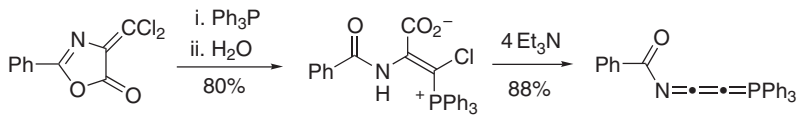
28 **29** (10)



30 **31** (11)



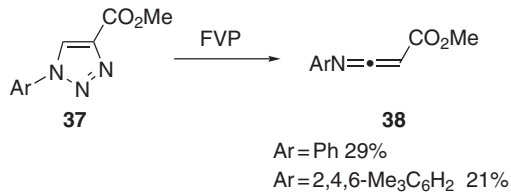
32 **33** (12)



34 **35** **36** (13)

(iv) Cleavage of triazoles and tetrazoles

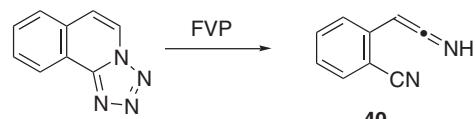
The formation of ketenimines by extrusion of nitrogen from *N*-aryltriazoles, previously achieved by photolysis, is also possible using FVP at 400–800 °C for triazole esters **37** to give ketenimine esters **38** isolable by distillation (Equation (14)) for Ar = Ph <1996JOC1363> and Ar = 2,4,6-$Me_3C_6H_2$ <1998JOC5779>. Products from the matrix photolysis of the tetrazoloisoquinoline **39** include the ketenimine **40** (Equation (15)) detected spectroscopically <2003JOC1470>.



37 **38**

Ar = Ph 29%

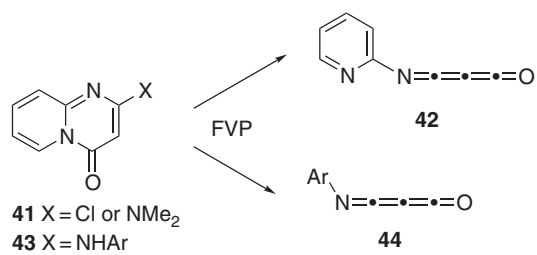
Ar = 2,4,6-$Me_3C_6H_2$ 21% (14)



39 **40** (15)

(v) Cleavage of other heterocycles

While FVP of the pyridopyrimidinone precursors **41** at 850 °C leads to quantitative formation of the cumulene **42** <1999JCS(P2)1087>, the apparently similar compounds **43** react differently under comparable conditions to give the cumulenes **44** (Scheme 2) <2002JOC8558>. The products of this type mentioned here have not been isolated but were identified only by matrix isolation IR studies and trapping; however, routes to isolable examples are covered in Section 3.17.1.2.5.

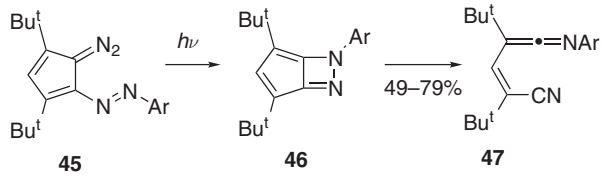


41 X = Cl or NMe_2
43 X = NHAr

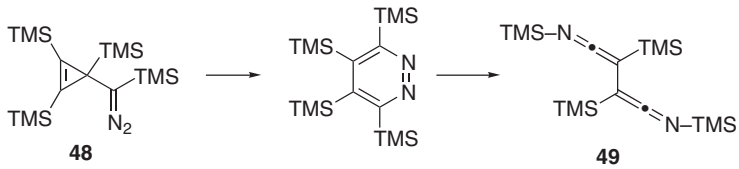
42 **44**

Scheme 2

Photolysis of compounds **45** leads, via a sequence of nitrogen extrusion, electrocyclization to give **46**, and ring cleavage, to the cyanovinyl ketenimines **47** isolated in 49–79% yield (Equation (16)) <1994CB1479>. The formation of bis(ketenimine) **49** among other products from heating the fully silylated cyclopropenyl diazomethane **48** at 60 °C is rationalized by formation and cleavage of an intermediate pyridazine (Equation (17)) <2001AG(E)1674, 2002JA13819>.



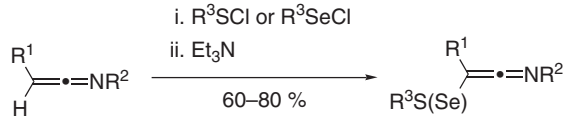
(16)



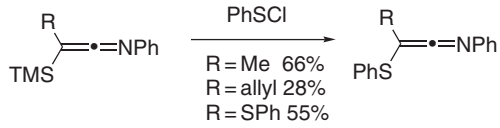
(17)

3.17.1.2.4 From other ketenimines

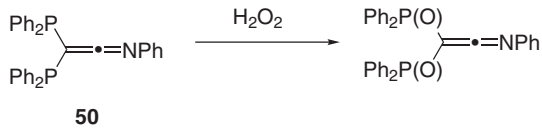
Since the publication of chapter 3.17.1.2.5 in <1995COFGT(3)555>, there have only been a few new developments in this area. Replacement of a ketenimine CH by PhS, BuS, or PhSe has been achieved in a convenient one-pot procedure in 60–80% yield by treatment with the appropriate sulfenyl- or selenenylchloride followed by triethylamine (Equation (18)) <1994JCS(P1)2899>. While this process can also be carried out for R^1 = TMS, silylketenimines lacking a CH undergo replacement of TMS by PhS upon treatment with PhSCl (Equation (19)), and PhSOCl can also be used to give the ketenimine sulfoxides <1999T5405>. Oxidation of the phosphine functions in the ketenimine **50** may be achieved with hydrogen peroxide although the process is complicated by formation of dimers (Equation (20)) <2002CEJ3872>.



(18)



(19)



50

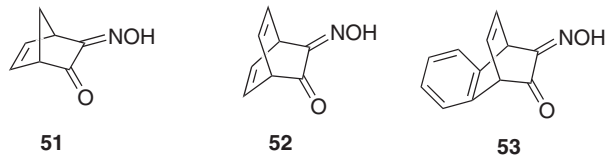
(20)

3.17.1.2.5 By miscellaneous pericyclic processes

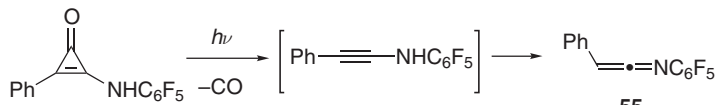
There have been few significant developments in this area since the publication of chapter 3.17.1.2.6 in <1995COFGT(3)555>.

Ketenimine, $H_2C{=}C{=}NH$, is detected together with other C_2H_3N isomers during photolysis of such precursors as vinyl azide, 1,2,3-triazole, and 1,2,4-triazole in a matrix at 10 K <1993CB2337>. The unusual cumulene ethenedione monoxime, $O{=}C{=}C{=}N{-}OH$, may be generated by photochemically induced retro-Diels–Alder reaction of precursors such as **51**–**53** in an argon matrix <1996LA303>. Flash photolysis of the cyclopropenone **54** in water results in loss of carbon

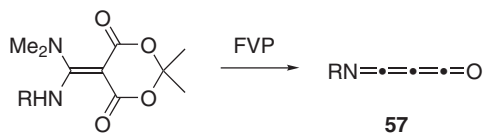
monoxide and isomerization of the resulting ynamine to give the ketenimine **55** at a rate which depends on the reaction conditions (Equation (21)) <1997JOC5363>. By using bulky groups R, the iminopropadienones **57**, obtained as described in <1995COFGT(3)555> by FVP of Meldrum's acid derivatives **56**, are stable enough to be isolated and characterized by NMR spectroscopy and MS (Equation (22)) <2002JOC2619>. For R = CH_2Bu^t the compound can be isolated by distillation, and for R = 2,4,6-$Me_3C_6H_2$ and 2-$Bu^tC_6H_4$ the products are isolated in 70–80% yield as solids.



51 **52** **53**



54 **55** (21)



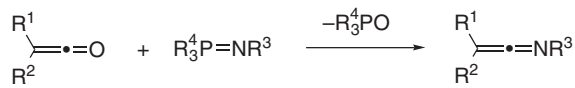
56 **57** (22)

R = Bu^tCH_2, 2,4,6-$Me_3C_6H_2$
2-$Bu^tC_6H_4$ 72–80%

3.17.1.3 Ketenimines from (CC + N) Precursors

3.17.1.3.1 From ketenes (or related precursors) and iminophosphoranes (or related precursors)

There have been several significant developments in this area since the publication of chapter 3.17.1.3.1 in <1995COFGT(3)555>. The general approach is shown in Equation (23) and previous work was generally confined to examples where $R^1 = R^2 = Ph$ and $R^4 = Ph$. The scope of the reaction has been expanded considerably both by using a wider variety of ketenes and using trimethylphosphonium imides, often generated *in situ* by treatment of azides with Me_3P. Representative new examples are given in Table 1.

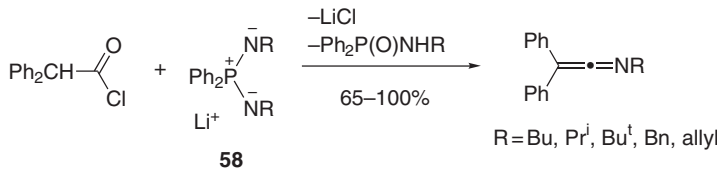


(23)

Table 1 New Ketenimines prepared according to Equation (23)

R^1	R^2	R^3	R^4	*Yield* (%)	*References*
Ph	Ph	$CH(TMS)_2$	Ph	71	<1995JOC6032>
TMS	H	$CH(TMS)_2$	Ph	42	<1995JOC6032>
Ph	Ph	Ar	Me	43–82	<2000JOC3633, 2002EJO4222>
Me	Ph	Ar	Me	30–60	<2002EJO4222>
TMS	H	Ar	Me	62–86	<1996S1199, 1997S963>
Et	Ph	$(CH_2)_2CH{=}CHAr$	Ph	62	<1994T5027>
Ph	Ph	C(=NAr)Ph	Ph	66–72	<2001TL2235>
Cl, Me, Ph	H	C(=NAr)Ph	Ph	60–71	<2001TL2235>

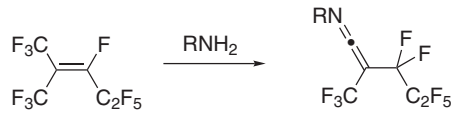
Reaction of diphenylacetyl chloride with a range of lithium phosphonium diimides **58** directly gives the ketenimines in 65–100% yield for a variety of alkyl groups R (Equation (24)) <1999JOM(584)68>.



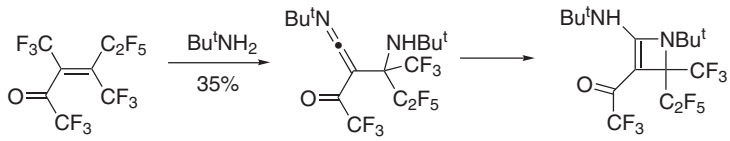
58 (24)

3.17.1.3.2 From haloalkenes or haloalkynes and amines or amine derivatives

In chapter 3.17.1.3.2 in <1995COFGT(3)555>, it was reported that the perfluoromethylpentene **59** reacted with *t*-butylamine to give ketenimine **60** (R = Bu^t) only as a minor by-product in 20% yield (Equation (25)). This process has been re-examined and, by working in acetonitrile with triethylamine present, compound **60** is obtained as the main product for R = Bu^t (90% yield) and R = cyclohexyl (83%). For R = Pr^i, however, only 25% of **60** is obtained accompanied by other products <2000RJOC99>. Reaction of the perfluorinated enone **61** with *t*-butylamine initially gives the ketenimine **62** as the main product (Equation (26)), but this undergoes slow cyclization at room temperature to give the isomer **63** <2000JCS(P1)1529>.



59 **60** (25)

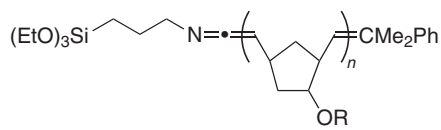


61 **62** **63** (26)

3.17.1.4 Ketenimines from (C + CN) Precursors

3.17.1.4.1 From phosphorus ylides and isocyanates or related compounds

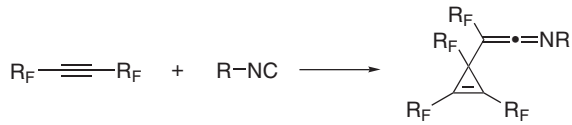
There have been few significant developments in the use of this method since the publication of chapter 3.17.1.4.1 in <1995COFGT(3)555>. Four examples of the reaction of fluorinated isocyanates $C_4F_9CH_2CH_2NCO$ and $C_6F_{13}CH_2CH_2NCO$ with stabilized ylides $Ph_3P{=}C(R^1)COR^2$ to give the ketenimines $R_FCH_2CH_2N{=}C{=}C(R^1)COR^2$ in yields of 74–83% have been reported <1993JFC(63)173>. The silylated isocyanate $(TMS)_2CH{-}NCO$ reacts with $Ph_3P{=}CMe_2$ to afford $(TMS)_2CH{-}N{=}C{=}CMe_2$ but only in 4% yield <1995JOC6032>. A somewhat analogous process is involved in the termination of the ring-opening metathesis polymerization (ROMP) of a substituted norbornene using $(EtO)_3Si{-}(CH_2)_3{-}NCO$ to give the ketenimine-functionalized polymer **64** <2002MI712>.



64

3.17.1.4.2 By alkylation of isocyanides

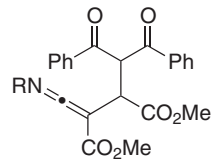
There have only been a few new developments in this area since the publication of chapter 3.17.1.4.2 in <1995COFGT(3)555>. The previously described reaction of isocyanides with hexafluorobut-2-yne to give products of structure **65** (Equation (27)) has now also been carried out for $R_F = CF_2CF_2Cl$ and R = cyclohexyl (53% yield) or Ph (48%) <2000JFC(102)323>. Reaction of isocyanides, RNC, with dibenzoylmethane and DMAD gives the ketenimine products **66** in 40–65% yield <1996M963>.



65

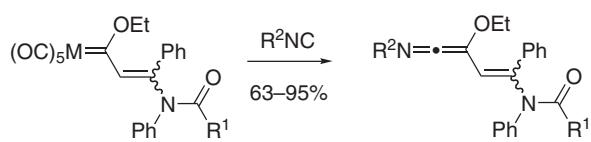
$R_F = CF_2CF_2Cl$
R = c-Hex 53%
R = Ph 48%

(27)



66

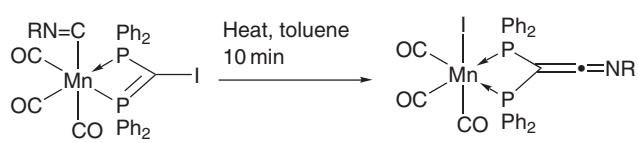
New examples involving transition metal carbene complexes include reaction of both $Cl(Pr^i{}_3P)_2Rh{=}CPh_2$ and $Cl(Pr^i{}_3Sb)_2Rh{=}CPh_2$ with Bu^tNC to give the ketenimine $Ph_2C{=}C{=}NBu^t$ <1997CEJ1375>, and treatment of both chromium and tungsten carbonyl complexes **67** with *t*-butyl or cyclohexyl isocyanide to give ketenimine products **68** in up to 95% yield (Equation (28)) <1994CB717>. A fascinating rearrangement process, which leads to compounds with a new mode of ketenimine to metal bonding, is involved in the isomerization of the manganese(I) complexes **69**, upon heating under reflux in toluene, to the products **70** (Equation (29)) <1998OM3835>.



67 M = Cr, W

68

(28)



69

70

R = Bu^t 90%
R = Ph yield not stated

(29)

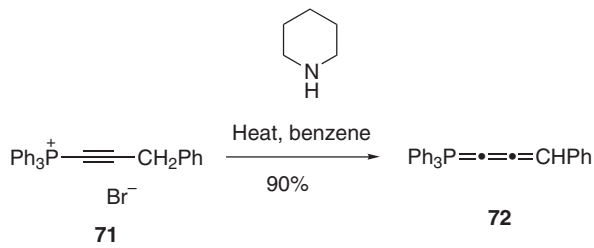
3.17.2 P, As, Sb, AND Bi ANALOGS OF KETENIMINES AND THEIR DERIVATIVES ($R_2C{=}C{=}P{-}R$, etc.)

3.17.2.1 λ^5-Phosphaallenes and $1\lambda^5$-Phosphacumulenes

Since the publication of chapter 3.17.2.1 in <1995COFGT(3)555>, there have only been a few significant developments in this area.

3.17.2.1.1 From precursors containing the CCP triad

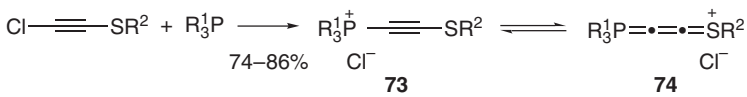
While base treatment of both allenyl- and propargylphosphonium salts was previously believed to result in the formation of phosphacumulenes $Ph_3P{=}C{=}C{=}CR_2$, these were never isolated. The first example of such a phosphacumulene **72** has now been isolated in 90% yield by treatment of alkynylphosphonium salt **71** with piperidine (Equation (30)) <2002BAU148>.



71 **72** (30)

3.17.2.1.2 From (CC + P) precursors

The formation of compound **36** containing both phosphacumulene and ketenimine functions has already been mentioned in Section 3.17.1.2.3.(iii). Five examples of the alkynylphosphonium salts **73** have been prepared as shown in Equation (31) and these are found to exist partly in the phosphacumulene form **74** <1999RJGC1247>.



73 **74** (31)

R^1 = Ph, PhCH=CH, $PhCH_2CH_2$
R^2 = Et, Pr

3.17.2.2 λ^3-Phosphaallenes and $1\lambda^3$-Phosphacumulenes

Since the publication of chapter 3.17.2.2 in <1995COFGT(3)555>, there has been a fair degree of progress in this field largely due to the group of Yoshifuji and involving compounds sterically protected by having a 2,4,6-tri-*t*-butylphenyl group (denoted here by Ar*) on phosphorus.

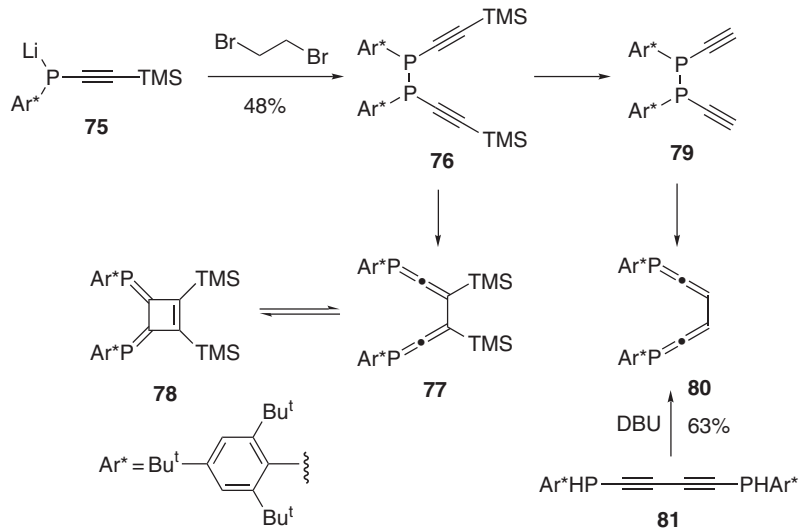
3.17.2.2.1 By the Peterson reaction and related olefinations

The previously reported route involving reaction of Ar*P=C(Li)TMS with Ph_2CO has been used to prepare samples of Ar*P=C=CPh_2 labeled with ^{13}C at either of the cumulene carbons starting from $^{13}CHCl_3$ or $Ph_2{}^{13}CO$ <1998JPC(A)10469>.

3.17.2.2.2 By other routes

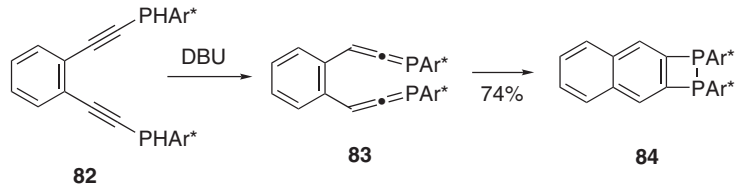
Oxidative coupling of the lithiated silyl alkynyl phosphine **75** with dibromoethane leads to **76** which can be isolated but slowly rearranges at room temperature to the bis(phosphaallene) form **77**

(Scheme 3) <1990CL2195>. On heating this reaches an equilibrium with the cyclic isomer **78**. If the silyl groups are removed from **76** to give **79**, this again rearranges to the isomer **80**, which can be isolated in 5% yield, but undergoes an irreversible cyclization to the compound analogous to **78** upon heating <1992BCJ2297>. Alternative access to compound **77** may be obtained by treating **75** with copper(I) chloride to give the product in 25% yield <1990AG(E)927>. More recently, the sequence of processes from **75** through **76** and **77** to **78** has also been demonstrated with other groups in place of TMS although only the final cyclobutene products were isolated in these cases, the intermediates corresponding to **76** and **77** being detected by NMR spectroscopy <2002OL569>.



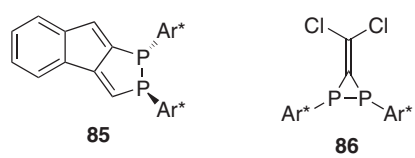
Scheme 3

Compound **80** can also be formed by isomerization of the bis(alkynylphosphine) **81** with DBU as shown, and from this route it is obtained as a mixture of *meso*- and *racemic*-diastereomers <1995TL6429>. Similar isomerization of the bis(alkynylphosphine) **82** with DBU gives ^{31}P NMR signals most likely corresponding to the bis(phosphaallene) **83** at −30 °C, but on warming to room temperature only the cyclized product **84** is obtained (Equation (32)) <1997LA121>. Compound **83** may also be an intermediate in the reaction of 1,2-diethynylbenzene with butyllithium followed by the chlorophosphine Ar*PHCl which gave the product **85** in 19% yield <1997LA121>.



(32)

New approaches to the diphosphabutatriene, Ar*P=C=C=PAr*, include reaction of the dichloromethylenediphosphirane **86** with lithium naphthalenide <1991CL491> and reaction of Ar*P=CCl_2 with BuLi followed by copper(II) chloride <1995CL747> which give the product in yields of 40% and 63%, respectively. The latter method has also been used to prepare the doubly ^{13}C-labeled compound starting from $^{13}CHCl_3$ <2002PCCP4931>.

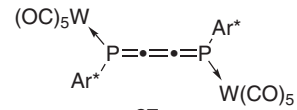


Significant progress has also been made in synthesis of simpler unhindered phosphaallenes <1994TL245>. Isomerization of HC≡C—PHMe with DBU at −20 °C leads to formation of H_2C=C=PMe, which can be detected by NMR spectroscopy and trapped by addition of

propane-2-thiol. Both this phosphaallene and the methylated analogs MeCH=C=PMe and Me_2C=C=PMe can be isolated in 30–40% yield from FVP of precursors of the type R_2C=C(Cl)—PHMe over potassium carbonate, and are sufficiently stable to be characterized by IR and NMR spectroscopy and MS.

3.17.2.2.3 Transition metal complexes of 1λ³-phosphaallenes and 1λ³-phosphacumulenes

Since the publication of chapter 3.17.2.2.3 in <1995COFGT(3)555>, there have been few major advances in this area but the bis(tungsten pentacarbonyl) complex **87** of the diphosphabutatriene has been prepared and its structure determined by X-ray crystallography <1998JOM(553)135>.



87

3.17.2.3 1-Arsacumulenes

There have been no significant developments in the synthesis of arsacumulenes since the publication of chapter 3.17.2.3 in <1995COFGT(3)555> and arsaallenes, as well as the antimony and bismuth analogs of both classes of compound, remain unknown.

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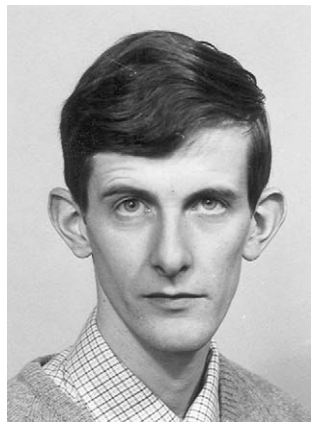
Biographical sketch



Alan Aitken was born in the Dumfries and Galloway area of SW Scotland. He studied at the University of Edinburgh where he obtained a B.Sc. in 1979 and his Ph.D. in 1982 under the direction of Dr. I. Gosney and Professor J. I. G. Cadogan. After spending 2 years as a Fulbright Scholar in the laboratories of Professor A. I. Meyers at Colorado State University he was awarded a Royal Society Warren Research Fellowship and moved to the University of St Andrews in 1984 where he has been a Senior Lecturer since 1997. His research interests are in the area of synthetic and mechanistic organic chemistry including asymmetric synthesis, synthetic use of flash vacuum pyrolysis, heterocyclic chemistry, organophosphorus, and organosulfur chemistry.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 605–619

3.18 Nitriles: General Methods and Aliphatic Nitriles

M. NORTH
King's College London, London, UK

3.18.1 GENERAL METHODS FOR NITRILE SYNTHESIS

This chapter updates the corresponding chapter published in COFGT (1995) <1995COFGT(3)611>, and covers the literature published between 1995 and 2003. A number of reviews dealing with the synthesis of nitriles have been published in COFGT (1995), though these deal with only one of the various approaches for the preparation of this functional group,

and are referenced in the appropriate section of this chapter. The format of this chapter is identical to the corresponding chapter in COFGT (1995), so the general methods used in the synthesis of nitriles have been classified as: by substitution, by addition, by elimination, synthesis from other nitriles, and miscellaneous methods.

3.18.1.1 Synthesis via Substitution Reactions

3.18.1.1.1 Nucleophilic substitutions

A number of developments have taken place in the use of the Mitsunobu reaction to prepare nitriles from alcohols. The combination of triphenylphosphine, diethylazodicarboxylate, and acetone cyanohydrin has been reported to convert alcohols (including propargylic alcohols <1995SC2575>) into the corresponding nitriles <1996SC909>. It has subsequently been reported that the use of tetramethylazodicarboxamide and tributylphosphine with acetone cyanohydrin gives higher yields for these reactions <1999TL7355>.

3.18.1.1.2 Electrophilic substitutions

No further advances have occurred in this area since the publication of chapter 3.18.1.1.2 in <1995COFGT(3)611>.

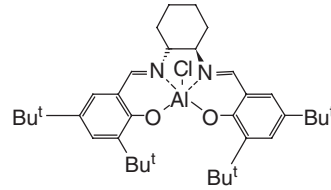
3.18.1.2 Synthesis via Addition Reactions

3.18.1.2.1 Addition to CC multiple bonds

Cyanide is an excellent "soft" nucleophile for Michael additions to conjugated alkenes. The use of diethylaluminum cyanide as the cyanide source allows this reaction to be carried out under homogeneous conditions in a nonprotic solvent <2001T127>. In a variation on this process, treatment of an α,β-unsaturated diester with potassium cyanide results in simultaneous Michael addition, ester hydrolysis, and decarboxylation as shown in Scheme 1 <1998SC3305>. The asymmetric addition of hydrogen cyanide to α,β-unsaturated imides is catalyzed by the aluminum–salen complex **1** <2003JA4442>. The reaction requires 10 mol.% of the catalyst and produces β-cyano imides with 87–98% enantiomeric excess.

Ar = Ph, 3,4-$Cl_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$

Scheme 1



1

Treatment of an alkene with 9-BBN to effect hydroboration followed by sodium cyanide to form a cyanoborate and work-up with a mixture of lead tetraacetate and sodium cyanide results in the overall *anti*-Markovnikov addition of hydrogen cyanide to the alkene <1998JCS(P1)3163>.

3.18.1.2.2 Addition to CX multiple bonds

This section discusses the addition of cyanide to carbonyl compounds or imines leading to racemic or achiral cyanohydrins or α-amino nitriles, respectively. For enantiospecific additions, see Sections 3.18.2.4.1 and 3.18.2.7, respectively. As discussed in COFGT (1995) <1995COFGT(3)611>, one of the most convenient ways of converting carbonyl compounds into cyanohydrins is by treatment with trimethylsilyl cyanide. The addition of trimethylsilyl cyanide to aldehydes and ketones occurs in the absence of a catalyst <1995JCS(P1)2383>, but is also catalyzed by a wide variety of chemicals, with acidic or basic character. A number of new catalysts have been reported for this reaction and are tabulated in Table 1. Ytterbium tricyanide appears to be a particularly active catalyst for both aldehydes and ketones, does not cause any 1,4-addition to α,β-unsaturated carbonyl compounds, and even works with easily enolizable ketones such as β-ketoesters <1995APOC413>. Indium trifluoride is an unusual catalyst in that reactions are carried out in water, and it is completely chemoselective for aldehydes in the presence of ketones <1998SL369>. Indium tribromide is an effective catalyst for the addition of trimethylsilyl cyanide to ketones <2001TL3041>, and unusually, it also catalyzes the sequential 1,4-addition of a nucleophile (indole or thiol) followed by 1,2-addition of trimethylsilyl cyanide to an α,β-unsaturated ketone, thus allowing the synthesis of β-(3-indoyl)- or β-thio-cyanohydrins <2002JOC3700>. The lithium complex **2** is not only a very active catalyst for additions to even sterically hindered ketones, it also gives very high diastereoselectivities where two diastereomeric products are possible <2001OL553>. This catalyst also catalyzes the addition of *t*-butyldimethylsilyl cyanide to ketones, again with high diastereoselectivity, though in this case it is necessary to use 25–50 mol.% of the catalyst.

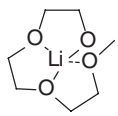
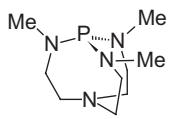
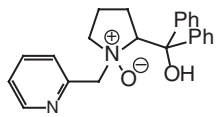
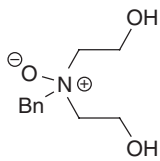
In addition to the well-defined catalysts included in Table 1, a number of insoluble catalysts for the addition of trimethylsilyl cyanide to carbonyl compounds have also been reported. A polymer-supported dicyanoketene acetal was prepared by Tanaka and Masaki and found to catalyze the addition of trimethylsilyl cyanide to aldehydes in high yield, but to only give low yields with ketones as substrates <1999SL1277>. Montmorillonite-K10 was reported to be an effective catalyst for the addition of trimethylsilyl cyanide to aldehydes <1998SC2043>, and potassium-exchanged zirconium hydrogen phosphate was found to be an effective catalyst for the addition to both aldehydes and ketones <1999SL315>.

The addition of trimethylsilyl cyanide to α,β-unsaturated ketones can occur by either a 1,2- or a 1,4-addition. It has been shown that low temperatures and basic catalysts favor 1,2-addition, whereas high temperatures and acidic catalysts favor 1,4-addition <1999TL5923, 2000T6533>.

Magnesium bromide has been reported to be a good catalyst for the diastereoselective addition of cyanide to α-alkoxyaldehydes to give selectively the *syn*-diastereomer of the product <2000OL57>. This reaction occurs with trimethylsilyl cyanide as the cyanide source, but better results are obtained using tetraethylammonium silver(II) cyanide as this allows reactions to be carried out at -78 °C, resulting in higher diastereoselectivities. In general, trimethylsilyl cyanide is not the best reagent for diastereoselective additions to chiral aldehydes and ketones, and diethylaluminum cyanide often gives better results, especially if the carbonyl compound contains a second functional group capable of forming a chelated complex. Particularly good results have been reported for the diastereoselective cyanation of α-sulfinylaldehydes <1998TA859>, α-sulfinyl ketones <1999TA2935, 2001TL261>, α-aminoaldehydes <2001TA347>, and β-aminoaldehydes <2002OL4519>.

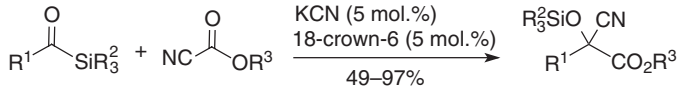
Acyl cyanides (RCOCN) and cyanoesters (ROCOCN) make convenient cyanating agents, and on reaction with carbonyl compounds they lead directly to cyanohydrin esters or carbonates which are more stable than free cyanohydrins or cyanohydrin trimethylsilyl ethers. The addition reaction is base-catalyzed, and Okimoto and Chiba <1996S1188> have shown that aqueous potassium carbonate is a suitable base for the addition of both acylcyanides and methyl cyanoformate to aldehydes, giving the cyanohydrin derivatives in 79–96% yield. The addition of methyl cyanoformate to aldehydes and ketones is induced by secondary amines, with diisopropylamine giving particularly good results <1999SL1423, 2000T5995>. A large excess of both methyl cyanoformate (5–10 equiv.) and diisopropylamine (20 equiv.) are required, however, in contrast,

Table 1 Catalysts for the addition of trimethylsilyl cyanide to aldehydes and ketones

Catalyst	*Mol.* (%)	*Aldehyde substrates?*	*Ketone substrates?*	*Yields* (%)	*References*
$Yb(CN)_3$	10	Yes	Yes	68–>99	<1995APOC413>
$Yb(OTf)_3$	2–10	Yes	Yes	55–95	<1997SL1379>
$Cu(OTf)_2$	5	Yes	Yes	70–95	<1998TL3823>
InF_3	30	Yes	No	75–95	<1998SL369>
$InBr_3$	1	Not studied	Yes	27–97	<2001TL3041>
R_2SnCl_2[a]	2–10	Yes	Yes[b]	71–97	<1996TL2525>
$BiBr_3$	0.5–1	Yes	Yes	75–92	<1997TL7215>
$LiClO_4$ or $LiBF_4$	10–300	Yes[c]	Yes	10–100	<1999TL491>
 **2**	0.1–5	Yes[c]	Yes	91–98	<2001OL553>
Tetracyanoethene	20	Yes	Yes[b]	74–93	<1995JCS(P1)2155>
$Me_3SiN(SO_2F)_2$	1	Yes	Yes	86–94	<1996SC1925>
	10	Yes	Yes	33–95	<2002JOM(646)161>
	10	Not studied	Yes	42–97	<2002SL793>
	10	Not studied	Yes	76–93	<2002SL793>
Iodine	5	Not studied	Yes	82–92	<2002TL9703>

[a] R = Bu or Ph. [b] Only methyl ketones were studied. [c] Only benzaldehyde studied.

the addition of ethyl cyanoformate to α,β-unsaturated aldehydes, leading to allylic cyanohydrin carbonates, is catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO), and requires only 1.5 equiv. of the cyanoformate and 10 mol.% of the catalyst to obtain yields in excess of 90% <2001JOC7191>. The reaction between methylaryl ketones and diethyl cyanophosphonate is catalyzed by lithium diisopropylamide (LDA) and leads to cyanohydrin diethylphosphate esters <2002JCS(P1)1115>. A combination of lithium cyanide and diethyl cyanophosphonate has also been used to convert aldehydes into cyanohydrin diethylphosphate esters <1999JA9143>. The reaction between acylsilanes and cyanoformate esters is catalyzed by a combination of potassium cyanide and 18-crown-6 and leads to the cyanohydrin trimethylsilyl ethers of α-ketoesters as shown in Scheme 2 <2002OL2957>.

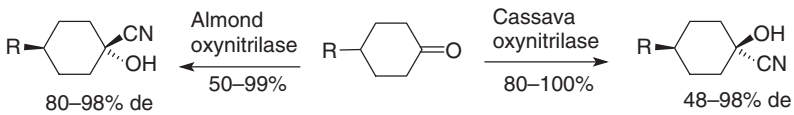


R^1 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, $CH_3(CH_2)_5$, *iso*-Pr, *t*-Bu, 2-furanyl
R^2_3 = Et_3, $Me_2{}^tBu$
R_3 = Et, Bn, *t*-Bu

Scheme 2

Cyanohydrin esters and carbonates can also be obtained by treatment of an aldehyde with aqueous sodium or potassium cyanide and an acid chloride or chloroformate ester in the presence of a phase transfer catalyst such as benzyltrimethylammonium chloride <1998TL4925, 2003TL1019>. Alternatively, α-bromonitriles react with carboxylic acids in the presence of triethylamine to give cyanohydrin esters <2001BMC33>. The reaction between an aldehyde, acetone cyanohydrin, and isopropenylacetate is catalyzed by $Cp^*_2Sm(THF)_2$ (10 mol.%) and leads to cyanohydrin acetates in 49–90% yield <1999JOC4214>. With α,β-unsaturated carbonyl compounds, 1,4-addition of cyanide occurs as well as (with aldehyde substrates) or instead of (with ketone substrates) 1,2-addition. The tin(II) bromide-catalyzed addition of trimethylsilyl cyanide to 2-naphthaldehyde in the presence of acetyl bromide provides a one-pot synthesis of the corresponding cyanohydrin acetate <2002TA1059>.

In most cases, the enzyme-catalyzed addition of cyanide to carbonyl compounds generates a nonracemic chiral cyanohydrin and so is discussed in Section 3.18.2.4.1. However, Effenberger and co-workers <2002AG(E)1876, 2002CJC671> have studied the enzyme-catalyzed hydrocyanation of 4-substituted cyclohexanones. The oxynitrilase enzymes from almonds and from cassava were found to catalyze the formation of opposite diastereomers of the 4-substituted cyclohexanone cyanohydrins as shown in Scheme 3.



R = Me, Et, Pr, iso-Pr, *t*-Bu, Ph, C(Me)=CH_2

Scheme 3

The three-component condensation of a carbonyl compound, an amine and potassium cyanide to form an α-aminonitrile, known as the Strecker reaction, is such a well-established process that there has been little new work reported in this area since 1995. It has, however, been reported that the reaction can be carried out under nonaqueous conditions by using indium trichloride as a catalyst in THF <2002T2529>.

A modern variation of the Strecker reaction uses trimethylsilyl cyanide in place of potassium or sodium cyanide. This has the advantage that all components of the reaction are soluble in organic solvents, thus allowing Strecker reactions to be carried out under nonaqueous conditions. It is sometimes difficult, however, to prepare α-aminonitriles derived from ketones, especially if the amine is also sterically hindered. It has been shown that this difficulty can be overcome by carrying out the reactions at high pressures, up to 600 MPa <2002TL9167, 2003TL447>. A number of catalysts have also been reported for this reaction, including lithium perchlorate <1998TL3049>, a polymer-supported scandium triflate <1996TL9221>, and ytterbium triflate <1997SL115>. The latter catalyst is interesting since it has been shown to catalyze the chemoselective addition of trimethylsilyl cyanide to an imine in the presence of an aldehyde, thus reversing the usual reactivity of these two functional groups <1997JA10049>. The use of acetone cyanohydrin as a cyanide source for the formation of an α-aminonitrile from a preformed imine has been reported <1996TL8655>, and dialkylcyanoboranes [$(R_2N)_2BCN$] have been shown to function as both the amine and cyanide source, giving α-aminonitriles when treated with an aldehyde <2002CC1392>.

It is also possible to use other nitrogen-based nucleophiles in place of the amine in a Strecker reaction. Thus, lithium perchlorate will catalyze the condensation of an aldehyde, a hydroxylamine, and trimethylsilyl cyanide leading to *N*-hydroxy-α-aminonitriles <2000TL2471> and the condensation between an aldehyde, a hydrazine, and trimethylsilyl cyanide to give α-cyanohydrazines <2002CL368>. The addition of trimethylsilyl cyanide to preformed *N*-benzoylhydrazones is also catalyzed by hafnium triflate <1999JOC8054>. Both trimethylsilyl cyanide and diethylaluminum cyanide add to nitrones in high yield even in the absence of a catalyst <1996JOC9028>. However, if the nitrone is chiral, then the addition of trimethylsilyl cyanide is generally more diastereoselective than the addition of diethylaluminum cyanide <2003TA367>.

Whilst the imine needed for a Strecker reaction is almost always generated from a carbonyl compound and a primary amine, it can also be generated by the oxidation of an amine. Thus, electrolysis of a tertiary amine in the presence of sodium cyanide leads via an imine or iminium ion to an α-aminonitrile <1997LA259, 1997LA2089, 1999EJO2645>. In a related process, treatment of a tertiary amine with singlet oxygen in the presence of trimethylsilyl cyanide has been used to form an α-aminonitrile <2001H(55)545>. Similarly, treatment of a tertiary amine with triphenylmethyltetrafluoroborate in the presence of potassium cyanide forms an α-aminonitrile <2002T3689>. Cyanohydrins can also be converted into α-aminonitriles in a one-pot procedure, simply by treatment with the appropriate amine <2000OL3337>.

3.18.1.3 Synthesis via Elimination Reactions

3.18.1.3.1 Elimination from carbonyl derivatives

A large number of dehydrating agents are known to induce the conversion of carbonyl derivatives into nitriles <1995COFGT(3)611>. Whilst most methods involve the initial formation of a nitrogen-containing aldehyde derivative (oxime, hydrazone, etc.), microwave irradiation or direct heating of a mixture of an aldehyde and hydroxylamine hydrochloride in NMP leads directly to the corresponding nitrile <1999T13265, 2001IJC(B)1000>. *O*-*t*-butyldimethylsilyl aldoximes can be converted into nitriles simply by heating with imidazole in DMF <1998SC2807>. Oximes can be dehydrated to nitriles by treatment with Burgess reagent or PEG-supported Burgess reagent in refluxing THF <2000SL1169> or by treatment with carbonyldiimidazole <2002JOC6228>.

N,*N*-Dimethyl hydrazones derived from aldehydes undergo oxidative elimination on treatment with dimethyldioxirane to form nitriles in >90% yield after reaction times of just 2–3 min at 0 °C <1998TL2009>. RAMP and SAMP hydrazones are versatile chiral auxiliaries in asymmetric synthesis. They are usually cleaved by hydrolytic or reductive methods, but treatment of an RAMP/SAMP hydrazone with MCPBA in the presence of solid sodium carbonate <1999TA1145> or magnesium monoperoxyphthalate buffered to pH 7 <2000EJOC3337> has been shown to result in elimination of the hydrazone to the corresponding nitrile without causing overoxidation of other functional groups within the substrate.

3.18.1.3.2 Elimination from carboxylic acid derivatives

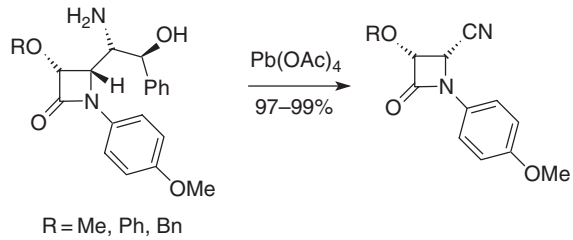
The dehydration of primary amides to nitriles has been reported to occur under very mild conditions, even at −78 °C, by using oxalyl chloride and DMSO as the dehydrating agent <2002T3561>. Alternatively, treatment of carboxylic acids with oxalyl chloride followed by 2,4-dinitrobenzenesulfonamide provides a one-pot procedure for the conversion of acids into nitriles <1998T9281>.

3.18.1.3.3 Elimination from nitro compounds

Treatment of primary nitro compounds with butyl isocyanate and triethylamine results in dehydration to form a nitrile <1997TL3391>.

3.18.1.3.4 *Elimination from amines and amino acids*

Oxidation of a β-aminoalcohol with lead tetraacetate results in oxidative cleavage of a carbon—carbon bond leading to a nitrile <1996T8989>. As the example shown in Scheme 4 illustrates these conditions are mild enough to preserve a β-lactam ring.



Scheme 4

3.18.1.4 Synthesis from Other Nitriles

The cyano- or nitrile functionality within a compound is particularly versatile and facilitates a number of reactions which lead to other nitriles. For example, α,β-unsaturated nitriles readily undergo Diels–Alder reactions, [2 + 2]-cycloadditions <2002H(57)665>, and Michael addition reactions <1997TL5881, 1998TL5775, 1999TL2331>. The latter process can also be used to form cyanocyclopropanes if the nucleophile contains a suitable leaving group <1997TL7951>. Tandem Michael additions and anion alkylations can also be carried out to simultaneously functionalize the α- and β-positions of the nitrile <2002T3371>.

Protons on a carbon adjacent to a nitrile are acidic (even if the nitrile contains an oxygen <1998SL1261> or nitrogen <1997JCR(S)254, 2002SL895> in the α-position) and can be removed by a suitable base to generate an enolate-like system that reacts with a wide variety of electrophiles and which undergoes Michael additions <1998JCR(S)226>. Many of these reactions lead to nitriles functionalized with specific functional groups and are discussed in the appropriate sections below. This methodology can also be used to prepare cyclic nitriles (for a review see <2002T1>), including cyclopropane derivatives <1999TA2583>, 2-cyano azetidines <2002TA297, 2002TA2619>, and macrocycles <1998TL7839>, and has also been used to cleave macrocycles from a polymeric support <1998SL1261>.

Cyanohydrins can be deoxygenated by treatment with thiocarbonyldiimidazole, DMAP, tributyltin hydride, and AIBN in the presence of light to form nitriles <2000OL1895>. When combined with the addition of cyanide to an aldehyde to form the cyanohydrin (see Section 3.18.1.2.2), this provides a methodology for the one-carbon homologation of an aldehyde to a nitrile. Treatment of a 1,1-dicyanide with tributyltin hydride and AIBN results in reductive decyanation, leading to mononitriles <1995TL5159>. The same reaction can be achieved with samarium(II) iodide <1995TL7661>.

3.18.1.5 Miscellaneous Methods of Synthesis

The rearrangement of an isonitrile to a nitrile normally requires very high temperatures (>250 °C). However, the reaction has been found to be catalyzed by samarium(II) iodide in HMPA and the catalyzed reaction occurs at −78 °C <1997CC821>. Under these remarkably mild reaction conditions, even a penicillin-derived isonitrile could be rearranged without decomposition.

3.18.2 ALIPHATIC NITRILE SYNTHESIS

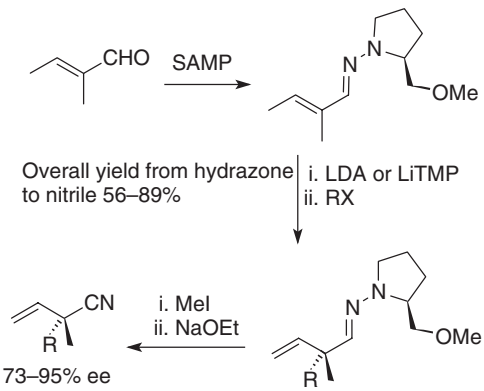
3.18.2.1 Saturated Unsubstituted Nitriles

No further advances have occurred in this area since the publication of chapter 3.18.2.1 in <1995COFGT(3)611>. These compounds are prepared using any of the general methods discussed in Section 3.18.1.

3.18.2.2 β- and More Remotely Unsaturated Nitriles

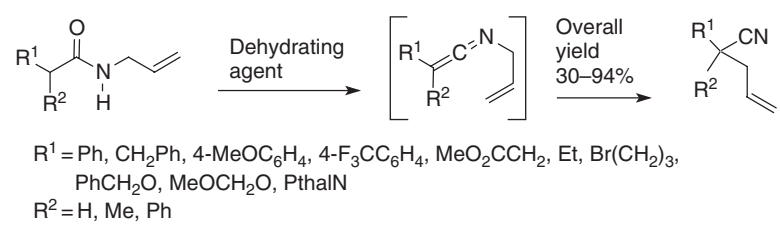
3.18.2.2.1 Aliphatic nitriles with one double bond

Allylic acetates and carbonates react with trimethylsilyl cyanide in the presence of tetrakis(triphenylphosphine)palladium(0) to give β,γ-unsaturated nitriles with reaction occurring at the less hindered end of the intermediate π-allyl palladium complex <1998OM4835>. β,γ-Unsaturated nitriles can also be prepared by a variation on the Knoevenagel condensation in which an aldehyde is condensed with cyanoacetic acid in the presence of piperidinium acetate, though this method lacks any stereocontrol <1998JCS(P1)3529>. Enantiomerically pure α,α-disubstituted β,γ-unsaturated nitriles can be prepared from α,β-unsaturated aldehydes by RAMP/SAMP methodology as shown in Scheme 5 <1996SL645>.

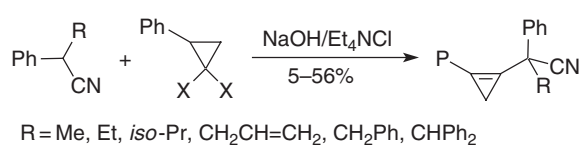


Scheme 5

Allylic amides can be converted into β,γ-unsaturated nitriles by a route involving an aza-Cope rearrangement as illustrated in Scheme 6. The rearrangement occurs at room temperature under neutral conditions, thus permitting a very mild synthesis of this class of nitriles <1996JOC55>. Nitriles bearing a (1-cyclopropenyl) group in the β-position can be prepared from benzylic nitriles and 1,1-dihalocyclopropanes as shown in Scheme 7 <1996S1073>.

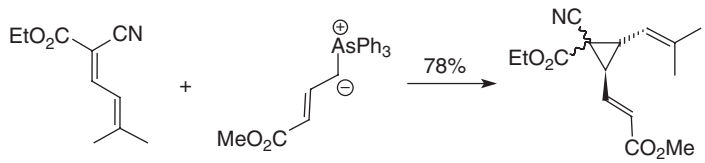


Scheme 6



Scheme 7

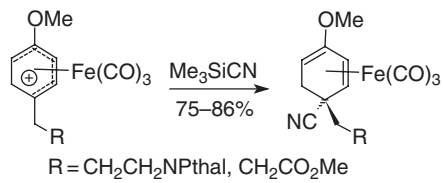
The palladium(0)-catalyzed reaction between the benzophenone imine of aminoacetonitrile and vinylepoxides leads to α-amino-ε-hydroxy-γ,δ-unsaturated nitriles <1997TL2167>. α-Cyanophosphonate anions undergo a Michael addition to acrylonitrile to give a new α-cyanophosphonate anion which undergoes a Wadsworth–Emmons reaction with an aldehyde to produce (*E*)-γ,δ-unsaturated nitriles <2000SC445>. A bis-γ,δ-unsaturated nitrile has been prepared from an arsonium ylid as shown in Scheme 8 <1997SL126>.



Scheme 8

3.18.2.2.2 Aliphatic nitriles with more than one double bond

The radical anion formed during the Birch reduction of an aromatic system can be trapped with iodoacetonitrile, leading to 3-cyanomethyl-cyclohexa-1,4-dienes <1996TL5853>. Iron dienyl cations react with trimethylsilyl cyanide to produce iron-complexed diene-containing nitriles as shown in Scheme 9 <1996TL4515, 1996JOC3996>.

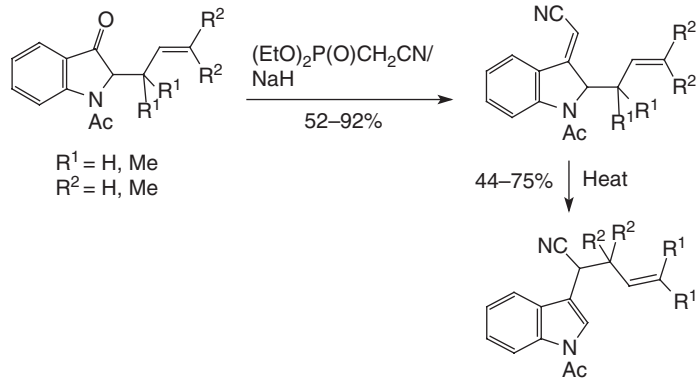


Scheme 9

3.18.2.2.3 Aliphatic nitriles with aryl or heteroaryl substituents

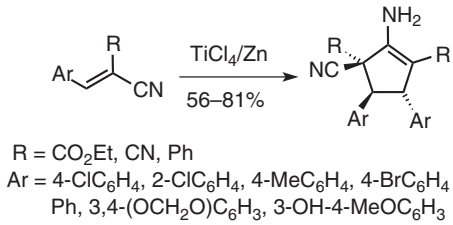
The direct displacement of benzylic halides by sodium cyanide can be carried out in a three-phase hexane/water/solid mixture by employing surfactant–clay composites as phase-transfer catalysts <1999GC95>. Best results are obtained by using tetramethylammonium chloride supported on montmorillonite K10 clay. Doubly benzylic chlorides ($Ar_2C(Cl)R$) undergo S_N1 cleavage upon treatment with silver hexafluoroantimonate and the resulting carbocations can be trapped with trimethylsilyl cyanide, leading to benzylic nitriles <1995JOC5925>. Dimethyl 2-cyano-cyclopropane-1,1-dicarboxylate undergoes ring opening when treated with nitrobenzene derivatives in the presence of potassium *t*-butoxide, leading to benzylic nitriles <1998TL9523>.

Treatment of an aromatic or heteroaromatic aldehyde with diethyl cyanophosphonate in the presence of samarium(II) iodide and a catalytic amount of lithium cyanide results in the formation of arylacetonitriles by deoxygenation of the intermediate cyanohydrin phosphonate <2003TL2903>. Reaction of pyrrole aldehydes withTosMIC also leads directly to pyrrole acetonitriles <1995SC787>. Aromatic ketones (ArCOR) can be converted into nitriles by reaction with 2-aminoacetonitrile to form an imine which on heating in DMF in the presence of potassium carbonate rearranges to a 2-aryl-alkylnitrile (ArCH(R)CN) <1999JCS(P2)2485, 2002JCS(P2)1033>. 2-Allyl-indolin-3-ones undergo a Wadsworth–Emmons reaction to form α,β-unsaturated nitriles which undergo reverse aromatic Cope rearrangements leading to indole alkylnitriles as shown in Scheme 10 <2001JOC1200>.



Scheme 10

β-Aryl-α,β-unsaturated nitriles undergo reductive dimerization when treated with titanium tetrachloride and zinc to form 1-amino-2-cyano-3,4-diaryl cyclopentenes as shown in Scheme 11 <1998S851>. (Aryl)chromium tricarbonyl arene complexes react with lithioacetonitrile to give chromium-complexed benzylic nitriles from which the chromium tricarbonyl unit can be removed by treatment with iodine <2000ICA(300-302)693>. The benzylic protons of a benzylic nitrile are sufficiently acidic to be removed even by potassium hydroxide, and the resulting nitrile stabilized anion will react with electrophiles such as potassium chloroacetate to give more functionalized benzylic nitriles <2001S1311>.



Scheme 11

3.18.2.2.4 Aliphatic nitriles with one or more CC triple bonds

No further advances have occurred in this area since the publication of chapter 3.18.2.2.4 in <1995COFGT(3)611>. These compounds are prepared using the general methods discussed in Section 3.18.1.

3.18.2.3 Halo-substituted Aliphatic Nitriles

Nitriles can be α-fluorinated by deprotonation followed by reaction of the nitrile-stabilized anion with $FClO_3$ <1998CC365>. The same reaction can also be accomplished using *N*-fluorobenzenesulfonimide as the electrophilic fluorine source <1999TL4149>. α-Thionitriles react with IF_5/Et_3N/HF to give α-fluoro-α-thionitriles <2002BCJ1597>. Another approach to α-fluoronitriles involves treatment of an aldehyde with trimethylsilyl cyanide to form a cyanohydrin trimethylsilyl ether (see Section 3.18.1.2.2) followed by addition of DAST to give the α-fluoronitrile. The resolution of α-fluoronitriles using nitrilase enzymes has also been reported <2001TA279>.

Ring opening of cyanoepoxides by hydrogen fluoride/pyridine provides access to β-fluorocyanohydrins, addition of fluoride occurring at the end of the epoxide remote to the cyano group <1996SC237>. The same process occurs when cyanoepoxides are treated with hydrogen chloride, leading to β-chlorocyanohydrins <1997BSF111>.

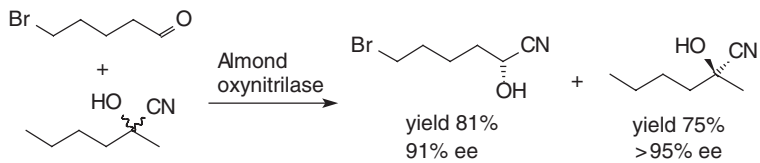
3.18.2.4 Aliphatic Nitriles Bearing an Oxygen-based Functional Group

3.18.2.4.1 α-Oxygenated nitriles

Methods for the synthesis of racemic or achiral α-oxygenated nitriles (cyanohydrin derivatives) by the addition of cyanide to carbonyl compounds were discussed in Section 3.18.1.2.2. In this section, methods for the synthesis of nonracemic cyanohydrins will be described. This is an area which has exploded in importance since the 1990s; a comprehensive 2003 review of the area <2003TA147> contains almost 150 references to the literature since 1993. Most of the interest is in the development of asymmetric catalysts for the addition of cyanide to carbonyl compounds and the catalysts can be classified as enzymes, diketopiperazines, Lewis acids, and Lewis bases, each of which will be discussed in turn.

Prior to 1995 <1995COFGT(3)611>, the only widely used enzyme for asymmetric cyanohydrin synthesis was the readily available (*R*)-oxynitrilase obtained from almonds (*Prunus amygdalus*). Since then, oxynitrilase enzymes have been isolated from many other sources and the most important (those with the broadest substrate tolerances and highest enantiospecificities) have been cloned and overexpressed. Thus, both (*R*)- and (*S*)-oxynitrilases which accept aldehydes and ketones as substrates are now commercially available. Enzymatic cyanohydrin synthesis has been the subject of a number of reviews <1997CC1933, 1999TCC194, 1999C3, 1999CRV3649, 2000CUOC283, 2003TA147>.

The (*R*)-oxynitrilase from almonds has been shown to accept ethyl ketones <1995TA2945> and bicyclo[3.2.0]hept-2-en-6-one <1999TL7407> as substrates in addition to the methyl ketones which were previously known to be substrates for this enzyme. Whilst the almond oxynitrilase enzyme can be used in a wide range of aqueous and organic solvents, it appears that the optimal conditions involve the use of an organic solvent and a minimal amount of water to form an emulsion <1998TA1835, 2001TA971>. Under these conditions the enzymatic addition is optimized, whereas the nonenzymatic addition of cyanide to the carbonyl compound is suppressed. The oxynitrilase enzyme has also been entrapped in a cross-linked poly(vinylalcohol) lens, allowing it to be easily reused through at least 21 reaction cycles <2001OL1969>. An ingenious application of the almond oxynitrilase enzyme is the transfer of hydrogen cyanide from a racemic ketone cyanohydrin to an aldehyde, thus allowing the simultaneous synthesis of the (*S*)-cyanohydrin of the ketone and the (*R*)-cyanohydrin of the aldehyde <1995CC989, 1997TA1551>. An example of this process is shown in Scheme 12. (*R*)-Oxynitrilases have also been isolated from apples, apricots, cherries, plums, peaches, and loquats <1997TA1225, 1999TA3531>. These enzymes are much less readily available than the almond enzyme, but may give better chemical yields and enantiomeric purities for specific substrates.



Scheme 12

Early work on (*S*)-oxynitrilases focused on the enzyme obtained from *Sorghum bicolor* as this was the only readily available natural source of an (*S*)-oxynitrilase <1996TA1105>. However, this enzyme was too difficult to isolate and had too narrow a substrate tolerance to become widely used, and advances in genetic engineering have allowed other (*S*)-oxynitrilases to be cloned and overexpressed. The first oxynitrilase enzyme to be obtained in this way was the enzyme isolated from cassava (*Manihot esculenta*) <1996AG(E)437>. The recombinant form of this enzyme was found to be 25 times more active than the natural enzyme, and to catalyze the addition of hydrogen cyanide to a wide range of aldehydes and methyl ketones <2000CEJ2564>, giving (*S*)-cyanohydrins with up to 98% enantiomeric excess.

A second (*S*)-oxynitrilase (isolated from the leaves of the rubber tree, *Hevea brasiliensis*) has also been cloned and overexpressed. This enzyme appears to give particularly good results with α,β-unsaturated aldehydes <1995TA845> as well as with benzaldehydes, furan-aldehydes, thiophene-aldehydes, and cyclohexane-carbaldehydes <1996T7833>. Propargylic aldehydes and

methyl ketones are also good substrates, provided the enzyme is used in a biphasic (aqueous buffer/methyl *t*-butylether) solvent system <1998T14477>. Aliphatic aldehydes with substituents at the α- or β-position however, are generally not good substrates for this enzyme <2001T2213, 2002T2979>. An interesting recent application of this enzyme is the enantiospecific addition of hydrogen cyanide to formylferrocene and to 1,1′-diformylferrocene, giving the corresponding cyanohydrin and biscyanohydrin with 96–99% enantiomeric excess <2003TA355>.

Interest in diketopiperazine-catalyzed addition of hydrogen cyanide to aldehydes has decreased markedly since the 1990s, probably due to the difficulty in studying the heterogeneous reaction and the failure of all attempts to optimize the catalyst structure beyond *cyclo*-[(*S*)-His-(*S*)-Phe] discovered by Inoue in 1979. Kellogg and co-workers <1997TA1987> have shown that the phenylalanine residue of *cyclo*-[(*S*)-His-(*S*)-Phe] can be replaced by an α-methylphenylalanine unit without loss of catalytic activity. Lipton and co-workers <1998JOC4604> discovered that addition of a cyanohydrin at the start of a reaction raises the enantiomeric excess of the product cyanohydrin. The added cyanohydrin can have a different structure to the cyanohydrin produced during the reaction, and can be racemic or achiral.

Probably the single most important development in asymmetric cyanohydrin synthesis since the 1990s has been the development of effective chiral Lewis acids for the asymmetric addition of trimethylsilyl cyanide to aldehydes and ketones. The COFGT (1995) cites just eight papers in this area <1995COFGT(3)611>, whereas Table 2 lists just the titanium-based systems that have been developed in subsequent years. A dendrimer-supported binaphthol ligand has also been prepared <2000CEJ3692> and was found to be at least as enantioselective in the addition of trimethylsilyl cyanide to pivaldehyde as the homogeneous ligand (entry **1** in Table 2). The enantioselectivity of the dendritic catalyst increased as the catalyst was reused during the first five cycles of reuse. Thereafter, the enantioselectivity decreased, but even after 20 cycles similar enantioselectivity to homogeneous binaphthol was observed.

Of the catalysts shown in Table 2, by far the most effective are the titanium complexes of cyclohexyl–salen ligand **3** and of phosphine oxide **4**. The titanium complexes of ligand **3** developed from an *in situ* formed species generated using titanium tetraisopropoxide <1996TA851, 1997JCS(P1)1293>, through a more active and isolable titanium dichloride complex <1998CC387, 1999JA3968>, to the most active catalyst **5** which is an isolable, bimetallic complex generated from ligand **3**, titanium tetraisopropoxide and water <1999JA3968>. Not only is catalyst **5** active at far higher substrate to catalyst ratios than any of the other complexes shown in Table 2, it is also active at room temperature and reactions with aldehyde substrates take just a few minutes. Catalyst **5** was also the first catalyst ever reported for the asymmetric addition of trimethylsilyl cyanide to ketones at atmospheric pressure <1999TL8147, 2001T771>. It has been reported that by changing the *t*-butyl groups of ligand **3** to *t*-pentyl groups, an even more enantioselective titanium complex can be formed <2002JOC2702>. However, it is not clear if the increase in enantioselectivity is actually due to the change in the substituents or to small differences in the reaction conditions. Another unique feature of catalyst **5** is that it is the only known catalyst for asymmetric cyanohydrin synthesis, which is compatible with potassium cyanide as the cyanide source, thus avoiding the use of volatile and hence hazardous hydrogen cyanide or trimethylsilyl cyanide. Thus, treatment of an aldehyde with potassium cyanide and acetic anhydride in the presence of 1 mol.% of catalyst **5** generates cyanohydrin acetates with 6–93% enantiomeric excess as shown in Scheme 13 <2002CC244, 2002HCA3301>.

Shibasaki has developed the titanium complexes of ligands **4** as highly effective catalysts for the asymmetric addition of trimethylsilyl cyanide to ketones. The initial ligand (X = Y = H) was reasonably active, but 10 mol.% of the catalyst was required to convert ketones into cyanohydrin trimethylsilyl ethers with 76–95% enantiomeric excess for reactions carried out at −30 °C to −50 °C <2000JA7412>. By changing X to an electron-withdrawing benzoyl group, the amount of catalyst needed could be reduced to 1–2.5 mol.%, the reaction temperature could be raised to −10 °C to −45 °C and the enantiomeric excess of the products were raised to 82–94% <2001TL691>. In some cases, still higher enantioselectivity was observed with the ligand in which X = Y = F <2003SL353>.

Whilst titanium has so far been the most popular metal ion for the development of chiral Lewis acids for asymmetric cyanohydrin synthesis, a number of other systems have also been studied. Ligand **3** has also been complexed to vanadium(IV) to form vanadyl complex [**3** V = O] and to vanadium(V) to form [**3** V = O·H_2O]$^+$ $EtSO_4^-$. The vanadium(IV) complex was found to catalyze the asymmetric addition of trimethylsilyl cyanide to aldehydes, and to be more enantioselective than the corresponding titanium(IV) complex **5** <2000OL1617, 2001T771>. Interestingly, the vanadium(V) complex was totally inactive for this reaction, but did catalyze the

Table 2 Chiral ligands for titanium-catalyzed asymmetric cyanohydrin synthesis

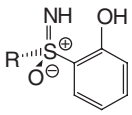
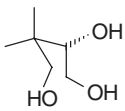
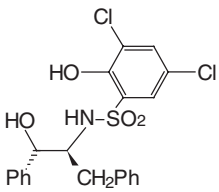
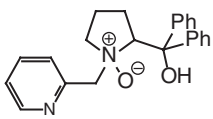
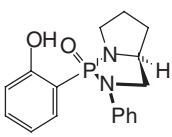
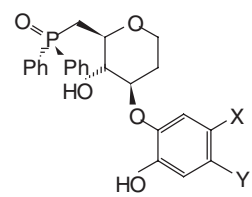
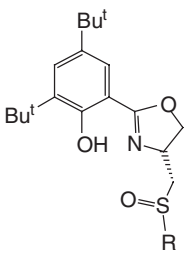
Chiral ligand	*Catalyst* (mol.%)	*Ketones as substrates*	*Enantiomeric excess* (%)	*References*
Binaphthol	20	No	0–75	<1997TL6229>
 R = Me, Et, i-Pr, *t*-butyl, CH_2CH_2Ph	20	No	37–91	<1995TL1625, 1996ACS305>
	1	Yes[a]	32–60	<1997TL6669>
	10	No	77–96	<2000CC1963>
	20	Yes	25–69	<2002SL1353>
	10	No	3–98	<1999TA1979>
 X = H, F, COPh Y = H, F X–Y = HC=CH–CH=CH **4**	1–10	Yes	69–97	<2000JA7412, 2001TL691, 2003SL353>
 R = Me, *t*-Bu	9	No	0–61	<2003SL236>

Table 2 (continued)

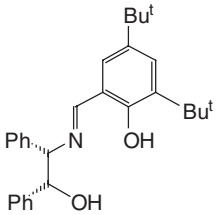
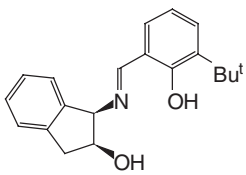
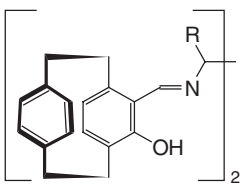
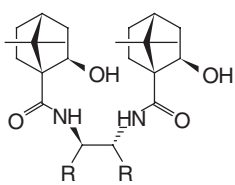
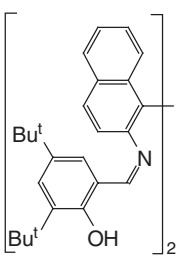
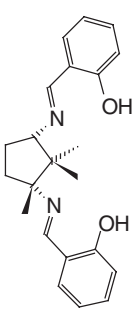
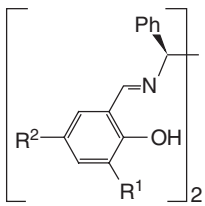
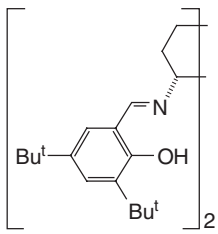
Chiral ligand	*Catalyst* (mol.%)	*Ketones as substrates*	*Enantiomeric excess* (%)	*References*
	20	No	49–92	<1995TA405, 1995TA2915>
	20	No	20–95	<2000OM2153, 2002TA149>
 R = H, CH_2CH_2	10	No	84	<1997TA3245>
 R = Ph, CH_2CH_2	15	No	87–99	<1998JOC6762, 2002CC54>
	20	No	63–93	<1999JCS(D)3303>
	20	No	30–73	<2001SC3031, 2001TA1579>

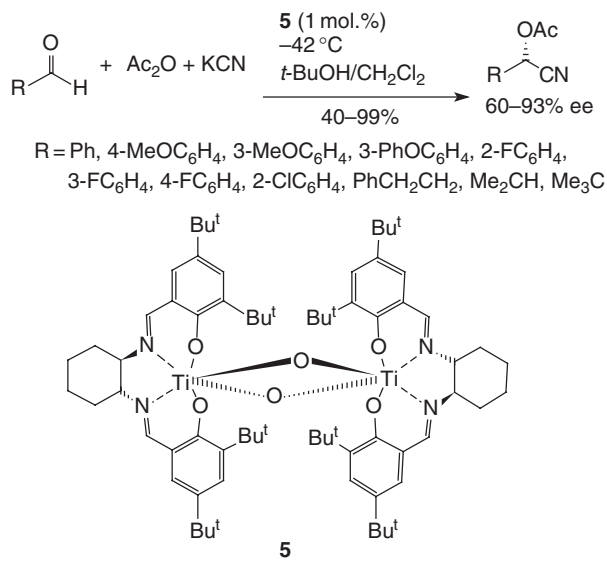
Table 2 (continued)

Chiral ligand	*Catalyst* (mol.%)	*Ketones as substrates*	*Enantiomeric excess* (%)	*References*
 R^1 = H, *t*-Bu, $CHPh_2$, OMe R^2 = H, *t*-Bu, Me, NO_2, OMe, Br, Cl	2–10	Yes[b]	22–87	<1996SL337, 1997T14327, 2003OL949>
 **3**	0.1	Yes	52–92	<1996TA851, 1997JCS(P1) 1293, 1998CC387, 1999JA3968, 1999TL8147, 2001T771, 2002CC244>

[a] Substituted acetophenones studied at high pressure (0.8 GPa). [b] Addition to ketones requires the additional presence of *N*,*N*-dimethylaniline *N*-oxide as a co-catalyst.

asymmetric addition of potassium cyanide to aldehydes as shown in Scheme 13 <2002HCA3301>. A silica-supported version of the vanadium(IV) complex has also been prepared and was found to be a slightly less enantioselective catalyst than the homogeneous complex <2003JCA(215)199>.

Holmes and Kagan <2000TL7453, 2000TL7457> have shown that the monolithium salts of binaphthol and **3** are also effective catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes, with the salt of **3** being the more enantioselective (ee of cyanohydrins 0–97%).

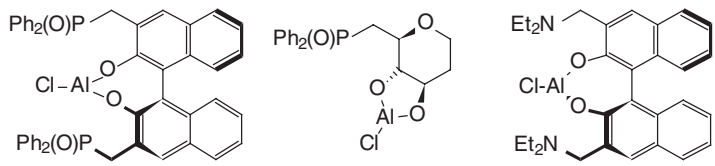


5

Scheme 13

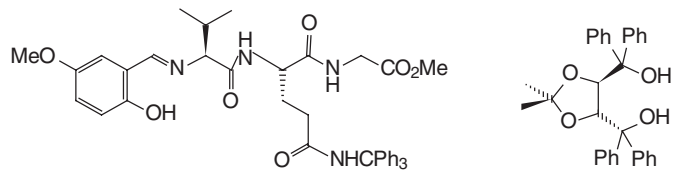
Interestingly, the absolute configuration of the cyanohydrins prepared using the lithium salt of ligand **3** is the opposite to that obtained using the titanium or vanadium complex of **3**. Hence, either enantiomer of a cyanohydrin can be prepared from either enantiomer of ligand **3** simply by choosing the appropriate metal complex. The same effect has been noted by Shibasaki for reactions using ligand **4**. Thus, whilst the titanium complex of ligand **4** catalyzed the formation of (*R*)-cyanohydrins, the corresponding samarium or gadolinium complexes catalyzed the formation of (*S*)-cyanohydrins with 62–97% enantiomeric excess <2001JA9908, 2002TL2923, 2002TL8647, 2003SL353, 2003H(59)369>.

Shibasaki <1999JA2641, 2001T805> has developed the aluminum–binol complex **6** as an effective catalyst for the asymmetric addition of trimethylsilyl cyanide to aldehydes. The effectiveness of the catalyst is due to the fact that it contains both Lewis-acidic and Lewis-basic sites, and it is only active in the presence of a phosphine oxide additive to change the geometry around the aluminum ion. Under optimal conditions at −40 °C, 9 mol.% of complex **6** will convert aldehydes into cyanohydrins with 83–98% enantiomeric excess. Aluminum complex **7** was subsequently developed by Shibasaki to function in the same way as complex **6** and was found to convert aldehydes into cyanohydrins with 70–80% enantiomeric excess without the need for any additives <2000TL2405>. Another variation on catalyst **6** is complex **8** developed by Nájera and co-workers. In the presence of triphenylphosphine oxide, 10 mol.% of complex **8** catalyzes the asymmetric addition of trimethylsilyl cyanide to aldehydes, giving cyanohydrins with 66% to >99% enantiomeric excess <2002OL2589>. Complex **8** also catalyzes the asymmetric addition of methyl cyanoformate (MeOCOCN) to aldehydes, leading directly to nonracemic cyanohydrin methylcarbonates with 0–80% enantiomeric excess <2003TA197>. The same reaction (using ethyl cyanoformate) has been shown by Shibasaki to be catalyzed by a yttrium/lithium polymetallic cluster derived from binaphthol <2002AG(E)3636>. With this catalyst, cyanohydrin ethyl carbonates are obtained with 87–96% enantiomeric excess from reactions carried out at −78 °C using 10 mol.% of the catalyst.



6 **7** **8**

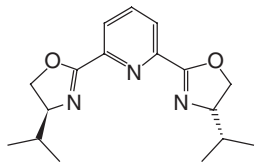
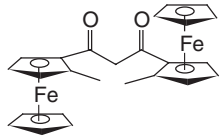
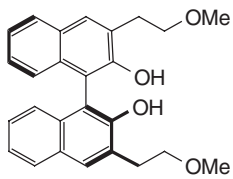
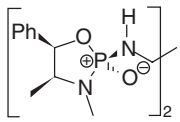
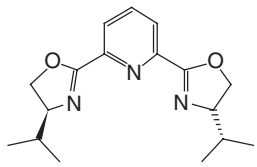
The aluminum complex of peptide-derived ligand **9** has been shown by Hoveyda and co-workers to be an effective catalyst for the asymmetric addition of trimethylsilyl cyanide to ketones <2002AG(E)1009>. Reactions carried out using 10–20 mol.% of the catalyst gave ketone-derived cyanohydrin trimethylsilyl ethers with 8–95% enantiomeric excess. Finally, the zirconium complex of TADDOL **10** has been shown to catalyze the asymmetric transfer of hydrogen cyanide from acetone cyanohydrin to aldehydes to give cyanohydrins with 29–91% enantiomeric excess <2001T867>. Various other metal/chiral ligand combinations have been reported to catalyze the asymmetric addition of trimethylsilyl cyanide to aldehydes, and these are detailed in Table 3.



9 **10**

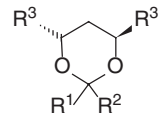
In 2001, Tian and Deng <2001JA6195>first reported the use of chiral Lewis bases in asymmetric cyanohydrin synthesis. They found that derivatives of the cinchona alkaloids quinine and quinidine would catalyze the asymmetric addition of ethyl cyanoformate to ketones leading to nonracemic cyanohydrin ethylcarbonates. Under optimized conditions at −24 °C, 15–35 mol.%

Table 3 Chiral ligands and metals for use as catalysts of the asymmetric addition of trimethylsilyl cyanide to aldehydes

Metal	*Chiral Ligand*	*Catalyst* (mol.%)	*Enantiomeric excess*	*References*
Aluminum		20	44	<1997TA1279>
Bismuth	Diethyltartrate	20	20–72	<1997TA3939>
Yttrium		1	10–91	<1996JOC2264, 1998T11405>
Lanthanum		10	48–73	<1998JCS(P1)2131>
Samarium		0.1–0.2	29–90	<1998JOC1356>
Ytterbium		10	6–67	<1999TL1763>

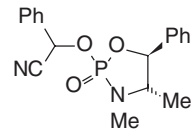
of the chiral Lewis base catalyzed the formation of cyanohydrin derivatives with 59–97% enantiomeric excess, and the two diastereomeric alkaloids produced opposite enantiomers of the cyanohydrins. The use of cinchona alkaloid derivatives for the asymmetric addition of trimethylsilyl cyanide to acetophenone was subsequently investigated by Matsumoto and co-workers; however, only very low levels of asymmetric induction (<10%) were observed <2002H(58)645>.

Two chiral auxiliary-based approaches to asymmetric cyanohydrin synthesis have been reported. Treatment of chiral acetals **11** with trimethylsilyl cyanide results in diastereoselective ring opening to give cyanohydrin ethers with 50–90% diastereomeric excess <1995SL1077>. Chiral cyanohydrin phosphate derivatives **12** derived from aldehydes can be deprotonated with butyllithium and reacted with alkylating agents to give the corresponding cyanohydrin derivatives derived from ketones. Cleavage of the chiral auxiliary leaves ketone derived cyanohydrins with >96% enantiomeric excess <1995AG(E)917, 1997JOC6882>. In addition to simple alkylations, the anions of compounds **12** also react with acid chlorides, and undergo Michael addition reactions, thus giving access to highly functionalized, chiral cyanohydrins <1997CEJ1273>.



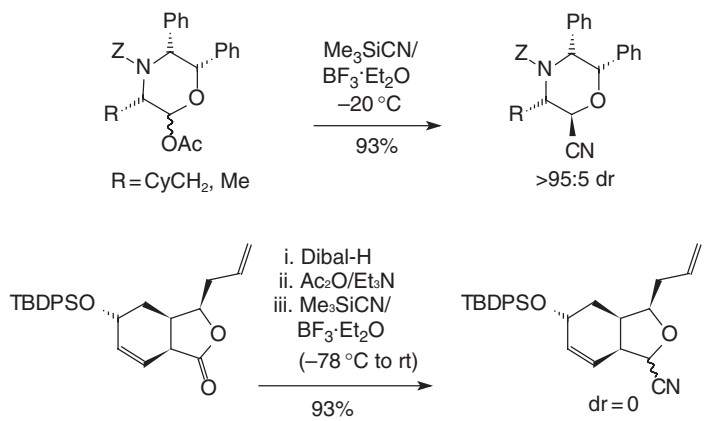
11

R^1 = Ph, 4-MeC_6H_4, 2-furanyl, C_5H_{11}, C_6H_{13}, Cy, Et_2CH, $PhCH_2CH_2$, PhCH=CH
R^2 = H or R^1-R^2 = $(CH_2)_5$
R^3 = Me, CO_2Et

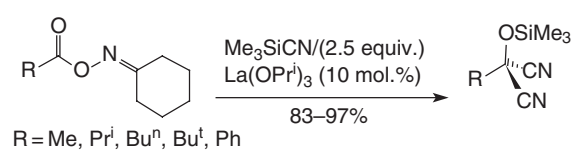


12

Other routes are also available for the synthesis of α-oxygenated nitriles. Tin(II) bromide catalyzes the addition of trimethylsilyl cyanide to 2-naphthaldehyde dimethylacetal to give the cyanohydrin methyl ether. Trimethylsilyl triflate has also been used to catalyze the addition of trimethylsilyl cyanide to a dibenzylacetal leading to a cyanohydrin benzyl ether <1998TL4971>. Boron trifluoride catalyzes the addition of trimethylsilyl cyanide to *O*-acetyl acetals, giving cyanohydrin ethers. Two examples <2001JA3472, 2001JA9021> of this chemistry are shown in Scheme 14. Lanthanum triisopropoxide catalyzes the addition of trimethylsilyl cyanide to oxime esters leading to α-trimethylsilyloxy dinitriles in >80% yield as shown in Scheme 15 <2000JOC6209>.

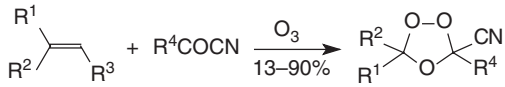


Scheme 14



Scheme 15

Whilst electron-deficient allylic alcohols are generally poor substrates for the Sharpless epoxidation, 2-cyano-allylic alcohols can be epoxidized in this way leading to cyanoepoxides with >95% enantiomeric excess <1995TA2249>. Ozonolysis of an alkene in the presence of an acyl cyanide leads to 3-cyano-1,2,4-trioxolanes as shown in Scheme 16 <1996JCS(P1)871>.

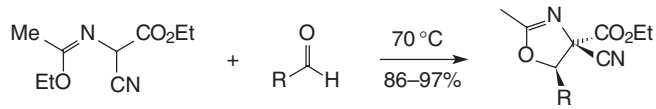


R^1 = Ph, Cy, H, *t*-Bu
R^2 = H, Ph, or R^1–R^2 = $(CH_2)_5$
R^3 = H, OMe, OEt
R^4 = Me, Ph, CH_2CHMe_2

Scheme 16

3.18.2.4.2 β-Oxygenated nitriles

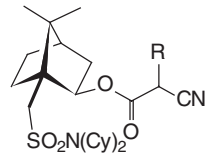
Reaction of a nitrile enolate with an aldehyde or ketone is one of the well-established methods for the synthesis of β-hydroxy nitriles. The reaction can be highly diastereoselective, and the scope, optimization, and limitations of this reaction have been studied <1997JOC6316>. By starting with a 4-chloronitrile, this process can be used to provide a one-pot synthesis of β-cyanotetrahydrofurans <2000SL1773>. An alternative to the standard conditions is to use samarium(II) iodide to induce the reaction between an α-bromonitrile and an aldehyde or ketone, though this method shows little or no diastereoselectivity <2000TL3039>. An enantioselective version of this reaction has been developed in which a (bisferrocenylphosphine)rhodium complex catalyzes the *anti*-selective aldol reaction between α-cyanopropionates and aldehydes <2000JOM(603)18>. A related reaction is the 1,3-dipolar cycloaddition reaction between nitrile **13** and an aldehyde leading to 4-cyano-2-oxazolines as shown in Scheme 17 <2000GC226>. Cativiela and co-workers <1995T5921, 1996T687, 1997TA311, 1997T5891, 1998T14963> have shown that the alkylation of enantiomerically pure cyanoesters **14** occurs diastereoselectively, leading to enantiomerically pure α,α-disubstituted cyanoacetates.



13

R = Ph, 2-pyridyl, 4-$MeOC_6H_4$, 2-BrC_6H_4, 2-HOC_6H_4, 3-HOC_6H_4

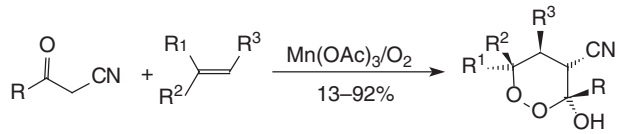
Scheme 17



R = Me, *iso*-Pr, CH_3CO_2, $PhCH_2$

14

The reaction between an aldehyde and the organoindium species obtained from 4-bromo-but-2-enonitrile proceeds with allylic transposition to give 3-cyano-4-hydroxy-alk-1-enes <1996SC3179>. Another indium-induced transformation is the reaction between an arylacyl cyanide (ArCOCN) and an α-bromonitrile which leads to β-ketonitriles in good yields <2002TL4813>. β-Ketonitriles can also be obtained by the reaction of a ketone with chlorosulfonylisocyanate <1997SL1432>. Treatment of a β-ketonitrile with an alkene in the presence of manganese(III) acetate and oxygen leads to cyclic α-hydroxy-β-cyano peroxides as shown in Scheme 18 <1996TL4949>.

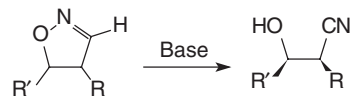


R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-naphthyl, 2-thienyl, (CH$_2$)$_4$CH$_3$
R^1 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, Me, H
R^2 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, Me, H
R^3 = Ph, H, or R^1–R^3 = (CH$_2$)$_6$

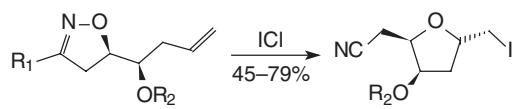
Scheme 18

Another common method for the synthesis of β-hydroxynitriles is the ring opening of epoxides by cyanide. With unsymmetrical epoxides, reaction occurs at the less-hindered end of the ring. Whilst sodium or potassium cyanide <1999TA2945, 1999TA4231> have been used as the cyanide source, the reaction conditions (polar solvents and strong acid or high temperature) are not compatible with some substrates. Other effective cyanide sources which overcome these limitations include acetone cyanohydrin <1996T7063>, lithium cyanide <1997SC3547>, and diethylaluminum cyanide <1999TL1041, 2002TA1321>. A related process for the synthesis of β-hydroxynitriles is the ring opening of cyclic sulfites derived from 1,2-diols which can be achieved using potassium cyanide in DMF at 100 °C <1996TA2411>.

Treatment of an isoxazoline with base results in ring opening to a β-hydroxy nitrile as shown in Scheme 19. The isoxazoline can be prepared from an alkene by reaction with fulminic acid (HCNO), thus providing a route for the *syn*-addition of cyanide and hydroxide to an alkene <1995TL3303>. Isoxazoles can be prepared by reaction of a β-ketoaldehyde with hydroxylamine, and undergo the same base-catalyzed ring opening leading to β-ketonitriles <2000T2075>. The base-induced ring opening of an isoxazoline requires a proton on the carbon adjacent to the nitrogen of the isoxazoline ring. However, with a suitable carbon-based substituent on this position and a suitably located alkene, ICl can induce a ring-opening–ring-closing fragmentation of isoxazolines leading to cyanomethyl substituted furans and pyrans as illustrated by the example in Scheme 20 <2000T711, 2002SL1691>.



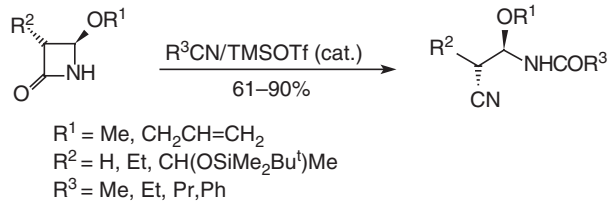
Scheme 19



R^1 = Ph$_3$C, PhCH(OTBDMS)
R^2 = SiMe$_2$Bu^t, SiPh$_2$Bu^t, MEM, MPM, MOM

Scheme 20

The Michael addition of an alcohol or alkoxide to an α,β-unsaturated nitrile leading to a β-alkoxynitrile is often straightforward. However, if either of the reactants is sterically hindered, then the reaction may fail. In these cases, it has been shown that the reaction is catalyzed by phosphines and is also accelerated by the application of high pressure (300 MPa) <2002T4311>. A very unusual reaction is the insertion of a nitrile into a suitably substituted β-lactam, catalyzed by trimethylsilyltriflate, leading to β-hydroxy-β-amidonitriles as shown in Scheme 21 <1996JCS(P1)2321>. Interestingly, the proposed mechanism has the nitrogen of the β-lactam becoming the nitrogen of the nitrile in the product and the nitrile reactant becomes the amide.

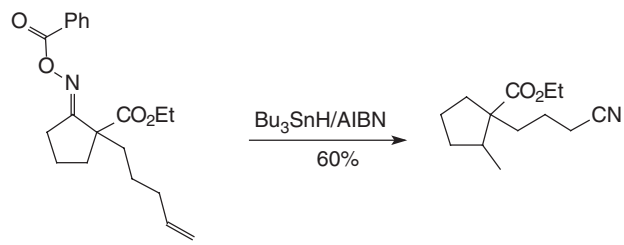


Scheme 21

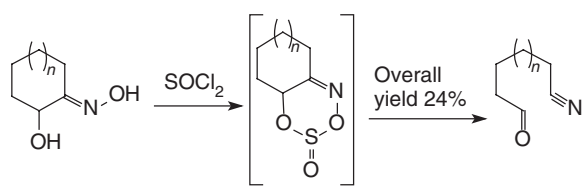
The resolution of racemic β-hydroxynitriles can be achieved by enzymatic esterification using vinylacetate as the acetate source and enzymes from *Candida rugosa, Pseudomonas fluorescens* <2000T1309>, or *Pseudomonas cepacia* <2001TA405>.

3.18.2.4.3 More remotely oxygenated nitriles

Treatment of the oxime benzoate of a cyclic β-ketoester with tributyltin hydride and AIBN results in fragmentation to form ω-cyano esters <1997SC323>. The reaction proceeds via an iminylradical which fragments to form the nitrile and a radical adjacent to the ester. The latter can be trapped by a suitably located double bond to produce cyclic products as illustrated in Scheme 22. Treatment of a β-hydroxyoxime with thionyl chloride results in fragmentation (presumably via a cyclic sulfite), leading to ω-cyanoaldehydes as shown in Scheme 23 <1995T13379>. Another fragmentation reaction involves treatment of a cyclic alkene with oxygen and sodium azide in the presence of light and copper(II) triflate. A radical mechanism leads to formation of a β-peroxyazide which undergoes radical-induced fragmentation to an ω-cyanoketone as shown in Scheme 24 <1997SL887>.

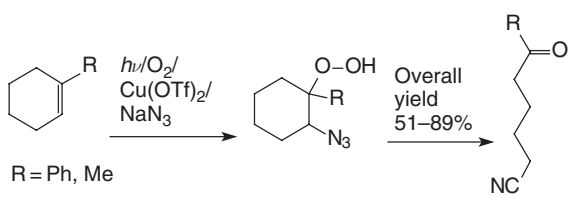


Scheme 22



Examples given are steroidal

Scheme 23

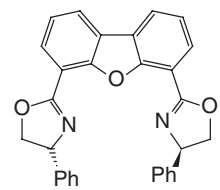


R = Ph, Me

Scheme 24

Nitrilase enzymes hydrolyze a nitrile to a carboxylic acid. When these enzymes are applied to α,ω-dinitriles, the enzymes will selectively hydrolyze one of the two nitriles, thus allowing the synthesis of ω-cyanoacids <1996TL6001, 2001TA3367>. Similarly, nitrile hydratase enzymes convert a nitrile into an amide and can be used to prepare ω-cyanoamides <2003CC386>. If the substrate for either of these enzymes is a meso-compound, then enantiomerically pure nitriles can be obtained in this way.

Bromoacetonitrile can be used as an electrophile in Evans' chiral enolate chemistry to prepare nonracemic β-cyanoimides <1996JCS(P1)621, 2002JOC6612>. The Michael addition of a nitrile anion onto an α,β-unsaturated ketone is a well-known process for the synthesis of γ-cyanoketones (see Section 3.18.1.4). This has been used as part of a modified Robinson annulation process leading to bicyclic γ-cyanoketones <2001SL214, 2003T1209>. The enantioselective Michael addition of malononitrile onto imides catalyzed by the combination of a chiral Lewis acid (the nickel complex of ligand **15**) and an achiral base has also been reported <2003TA635>. Similar chemistry can be carried out starting from α-cyanopropionates using a rhodium(bisoxazoline) complex <2002CEJ2968> or using α-cyanophosphonates and a (bisferrocenylphosphine)-rhodium complex <2000BCJ2559>.



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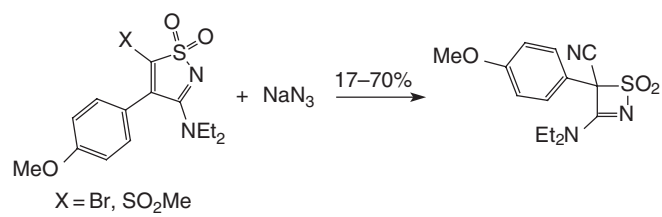
3.18.2.5 Aliphatic Nitriles Bearing a Sulfur-based Functional Group

Treatment of a benzylic nitrile with butyllithium followed by phenyl *p*-toluenesulfonate leads to benzylic α-cyanosulfones <1995SC4063>. The chemistry is compatible with a variety of functional groups on the aromatic ring of the benzylic nitrile, and with (2-thienyl)acetonitrile. Another route to benzylic α-cyanosulfones involves treatment of heterocycles **16** with sodium azide as shown in Scheme 25 <2002T5173>.

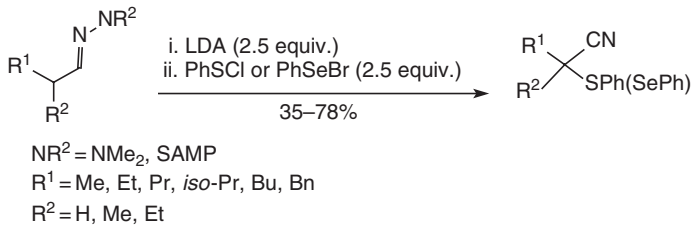


X = Br, SO_2Me

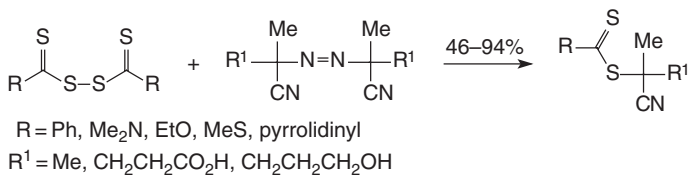
16

Scheme 25

Dimethylhydrazones react with LDA and either phenylsulfenyl chloride or phenylselenyl bromide to give α-thio- and α-selenonitriles, respectively, as shown in Scheme 26 <2002T3275>. Treatment of an α-acetoxysulfide with trimethylsilyl cyanide in the presence of tin tetrachloride affords α-cyanosulfides <1995TL2599>. Enantiomerically pure cyanohydrins are available by a number of methodologies (see Section 3.18.2.4.1). They can be activated as aryl- or methylsulfonates and then reacted with a variety of sulfur-based nucleophiles including potassium thioacetate, thioacetic acid, potassium ethylxanthogenate, potassium thiocyanate, thiols, and thiophenols to give a variety of α-thionitriles with inversion of configuration at the stereocenter <1999TA1765>. Treatment of a bis(thiocarbonyl) disulfide with an α-cyano azo compound leads to α-cyanodithioesters, dithiocarbamates, xanthates, and trithiocarbamates as shown in Scheme 27 <1999TL2435>.

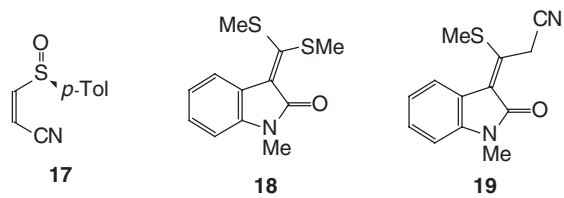


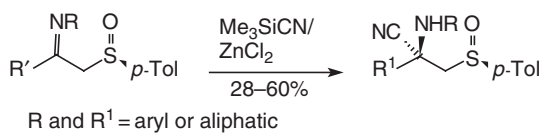
Scheme 26



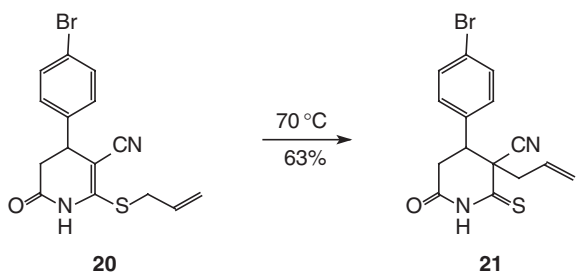
Scheme 27

Enantiomerically pure cyanosulfoxide **17** is an excellent dienophile, reacting with cyclic and acyclic dienes to give β-cyanosulfoxides <2000JOC7938>. Treatment of dithioketene acetal **18** with acetonitrile and butyllithium gives β-methylthionitrile **19** <2001T781>. Treatment of chiral α-sulfinylketimines with trimethylsilyl cyanide in the presence of zinc chloride provides a stereocontrolled synthesis of β-amino-β-cyanosulfoxides as shown in Scheme 28 <2002T3217>. *S*-Allyl-α,β-unsaturated nitrile derivatives **20** undergo a Claisen rearrangement on refluxing in benzene to give α-cyanothioimides **21** as shown in Scheme 29 <1997RCB990>.





Scheme 28



Scheme 29

3.18.2.6 Aliphatic Nitriles Bearing an Se- or Te-Based Functional Group

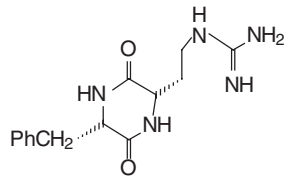
The only new method for the synthesis of α-selenonitriles is also applicable to the synthesis of α-thionitriles and so was discussed in Section 3.18.2.5.

3.18.2.7 Aliphatic Nitriles Bearing a Nitrogen-based Functional Group

A major advance since the publication of COFGT (1995) has been the development of asymmetric catalysts for the enantioselective addition of cyanide to imines, leading to nonracemic α-aminonitriles. This area has been the subject of two reviews <1999CRV1069, 2000CSR359>.

The first reported catalyst was diketopiperazine **22** developed by Lipton and co-workers in 1996 <1996JA4910>. Catalyst **22** (2 mol.%) catalyzes the asymmetric addition of hydrogen cyanide to *N*-benzhydrylimines with up to >99% enantiomeric excess for reactions carried out at −25 °C to −75 °C. Best results are obtained with electron-rich aromatic aldehydes; aliphatic, heteroaromatic, and electron-deficient aromatic aldehydes give products with low enantiomeric excesses. Subsequently, Corey and Grogan <1999OL157> demonstrated that bicyclic guanidine **23** was also a catalyst for this reaction. The use of 10 mol.% of catalyst **23** at temperatures between −20 and −40 °C converted *N*-benzhydrylimines of aromatic aldehydes into α-aminonitriles with 50–88% enantiomeric excess.

Jacobsen and co-workers used combinatorial methods to develop compounds **24** and **25** as catalysts for the asymmetric addition of hydrogen cyanide to both aldehydes and methyl ketones <2000AG(E)1279, 2000OL867, 2002JA10012>. Catalyst **25** is the more enantioselective catalyst, and at −78 °C, 1 mol.% of this catalyst produces α-aminonitriles with 86–99% enantiomeric excess. Bis-*N*-oxide **26** has been shown to induce the asymmetric addition of hydrogen cyanide to *N*-benzhydrylimines derived from aromatic aldehydes, giving α-aminonitriles with 37–73% enantiomeric excess. However, it was necessary to use a full equivalent of *N*-oxide **26** <2001SL1551>.



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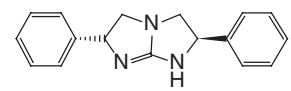

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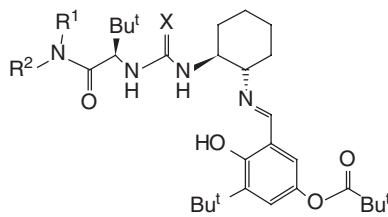
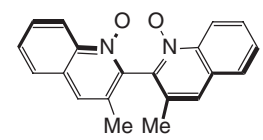


24: X = O, R^1 = $PhCH_2$, R^2 = H

25: X = S, R^1 = Me, R^2 = Me



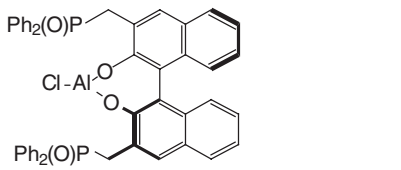
26

The above methods are all based on metal-free catalysts; however, a number of chiral metal complexes have also been used to catalyze the asymmetric addition of cyanide to imines. In 1998, Sigman and Jacobsen showed that aluminum(salen) complex **1** would catalyze the asymmetric addition of trimethylsilyl cyanide or hydrogen cyanide to *N*-allylimines <1998JA5315>. Use of 5 mol.% of the catalyst at −70 °C resulted in the formation of α-aminonitriles with 37–95% enantiomeric excess. Shibasaki and co-workers have investigated the asymmetric addition of trimethylsilyl cyanide to *N*-fluorenylimines catalyzed by binol complex **27** <2000AG(E)1650, 2000CPB1586> or its polymer-supported analog **28** <2001TL279>. These binol complexes were designed as bifunctional Lewis acids and Lewis bases to simultaneously activate both the imine and trimethylsilyl cyanide. At −40 °C, 9 mol.% of catalyst **27** produced α-aminonitriles with 70–95% enantiomeric excess. The polymer-supported catalyst **28** showed comparable enantioselectivity (83–87%) and could be recovered and reused 4 times.

Hoveyda and co-workers <1999JA4284> used combinatorial methods to develop the titanium complexes of peptide-derived Schiff bases **29** as catalysts for the asymmetric addition of trimethylsilyl cyanide to a wide range of imines. Using 10 mol.% of the catalyst at 4 °C,

α-aminonitriles with 85% to >99% enantiomeric excess could be obtained. However, to obtain optimal results it was necessary to optimize the substituents (X) on the aromatic ring of the Schiff base for each substrate. Recently, the titanium complex of *N*-salicyl-β-aminoalcohol **30** was found to be an effective catalyst for the asymmetric addition of trimethylsilyl cyanide to aryl-*N*-benzylimines <2003TL3805>. The optimal conditions involved the use of 10 mol.% of the catalyst and produced α-aminonitriles with 44–81% enantiomeric excess.

Kobayashi and co-workers <2000CHIR540, 2000JA762> have developed bimetallic zirconium(binol) complex **31** as a catalyst for the addition of hydrogen cyanide or tributyltin cyanide to aldimines. A novel feature of this chemistry is that the catalyst would also catalyze the three-component condensation of an aldehyde, amine, and hydrogen cyanide. In both cases, optimal results are obtained using 5 mol.% of the catalyst at temperatures of −65 °C to −45 °C and with *N*-*o*-hydroxyphenyl imines. Under these conditions, α-aminonitriles can be obtained with 74–94% enantiomeric excess from both aromatic and aliphatic aldehydes. A scandium–lithium bimetallic binol complex **32** has also been used to catalyze the asymmetric addition of trimethylsilyl cyanide to the *N*-benzylimines of benzaldehyde, 2-naphthaldehyde, and acetophenone <2001TA1147>. At −20 °C, 10 mol.% of the catalyst converted the three imines into α-aminonitriles with 95%, 65%, and 55% enantiomeric excess respectively, though the conversions were less than 50% under these conditions.



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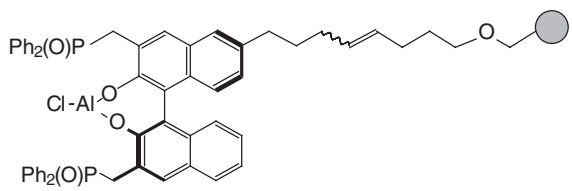

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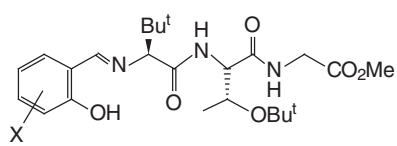
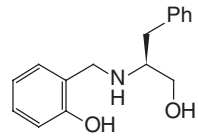
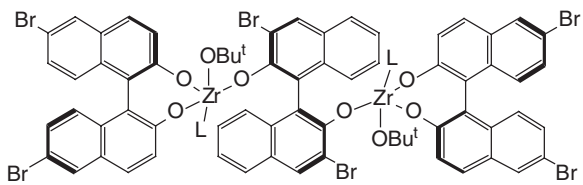


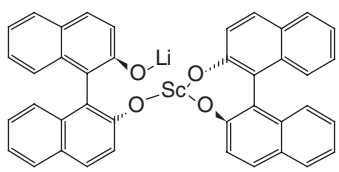
29 X = 5-MeO, 3,5 DiCl, or 3,5 DiBr



30



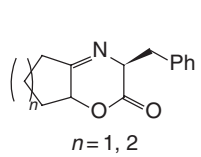
31 L = *N*-methylimidazole



32

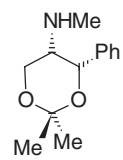
An alternative method for the preparation of nonracemic α-aminonitriles is to use a chiral auxiliary located on the nitrogen atom of an imine. Traditionally, this has been achieved using chiral auxiliaries derived from α-methylbenzylamine <1997S32, 1999JOC93, 2000JOC4440, 2001TL5191, 2002TA2241> or phenylglycidol <1995TL7081, 1996BMCL2243, 1996TL3023, 1998BMCL1569, 1998TA3095, 1999T11295, 2000JOC7208, 2000TA4537, 2001CC475, 2001T6361, 2001T6383, 2002EJO834, 2002OL695, 2002TL2827, 2003JOC1401>. Both of these auxiliaries are compatible with a variety of cyanide sources including trimethylsilyl cyanide, hydrogen cyanide, potassium cyanide, and acetone cyanohydrin, though in general the use of phenylglycidol results in higher diastereoselectivities. It has been reported, however, that the diastereoselectivity observed during the addition of trimethylsilyl cyanide to *N*-α-methylbenzylimines is significantly enhanced by the addition of a stoichiometric amount of (*R*),(*R*)-tartaric acid, and 10 mol.% of *N*,*N*′-dimethyl-(*R*),(*R*)-1,2-diphenyl-1,2-diaminoethane <2000TA3471>.

The use of phenylglycinamide as a chiral auxiliary for the Stecker reaction has also been reported <2001OL1121>. In this case, the diastereomeric adducts can be equilibrated and one diastereomer selectively crystallizes from the reaction mixture, thus allowing it to be obtained with both high yield and high diastereoselectivity. However, only two examples (pivaldehyde and 3,4-dimethoxybenzyl methyl ketone) have been reported. In a related and seemingly more general process, racemic α-aminonitriles can be crystallized with mandelic acid under equilibrating conditions, again allowing one diastereomeric salt to precipitate in high yield and with high diastereomeric purity <1998JCS(P1)3747>. Compounds **33** derived from an amino acid and an α-hydroxyketone undergo diastereoselective addition of cyanide to the carbon–nitrogen double bond, thus allowing the synthesis of β-hydroxy-α-aminonitriles <1997CHIR459>. Amine **34** reacts with *N*,*N*-dibenzyl-3-aminopropanal to give an iminium ion which reacts with hydrogen cyanide to give a 3:2 ratio of diastereomeric α,β-diaminonitriles which can separated by chromatography <1999JCS(P1)1617>. Alternatively, the α,β-diaminonitrile can be deprotonated adjacent to the nitrile and reacted with α,β-unsaturated esters to give Michael adducts with 91–93% diastereomeric excess.

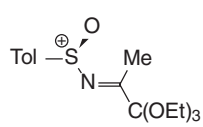


n = 1, 2

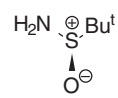
33



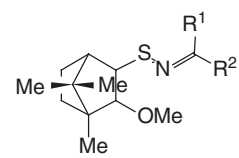
34



35

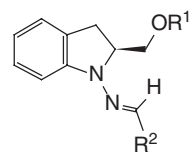


36



R^1 = H, Me
R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$O_2NC_6H_4$, Et, CH_2CHMe_2

37



R^1 = Me, CH_2OMe, $SiMe_2Bu^t$
R^2 = Et, Bu, *iso*-Pr, *t*-Bu, $(CH_2)_4OTs$

38

Various heteroatom-based chiral auxiliaries have also been used in asymmetric α-aminonitrile synthesis. In 1995, Hua and co-workers <1995TA349> reported the addition of diethylaluminum cyanide to *p*-toluenesulfinimide **35**, though the diastereoselectivity was only 7:4. This process was subsequently optimized by Davis and co-workers <2000JOC8704> who showed that by addition

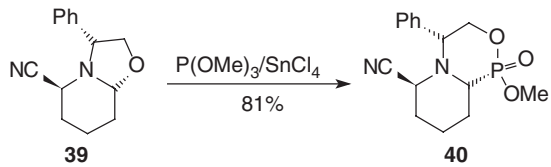
of isopropanol to the reaction mixture, a variety of ketone-derived *p*-toluenesulfinimides underwent diastereoselective cyanide addition with diastereomeric excesses as high as 98%. Both Davis and co-workers <2000JOC8704> and Mabic and Cordi <2001T8861> have also investigated the addition of cyanide (from diethylaluminum cyanide/isopropanol or trimethylsilyl cyanide) to imines derived from sulfinamide **36**, and in general, this chiral auxiliary gave better diastereocontrol than the toluene-derived sulfinimide. Camphor-derived sulfenimines **37** react with trimethylsilyl cyanide to give α-aminonitriles with 16–74% diastereomeric excess <1996SC63>. The highest diastereoselectivity is obtained for sulfenimines derived from benzaldehyde derivatives. Choi and Kim have shown that chiral hydrazones **38** undergo highly diastereocontrolled addition of trimethylsilyl cyanide catalyzed by diethylaluminum chloride to give α-cyanohydrazines with up to 96% diastereomeric excess <1996TL7795>.

Enantiomerically pure cyanohydrins are readily available by a number of methods (see Section 3.18.2.4.1), and a modified Mitsunobu reaction using $BocHNSO_2CH_2CH_2SiMe_3$ as the nucleophile has been developed to convert them into nonracemic α-aminonitriles with inversion of configuration <1997SL529>. The ring-opening of an *N*-acylaziridine has been used to prepare a β-cyanoamide <2000TA567>.

α,β-Unsaturated α-amidonitriles are chemoselectively reduced by sodium hydrogen telluride, to form α-amidonitriles in 65–85% yield <1997SC939>. The ring-opening of aziridines by trimethylsilyl cyanide is catalyzed by tetrabutylammonium fluoride, giving β-aminonitriles in 79–99% yield <2000JOC1344>. Reaction occurs exclusively at the less-hindered end of the aziridine, and with complete inversion of configuration.

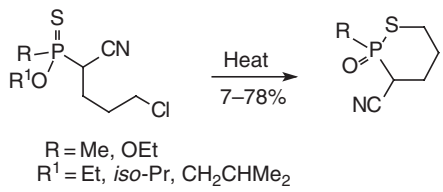
3.18.2.8 Aliphatic Nitriles Bearing a P-, As-, Sb-, or Bi-Based Functional Group

There are no general methods to report in this section. However, treatment of stereochemically pure α-aminonitrile **39** with trimethylphosphite in the presence of tin tetrachloride leads to phosphorus-containing nitrile **40** as a 71:28:1 mixture of diastereomers as shown in Scheme 30 <1997T3627>. α-Cyano phosphorus-containing heterocycles can be prepared by the route shown in Scheme 31 <1999MC158>, and bicyclic α-cyanophosphonate **41** has been prepared as shown in Scheme 32 <1998PS(132)265>.

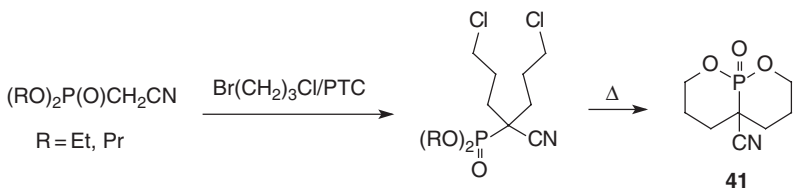


39 **40**

Scheme 30



Scheme 31



41

Scheme 32

3.18.2.9 Aliphatic Nitriles Bearing an Si- or B-Based Functional Group

The ring-opening fragmentation of isoxazolines discussed in Section 3.18.2.4.2 has been used to prepare β-silyl-β-hydroxynitriles from silylated isoxazolines <1996JOM(521)235>. Treatment of an α-chloroboronate with lithioacetonitrile provides access to β-cyanoboronates <1998TL2423>.

3.18.2.10 Aliphatic Nitriles Bearing a Metal Functionality

No further advances have occurred in this area since the publication of chapter 3.18.2.10 in <1995COFGT(3)611>.

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Biographical sketch

Michael North was born in Blackburn. He studied at Durham University, where he obtained a B.Sc. in 1985 and subsequently at Oxford where he obtained his Ph.D. in 1988 under the direction of Professor Sir J. E. Baldwin. After spending two years as a postdoctoral researcher in the laboratories of Professor G. Pattenden at Nottingham, he was appointed to a lectureship in organic chemistry at the University of Wales, Bangor. In 1999 he moved to King's College London as reader of synthetic organic chemistry, and in 2001 was promoted to a chair in synthetic organic chemistry. In 2001 he was awarded the Descartes prize for collaborative research by the EU. He moved to his current post of professor of organic chemistry at the University of Newcastle Upon Tyne in September 2004. His scientific interests cover peptide synthesis and conformational analysis, and asymmetric catalysts, especially asymmetric cyanohydrin synthesis and asymmetric enolate alkylation.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 621–655

3.19
α,β-Unsaturated and Aryl Nitriles

M. J. KIEFEL
Griffith University, Southport, QLD, Australia

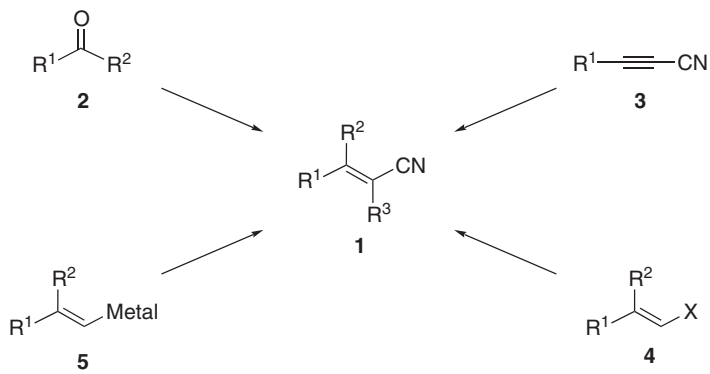
3.19.1 GENERAL METHODS

Nitriles represent one of the classical functional groups of organic chemistry. The importance of the carbon—nitrogen triple bond lies in its ease of introduction, as well as its exceptional reactivity. The unique reactivity of nitriles is due to a combination of unsaturation, polarizability, and low steric demand. Synthetic chemists have long recognized the value of the nitrile group and its characteristic reactivity in the synthesis of highly functionalized molecules, most notably in relation to the synthesis of heterocyclic compounds.

The synthesis of α,β-unsaturated and aryl nitriles is similarly of great interest to synthetic chemists and industrial chemists. Perhaps the most exploited of these are the α,β-unsaturated nitriles which have found extensive use in the synthesis of carbocycles and heterocycles. α,β-Unsaturated nitriles are also valuable starting materials for conjugate addition reactions leading to highly functionalized nitriles, and this area has been reviewed recently <2003CRV2035>. Since this account is devoted to the synthesis of α,β-unsaturated and aryl nitriles themselves, and not the use of such functionality as intermediates in the synthesis of other compounds, the interested reader is directed to several excellent reviews to become more acquainted with this field <1983H(20)519, B-1983MI319-01, B-1983MI319-02, 1991COS(6)225, 2003CRV2035>. The comprehensive nature of these outstanding articles, together with the previous coverage of this topic in the first issue of this series <1995COFGT(3)641>, dictates that this account focuses on

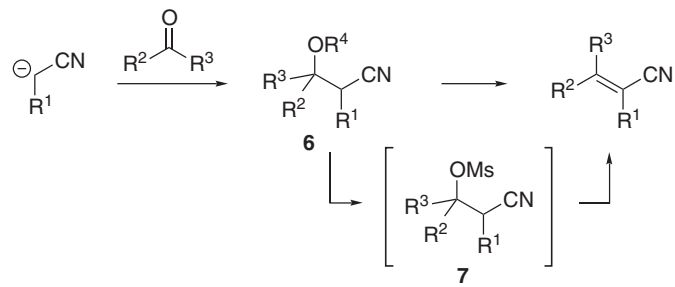
the advances in the synthesis of α,β-unsaturated and arylnitriles since the 1990s. Where appropriate, due reference will be made to work cited in COFGT (1995) <1995COFGT(3)641>, but this will not be done at the expense of clarity.

Four general strategies have emerged for the synthesis of α,β-unsaturated nitriles, and these are summarized in their broadest terms in Scheme 1. Whilst specific examples of these general approaches will be presented throughout this chapter, it is appropriate at this stage to give an overview of these techniques. Condensation of nitrile anions with carbonyl compounds (e.g., **2** → **1**) is one of the most commonly used methods, primarily due to the ready availability of the appropriate carbonyl precursors. The conjugate addition to, or reduction of, alkyne nitriles (e.g., **3** → **1**), the reaction of cyanide with vinyl halides or vinyltriflates (e.g., **4** → **1**), and the cyanation of vinyl anions (e.g., **5** → **1**), have also provided convenient access to α,β-unsaturated nitriles <1995COFGT(3)641, 2002JOC3668, 1991COS(6)225>.



Scheme 1

The condensation of nitrile anions with carbonyl compounds generates β-alkoxynitriles **6** <1998T4211, 1998AG(E)2252, 2000OL2443> that can be subsequently dehydrated (Scheme 2). If the intermediate β-alkoxynitrile contains phosphorus (**6**, $R^4 = PPh_3$), then the elimination of the corresponding oxide occurs directly, providing the target α,β-unsaturated nitrile in a single synthetic step <1984SC565, 1977S126, 1994TL1581>. When condensing aromatic acetonitriles with aryl aldehydes or ketones, the dehydration of **6** ($R^4 = H$) is facilitated by the aromatic substituents (see, e.g., <1986JHC1747>). For aliphatic systems, the dehydration of **6** ($R^4 = H$) is less favored, and often the β-hydroxynitrile intermediate (**6**, $R^4 = H$) must be derivatized (e.g., to the methanesulfonate **7**) in order to facilitate elimination and provide the requisite α,β-unsaturated nitrile. However, the elimination of β-hydroxy nitriles involving the formal elimination of superoxide has been reported for cyclohexene derivatives <1999MI319-01>.

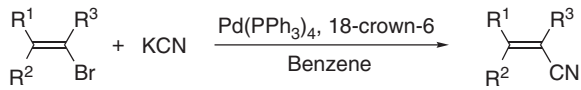


Scheme 2

The alkenylation of carbonyl compounds using Wittig, Wittig–Horner, or Horner–Wadsworth–Emmons condensations are considered as one of the more straightforward routes for the synthesis of α,β-unsaturated nitriles <1961JCS1266, 1973T2437, 1977OR73, 1995COFGT(3)641>. The stereochemical outcome of these olefinations is generally poorly defined <1989CRV901>, although modifications of the phosphorus reagent (e.g., introduction of bulky groups on the

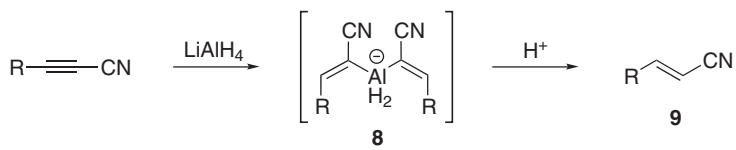
α-carbon) <1994TL1581> or the use of a phosphine oxide reagent in the presence of base <1977S126> can lead to improved stereochemical outcomes. Further examples of improved stereochemical outcomes for these types of condensations will be discussed later in this chapter.

Nucleophilic displacement of vinyl halides with cyanide anion is another general method for the preparation of α,β-unsaturated nitriles. Whilst vinyl halides generally have low reactivity toward nucleophilic displacement <1991COS(6)225>, the use of copper cyanide and base under high temperatures (>200 °C) can accomplish the desired outcome. Milder conditions (<100 °C) using potassium cyanide and catalytic Pd(0) in the presence of crown ethers (Equation (1)) can provide excellent yields of α,β-unsaturated nitriles in a highly stereospecific manner <1977TL4429>. Similarly, treatment of vinyltrifluoromethanesulfonates with Pd(0) in the presence of 12-crown-4 also provides an efficient avenue into α,β-unsaturated nitriles <1993CJC1867>.

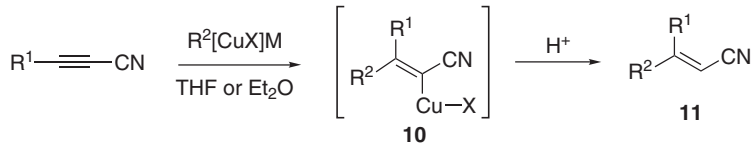


(1)

The reduction of α,β-alkyne nitriles (see Section 3.19.4 for the preparation of nitriles bearing an α,β-triple bond) is also a method that can be utilized in the synthesis of α,β-alkenic nitriles <1995COFGT(3)641>. Lithium aluminum hydride adds in a *trans*-manner to alkynenitriles providing the alanate **8** (Scheme 3), which upon acidification gives the (*E*)-α,β-unsaturated nitriles **9** <1979S430>. Addition of organocopper(I) reagents to alkyne nitriles gives the α-cyanocuprate intermediate **10** (Scheme 4) which provides the 2-alkenenitrile **11** after acidification <1978S454>. It is interesting to note that in this instance the CN and R^1 groups are *cis* with respect to each other (cf. Scheme 3).



Scheme 3



Scheme 4

There are several examples in the patent literature pertaining to the synthesis of α,β-unsaturated nitriles. Given that the majority of these patents appear to relate to the industrial preparation of α,β-unsaturated nitriles, the coverage here will be brief. A number of these industrial processes react an olefin at elevated temperatures in the presence of ammonia and oxygen (ammoxidation), often employing a molybdenum catalyst <2003WOP03097583, 2000USP6037304, 1997WOP9733863, 2003JAP03320248, 2003WOP03089407, 1999JAP11349545, 1996WOP9631465>. The patents generally vary in the type of molybdenum catalyst employed, commence with an alkane instead of an olefin, or use different equipment in order to more efficiently isolate the desired components from this process.

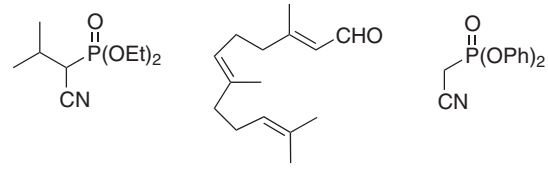
Throughout the preparation of this overview, there were several occasions where it was difficult to appropriately classify the type of α,β-unsaturated nitrile being prepared based upon the various subsections within this article. Primarily this difficulty was due to the fact that many papers describe the synthesis of α,β-unsaturated nitriles with a range of different functionalities. In keeping with clarity and space constraints, repetition of a method that is, for example, equally applicable to the synthesis of α,β-unsaturated nitriles without further unsaturation (Section 3.19.2.1) as well as with oxygen-based substituents (Section 3.19.2.4) has been avoided. The interested reader is therefore encouraged to look at other sections within this article, rather than just at a specific section that contains the additional functionality of interest.

3.19.2 NITRILES BEARING AN α,β-VINYLIC BOND

3.19.2.1 α,β-Alkenic Nitriles without Further Unsaturation

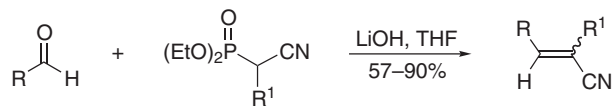
As mentioned above, the alkenation of aldehydes or ketones is an important route into α,β-unsaturated nitriles. One of the important issues that has emerged since the 1990s in this area of research is obtaining the desired α,β-unsaturated nitrile with defined stereochemistry about the double bond. In this regard, it has previously been shown that a degree of (*Z*)-selectivity could be achieved by using a bulky group on the phosphononitrile **12** when employed in a Horner–Emmons reaction with the aldehyde **13** <1990TL3317>. Following on from this work the same group has examined the reaction conditions used to couple **12** and **13** with a view to trying to enhance the (*Z*)-selectivity <1994TL1581>. It was found that the influence of solvent was crucial to the stereochemical outcome, with the least polar solvents (excluding hexane) giving higher (*Z*)-selectivity. Lower reaction temperatures (−78 °C) and the use of Bu^nLi, LHMDS, or KHMDS as base in toluene provided the best (*Z*)-selectivities (up to 35:1) <1994TL1581>.

Following from a report that good *cis*-selectivity could be achieved using a modified Horner–Wadsworth–Emmons reagent in the synthesis of unsaturated esters <1995TL4105>, the preparation and use of the cyanomethylenephosphonate **14** has been described <1998TL1461>. It was found that treatment of **14** with a variety of alkyl aldehydes in the presence of potassium *t*-butoxide afforded the corresponding α,β-unsaturated nitriles in high chemical yield and generally better than 4:1 (*Z*):(*E*) selectivity. Generally it was observed that bulkier aldehydes gave better (*Z*)-selectivity <1998TL1461>.



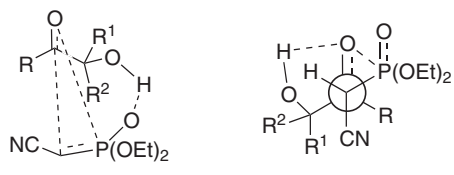
12 **13** **14**

The exclusive formation of (*E*)-α,β-unsaturated nitriles can be accomplished using Horner–Wadsworth–Emmons olefination that is promoted by lithium hydroxide <2003TL1333>. Whilst the coupling between aryl and alkyl aldehydes **15** and the cyanophosphoranes **16** in THF containing lithium hydroxide gives excellent yields of the α,β-unsaturated nitriles **17** (Equation (2)), the (*E*):(*Z*)-selectivity is generally in the range of 2:1 up to 9:1. However, when α-hydroxy ketones were employed as the substrates in couplings with **16**, the (*E*)-products were obtained exclusively <2003TL1333>. The authors rationalize this by suggesting that there is a possible interaction between the α-hydroxyl group and the phosphonate oxygen, giving rise to the transition state **18** which, after *syn*-elimination of the phosphate, would furnish the (*E*)-olefin. Alternatively, it is possible that a hydrogen bond between the hydroxyl group and the carbonyl group could lead to the less sterically encumbered transition state **19**, which would also lead to the (*E*)-olefin after elimination. In support of the important role of the α-hydroxyl group is the observation that functionalization of the hydroxyl group (as ether, ester, or silyl derivatives) removes the observed (*E*)-selectivity <2003TL1333>.



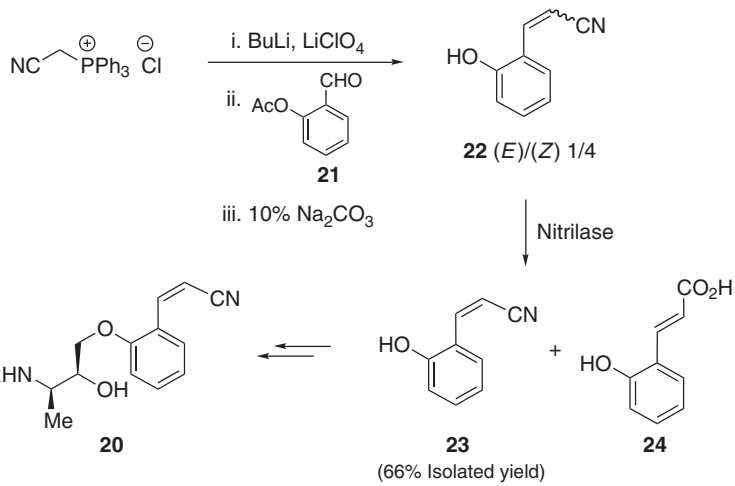
15 **16** **17** (2)

R = alkyl, aryl; R^1 = H or Me



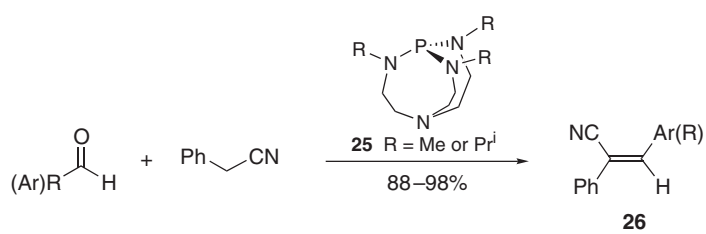
18 **19**

The issue of (*E*),(*Z*)-stereoselectivity in the formation of α,β-unsaturated nitriles has been addressed in an alternative approach. In work toward the synthesis of β-lactamase inhibitors, it was found that the (*Z*)-isomer of 2β-acrylonitrile penam sulfone is 20 times more active than the corresponding (*E*)-isomer <1996JMC3712>. Whilst the (*Z*)-selectivity of Wittig reactions to prepare α,β-unsaturated nitriles can be improved by the addition of lithium salts <1996JMC3712>, separation of the desired pure (*Z*)-isomers required extensive purification. In an attempt to alleviate the problem of separation of (*Z*)- and (*E*)-isomers of α,β-unsaturated nitriles, it has been found that the recombinant nitrilase AtNIT1 from *Arabidopsis thaliana* hydrolyzes (*E*)-isomers exclusively to the corresponding (*E*)-carboxylic acids <2001TA2581>. In this way a series of (*E*),(*Z*)-isomeric mixtures of α,β-unsaturated nitriles could be separated. By way of example, the β-antagonist **20** was prepared by initial Wittig reaction on the aryl aldehyde **21** in the presence of lithium perchlorate to give the isomeric α,β-unsaturated nitriles **22** (Scheme 5). Enzymatic hydrolysis of the isomers **22** gave the desired (*Z*)-α,β-unsaturated nitrile **23** together with the (*E*)-carboxylic acid **24**. The nitrile **23** could be easily separated from the acid **24** using an aqueous bicarbonate wash, and **23** was subsequently elaborated into **20** <2001TA2581>.



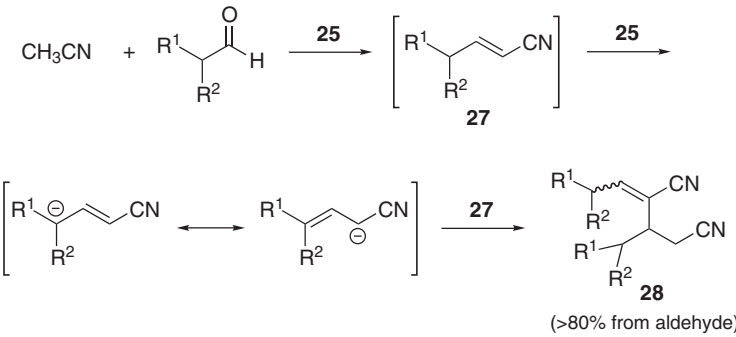
Scheme 5

The reaction of the anion derived from acetonitrile with carbonyl compounds is another commonly used method for the synthesis of α,β-unsaturated nitriles. Typically this involves the use of strong ionic bases (e.g., Bu^nLi) to deprotonate the acetonitrile derivative, and is often hampered by the generation of unwanted side products and the lack of tolerance for base-sensitive functionality <1979JOC4640>. In an attempt to overcome this problem, the nonionic superbases **25** have been developed and employed in the synthesis of α,β-unsaturated nitriles. In a typical experiment, exposure of either aliphatic or aromatic aldehydes to benzylcyanide in the presence of a catalytic amount of the base **25** results in excellent yields of the corresponding (*E*)-α,β-unsaturated nitriles **26** (Equation (3)) <1998JOC3961>. Similar results were obtained with acetonitrile, although the (*E*):(*Z*)-selectivity was not as pronounced.



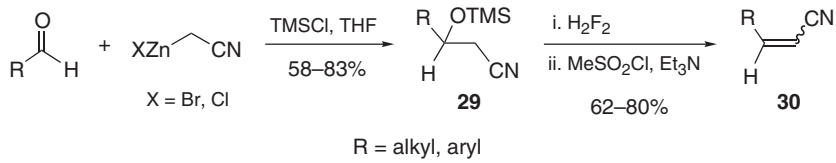
(3)

Interestingly, if the nonionic superbase **25** is employed to couple secondary aldehydes with acetonitrile, the initially formed α,β-unsaturated nitrile **27** (Scheme 6) is subsequently deprotonated and undergoes a self-condensation to afford the dimeric species **28** <1998JOC10057>.

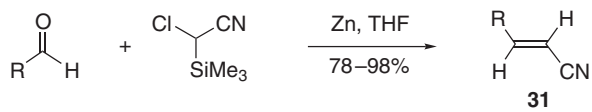


Scheme 6

Carbonyl compounds can be condensed with α-haloacetonitriles in the presence of zinc and trimethyl chlorosilane to afford β-trimethylsilyloxy nitriles **29** which can be dehydrated to the alkene nitrile **30** after fluoride treatment and elimination of the subsequently formed methanesulfonate (Scheme 7) <1990TL2205>. These same authors have also shown that predominantly (*Z*)-alkene nitriles can be obtained through a zinc-promoted Reformatsky–Peterson reaction with carbonyl compounds <1990TL2209>. Using trimethylsilylchloroacetonitrile, reaction of a carbonyl compound in the presence of zinc powder gives the α,β-unsaturated nitrile **31** (Equation (4)) after aqueous ammonia work-up. The yields for this transformation are consistently high (generally >80%) and the reaction can be carried out on a variety of aliphatic or aromatic carbonyl compounds <1990TL2209>.

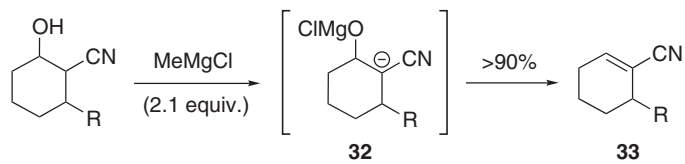


Scheme 7



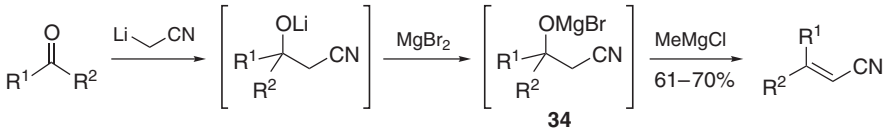
(4)

The elimination of β-hydroxy nitriles has been used in a number of syntheses of α,β-alkene nitriles. Based upon the observation that Grignard reagents do not generally react with nitriles <1987JOC3901>, it was found that double deprotonation of β-hydroxy nitriles generates the dianion **32** that readily ejects MgO to provide the unsaturated nitrile **33** in excellent yield (Scheme 8) <1999OL1547>. Subsequent to this it has been shown that a range of β-hydroxy nitriles undergo this facile elimination of ClMgO upon double deprotonation with MeMgCl to give excellent yields of a series of highly substituted α,β-unsaturated nitriles <2000TL8847>. This method is especially useful for the synthesis of α,β-unsaturated nitriles from hindered ketones that are otherwise difficult to obtain <2002JOC3668>.



Scheme 8

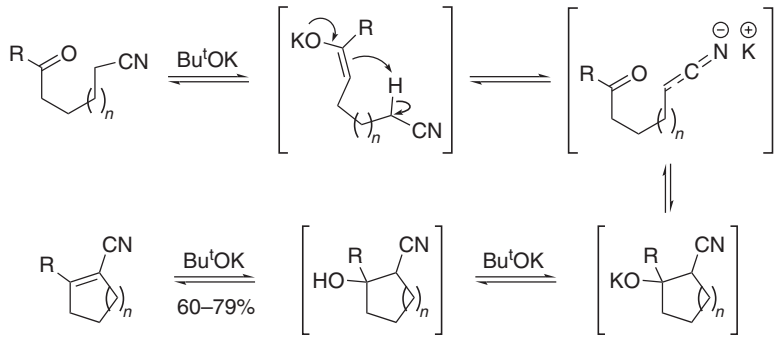
In an alternative yet complementary approach, sequential addition of lithioacetonitrile and $MgBr_2$ to aldehydes and ketones generates magnesium alkoxides (e.g., **34**) (Scheme 9) *in situ* that eliminate BrMgO upon addition of MeMgCl to give α,β-unsaturated nitriles <2002JOC3668>.



R^1 = alkyl; R^2 = H, alkyl, aryl

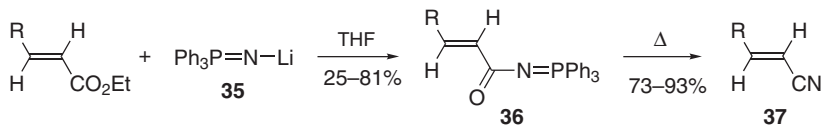
Scheme 9

Despite the value of cyclic alkenenitriles in the synthesis of substituted carbocycles, their synthesis is challenging because of the inherent difficulty in performing an efficient cyclization–olefination sequence in a single operation. This is particularly the case if the approach involves attempted intramolecular condensation of a nitrile anion with a remote carbonyl group, since there is generally a preference for the more acidic carbonyl group to form an enolate with subsequent addition to the nitrile group. In a novel approach to overcome this problem, a series of carbocyclic and heterocyclic alkenenitriles have been prepared in good yield by treatment of oxonitriles with an excess of either Bu^tOK or Bu^iOK <2002JOC9414>. It is postulated that the reaction occurs via sequential anion equilibration, cyclization, and elimination as depicted in Scheme 10.



Scheme 10

The reaction of α,β-unsaturated esters with the lithiated phosphinimine **35** (Scheme 11) results in the formation of the unsaturated acylphosphinimines **36** <1999HAC49>. Upon heating (at 65–110 °C) in toluene, compounds **36** undergo an intramolecular aza-Wittig reaction (Scheme 11) to afford the corresponding α,β-unsaturated nitriles **37** in generally excellent yield.



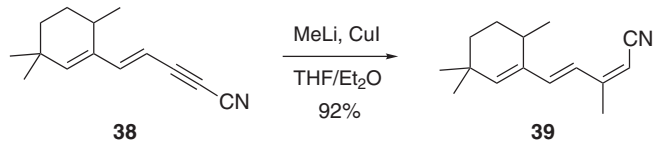
R = alkyl, aryl, heteroaryl

Scheme 11

3.19.2.2 α,β-Alkenic Nitriles with Further Unsaturation

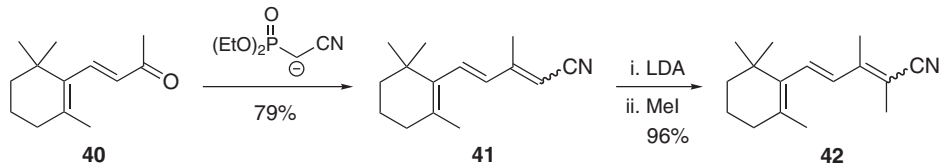
There have been several syntheses of α,β-unsaturated nitriles that contain further unsaturation since the 1990s. However, a number of these reports also contain the synthesis of α,β-unsaturated nitriles without further unsaturation, and have therefore been discussed in the preceeding section. The addition of organocopper reagents to enynenitriles results in exclusively 1,4-addition, whereas

most dienenitriles react with cuprates by 1,6-addition <2003CRV2035>. This type of reactivity was used to excellent effect in a synthesis of retinoids, wherein the dienynenitrile **38** was treated with MeLi and CuI to afford exclusively the triene nitrile **39** (Equation (5)), which was further elaborated to the target compounds <1996JOC3542>.



38 **39** (5)

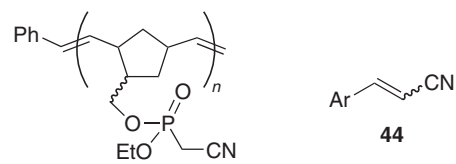
The synthesis of a variety of 10-, 14-, and 10,14-substituted retinal derivatives via alkene nitriles has also been accomplished using Horner–Emmons chemistry. For example, condensation of the aldehyde **40** with the anion derived from diethyl cyanomethylphosphonate afforded the α,β-unsaturated nitrile **41** in high yield as a mixture of (*E*)- and (*Z*)-isomers (Scheme 12) <2001JOC1269>. Deprotonation of **41** and quenching with iodomethane smoothly provided the substituted alkenenitrile **42** which was further elaborated into substituted retinal derivatives.



40 **41** **42**

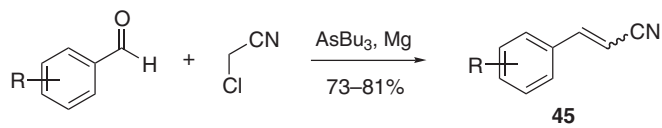
Scheme 12

The emergence over recent years of the value of combinatorial chemistry has prompted the development of Horner–Emmons reagents bound to a polymer. One such example is the ROMPGEL reagent **43** which has been condensed with a variety of aryl aldehydes to give the α,β-unsaturated nitriles **44** in consistently high yield (>85%) and typically better than 4:1 selectivity for the (*E*)-isomer <1999OL579>.



43 **44**

Aryl α,β-unsaturated nitriles (e.g., **45**) have also been prepared from the corresponding aldehyde by condensation with benzyl nitrile in the presence of base <1996MI319-02>. Similarly, iodine-catalyzed condensation between aryl aldehydes and chloroacetonitrile promoted by tributylarsine and magnesium provides consistently high yields of the corresponding α,β-unsaturated nitriles (Equation (6)) <1996SC4693>.

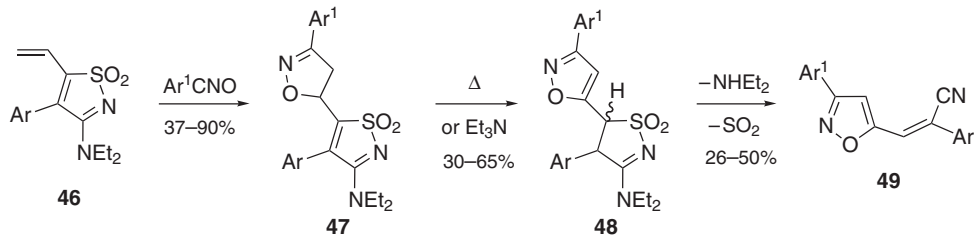


45 (6)

R = H, Me, Cl, Br, NO_2

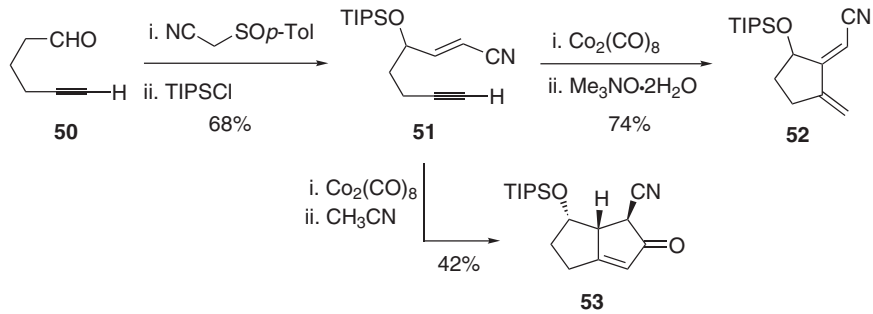
In an investigation into the reactivity of 3-amino-isothiazole 1,1-dioxides **46** toward 1,3-dipoles (such as nitrile oxides), it was found that the cycloaddition occurred with complete regioselectivity giving rise to the cycloadduct **47** (Scheme 13). Heating **47** in a high boiling solvent resulted in the formation of the isoxazole **48** which, upon heating at its melting point, resulted in the pyrolytic transformation to the α,β-unsaturated nitrile **49** <1998T11285>. The unsaturated nitrile **49** was obtained exclusively as the isomer shown, irrespective of whichever

isomer of **48** was used as substrate for the reaction. The assignment of the isomeric configuration of **49** was confirmed either by ^{1}H NMR n.O.e. experiments or, in one instance, by X-ray crystallographic analysis <1998T11285>.



Scheme 13

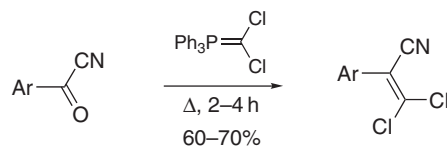
The intramolecular cyclization of enynes is also a useful avenue into functionalized α,β-unsaturated nitriles. Condensation between the aldehyde **50** and *p*-tolylsulfinylacetonitrile gave the γ-*oxo*-alkenenitrile **51** which, upon treatment with dicobalt hexacarbonyl promoted by $Me_3NO_2{\cdot}2H_2O$, gave the diene **52** as the (*E*)-isomer as shown in Scheme 14 <2003JOC2975>. Interestingly, under Pauson–Khand cyclization conditions (dicobalt hexacarbonyl in refluxing acetonitrile), the γ-*oxo*-alkene nitrile **51** gave predominantly the *endo*-cyclization product **53**.



Scheme 14

3.19.2.3 α,β-Alkenic Nitriles with Halo-substituents

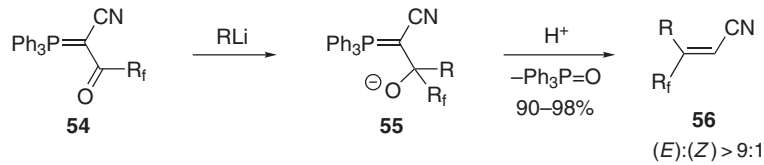
Halogen-substituted α,β-unsaturated nitriles are quite useful intermediates in organic synthesis, particularly in the synthesis of biologically active natural products (see, e.g., <1995P597, 1983JMC1551>). α-Halo-substituted-α,β-unsaturated nitriles are generally prepared by condensation reactions between a carbonyl compound and an α-halogenated phosphorane <1995COFGT(3)641>. An example of this type of process is shown in Equation (7), wherein 2-arylacrylonitriles are reacted with triphenylphosphine in the presence of a large excess of carbon tetrachloride, to give the desired aryl-3,3-dichloroacrylonitriles in good yield <1973JOC479>. This reaction fails when aliphatic acyl cyanides are used as substrates. Since the publication of COFGT (1995) (Section 3.19.2.3) <1995COFGT(3)641>, there have been a limited number of additional publications in this area.



(7)

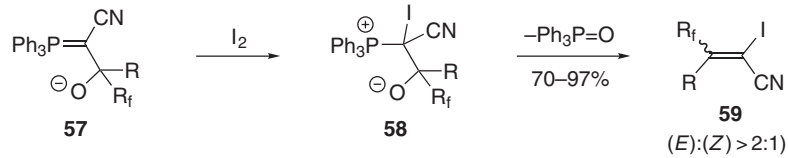
Perhaps the area of greatest activity since the early 1990s is the synthesis of perfluoroalkylated α,β-unsaturated nitriles. The observation that treatment of perfluoroacylcyanomethylenetriphenylphosphoranes **54** (Scheme 15) with an aryl- or alkynyllithium reagent leads to the ylide anion **55** which, upon acidification, undergoes a spontaneous intramolecular Wittig reaction to give the

fluorinated α,β-unsaturated nitrile **56** ((*E*)-isomer shown) <1991JCS(P1)487> has prompted the same group to expand on their initial findings. In a similar approach, the intermediate ylide anion **57**, generated in the same way as **55**, is treated with iodine (or 1,2-diiodoethane) to generate the intermediate iodinated derivative **58** which then eliminates triphenylphosphine oxide to give a mixture of (*E*)- and (*Z*)-α-iodo-α,β-unsaturated nitriles **59** (Scheme 16) <1996JFC(80)153>. Of a series of analogs of **59** prepared in this way, generally the (*E*)-isomer was the major component.



$R_f = CF_3, C_3F_7$; R = aryl, alkynyl

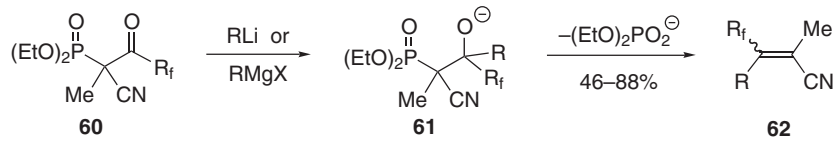
Scheme 15



$R_f = CF_3, C_2F_5, C_3F_7$; R = alkyl, aryl

Scheme 16

Perfluoroalkylated α,β-unsaturated nitriles have also been prepared through the use of Horner–Wadsworth–Emmons chemistry with cyanoethylphosphonates. In a similar way to that shown above, treatment of the phosphonate **60** with an organolithium reagent results in addition to the carbonyl group leading to the intermediate **61** (Scheme 17) which undergoes an elimination to give the α,β-unsaturated nitrile **62** <1997JFC(86)173>. Generally, **62** is formed with a slight preference for the (*E*)-isomer. Interestingly, treatment of the same intermediate **60** with Grignard reagents affords the product **62** as predominantly the (*Z*)-isomer (up to 89:11 (*Z*):(*E*) ratio when R = PhC≡C) <2002MI319-03>.



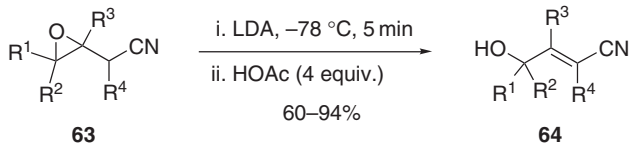
$R_f = CF_3, C_2F_5, C_3F_7$; R = aryl, alkynyl

Scheme 17

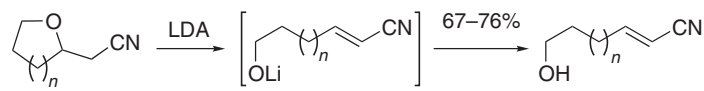
3.19.2.4 α,β-Alkenic Nitriles with Oxygen-based Substituents

Oxygen-containing α,β-unsaturated nitriles are extremely useful intermediates in the synthesis of heterocycles. Hydroxy-containing alkene nitriles represent the ideal substrates for exploring stereoselective conjugate additions to the nitrile functionality, since the hydroxyl group stereochemistry is effectively relayed to the newly formed bonds (see <2003JOC4235> and references therein). Whilst α,β-unsaturated nitriles can be prepared from a variety of precursors (*vide infra*), fewer methods exist for the synthesis of hydroxylated alkene nitriles. γ-Hydroxy unsaturated nitriles have been prepared by cyanide or acetonitrile additions to vinyl iodides, aldehydes, and ketones; however, there is no single method for synthesizing unsaturated nitriles with hydroxylation at carbons successively removed from the unsaturated nitrile moiety. In one example, epoxidation of commercially available β,γ-unsaturated nitriles affords epoxy nitriles **63** (Equation (8)) which upon brief

exposure to LDA at −78 °C followed by immediate quenching with acetic acid affords the corresponding hydroxy α,β-unsaturated nitriles **64** in high yield <2001JOC2171>. In this way a series of di- and tri-substituted γ-hydroxy α,β-alkene nitriles were prepared, and all of the products were obtained exclusively as the (*E*)-isomers. Interestingly, the ring opening of larger rings (furan and pyran) also occurs efficiently under these reaction conditions (Equation (9)), giving rise to the corresponding α,β-unsaturated nitriles with the hydroxyl further removed from the unsaturation <2001JOC2171>.

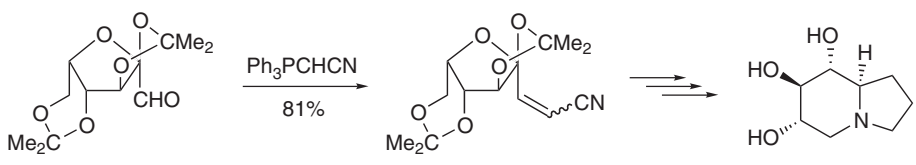


63 **64** (8)



n = 1, 2 (9)

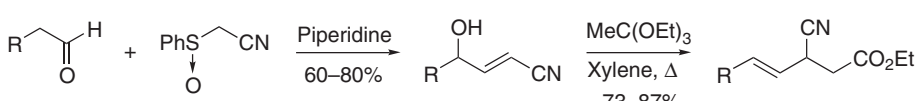
The addition of (cyanomethylene)triphenylphosphorane to the D-*xylo*-hexos-2-ulofuranose derivative **65** afforded predominantly the carbohydrate-based (*E*)-unsaturated nitrile **66** which was further elaborated into 1-deoxycastanospermine **67** (Scheme 18) <1999EJO1269>.



65 **66** (*E*)/(*Z*) 9/1

Scheme 18

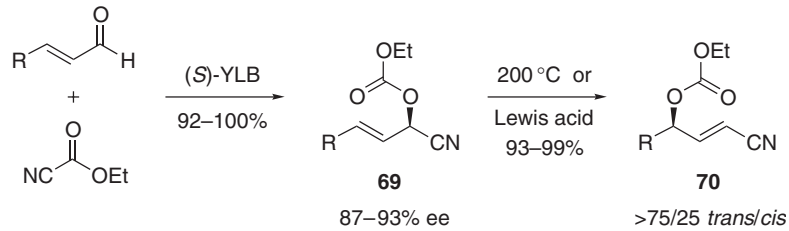
Reaction of a series of aliphatic aldehydes with (phenylsulfinyl)acetonitrile efficiently gives the γ-hydroxy α,β-unsaturated nitriles **67** which, when treated with triethylorthoacetate, undergo a Claisen–Johnson orthoester rearrangement to the corresponding 3-cyanoesters **68** (Scheme 19) <2001EJO713>. The use of a [3,3]-sigmatropic rearrangement has also been utilized in an approach toward the synthesis of Patulolide C. Catalytic asymmetric cyanation on aliphatic or aromatic aldehydes using ethylcyanoformate promoted by YLi_3-tris(binapthoxide) (YLB) <2002AG(E)3636> affords optically active cyanohydrin carbonates **69** in >90% ee (Scheme 20). Thermal (200 °C) [3,3]-sigmatropic rearrangement of **69** gave the γ-*oxy*-α,β-unsaturated nitrile **70** in high yield predominantly as the *trans*-isomer without racemization <2003OL3021>. Similarly, treatment of **69** under Lewis acid-promoted conditions also afforded predominantly the *trans*-isomer of **70**, although partial racemization did occur under these conditions <2003OL3021>.



67 **68**

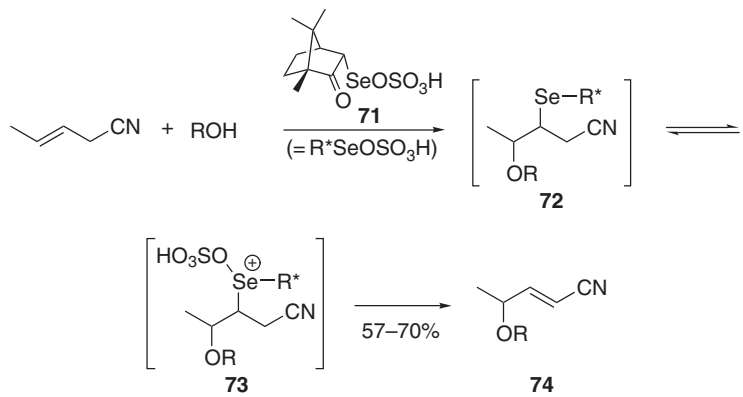
R = *n*-C_6H_{13}, $Cl(CH_2)_4$, Pr^i, $BnO(CH_2)_3$, $CH_2{=}CH(CH_2)_6$, $PhCH_2$

Scheme 19



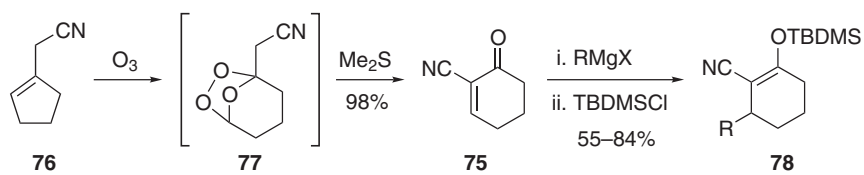
Scheme 20

An asymmetric oxyselenation–deselenation sequence on β,γ-unsaturated nitriles using camphor diselenide and ammonium persulfate in methanol, ethylene glycol, or water affords enantiomerically enriched α,β-unsaturated nitriles <1999TA747>. The reaction proceeds via initial reaction of the camphor diselenide with the ammonium persulfate, giving rise to the camphor selenenylsulfate **71** which reacts with the alkene to give the oxyselenated product **72** (Scheme 21). Further reaction of **72** with ammonium persulfate generates the selenonium ion **73** which undergoes an elimination to generate the observed product **74** <1999TA747>.

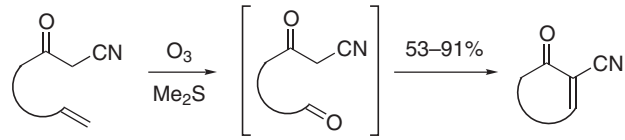


Scheme 21

In a series of reports by the Fleming group, β-oxygenated α,β-unsaturated nitriles have been used as valuable tools in the synthesis of a range of natural product structural units. In one report <1997JOC3036> the β-*oxo*-α,β-unsaturated nitrile **75** is obtained in near quantitative yield by a domino ozonolysis–aldol sequence from the β,γ-alkenenitrile **76** via the ozonide **77** (Scheme 22). This domino ozonolysis–aldol sequence is also applicable to a range of substituted acyclic ketonitrile substrates, with yields of the corresponding five- and six-membered *oxo*-α,β-alkenenitriles being generally >80% (Equation (10)) <1997JOC3036, 1999JOC2830>. The oxonitrile **75** reacts with Grignard reagents affording the conjugate addition products **78** (Scheme 22) in good-to-excellent yields after trapping of the intermediate enolate as the silylether <1997JOC4883>.

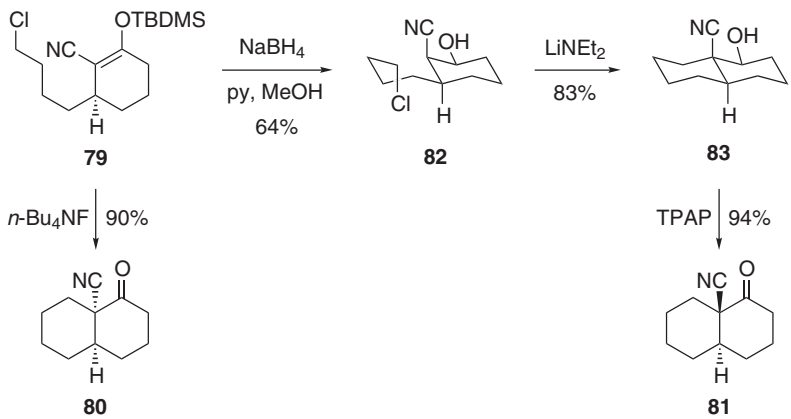


Scheme 22



(10)

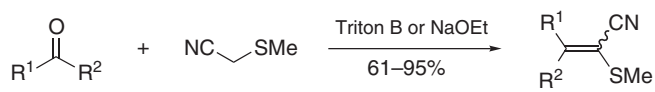
β-Siloxy unsaturated nitriles allow the generation of either ketone enolates or nitrile anions, providing a potential means of stereocontrol in alkylations with appropriately positioned electrophiles. This concept has been utilized to great effect in the stereoselective synthesis of *cis*- and *trans*-decalins <1999OL1547, 2003T737>. Thus, desilylation (*n*-Bu_4NF) of the β-siloxy unsaturated nitrile **79** (Scheme 23), itself generated from **75** by reaction with chlorobutyl Grignard reagent, afforded exclusively the *cis*-decalin **80** in 90% yield <1999OL1547>. For preparation of the corresponding *trans*-decalin **81**, the silyl group in **79** was removed, the enolate protonated, and the resulting ketone reduced to produce predominantly the β-hydroxynitrile **82**. Cyclization of **82** by treatment with excess $LiNEt_2$ gave the decalin **83** which was oxidized to the *trans*-decalin **81** (Scheme 23). This method has also been used to prepare more highly substituted *cis*- and *trans*-decalins that are potential precursors to terpenoid natural products <1999OL1547, 2003T737>.



Scheme 23

3.19.2.5 α,β-Alkenic Nitriles with Sulfur-based Substituents

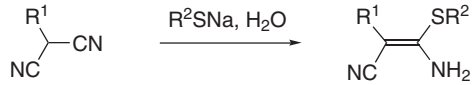
There have been few advances in this area since the publication of chapter 3.19.2.5 in <1995COFGT(3)641>. As with the preparation of alkoxy-α,β-unsaturated nitriles by condensation between carbonyl compounds and the anion derived from alkoxyacetonitrile (section 3.19.2.4, <1995COFGT(3)641>), the anion derived from methyl thioacetonitrile reacts with carbonyl compounds to form α-methylthio-α,β-alkenic nitriles (Equation (11)). The α-methylthio-α,β-alkenic nitriles shown in Equation (11) are generally obtained as ~1:1 mixtures of (*E*):(*Z*) isomers, although in some instances (e.g., R^1 = Ph, R^2 = Me) a 5:1 ratio of (*E*):(*Z*) isomers was obtained <1988SC2111>. The same outcome results from the exposure of carbonyl compounds to the Peterson reagent cyano(methylthio)methyltrimethylsilane in the presence of LDA <1988SC2111, 1995COFGT(3)641>.



(11)

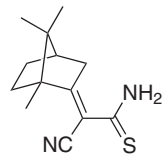
R^1 = alkyl, aryl; R^2 = H, alkyl

An efficient synthesis of β-alkylthio-α,β-unsaturated nitriles involves exposure of substituted malononitriles to sodium alkylthiolate (Equation (12)) <1988S813, 1995COFGT(3)641>. The addition of thiols to allenyl nitriles, as well as the condensation of acetonitrile with thioesters in the presence of Bu^nLi, can both be utilized to furnish β-thio-α,β-alkenic nitriles <1995COFGT(3)641>.

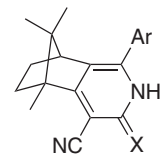


(12)

More recently, reaction between camphor and cyanothioacetamide under phase-transfer catalysis provided the camphorylidene derivative **84** <2003SUL55>. Subsequent reaction of **84** with arylidene derivatives cyanothioacetamide or cyanoacetamide leads to the 2-thioxo and 2-oxopyridine derivatives **85**. Treatment of the pyridinones (**85**, X = O) with P_4S_{10} results in the smooth formation of the corresponding pyridinethiones (**85**, X = S) <2003SUL55>.

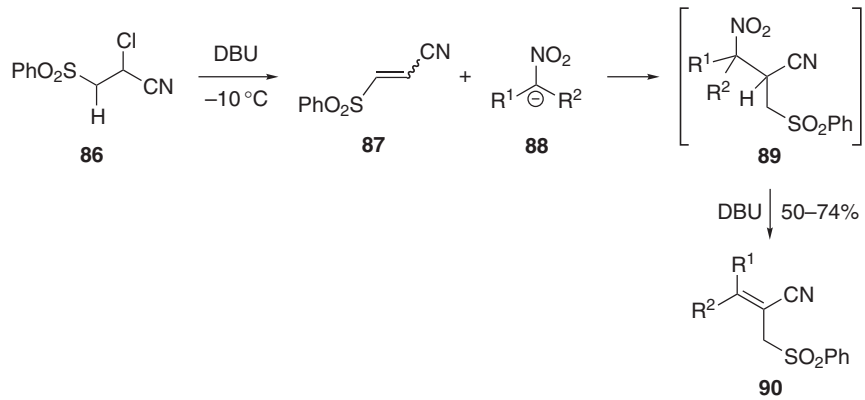


84



85 X = S or O

Polyfunctionalized sulfur-containing α,β-unsaturated nitriles have been obtained by reaction of nitroalkanes with 2-chloro-3-phenylsulfonylpropanenitrile **86** in the presence of base <2003TL9033>. The reaction proceeds by initial elimination of HCl from **86** leading to the unsaturated nitrile **87** (Scheme 24) and the simultaneous formation of the anion **88**. Conjugate addition of **88** to **87** gave the Michael adduct **89** which then eliminates nitrous acid to give the desired α,β-unsaturated nitrile **90**. The product **90** was generally formed with complete (*E*)-selectivity <2003TL9033>.



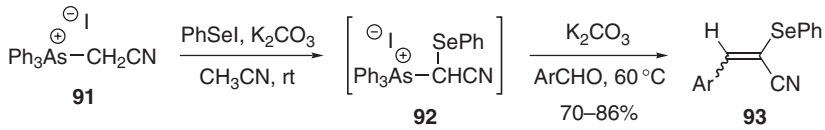
86 **87** **88** **89** **90**

Scheme 24

3.19.2.6 α,β-Alkenic Nitriles with Se- and Te-Based Substituents

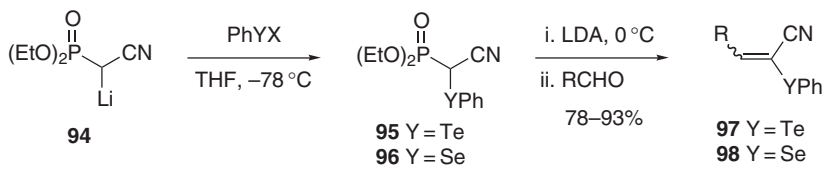
There have been a limited number of reports in this area since the publication of chapter 3.19.2.6 in <1995COFGT(3)641>. As previously described <1995COFGT(3)641> whilst the oxidative elimination of selenoxides has been used in the synthesis of α,β-unsaturated nitriles, the actual synthesis of α,β-alkenic nitriles that themselves contain selenium-based substituents is far less common. In a series of reports from the same group, the synthesis of several α-phenylseleno-α,β-unsaturated nitriles has been described. In one example, the stable arsonium salt **91** was obtained by reaction between triphenylarsine and chloroacetonitrile in the presence of potassium iodide <1999MI319-02, 2002SC1775>. Reaction between **91** and phenylselenenyl iodide in the presence of anhydrous K_2CO_3 afforded the salt **92** which, without isolation, was condensed with aromatic

aldehydes to give the desired α-seleno-α,β-unsaturated nitriles **93** in consistently high yields (Scheme 25). In a minor modification to this procedure, potassium *t*-butoxide was added to **91** followed by the addition of PhSeI and then the aldehyde <2002SC1775>.



Scheme 25

In what is perhaps the only report describing the synthesis of α,β-alkenic nitriles with tellurium-based substituents, reaction of the lithiated cyanomethylphosphonate **94** with benzenetellurenyl bromide afforded the α-phenyltellurium intermediate **95** (Scheme 26) which, upon treatment with LDA (excess) and an aliphatic aldehyde, afforded the target α-phenyltelluride-α,β-unsaturated nitrile **97** <2001T5953>. Interestingly, the use of aromatic aldehydes in the reaction with **95** resulted in unstable products that could not be isolated. The same process is also applicable to the synthesis of the corresponding selenium-containing α,β-alkenic nitrile **98**, using benzeneselenenyl chloride instead of benzenetellurenyl bromide to afford **96**. In the selenium case, both aliphatic and aromatic aldehydes are tolerated, with **98** being obtained in generally >80% yield <2001T5953>.

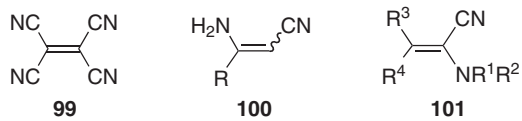


when Y = Te, R = alkyl; when Y = Se, R = alkyl, aryl

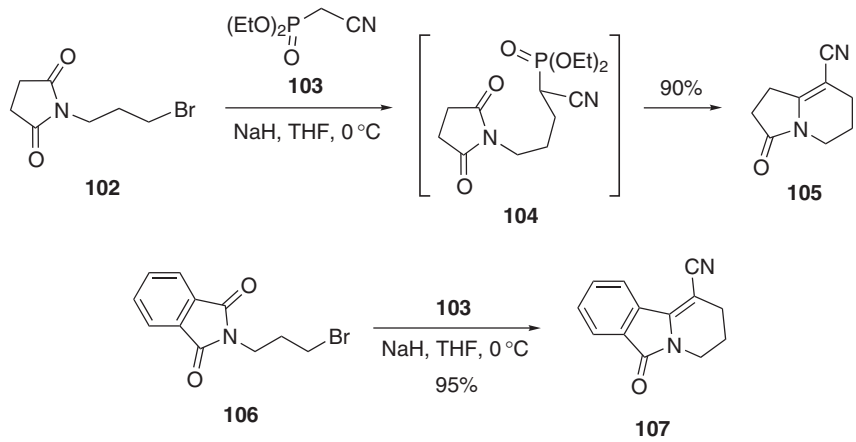
Scheme 26

3.19.2.7 α,β-Alkenic Nitriles with Nitrogen-based Substituents

Tetracyanoethylene (TCNE, **99**) is perhaps the best known and certainly the most widely used α,β-alkenic nitrile with nitrogen-based substituents. A comprehensive review of the synthesis and chemistry of TCNE appeared in 1986 <1986S249>, and since then there have been few further advances in this area. β-Enaminonitriles (e.g., **100**) are extremely useful compounds for the synthesis of heterocyclic systems, and an excellent article in the early 1990s <1993CRV1991> covers this area of chemistry in far more detail than is possible here. Generally, the preparation of simple β-enaminonitriles, e.g., **100**, can be accomplished by the dimerization of substituted nitriles, or via the hydride reduction of substituted malononitriles. The synthesis of α-amino-α,β-alkenic nitriles (e.g., **101**) is also an area of intense interest. A simple access to these compounds is via the deprotonation of saturated α-aminonitriles with strong base, or via the cyanation of enamines themselves. For a more detailed account of these general methods, see chapter 3.19.2.7 in <1995COFGT(3)641> and references therein.

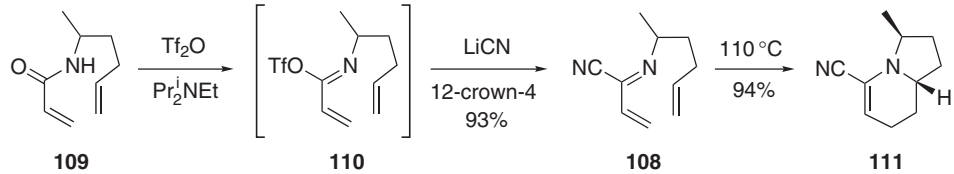


In the synthesis of some novel heterocyclic compounds, it was found that condensation between the imide **102** and the anion derived from the β-cyanophosphonate **103** initially resulted in the generation of **104** (Scheme 27), which undergoes an intramolecular Horner–Wadsworth–Emmons reaction leading to the heterocycle **105** <1999EJO3489>. The reaction works equally well with the imide **106**, leading to the formation of the tricyclic derivative **107** in 95% yield <1999EJO3489>.



Scheme 27

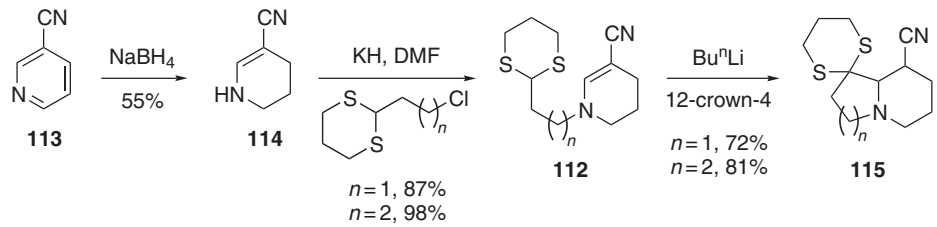
In an elegant synthesis of indolizidine and quinolizidine alkaloids, the presence of a 2-cyano substituent in 1-aza-1,3-butadienes (e.g., **108**) (Scheme 28) is required to sufficiently activate the diene for an intramolecular Diels–Alder reaction <1997JOC2093>. The 2-cyano-1,3-butadiene **108** was itself prepared by treatment of the amide **109** with triflic anhydride, leading to the intermediate imidoyltriflate **110** which was then reacted with lithium cyanide. In this way the requisite diene **108** was generated in excellent yield, and subsequently furnished the cycloadduct **111**, predominantly (4:1) as the isomer shown (Scheme 28).



109 **110** **108** **111**

Scheme 28

The synthesis of the backbone of indolizidine and quinolizidine alkaloids has also been achieved from the dithiane anion of the enamino nitrile **112** (Scheme 29) <1997JOC1305>. In this instance, the enamino nitrile **112** was obtained by reduction of the nicotinonitrile **113** to the tetrahydropyridine **114**, followed by alkylation with dithianes. The enaminonitriles **112** cyclize to the requisite alkaloid templates **115** in the presence of Bu^nLi and 12-crown-4, with the nitrile group exhibiting a strong thermodynamic preference for an axial orientation <1997JOC1305>.

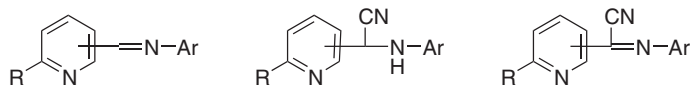


113 **114** **112** **115**

Scheme 29

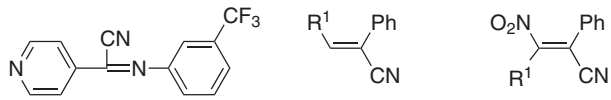
The addition of trimethylsilylcyanide to imines (e.g., **116**) furnished the expected α-amino-nitriles **117** together with the unexpected α,β-unsaturated nitriles **118** <2001APOC733>. Although the isolated yields of the α,β-unsaturated nitriles **118** were generally low (<30%), in some

instances, e.g., **119**, they were the only product obtained. The nitration of a series of α,β-alkenic nitriles **120** using NO—NO_2 provides the corresponding (Z)-β-nitro-α,β-unsaturated nitriles **121** in 75–90% yield <1999OPP117>.



116 **117** **118**

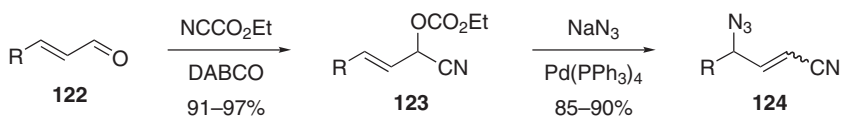
R = H, Me; Ar = 3- or 4-CF_3-C_6H_4



119 **120** **121**

R^1 = H, Me, Ph, styryl, 2-thienyl

The synthesis of γ-azido-α,β-alkenic nitriles is of interest because of their use in the synthesis of a diverse array of biologically active compounds such as unnatural γ-amino acids. In a simple and efficient procedure for preparing γ-azido-α,β-unsaturated nitriles, cyanation of unsaturated aldehydes **122** is efficiently achieved by reaction with ethyl cyanoformate in base to give the cyanohydrin carbonates **123** (Scheme 30) <2001JOC7191>. Palladium-catalyzed allylic substitution on **123** with azide ion then smoothly affords the corresponding γ-azido-α,β-alkenic nitriles **124** as mixtures of (*E*):(*Z*)-isomers.



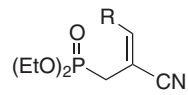
122 **123** **124**

R = Me, Pr, CH_2OBn, CH_2OTBS

Scheme 30

3.19.2.8 α,β-Alkenic Nitriles with P-, As-, Sb-, and Bi-Based Substituents

No further advances have occurred in this area since the publication of chapter 3.19.2.8 in <1995COFGT(3)641>. Indeed, α,β-alkenic nitriles with arsenic-, antimony-, or bismuth-based substituents appear to be unknown, whilst α,β-alkenic nitriles with phosphorus-based substituents (e.g., **125**) are generally obtained as intermediates in the condensation of carbonyl compounds with phosphonates, and usually react *in situ*. Although the cyanophosphonate **125** is highly reactive, it has been isolated in moderate yield <1983S917>.

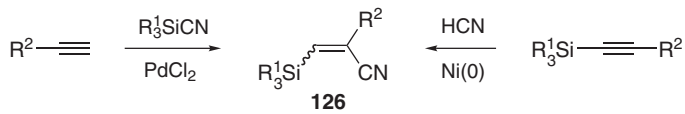


125

3.19.2.9 α,β-Alkenic Nitriles with Si- and B-Based Substituents

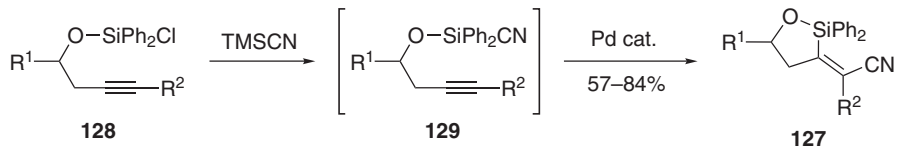
As is the case with phosphorus-based α,β-alkenic nitriles described above, the few reports of silicon-based α,β-unsaturated nitriles generally describe such molecules as reactive intermediates rather than isolated target compounds <1995COFGT(3)641>. Silylated alkynes can be cyanated

with hydrogen cyanide in the presence of a nickel catalyst to give the β-silylated α,β-alkenic nitrile **126** (Equation (13)), whilst alkynes themselves, upon treatment with TMSCN in the presence of a palladium catalyst, also afford **126** (see chapter 3.19.2.9 in <1995COFGT(3)641> and references therein for further discussion).



(13)

There have been few reports on the synthesis of silylated α,β-alkenic nitriles since the 1990s. The unusual tetrahydrofuran derivative **127** was obtained by the intramolecular palladium-catalyzed cyanosilylation of the homopropargylic alcohol derivative **128** via the intermediate **129** (Scheme 31) <1994TL8635>. The use of propargyl or 4-pentyn-1-ol substrates in this reaction gave complex mixtures of products, indicating that formation of the five-membered ring in **127** is the most favored for the intramolecular cyclization.



R^1 = H, Me; R^2 = H, Me, Bu

Scheme 31

3.19.2.10 α,β-Alkenic Nitriles with Metal Substituents

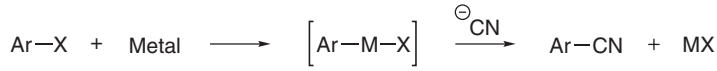
α,β-Alkenic nitriles with metal substituents are highly reactive species and as such have not been isolated. Such species are therefore considered as transient intermediates and will not be specifically discussed here. However, it is worth remembering that such species, formed by deprotonation of α,β-unsaturated nitriles by strong base, are valuable intermediates in the preparation of substituted α,β-alkenic nitriles.

3.19.3 NITRILES BEARING AN α,β-ARYL OR -HETARYL SUBSTITUENT

3.19.3.1 General Methods

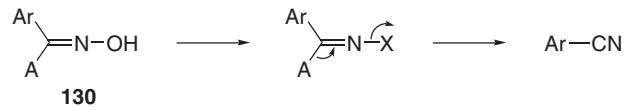
As with aliphatic and α,β-alkenic nitriles, aryl nitriles are important compounds because of the unique reactivity of the nitrile group and its subsequent use in the synthesis of important functionality such as novel heterocyclic systems of biological interest. One such example is the transformation of aryl nitriles into substituted 1*H*-tetrazoles as carboxylic acid isosteres <2002BMC3379>. Other recent examples include the use of aryl nitriles in a route to arylaminocyclopropane derivatives <2003JOC7133> or their use in cross-coupling reactions <2003TL1907>.

Despite the importance of aryl nitriles, there have been few significant changes in the way in which they are prepared over recent years. The most commonly employed method for the preparation of aryl nitriles involves reaction between an aryl halide and cyanide ion (Equation (14)). When the transformation shown in Equation (14) is conducted with copper cyanide at elevated temperatures (150–250 °C), it is referred to as the Rosenmund–von Braun reaction, which was first reported in 1919 (for a review, see <1987CRV779>). There are a number of modifications on this theme, particularly in relation to the use of either palladium or nickel catalysts in order to carry out this transformations under milder conditions than those of the Rosenmund–von Braun reaction. In all of these transformations, the nature and position of other substituents on the aromatic ring has an effect on the outcome. In general, the aromatic ring may contain various substituents (but not nitro groups because they interact unfavorably with the metal catalyst) although *ortho*-substituents tend to give rise to lower yields.



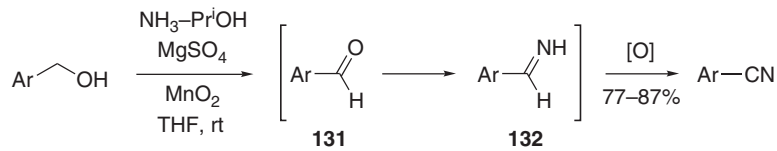
(14)

Other transformations are also possible for the synthesis of aryl nitriles. The dehydration of oximes is the most common of the elimination reactions leading to aryl nitriles, and since aryl aldehydes can be readily transformed into the corresponding oxime, this approach allows the direct transformation of aryl aldehydes to aryl nitriles <B-1983MI319-02>. The Beckmann fragmentation of ketoximes is also a useful route, but requires that the substituent on the α-carbon ("A" in **130**) is able to stabilize (or bear) a positive charge (Scheme 32). Aromatic amides can also be efficiently transformed into aryl nitriles under very mild conditions using chlorosulfonyl isocyanate in triethylamine. The interested reader is directed to chapter 3.19.3 in <1995COFGT(3)641> as well as three excellent reviews <B-1983MI319-02, 1987CRV779, 1991COS(6)225> for a more detailed discussion.



Scheme 32

Another important and highly versatile approach to aryl nitriles involves an *in situ* oxidation–imination–aldimine oxidation sequence that directly converts benzylic alcohols into aryl nitriles (Scheme 33) <2002SL1291>. This transformation follows from the earlier work <2001SL230> which showed that aryl aldehydes could be converted to the corresponding nitriles by treatment with ammonia in isopropanol and THF containing magnesium sulfate and manganese dioxide. In the conversion of benzylic alcohols into arylnitriles (Scheme 33), it is believed that the initially formed aldehyde **131** is transformed into the aldimine **132** followed by oxidation to the nitrile by manganese dioxide <2002SL1291, 2001SL230>. In this way a series of aryl and heteroaryl nitriles were obtained in excellent yield. Propargylic alcohols also undergo this transformation <2002SL1291>.



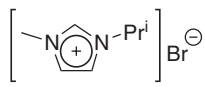
Scheme 33

3.19.3.2 Benzonitrile and Substituted Benzonitriles

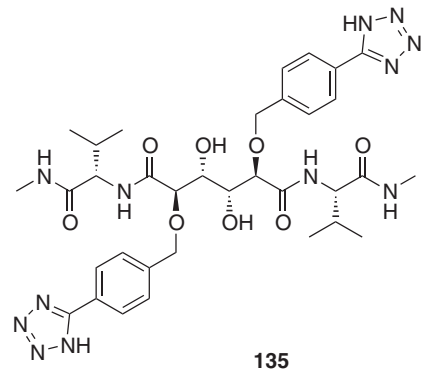
The displacement of aromatic halides with cyanide ion in the synthesis of α,β-aryl nitriles, such as the Rosenmund–von Braun reaction, remains one of the most popular routes employed. Considerable effort, however, has gone into establishing conditions that are less severe than those first developed around 80 years ago, particularly because of the usefulness of aryl nitriles as intermediates in the pharmaceutical industry. Over recent years there has been a trend toward developing safer, more environmentally friendly chemistry, and this is also true for the synthesis of aryl nitriles from aryl halides. In one such example the use of ionic liquids (e.g., 1-*n*-butylmethyl-imidazolium halide salts (bmiX)) has been found to be an effective reusable reaction media for the Rosenmund–von Braun reaction of aryl halides with sodium cyanide in the presence of copper(I) salts <2002TL387>. Thus, exposure of a series of aryl halides to cyanide ion in the presence of a copper(I) catalyst immobilized in the ionic liquid bmiX gave the resultant aryl nitrile derivatives **133** in generally high yield after heating at **120** °C for 24 h (Equation (15)). Of the various substrates used in this reaction, it was found that the electronic character of any substituents on the aromatic ring (e.g., methoxy or cyano groups) appeared to have little effect on the outcome of the reaction. Importantly, the product **133** is readily isolated from the mixture using simple extraction with organic solvent, and the ionic liquid with immobilized copper(I) catalyst can be reused repeatedly without any apparent loss of efficiency <2002TL387>.

$$\mathrm{Ar{-}X} + \mathrm{NaCN} \xrightarrow[120\,^{\circ}\mathrm{C}]{\mathrm{CuI\ (2\ equiv.),\ bmiX}} \underset{\mathbf{133}}{\mathrm{Ar{-}CN}} \quad 65\text{–}100\% \qquad (15)$$

In a modification of this approach using the ionic liquid **134**, in conjunction with microwave heating of the reaction, aryl nitriles could be obtained from the corresponding aryl iodides or aryl bromides (but not aryl chlorides) in consistently good yield (55–75%) after only 3 min (for aryl iodide substrates) or 10 min (for aryl bromide substrates) <2003T2253>. The microwave-assisted cyanation of aryl bromides has also provided a milder method for the synthesis of aryl nitriles. In the presence of zinc cyanide and catalytic $Pd(PPh_3)_4$, a series of benzonitrile derivatives have been obtained after 2 min (magnetron input power of 60 W) in >84% isolated yield <2000JOC7984>. This approach was used to great effect in the synthesis of the HIV-1 protease inhibitor **135** in a one-pot microwave-promoted cyanation followed by a cycloaddition reaction on the nitriles to introduce the tetrazole rings as carboxylic acid isosteres <2000JOC7984>.



134

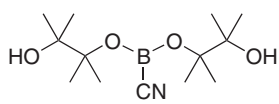


135

One of the limitations with these types of transformations is the generally poor results obtained with aryl chloride substrates, which is due to the fact that the C—Cl bond in aryl chlorides is far more difficult to activate than C—I or C—Br bonds <1994CRV1047>. This lack of reactivity has been overcome by the development of a new palladium catalyst, generated by the addition of 1,5-bis(diphenylphosphino)pentane to $Pd(OAc)_2$, for use in the cyanation of aryl chlorides with potassium cyanide (Equation (16)) <2001TL6707>. Critical to the success of this reaction is the use of catalytic TMEDA. In a series of examples, it was shown that activated aryl chlorides (e.g., methyl 4-chlorobenzoate, 2-chlorobenzonitrile, 4-chloroacetophenone) gave excellent yields (75–96%) of the corresponding nitriles, whilst nonactivated substrates (e.g., chlorobenzene, 3-chlorotoluene) gave poorer yields (17–33%) of aryl nitriles <2001TL6707>.

$$\mathrm{Cl}\text{–}\mathrm{C_6H_4}\text{–}\mathrm{R} \xrightarrow[\text{Toluene}\ 160\,^{\circ}\mathrm{C},\ 16\,\mathrm{h}]{\mathrm{Pd(OAc)_2/dppe},\ \text{cat. TMEDA, KCN}} \mathrm{NC}\text{–}\mathrm{C_6H_4}\text{–}\mathrm{R} \quad 17\text{–}96\% \qquad (16)$$

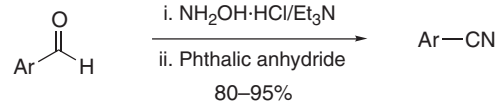
A series of benzonitrile derivatives have also been obtained from the corresponding aryl halides using the novel dialkylcyanoboronate **136** as a cyanide source in the presence of $Pd(PPh_3)_4$ catalyst (Equation (17)) <2001T1581>. The yields of benzonitriles obtained in this way were quite variable, depending on the substitution pattern of the aromatic ring, and some substrates (e.g., 1,4-diiodobenzene) were very slow to react (only 13% conversion to 4-iodobenzonitrile after 42 h).



136

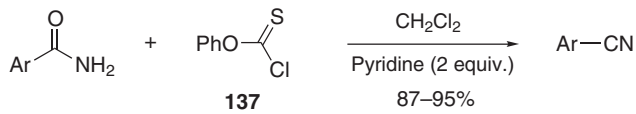
$$\mathbf{136} + \mathrm{Ar{-}X} \xrightarrow[K_3PO_4,\ \mathrm{THF},\ 50\,^{\circ}\mathrm{C}]{Pd(PPh_3)_4/PPh_3} \mathrm{Ar{-}CN} \quad 32\text{–}89\% \qquad (17)$$

The reaction of aryl aldehydes with hydroxyamine is also a useful avenue into substituted benzonitrile derivatives. Of the many possible routes for achieving this transformation (see <1995COFGT(3)641> and <1998TL4047> and references therein), a recent improvement on this general approach utilizes hydroxyamine with phthalic anhydride in a one-pot transformation of aryl aldehydes into the corresponding aryl nitriles in excellent yield (Equation (18)) <1998TL4047>. It is believed that this reaction occurs via nucleophilic attack of the aldoxime hydroxyl onto the phthalic anhydride ring followed by an intramolecular 1,2-elimination <1998TL4047>.



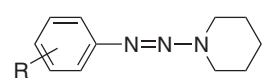
(18)

Aromatic amides are another useful substrate for the generation of the corresponding aryl nitriles. Of the possible methods that can be employed, including the dehydration of carboxamides with phosphorus pentoxide, thionylchloride, boron trifluoride, or phase-transfer catalysis, many of these processes have limitations especially in relation to the type of substrate that can be utilized and the harsh reaction conditions that are needed in some instances (see <1999TL747> and references therein). Many of these problems have been overcome by the development of a mild and efficient process wherein the arylamide is treated with the arylchlorothionoformate **137** in the presence of pyridine at room temperature for a few hours (Equation (19) <1999TL747>. In this way, several benzonitrile derivatives, including methoxy- and nitro-substituted compounds, were obtained by dehydration from the corresponding amides in excellent yields. The reaction is also applicable to α,β-unsaturated and aliphatic amides.



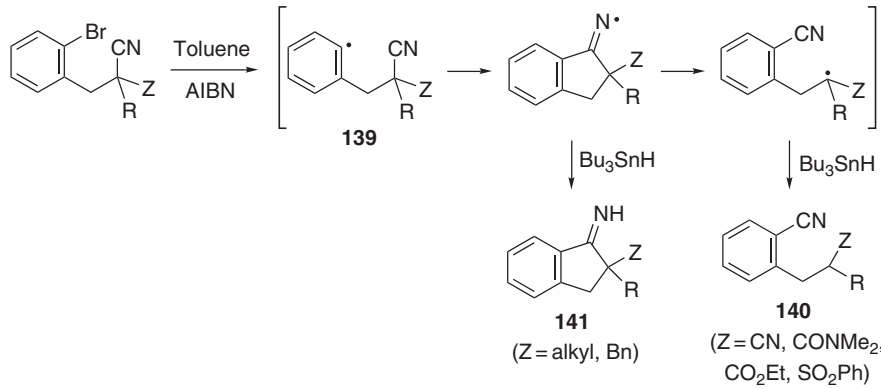
(19)

Aryl triazine derivatives (e.g., **138**), prepared from the corresponding amines, can be easily converted into benzonitriles by treatment with zinc perchlorate/zinc cyanide in refluxing acetonitrile <2001TL3553>. A range of 2- and 4-substituted triazines undergo this transformation, and the yields of benzonitrile products obtained are generally >70% (except for 4-alkyl-substituted derivatives which were generally obtained in <50% yield). The reaction of aryl bromides with Bu^tLi at −94 °C results in the formation of the corresponding aryllithium species (Ar—Li), which can be reacted with tosyl cyanide to furnish the corresponding benzonitrile compounds in generally high yield <1995JOC2948>. In this way it was found that the aryllithium species was superior to the arylcuprate species (Ar—Cu), and that the method is amenable to the preparation of various substituted benzonitrile derivatives.



138

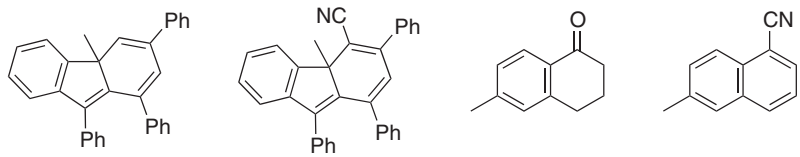
In an attempt to better understand the enigmatic reactivity of radical cyclization onto nitriles, it was found that 5-*exo*-cyclizations of arylradicals **139** undergo nitrile translocation (β-scission) to the benzonitrile derivatives **140** when the α-substituent is an electron-withdrawing group (Scheme 34) <2000TL8989>. The rate of translocation is faster than the 5- or 6-*exo* cyclization onto alkenes or the 1,5-hydrogen abstraction of allylic hydrogens. The nitrile translocation does not occur if the α-substituent in **139** is electron donating, in this case giving the cyclized imine **141** <2000TL8989>.



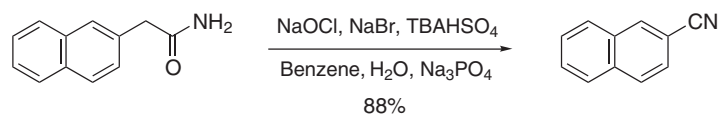
Scheme 34

3.19.3.3 Polycyclic Aromatic Nitriles

Syntheses of polycyclic aromatic nitriles are not widely reported in their own right, since many of the methodologies presented in Sections 3.19.3.1 and 3.19.3.2 are as equally applicable to polycyclic systems as they are to simpler aromatic systems. As discussed earlier, the addition of cyanide ion is a useful procedure for the synthesis of polycyclic aromatic nitriles. Examples include the addition of cyanide ion to the fluorene derivative **142**, to provide the polycyclic aromatic nitrile derivative **143** after oxidation <1995COFGT(3)641, 1970JOC30>. The reaction of aromatic carbonyl derivatives such as the tetralone **144** with TMSCN ultimately leads to the arylnitrile **145** after treatment of the intermediate trimethylsilylcyanohydrin with phosphorylchloride in pyridine followed by aromatization <1983JOC5134>.



Treatment of aryl-substituted acetamides with a hypochlorite liquid triphasic system results in the loss of one carbon via a Hofmann rearrangement (Equation (20)) producing aryl nitriles in moderate yield <1994S1127>. 2-Naphthalenecarboxamide can also be transformed into 2-cyanonaphthalene, by treatment with arylchlorothionoformate in high yield <1999TL747>.



(20)

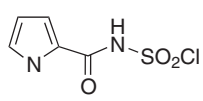
The use of ionic liquids in a Rosenmund–von Braun reaction with aryl halides has also provided access into polycyclic aromatic nitriles <2002TL387>. Both 1- and 2-bromonaphthalene undergo the reaction with CuCN in the presence of the ionic liquid bmiBr, giving the corresponding cyanonaphthalene derivatives in >70% yield.

3.19.3.4 Heterocyclic Aromatic Nitriles

The syntheses of heterocyclic aromatic nitriles are generally carried out in the same way as for the synthesis of other aromatic nitriles (Sections 3.19.3.1 and 3.19.3.2). As with simple aromatic nitriles, the most widely used method for the preparation of heterocyclic aromatic nitriles involves the cyanation of heterocyclic aromatic substrates. An excellent review (see <1987CRV779>) provides a detailed insight into the displacement of a heterocyclic aromatic halides with cyanide

ion. Three other reviews also provide valuable information on the preparation of heteroaryl nitriles, with one article focusing on the use of cyanoacetamide in heterocyclic synthesis in general <1986H(24)2023>, while the other two articles highlight the importance of nitriles in heterocyclic synthesis <1983H(20)519, 1987H(26)497>.

Apart from the displacement of halides with cyanide ion there are other methods that are routinely used in the synthesis of heteroaryl nitriles. The cyanation of pyrroles, indoles, thiophenes, and furans has been accomplished using chlorosulfonylisocyanate in generally excellent yields. The reaction proceeds through a chlorosulfonylcarboxamide intermediate, such as **146** in the pyrrole series, which liberates HCl and SO_3 upon the addition of *N*,*N*-dimethylformamide <1981CJC2673, 1983T3881, 1995COFGT(3)641>. It is important to note here that the nature of other substituents on the heterocyclic ring can alter the position of cyanation. For example, if a deactivating group is in the 2-position of pyrrole, then cyanation with chlorosulfonylisocyanate occurs at the 4-position, whereas 2-substituted furans give 5-cyanofurans under these conditions <1981CJC2673, 1983T3881, 1995COFGT(3)641>. Trimethylsilyl cyanide is also a valuable reagent for the synthesis of heteroaryl nitriles. Treatment of pyridine *N*-oxide with this reagent, in a modification of the Reissert–Henze reaction, provides 2-cyanopyridines in high yield via the silyl ether **147**, whilst reaction between trimethylsilyl cyanide and alkynes in the presence of a palladium or nickel catalyst affords the cyanopyrroles **148** in excellent yields <1995COFGT(3)641>.



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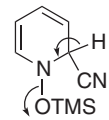

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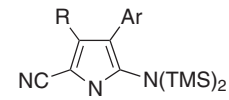
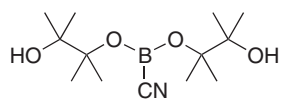


148

The use of a metal catalyst has also been employed more recently for the synthesis of heteroaryl nitriles. In one such example, exposure of 2-iodothiophene to the dialkylcyanoboronate **136** in the presence of a palladium catalyst gave 2-cyanothiophene **149** in 84% yield <2001T1581>. In the same way the 3-cyanoindole derivative **150** was obtained from the corresponding 3-iodoindole; however, the isolated yield of **150** (49%) was only modest. The mechanism of this transformation is considered to be comparable to that of a cross-coupling reaction <2001T1581>. 3-Cyanothiophene and 3-cyanopyridine can also be prepared from the corresponding bromo-derivatives by treatment with zinc cyanide and a palladium catalyst <2000JOC7984>. In this example, the use of microwave irradiation provides the heteroaryl nitriles in >80% isolated yield in only 2 min, compared to several hours using thermal heating.



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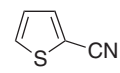

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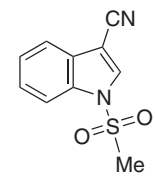
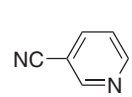


150

The new palladium catalyst, generated by the addition of 1,5-bis(diphenylphosphino)pentane to $Pd(OAc)_2$ referred to earlier (see Equation (16), Section 3.19.3.2) <2001TL6707>, has also been used to prepare the heteroaryl nitriles **151** and **152** in 46% and 74% yield, respectively.



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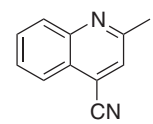
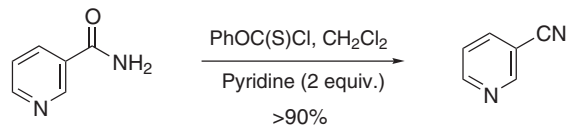


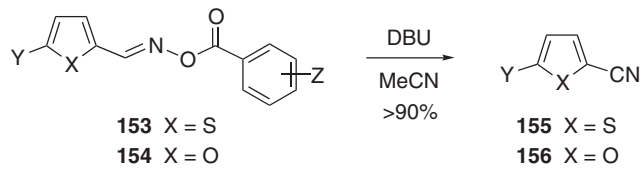
152

The conversion of heteroaryl carboxamides into the corresponding heteroaryl nitriles can be accomplished in excellent yield by treatment with arylchlorothionoformate in the presence of base (Equation (21)) <1999TL747>. In this way, 3-cyanopyridine and 2-ethyl-4-cyanopyridine were obtained in >90% yield from the corresponding nicotinamides.



(21)

Treatment of (*Z*)-thiophene- or (*Z*)-furan-2-carbaldehyde *O*-benzoyloximes, **153** and **154**, respectively, with DBU in acetonitrile provides the corresponding heteroaryl nitriles **155** and **156** in excellent yield (Equation (22)) <1998JOC8304>. In a detailed analysis of the mechanism of this elimination reaction, using kinetic isotope effects and various aryl substituents, it was found that an E2 mechanism is operating and the transition-state structure changes toward a product-like structure as the β-aryl group is altered <1998JOC8304>.



153 X = S
154 X = O

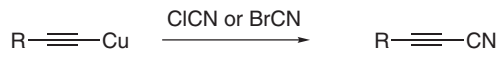
155 X = S
156 X = O

(22)

Y = H, Me, MeO, Br, NO_2; Z = H, *m*-Br, *p*-NO_2

3.19.4 NITRILES BEARING AN α,β-TRIPLE BOND

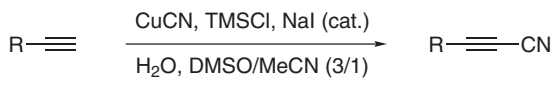
As mentioned earlier (Section 3.19.1), α,β-alkynenitriles are valuable precursors for the preparation of α,β-unsaturated nitriles. The use of α,β-alkynic nitriles as substrates for conjugate addition reactions leading to unsaturated nitriles has recently been discussed in detail <2003CRV2035>. Some of the early methods for the synthesis of α,β-alkynenitriles, including the reaction of metallated alkynides (e.g., **157**) with cyanogen chloride or cyanogen bromide (Equation (23)), suffered from both modest yields and the use of highly toxic reagents <1995COFGT(3)641>. Metallated alkynides can also react with *p*-toluenesulfonyl cyanide leading to α,β-alkynic nitriles, with alkynic organozinc iodides providing the desired products in excellent (81–90%) yield <1993TL4623>.



157

(23)

Since the early 1990s a number of milder, more efficient, and safer methods for the preparation of α,β-alkynic nitriles have emerged. In one example, the iodine-catalyzed cyanation of terminal alkynes using copper(I) cyanide provides generally excellent yields of the α,β-alkynic nitriles, provided that dimethylsulfoxide and acetonitrile are employed as the solvent in a ratio of 3:1 (Equation (24)) <1993TL5911>. The pyrolysis of dichloronitriles (e.g., **158**) or β-ketoalkylidenephosphoranes (e.g., **159**) at temperatures above 200 °C can also lead to α,β-alkynic nitriles <1995COFGT(3)641>.



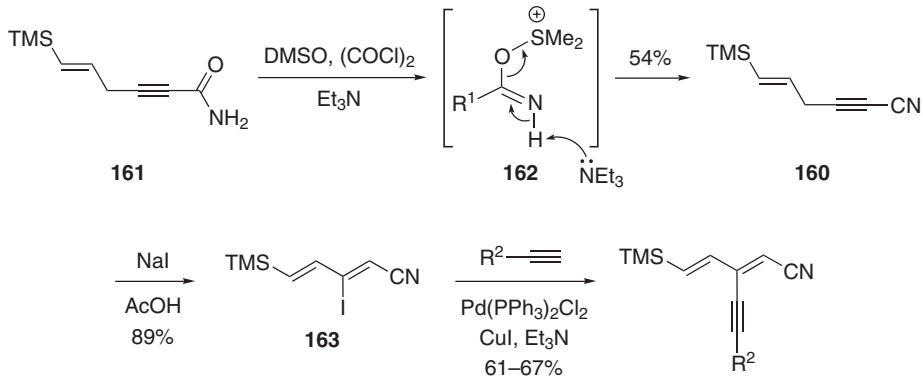
R = alkyl, aryl

(24)

158 **159**

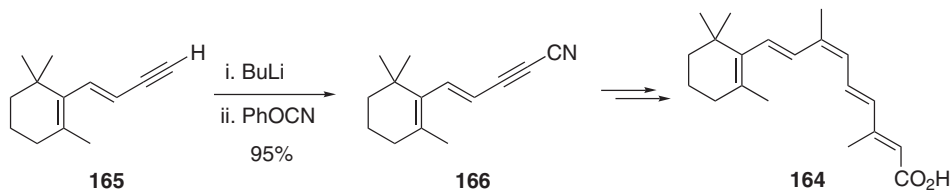
The dehydration of amides to provide nitriles can be accomplished by a number of methods, including the use of phosphorus pentoxide at elevated temperatures, or with thionyl chloride or titanium tetrachloride (see <1997TL2099> and references therein). These conditions tend to be

quite harsh and therefore restrict the types of functional groups that can be present in the substrate. More recently, an extremely mild method involving the use of oxalyl chloride and DMSO in the presence of triethylamine (Swern oxidation conditions) has been shown to be effective for the conversion of primary amides into nitriles in excellent (>80%) yield <1997TL2099>. This method has been utilized by others in the synthesis of the α,β-alkynic nitrile **160** from the corresponding amide **161** (Scheme 35), and is considered to proceed through the intermediate **162** <1998T12399, 2002T9547>. The α,β-alkynic nitrile **160** was subsequently treated with NaI to afford the α,β-unsaturated nitrile **163** which was further modified into a series of conjugated dienynes <2002T9547>.



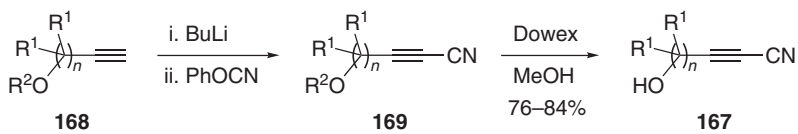
Scheme 35

The use of lithiated acetylenides has also proven to be a mild procedure for the preparation of α,β-alkynic nitriles. In a simple and efficient synthesis of 9-*cis*-retinoic acid **164** (Scheme 36), treatment of the alkyne **165** with Bu^{n}Li followed by the addition of phenylcyanate (the use of which was first reported for this type of cyanation in 1980 <1980S150> affords the α,β-alkynic nitrile **166** <1996JOC3542>. Elaboration of **166** to **164** was accomplished in four steps.



Scheme 36

Lithiated acetylenides have also been successfully employed in the synthesis of the α,β-alkenic nitriles **167** for use in chelation-controlled conjugate addition reactions (Scheme 37) <2002OL659, 2003T5585>. An important consideration in this work is the tendency of compounds like **167** (n = 1, R^1 = H) to undergo base-promoted polymerization. This was overcome by the use of the tetrahydropyranyl ether in the substrate **168** (n = 1 or 2, R^1 = H, R^2 = THP) and its subsequent removal from **169** with acidic Dowex resin, thus eliminating the need for chromatographic purification of **167**. For the tertiary alcohol **168** (n = 1, R^1 = Me, R^2 = H) (Scheme 37), the presence of the two methyl groups imparts enough steric hindrance to prevent polymerization, and so a double lithiation–cyanation sequence directly furnishes the product **167** (n = 1, R^1 = Me) <2003T5585>.



n = 1, 2; R^1 = H, Me; R^2 = THP, H

Scheme 37

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Biographical sketch

Milton J. Kiefel was born in Victoria, Australia, and studied at The University of Melbourne, where he obtained a B.Sc. (Hons) in 1986 and his Ph.D. in 1990, under the direction of Dr. Melvyn Gill. During 1991 and 1992 he undertook a postdoctoral position with Professor Gerald Pattenden (University of Nottingham, UK), before returning to Australia in 1993 as a Research Fellow within the research group of Professor Mark von Itzstein at the Victorian College of Pharmacy (Monash University). In 2000 he was appointed as a lecturer at Griffith University within the Institute for Glycomics (formerly called the Centre for Biomolecular Science & Drug Discovery). His research interests focus on the synthesis of novel carbohydrates and glycomimetics, particularly in relation to sialic acids, as probes for carbohydrate-recognizing proteins and as potential drug candidates. He also has an interest in the development of novel strategies for the synthesis of carbohydrates of biological interest.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 657–684

3.20 *N*-Substituted Nitriles and Other Heteroanalogs of Nitriles of the Type RCZ

C. ESCOLANO and S. VÁZQUEZ
Universitat de Barcelona, Barcelona, Spain

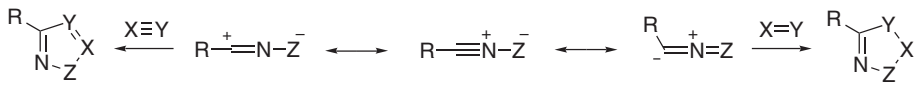
3.20.1 *N*-SUBSTITUTED NITRILES

The chemistry of *N*-substituted nitriles was reviewed in chapter 3.20 by Paton in COFGT (1995) <1995COFGT(3)677>. In order to provide for continuity, this chapter summarizes the major points from the previous chapter and includes some material already covered in COFGT (1995).

3.20.1.1 General Methods for the Formation of Nitrilium Betaines

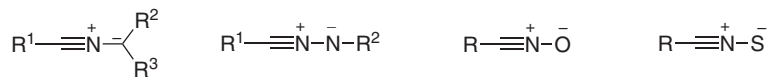
Nitrilium betaines are propargyl–allenyl-type 1,3-dipoles with nitrogen as the central atom and can be represented as shown in Scheme 1. They undergo concerted inter- and intramolecular 1,3-dipolar cycloaddition reactions with a variety of double- and triple-bonded dipolarophiles

<B-2002MI001>, including heteroaromatics <1995MI169> (Scheme 1). Asymmetric 1,3-dipolar cycloadditions for the construction of enantiomerically pure heterocycles <1998CRV863, 2001OPP103>, cycloadditions under microwave-irradiation conditions <2000EJO3659, 2004H(63)903>, and 1,3-dipolar cycloadditions adapted to solid-phase organic synthesis <2001CRV137> have been developed. Transition metal complexation in the 1,3-dipolar cycloaddition of nitrile imines and nitrile oxides was recently reviewed <2003H(59)823>. Mass spectrometric studies carried out on nitrilium betaines have been reviewed <2000MI367>.



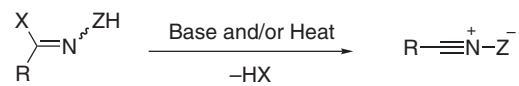
Scheme 1

Four classes of nitrilium betaines will be discussed here: nitrile ylides, nitrile imides, nitrile oxides, and nitrile sulfides (Scheme 2). There have been no synthetic advances in the area of nitrile selenides <1998JPC(A)9021>. Methods for the formation of nitrilium ions are considered in the final section. Almost nothing is known about nitrilium betaines containing a third-row element (Z = SiR_2, PR in Scheme 1). However, Streubel and co-workers <1998CEJ1542, 2002HAC72> have reported the trapping of nitrilium phosphane ylide complexes.



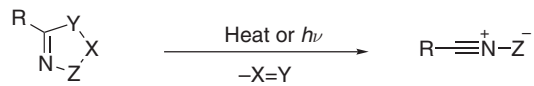
Scheme 2

No single method is applicable for the generation of all four classes of nitrilium betaines. Nitrile ylides, nitrile imides, and nitrile oxides can be obtained from the appropriately substituted imino compounds (RCX = NZH). The elimination is usually accomplished by treatment with a base or by thermolysis (Equation (1)).



X = Cl, Br; Z = CR_2, NR, O (1)

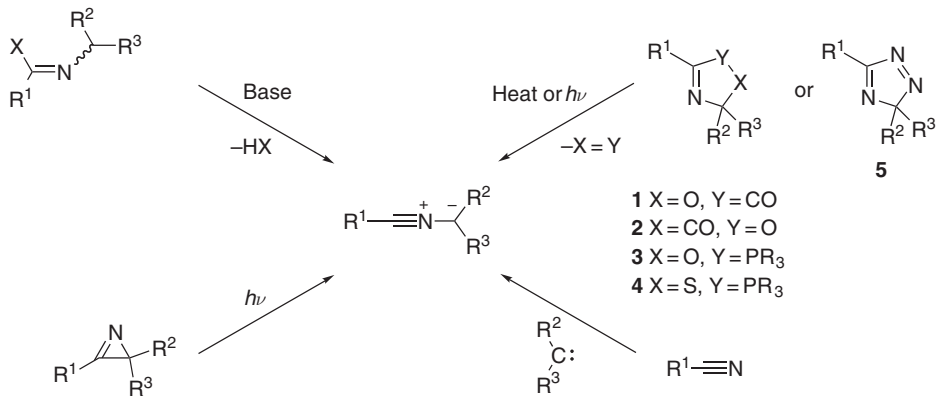
Thermal or photochemical fragmentation of a five-membered heterocyclic compound that already incorporates the C═N—Z moiety is also a general approach to nitrilium betaines <2001EJO2209>. This is still the method of choice for nitrile sulfides and is also used for nitrile ylides and nitrile imides (Equation (2)).



X = Y = Z = N
X = Y = N, Z = CR_2
X = CO, Y = O, Z = S (2)

3.20.1.2 Nitrile Ylides

Nitrile ylides are known to be useful intermediates in the synthesis of five-membered *N*-heterocycles, undergoing 1,3-dipolar cycloadditions with CC—, CN—, CO—, NN—, NO—, and CS— multiple bonds and have been used extensively for the synthesis of pyrroles and reduced pyrroles <1990HOU(E14)1, B-2002MI473>. The 1,7-electrocyclization of diene-conjugated nitrile ylides is of synthetic interest <1999AHC(73)97>. Paton <1995COFGT(3)677> and, more recently, Clark <B-2002MI1> have summarized the more established methods for nitrile ylide generation and no new methods have been developed (Scheme 3). Only some new interesting applications of these known methodologies will be discussed here.



Scheme 3

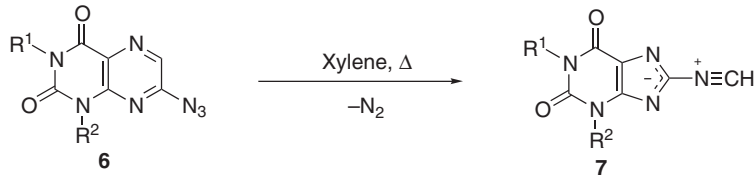
Nitrile ylides can be prepared by the well-established 1,3-dehydrochlorination of imidoyl chlorides, which are themselves readily prepared from the corresponding amides and thionyl chloride <B-2002MI1>. This method has been used for the synthesis of a new class of phosphorylated nitrile ylides <1996JCS(P1)1893> and some relatively stable, novel trifluoromethyl-substituted nitrile ylides <2001JCS(P2)1239>. Although triethylamine was originally employed by Huisgen and this base is still widely used <1997TL6933, 2002T3003>, other strong non-nucleophilic bases such as potassium *t*-butoxide <1999JOC2361, 2001JCS(P1)2781>, LDA <2004JOC4663> or LHMDS <1999JCS(P1)443> are commonly used, thus allowing the generation of nitrile ylides at low temperatures. It has been found that some nitrile ylides undergo [3 + 2]-cycloaddition reactions with their imidoyl chloride precursors to give imidazoles <2001JCS(P1)2781>.

Photoirradiation of "easily available" 2*H*-azirines <2003JOC9105> results in ring opening at the C—C bond to afford nitrile ylides. Laser flash photolysis of 2*H*-azirines is probably the most powerful method to study the characteristics and reactivity of nitrile ylides <1995BCJ2905, 1995MI73, 1997JA11605>. This method is also a convenient route for synthetic purposes <1994BSF973>.

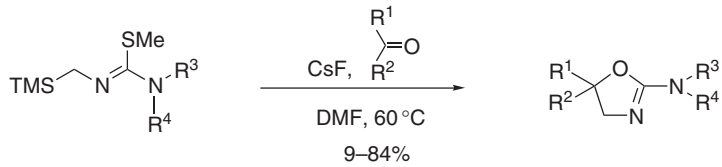
Nitrile ylides can be prepared by addition to nitriles of singlet carbenes, generated by photolysis of diazirines <1999JPC(A)8187> or diazomethane, or of rhodium carbenoids, derived from α-diazocarbonyl compounds <B-2002MI279>.

Nitrile ylides are also available from thermally or photochemically induced fragmentation of several heterocyclic systems **1**–**5** <2001EJO2209>. The generation of nitrile ylides by thermolysis of 1,4,2-oxazaphospholines, **3** has been recently reviewed <B-2002MI286>. Thermolysis of 1,2,4-triazoles, **5**, also generates nitrile ylides <1997JHC797>. Heimgartner and co-workers <1998H(47)781> have further studied the thermally induced fragmentation of 4-alkoxy-1,3-oxazol-5(2*H*)-ones (**1**, R^1 = alkoxy) as a source of nitrile ylides bearing an alkoxy substituent at the nitrile C-atom.

There are also some rather unusual methods of preparing nitrile ylides, which involve rearrangement rather than fragmentation (Scheme 4). For example, the nitrile ylides **7**, stable enough to be spectroscopically characterized, were produced by thermally induced pyrazine ring contraction of azidolumazines **6** <1989H(28)203>. Rather serendipitously, Hart and co-workers <2001JA5892> found that thermal fragmentation of an iminobenzoxazine led to a nitrile ylide.



$R^1 = CH_3, C_8H_{17}$
$R^2 = CH(CH_3)_2, CH_2C(CH_3)_3$



$R^3, R^4 = -(CH_2)_5-$, Et
$R^3 = Ph, R^4 = Me$

$R^1 = 4\text{-}ClC_6H_4$, Ph, $4\text{-}MeOC_6H_4$, $4\text{-}CF_3C_6H_4$, PhCH=CH, $Me(CH_2)_4$, Me_2CH, $-(CH_2)_5-$
$R^2 = H$, Me

Scheme 4

Treatment of α-silyl thioimidates with fluoride ion gives nitrile ylides. The precursors are prepared in a single step by treatment of a nitrile with (trimethylsilyl)methyl triflate in the presence of a thiol <1986JA6739>. A related procedure allows the generation of aminonitrile ylides <1997H(45)1405>.

Very recently it has been reported that the photolysis of 3-pyridylcarbene and 3-pyridylnitrene results in ring opening to nitrile ylides <2003JA9083, 2004JA237>.

3.20.1.3 Nitrile Imides

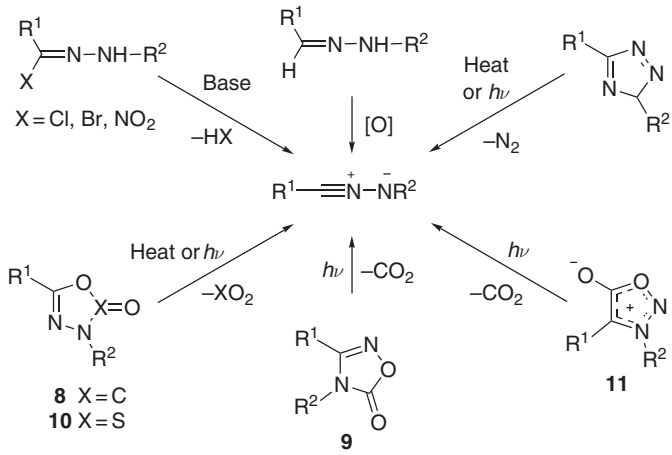
Nitrile imides (nitrile imines or nitrilimines) are important building blocks in organic synthesis <1990HOU(E14)33>, particularly in 1,3-dipolar cycloadditions, for the construction of a variety of nitrogen-containing heterocycles <2002JHC1, 2002MI92, B-2002MI473, 2003CUOC771> and their ring-fused derivatives <1993CRV2731, 1995MI169>. Broggini and co-workers <1998H(47)541> have reviewed the intramolecular 1,3-cycloadditions of nitrile imides. This review also covers their 1,5- and 1,7-electrocyclizations. The 1,7-electrocyclization of diene-conjugated nitrile imides has synthetic interest <1999AHC(73)97>.

3.20.1.3.1 Generation of transient nitrile imides

No new methods have been introduced for the synthesis of transient nitrile imides since the publication of chapter 3.20.1.3 in <1995COFGT(3)677>. Only some representative new examples and new condition reactions will be summarized here.

Earlier, nitrile imides were generated by the dehydrogenation of araldehyde hydrazones with $Pb(OAc)_4$ <1982BCJ2456>, $Hg(OAc)_2$, 1-chlorobenzotriazole, or, more recently, with chloramine-T <2002HAC677> or $PhI(OAc)_2$ <1995SC1617>. Nowadays, the simplest and most common access to nitrile imides is centered on the base-mediated dehydrohalogenation of hydrazonoyl halides, readily available by treating hydrazides with chlorinating agents <1993CRV2731, 1995COFGT(3)677> or by chlorination of aldehyde hydrazones with *N*-chlorosuccinimide (NCS) <2002T5821>. Bromination of aldehyde hydrazones with *N*-bromosuccinimide (NBS) with <1996T661, 2001TA469> or without dimethyl sulfide <1999TL1587> provides access to the corresponding bromides. Often, the halogenation step and the dehydrohalogenation are carried out without isolation of the hydrazonoyl halide. The coupling of diazonium salts with halogenated active-methylene compounds such as 2-chloro-3-oxobutanoates is widely employed for the preparation of *C*-acetyl and *C*-alkoxycarbonyl hydrazonoyl chlorides <2000H(53)831, 2000H(53)917>. This method has been applied to the synthesis of homochiral nitrile imides <2001SC3799>.

Although the most common base used for the dehydrohalogenation step is triethylamine <2000EJO1773, 2003OBC822, 2003SC19>, other bases, such as Ag_2CO_3, which ensures smooth generation of nitrile imides at room temperature so minimizing degradative processes of the 1,3-dipole <1981JOC1402, 1995H(40)777, 1998T2843, 1998T14859>, AgOAc <2003TL1425>, Ag_2O <2002JHC957>, or sparteine <2002TA2491> are used. Some nitrile imides have been generated in aqueous media from hydrazonoyl chlorides using NaOH <2000JCS(P1)3742> or Na_2CO_3 <2002NJC1340> as base (Scheme 5).



Scheme 5

Nitrile imides can be generated by thermal or photochemical extrusion of nitrogen from tetrazoles <1993CRV2731, 1997MI195, 1998H(47)541, 2001EJO2209>. Some of these precursors are easily available. Maier and co-workers <1996LA1041> reported that FVP at 800 °C or photolysis in cryogenic matrices of tetrazole allowed the matrix-IR identification of the parent nitrilimine (HCNNH). Also, in this work, parent nitrilimine was generated by photolyzing 1,2,3- and 1,2,4-triazole in argon matrices. Earlier, nitrilimine had been detected mass spectrometrically in the gas phase employing 1,2,4-triazole as precursor <1994HCA2354>.

No further examples of the use of oxadiazolones **8** or **9**, 1,2,3,4-oxathiadiazol-2-oxides **10**, or mesoionic compound **11** as precursors of nitrile imides have been described.

3.20.1.3.2 Preparation of stable nitrile imides

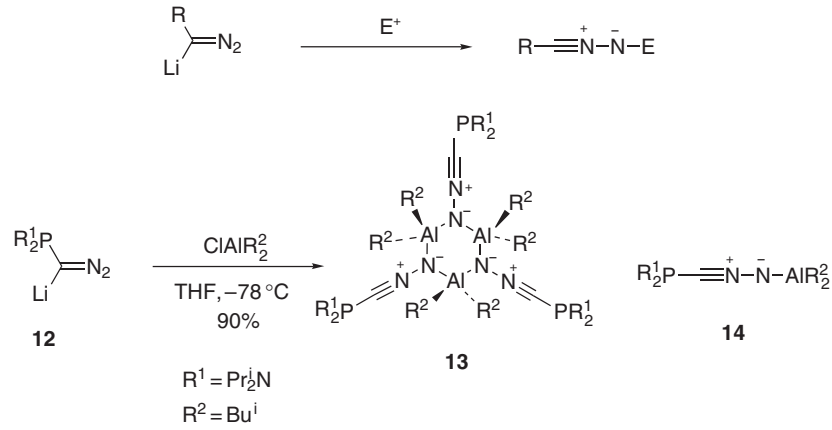
Bertrand and co-workers <1994AG(E)527> have recently shown that suitably substituted nitrile imides can exist as stable compounds in the solid state and in solution. The intermolecular cycloadditions of stable nitrile imides with a wide range of dipolarophiles have been studied.

Stable nitrile imides were originally prepared by treatment of the lithium salt of a thiophosphinoyldiazomethane with chlorophosphanes (Equation (3)). This general method has been used for the preparation of derivatives possessing a chiral substituent either at the carbon or at the nitrogen terminus <1997JA2819>.

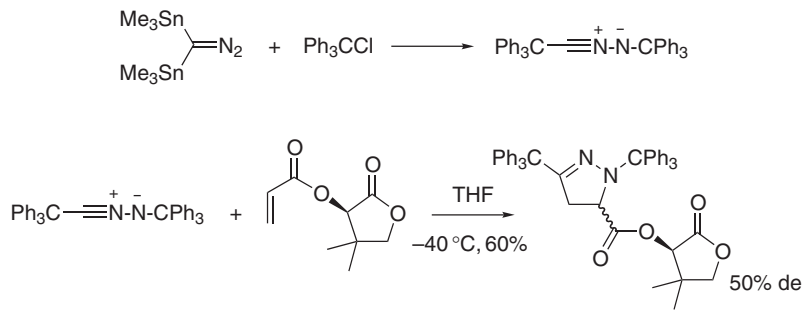
$$(Pr^i_2N)_2P(S)C(Li)=N_2 + (Pr^i_2N)_2PCl \longrightarrow LiCl + (Pr^i_2N)_2P(S)C\equiv N^+\text{-}N^-P(NPr^i_2)_2 \quad (3)$$

Starting from diazolithium precursors several stable nitrile imides have been prepared by reaction with chlorosilanes, chloroboranes, chlorophosphanes <1992JA6059>, and dialkylaluminum chlorides <1998AG(E)989>. Interestingly, reaction of the lithium salt of [bis(diisopropylamino)-phosphanyl]diazomethane **12** with $ClAl(iBu)_2$ gave **13**, a trimer of nitrilimine **14** (Scheme 6).

Bis(trialkylstannyl)diazo-compounds also are precursors of stable nitrile imides and their chemistry has been recently reviewed <1996RHA137>. These precursors allowed the preparation of the stable *C*,*N*-bis-trityl derivative that was used for the first diastereoselective [3 + 2]-cycloaddition involving a nitrile imide <1997JA2819> (Scheme 7).



Scheme 6



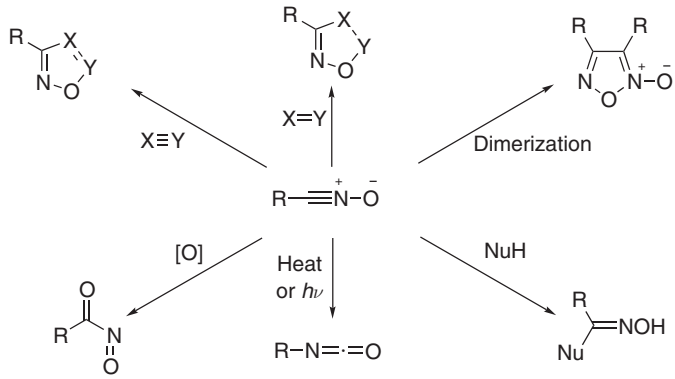
Scheme 7

Interestingly, it is possible to chemically manipulate some stable nitrile imides, thus allowing the synthesis of new nitrile imides <1994AG(E)527>.

3.20.1.4 Nitrile Oxides

Nitrile oxides are versatile intermediates that have found widespread application in organic synthesis <B-2002MI361>. This is due to at least two reasons. First, 1,3-dipolar cycloadditions of nitrile oxides provide efficient access to a number of useful heterocyclic compounds <1994AHC(60)261, 1997MI225, 2001RCR405, 2001RCR641, 2002MI248, 2002SL1371, 2003CUOC397>, including asymmetric versions <1998CRV863, 2001OPP103, 2003SL1075, 2004JA5366> and, second, the reaction products are used as starting materials for other compounds: γ-amino alcohols, 1,3-diols, β-hydroxy ketones, β-amino ketones, β-diketones, α,β-unsaturated ketones, β-hydroxy nitriles, acids, esters, and amides. In addition, nitrile oxides undergo other synthetically useful processes such as ene-like reactions, 1,3-addition with C-nucleophiles <1997MI141>, and oxidation to nitrosocarbonyl compounds <2000EJO2613>.

A few nitrile oxides with bulky aryl substituents are isolable, but most are unstable and are generated *in situ* in the presence of the dipolarophile in order to minimize side reactions, mainly rearrangement to the isomeric isocyanates <1999T6435> and dimerization to either 1,4,2,5-dioxadiazines <2001MI1355> or furazan *N*-oxides (furoxans). Furoxans can usefully be converted into 1,2-dioximes, 1,2-diketones, 1,2-diols, or 1,2-diamines <1999JOC8428>. The intramolecular dimerization of nitrile oxides furnished bicyclic furoxans <1997JCS(P1)2461, 1999JOC8428>. Interestingly, the tendency of nitrile oxides to undergo dimerization to furoxans is reduced under solid-phase conditions <2002EJO1175> and in ionic liquids <2003TL5327> (Scheme 8).



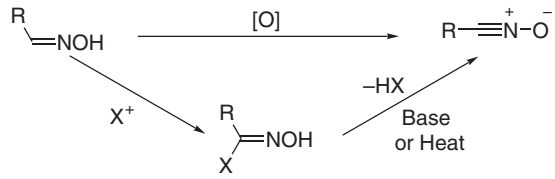
Scheme 8

3.20.1.4.1 From aldoximes

Hydroximoyl chlorides, which were classically prepared from the parent aldoximes using chlorine, undergo facile dehydrochlorination to the nitrile oxide in the presence of triethylamine; in the absence of base the nitrile oxide may be generated by thermolysis in an inert solvent such as toluene. The competing dimerization to furoxans is minimized by slow addition of triethylamine to a solution of the hydroximoyl chloride. Reaction of hydroximoyl chlorides with ethylzinc also generates nitrile oxides <2003SL1075>. Direct chlorination of aldoximes can be a capricious reaction <2002T8505> and so nowadays milder reagents such as NCS, NBS, or nitrosyl chloride, are used <1995COFGT(3)677>. The reaction of hypochlorous acid with aldoximes also provides hydroximoyl chlorides <1992JOC6649>.

There are also several one-pot halogenation/dehydrohalogenation methods including treatment of aldoximes with NCS <1995SL907, 2002OL977>, NBS <1996BMC209>, chloramine-T <2003JOC1567>, or aq. NaOCl <1999OL1795, 2001OL2575>. Recently, Carreira and co-workers <2001AG(E)2082, 2001JOC6410, 2003SL1075> have reported a protocol that permits the preparation of nitrile oxides by reaction of aldoximes with *t*-BuOCl at −78 °C followed by reaction of the solution of the corresponding hydroximoyl chloride with a base. Under these mild conditions dimerization and decomposition are minimized.

Other reagents for the *in situ* generation of nitrile oxides from aldoximes are 1-chlorobenzotriazole <1990SC1373>, $PhICl_2$ <1991SC1625>, CAN <1999BCJ2277>, manganese dioxide <1999TL5605>, and trichloroisocyanuric acid <2001SC3075>. For solid-phase and parallel synthesis, although NBS can be used <2002OL323>, NCS <2000JCO6, 2002EJO1175> and NaOCl <2000TL5617, 2002OL741> are the more popular choices (Scheme 9).



Scheme 9

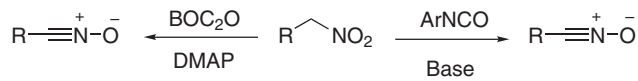
Nitrolic acids ($O_2NCR{=}NOH$), prepared by addition of dinitrogen tetraoxide to aldoximes or by reaction of primary bromo- or nitro-derivatives with acetic acid and sodium nitrite, are also efficient precursors of nitrile oxides under neutral conditions <1998SL385, 2000TL1191>.

3.20.1.4.2 From nitromethyl compounds

The dehydration of primary nitroalkanes to nitrile oxides with phenyl-isocyanate in the presence of a base such as triethylamine ("Mukaiyama's method") is a practicable way for *in situ* generation of these reactive dipoles. Although this method has a widespread use, even in complex

polyfunctionalized substrates and in the generation of polymer-bound nitrile oxides <1995JOC4196>, it also has some drawbacks. The diaryl urea, formed as a side product, complicates the purification stage, the reaction requires high temperatures and/or prolonged reaction times, and the use of isocyanates is incompatible with free hydroxyl groups. In order to avoid the purification problem, diisocyanates such as 1,4-phenylene diisocyanate <1998JOC5272>, toluene 2,4-diisocyanate (TDI) <1988CC1339>, or 4,4′-methylenebis(phenylisocyanate) (MDI) <1999TL7955> are sometimes used. Owing to the polymeric nature of the urea formed from these diisocyanates, the cycloadducts can be easily purified by simple filtration. Alternative dehydrating agents include phosphorus oxychloride, oxalyl chloride, Burgess salt, and DAST <1997TL1547>.

Hassner and co-workers <1997S309> reported a method for the preparation of nitrile oxides from nitroalkanes at room temperature using di-*t*-butyldicarbonate (BOC_2O) and a catalytic amount of DMAP (Scheme 10). This method has rapidly gained in popularity and it is now widely used, even in solid-phase synthesis <2002JCO652>.



Scheme 10

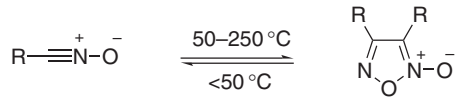
Nitrile oxides can also be efficiently generated from nitroalkanes using 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride in the presence of DMAP with or without microwave radiation. This procedure has been applied to solid-phase synthesis <2003T5437>. Reaction of α-unsubstituted nitroacetates with $Mn(OAc)_3$ also generates nitrile oxides <2002T7821>. Finally, reaction of methyl nitroacetate with diazomethane gave the corresponding nitronate that underwent spontaneous or Lewis-acid catalyzed β-elimination to methoxycarbonyl formonitrile <1998TL8865>.

3.20.1.4.3 From α-nitroalkanoate esters

No further advances have occurred in this area since the publication of chapter 3.20 in COFGT (1995) <1995COFGT(3)677>.

3.20.1.4.4 From furazan N-oxides

Dimerization of nitrile oxides leading to furoxans (furazan *N*-oxides) remains a reaction of low synthetic interest <1999JOC8428, 2003JA15420>. However, the dimerization process is reversible, at least for very highly substituted nitrile oxides <1981JOC316, 1985JA6023>, and thermolysis of furoxans gives rise to nitrile oxides <1998H(47)271, 1997JST(408/409)161>. The reversibility of this process has allowed the use of furoxans as stable masking groups for nitrile oxides <2001JOC6410> (Equation (4)).



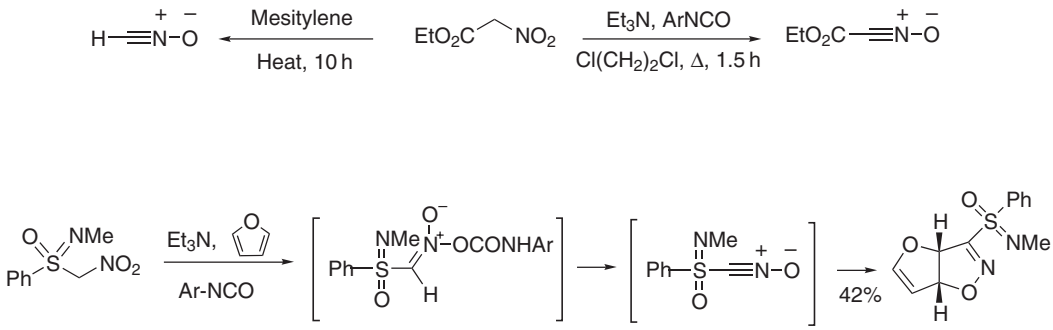
(4)

3.20.1.4.5 Generation of fulminic acid and heteroatom-substituted analogs

Fulminic acid, the parent nitrile oxide, and several of its salts have a long and fascinating history <2000JCE851>. Paton found that under Mukaiyama's conditions, ethyl nitroacetate gave the expected ethoxycarbonyl formonitrile oxide. However, thermolysis of ethyl nitroacetate led to fulminic acid <1994TL9251>.

Chloroformonitrile and bromoformonitrile oxides have been prepared from the corresponding dihaloformaldoxime species, cyanogen oxide from its furoxan dimer, and cyanogen dioxide from dichloroglyoxime or by thermal bromine elimination from dibromofuroxan <1997JST(408/409)161>.

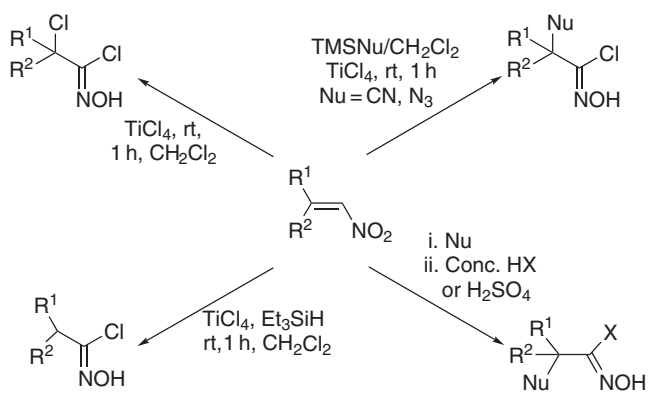
The first sulfoximinyl nitrile oxide has been generated from racemic *N*-methyl-*S*-(nitromethyl)-*S*-phenylsulfoximine using Mukaiyama's procedure (Scheme 11) <2002JOC2859>.



Scheme 11

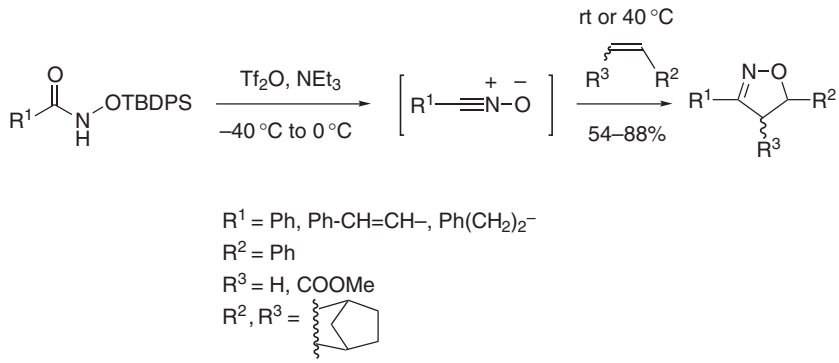
3.20.1.4.6 New methods for nitrile oxide generation

Related to previous methods, Kumaran and Kulkarni have developed a general, one-step, mild route for the synthesis of several α-functionalized and nonfunctionalized hydroximoyl chlorides from conjugated nitroalkenes, nitroalkanes, and titanium tetrachloride <1997JOC1516>. Alternatively, reaction of β-nitrostyrenes with various nucleophiles followed by HCl addition at low temperature gave hydroximoyl chlorides <1998T13997> that are precursors of nitrile oxides (see preceding section). This procedure has been adapted for the one-pot generation of nitrile oxides from nitroalkenes through a sequence of nitroalkene conjugate addition, nitronate transformation, and β-elimination <1999T12493> (Scheme 12).



Scheme 12

Carreira and co-workers <2000OL539> have found that *O*-*t*-butyldiphenylsilyl hydroxamates serve as stable, readily accessible, crystalline precursors to nitrile oxides when treated with trifluoromethanesulfonic anhydride and triethylamine (Equation (5)).

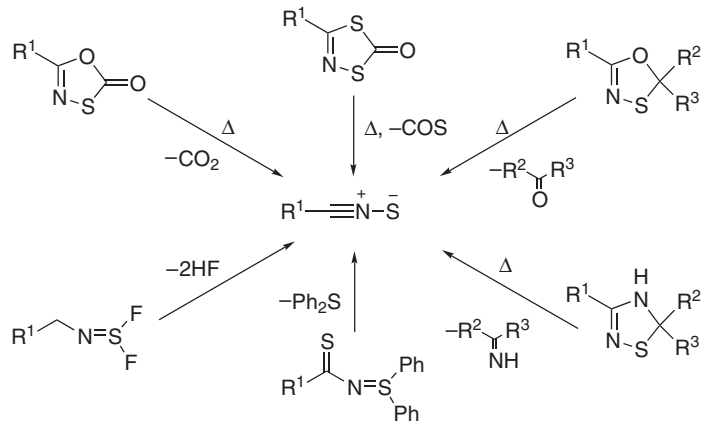


(5)

It has been reported that alkyl aryl β-diketones are smoothly converted into aryl acyl nitrile oxides by the action of a nitrating mixture <1996SC3401>. Ariga and co-workers found that 2-methyl-4-nitro-3-isoxazolin-5-one generates a nitrile oxide bearing a carbamoyl group under very mild conditions <1998TL4851>.

3.20.1.5 Nitrile Sulfides

Although much less stable than the corresponding nitrile oxides, to the extent that their isolation in the pure state is not possible even for sterically hindered derivatives <1994CJC1143, 1995CJC212>, nitrile sulfides have been used in 1,3-dipolar cycloaddition reactions in solution, providing routes to several classes of heterocycles accessible only with difficulty by other means <1995COFGT(3)677>. They are usually generated *in situ*, in the presence of a dipolarophile, by thermal decomposition of a five-membered ring containing the CNS moiety. Scheme 13 summarizes the different methods for nitrile sulfide generation. The method of choice generally involves thermolysis of substituted 1,3,4-oxathiazol-2-ones <2000MI720, 2002MI15>, although Paton and co-workers <2002MI121> have recently expanded the usefulness of 1,4,2-dithiazol-5-ones as precursors of nitrile sulfides. Thermolysis of 1,2,5-thiadiazoles does not produce nitrile sulfides but gives sulfur and the corresponding nitrile <2001JPC(A)6258>.



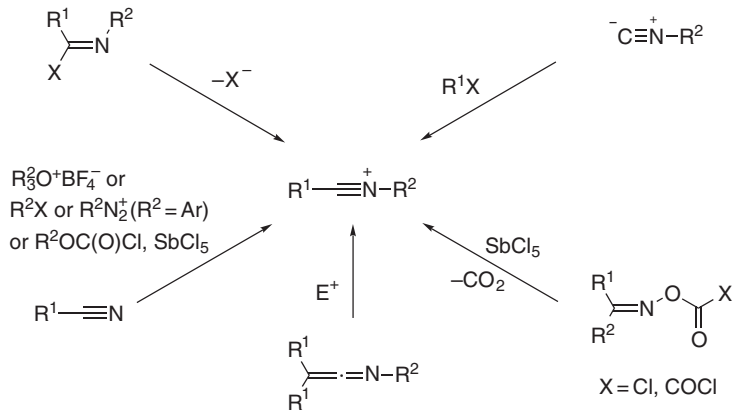
Scheme 13

The parent thiofulminic acid (HCNS) and other simple nitrile sulfide derivatives have been generated and identified as in the gas phase <1999JCS(P2)1683, 2003MI241>.

3.20.1.6 Nitrilium Ions

Nitrilium ions are intermediates in numerous reactions, e.g., in the Beckmann rearrangement and in the Ritter, Bischler–Napieralski, Houben–Hoesch, Passerini, and Ugi reactions <2000JOC3569>. The reactivity of nitrilium salts with alkenes, alkynes, arenes <2000JOC3569>, and carbonyl compounds <1996JPR598> has been studied.

Nitrilium salts are obtained by *N*-alkylation of nitriles with, for example, alkyl halides <2002JA5294>, chloroformates in the presence of Lewis acids such as antimony pentachloride or aluminum chloride <1993S426>, oxonium salts, or alkyl fluorosulfonates or triflates <1995S253, 1996ACS623>. *N*-Arylnitrilium salts are formed from aryldiazonium salts and nitriles or by treatment of readily accessible imidoyl halides <1995COFGT(3)677> with Lewis acids <1995S253>. The direct conversion of carboxamides into nitrilium ions has been carried out. Alternatively, rearrangement of *O*-(chlorooxalyl)oximes, or of other imines with non-nucleophilic leaving groups, in the presence of Lewis acids affords *N*-Aryl- and *N*-alkyl nitrilium salts <1995S253>. Reaction of isonitriles with alkyl- or, more interestingly, acyl halides generates *C*-alkyl and *C*-acyl nitrilium ions, respectively (Scheme 14). The latter are very useful intermediates in heterocycle synthesis <1999T9947>.



Scheme 14

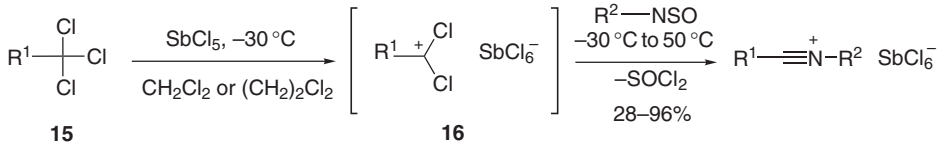
Jochims and co-workers <1995S253> have shown that aryl- and vinyl-trichloromethanes **15** are transformed with antimony pentachloride to α,α-dichlorocarbenium salts **16**, which react with sulfinylamines to afford nitrilium salts in good yields. The reaction is especially useful for *N*-aryl nitrilium salts, which are not easily obtained otherwise. Moreover, sulfinylamines are readily prepared from amines and $SOCl_2$.

The same group reported that 2-azoniaallene salts **17** react with isocyanates to give nitrilium salts in moderate to good yields <1995S820>. Finally, flash photolysis of benzimidate esters **18** led to benzonitrilium ions <2002JCS(P2)312> (Scheme 15).

3.20.2 *N*-SUBSTITUTED ANALOGS OF NITRILES BEARING A HETEROATOM OTHER THAN NITROGEN

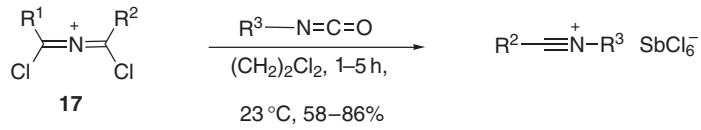
3.20.2.1 Phosphaalkyne Synthesis

Although the synthetic difficulty and extreme instability of the initially reported phosphaalkynes, RC≡P, precluded any significant development of their chemistry for years, recently, numerous phosphaalkynes have been reported, which are rather stable, primarily due to the presence of bulky substituents on the carbon atom, such as *t*-butyl-, adamantyl-, and mesitylphosphaalkyne.



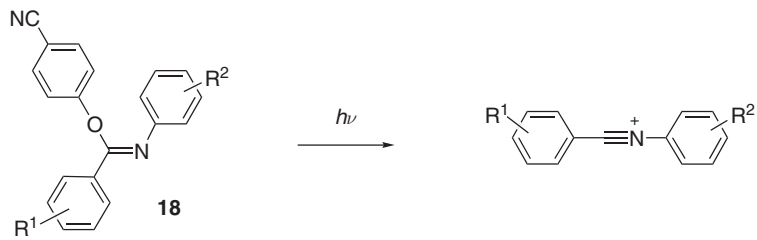
15 16

R^1 = PhCH=CH, Cl_2C=CCl, Ph, 4-ClC_6H_4
R^2 = C_6H_{13}, c-C_6H_{11}, Ph, 4-MeC_6H_4, Bu^i, $(CH_2)_2Ph$, $(CH_2)_3Ph$, 4-MeO, 3,5-$Cl_2C_6H_3$, C_6H_{13}



17

R^1 = Ph, 4-ClC_6H_4, Cl_2C=Cl
R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4
R^3 = Me, Et, Pr, Ph, Pr^i



18

R^1 = H, 4-MeO, 4-Me, 3-Me, 3-MeO, 4-Cl, 3-Cl, 3-CF_3, 4-CF_3
R^2 = H, 4-MeO, 4-PhO, 4-Me, 3-Me, 4-Cl, 3-Cl, 3-CF_3, 4-CF_3

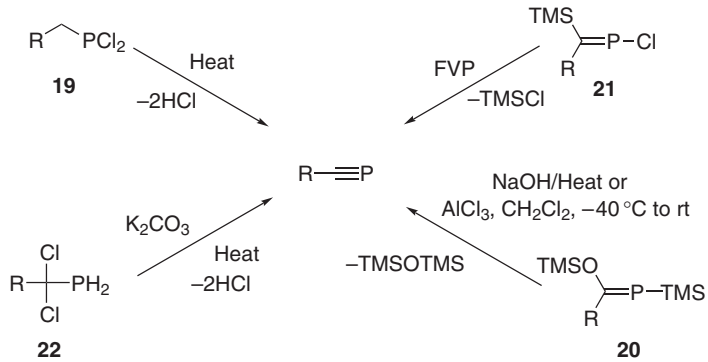
Scheme 15

In recent years, several reviews have appeared dealing with the organic and inorganic chemistry of phosphaalkynes <1989T6019, 1995CCR(145)201, 2003AG(E)1578>. Phosphaalkynes have been found to react more like alkynes than nitriles in a variety of reactions. The cycloaddition chemistry of phosphaalkynes is extremely well developed <2003AG(E)1578>. Phosphaalkynes are intensively used as partners and ligands for a variety of transition metals and are ideal starting materials for the formation of organophosphorus cage compounds because of their enormous potential for thermal or metal-induced cycloaddition and cyclooligomerization reactions <1997AOC(41)1, 1997CB823, 2002CEJ2622>.

Several simple phosphaalkynes have been generated in the gas phase by elimination reactions from suitable precursors, e.g., dichlorophosphanes **19** <1994CRV1413>. The liquid-phase generation of phosphaalkynes involves two kinds of reactions: base-induced β-eliminations and rearrangements. The more reliable method and the only one routinely used involves high-temperature base-catalyzed elimination of hexamethyldisiloxane from phosphaalkenes **20** <1989T6019, 1994CRV1413>. Regitz and co-workers <1996CB489, 1998S1305> found that this elimination can be carried out at lower temperatures in the presence of a stoichiometric amount of $AlCl_3$ in CH_2Cl_2. Alternative approaches to phosphaalkynes include FVP-induced β-elimination of trimethyl silyl chloride from chlorophosphaalkenes **21** or base-mediated dehydrochlorination of α,α-dichlorophosphanes, **22** <2001JOC7864> (Scheme 16). Rearrangement approaches to phosphaalkynes <1994OM2444>, the thermolysis of phosphinodiazo compounds <1996OM4904>, and other less general and less predictable methods <1992CC1799> were previously reviewed <1995COFGT(3)677> and will not be covered again here.

Very recently, Yoshifuji and co-workers <2004JOC5065> have prepared some phosphaethynes bearing bulky aryl groups by $NiBr_2$ $(PPh_3)_2$-mediated dehalogenation reactions of dibromomethylarylphosphines.

The chemistry of arsaalkynes is only poorly developed <1996CB367>. Although ethylidynearsine was generated (and spectroscopically characterized) by the base-induced rearrangement of ethynylarsine under vacuum gas–solid reaction conditions <1995OM4732>, and this method was also successfully used for propylidynearsine, this approach is not general <1995IC5694>.



Scheme 16

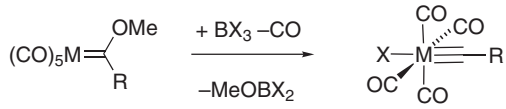
3.20.2.2 Methods for the Synthesis of Alkylidyne–Transition-Metal Compounds

Compounds containing a transition metal to carbon triple bond are called carbynes or alkylidyne complexes. As in carbene complexes, the metal can be in a low (Fischer-type) or high oxidation state (Schrock-type). Generally, the carbyne ligand of Fischer complexes displays electrophilic behavior, while Schrock alkylidene complexes usually exhibit nucleophilic reactivity. They are known for a wide variety of transition metals, although Schrock-type systems are generally restricted to Mo, W, Re, and Os. Although discovered in 1973, experimental research on carbyne complexes increased considerably only after the discovery in 1981 that [(tBuO)$_3$W(CMe)] is an active catalyst in alkyne-metathesis reactions <1999AG(E)478, 2001JCS(D)2541, 2003AG(E)4592, B-2003MI001>. Both types of carbyne complexes have now become versatile compounds for many synthetic and catalytic processes and their chemistry has been the subject of several reviews <B-1993MI001, 1995CRV2281, 1996SL806, 2001CCR(218)43, 2002CRV145, 2002CCR(231)109, 2002MI283>. Advances in the synthesis and reactivity of alkylidyne complexes are annually reviewed by Herndon <2003CCR(243)3>.

Fischer <B-1988MI3> and Paton <1995COFGT(3)677> reviewed the synthetic approaches to these compounds and only new representative examples will be shown here.

3.20.2.2.1 Synthesis from nonalkylidyne precursors

Carbene complexes are useful starting compounds for carbynes. For example, Lewis-acid-assisted abstraction of an alkoxy group from an alkoxycarbene led to neutral or cationic <B-1988MI3, 2002CCR(231)109> carbyne complexes. Boron trihalides are the most used Lewis acids, but others, such as silver salts or trimethyl silyl triflate <1998JA11008>, are also used (Scheme 17).

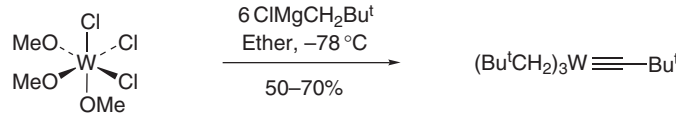


M = Cr, Mo, W; X = Cl, Br, I

Scheme 17

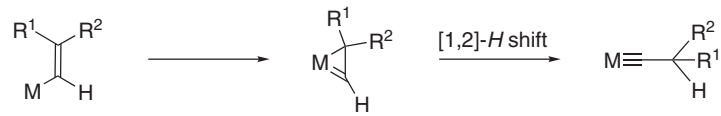
Abstraction with base of an α-hydrogen atom from a carbene ligand $L_nM = CHR$ is used for the preparation of carbyne complexes <2001JCS(D)2541>. Similarly, α,α-hydrogen abstraction from alkyl complexes led to carbynes. Equation (6) shows the first practical synthesis of a Schrock-type carbyne complex of tungsten; the reaction probably proceeds via

α-hydrogen abstraction at some stage to give a neopentylidene complex, followed by α-abstraction from it to give, after complete alkylation at the metal center, the carbyne complex <2002MI283>.



(6)

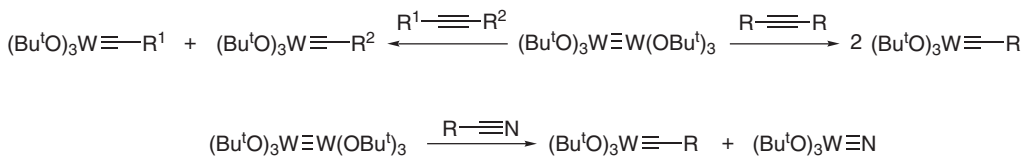
Carbynes are also accessible via rearrangements <B-1988MI3, 2002MI283>. Thus, vinyl complexes can rearrange via a [1,2]-*H* shift to carbyne complexes (Equation (7)) and nucleophiles in $L_nM = C(Nu)R$ rearrange to carbynes $L_{n-1}(Nu)M{\equiv}CR$.



(7)

A one-pot procedure of formal abstraction of oxide, O^{2-}, from acyl ligands with strong Lewis acids followed by addition of a ligand is a highly practical method to prepare carbyne complexes <2003JOM(671)52>.

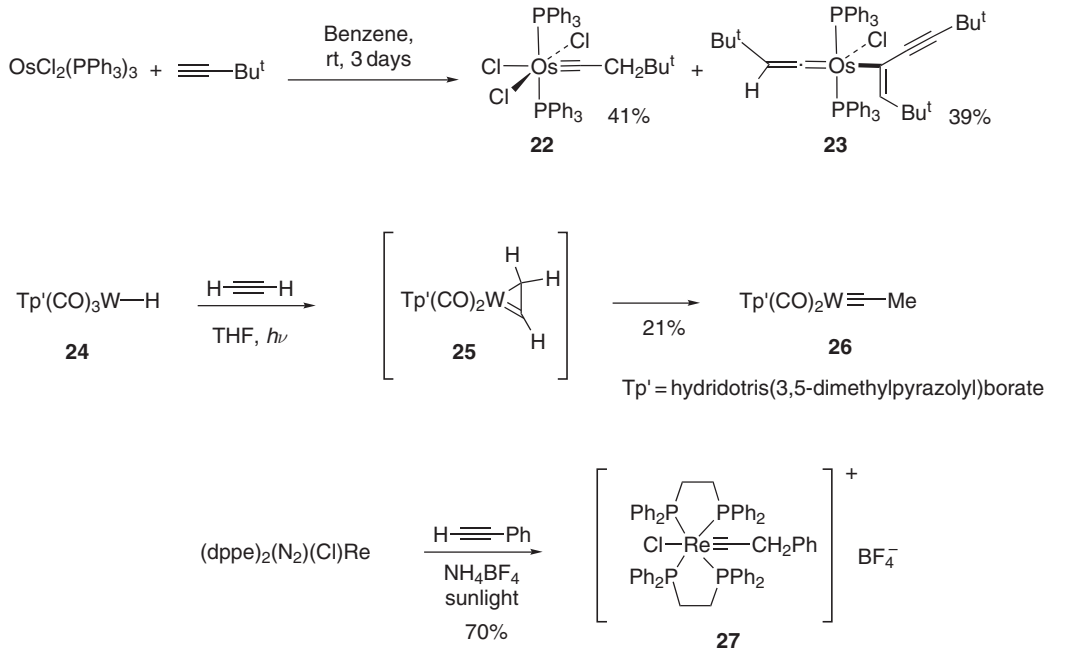
Symmetrical alkynes provide access to carbyne complexes upon metathesis with symmetrical triply bonded tungsten and molybdenum complexes <2002CRV145>. Unsymmetrical alkynes can be cleaved giving a 1:1 mixture of the two carbyne products <1999CC589>. Nitriles react similarly producing both carbyne and nitrido compounds <1997CC1263, 1998JOM(569)125> (Scheme 18).



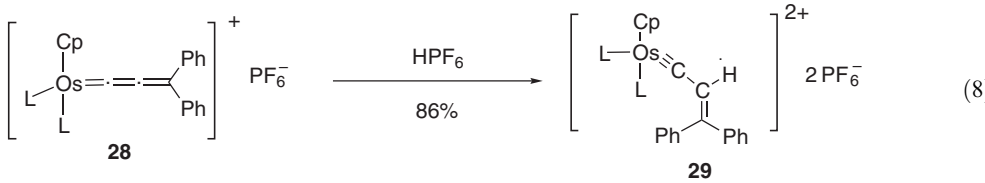
Scheme 18

More recent approaches to carbynes involve reaction of osmium, tungsten, and rhenium complexes with acetylenes. For example, reaction of $OsCl_2(PPh_3)_3$ with *t*-butylacetylene led to a mixture of carbyne complex **22** and vinylidene complex **23** <2000OM3757, 2001AG(E)1951>, reaction of complex **24** with acetylene gave carbyne complex **26** and η^2-vinyl complex **25**, which converted into **26** upon thermolysis <2000OM1497>, and sunlight-irradiation of terminal alkynes in the presence of $(dppe)_2(N_2)(Cl)Re$ gave the cationic rhenium carbyne complex **27** <1997OM4469>. Alternatively, reaction of $Os(H)_2Cl_2L_2$ with styrene (1:2 molar ratio) produced the carbyne complex $OsHCl_2(CCH_2Ph)L_2$ <1993JA4683, 1999EJI951, 2001JOM(617/618)56> (Scheme 19).

Finally, protonation of vinylidene, allenylidene, or alkynyl complexes gave cationic carbyne complexes <2003CCR(243)3>, e.g., **28** was transformed into **29** upon protonation <2000OM2585> (Equation (8)).



Scheme 19



(8)

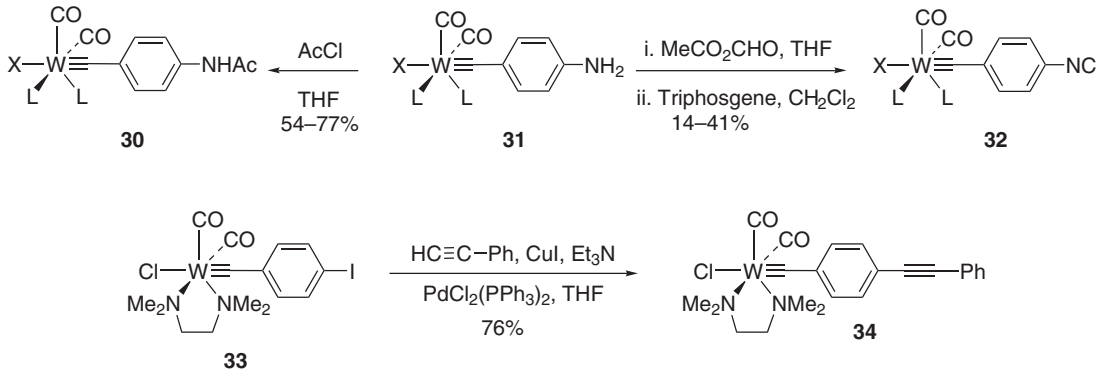
3.20.2.2.2 *Modification of alkylidyne–metal complexes*

Alkylidyne complexes can be modified in various ways: by modification of the metal–ligand framework, by modification of the carbyne ligand, and by oxidation/reduction of the metal center.

The metal center of such complexes is often surrounded by ligands such as CO, nitrogen donor ligands, ethers, or halogen groups. Strongly coordinating ligands such as tertiary phosphines or cyclopentadienyl frequently react with the metal center to substitute these labile ligands. For example, sodium cyclopentadienide reacts with [W(CAd)(dme)(TfO)(OBu^t)$_2$, Ad = 1-adamantyl] at a low temperature to give CpW(CAd)(OBu^t)$_2$ in high yield and addition of Grignard reagents to CpW(CAd)Cl_2 gives CpW(CAd)R_2 <1998JOM(569)125>. Substitution of chloride by trialkyl silyl groups has also been reported <2002JMOC(190)101>. The complex W(CPh)(OBu^t)$_3$ reacts with BCl_3 in DME to give W(CPh)(dme)Cl_3 <1997OM3572>.

A variety of new complexes can be obtained from a pre-existing carbyne complex and an alkyne by a metathesis process <1995CRV2281, 2002CRV145, 2002MI283>. Many alkylidyne complexes have been synthesized by modification of the carbyne ligand. A chloride substituent on a carbyne carbon can be displaced by nucleophiles to form new alkylidyne complexes <1995CRV2281>. Tungsten complexes **31** were prepared and subjected to transformations typical of an amine group to give **30** and **32** <1998JCS(D)475> and the analogous complex **33** underwent Sonogashira coupling to produce **34** <1998JCS(D)2373> (Scheme 20).

It is also possible to synthesize new alkylidyne complexes by oxidation <2002CRV145, 2002MI283> and reduction <1999CC589> of alkylidyne complexes.



Scheme 20

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Biographical sketch

Carmen Escolano was born in Barcelona and studied Pharmacy at the Universitat de Barcelona, where she also obtained her Ph.D. degree in 1998 under the guidance of Prof. J. Bonjoch and Dr. J. Quirante for her studies in aminoradicals and its application to the total synthesis of natural products. After spending the summer of 1998 doing QSAR studies in the team of Prof. C. R. Ganellin (University College London), she joined the group of Prof. K. Jones at Kingston University (Surrey, United Kingdom) as Marie Curie Research Fellow for 2 years working on the synthesis of martinelline. In 2001 she returned to Universitat de Barcelona and currently she is working in the group of Prof. J. Bosch and Prof. M. Amat as "Investigador Ramón y Cajal." Her present research interest is focused on chiral bicyclic lactams as synthons for the enantioselective synthesis of alkaloids and bioactive compounds.

Santiago Vázquez was born in Barcelona in 1968. He studied Pharmacy (1986–1991) at the Universitat de Barcelona. He obtained his Ph.D. in Organic and Medicinal Chemistry at the same university in 1996 under the direction of Professor P. Camps. After spending 2 years (1998–1999) in the Christopher Ingold Laboratories (University College London) with Professor William B. Motherwell as a Marie Curie Research Fellow, he returned to Barcelona. In 2001 he took up his present position as "Investigador Ramón y Cajal" at Universitat de Barcelona. His scientific interests include polycyclic cage compounds, drug synthesis, and free radical and computational chemistry.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 685–704

3.21 Isocyanides and Their Heteroanalogs (RZC)

J. R. FULTON
King's College London, London, UK

3.21.1 ISOCYANIDES

3.21.1.1 General Methods for Isocyanide Synthesis

Isocyanides continue to be a versatile synthetic tool as they are key intermediates in several multicomponent reactions. In COFGT (1995) (chapter 3.21), several different methodologies toward the synthesis of isocyanides were outlined. Since then, a few new, but significant, synthetic routes into isocyanides have been discovered. The bulk of the isocyanide compounds generated have been synthesized by expansion of known methodology.

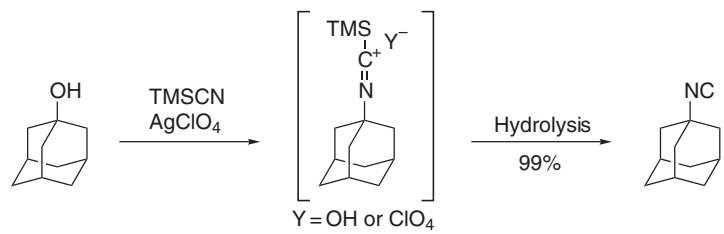
The synthesis of isocyanides can still be broken down into seven different basic routes. These are:
(i) the alkylation and alkynylation of cyanides;
(ii) the reaction of primary amines with dichlorocarbene;
(iii) the dehydration of amide aldehydes;

(iv) further elaboration of isocyanides;
(v) use of organometallic isocyanides;
(vi) reduction of isocyanates, isothiocyanates, isoselenocyanates, and isocyanide dihalides; and
(vii) miscellaneous methods.

These routes will be outlined in the following sections, with a few key examples to illustrate some of the observed selectivity.

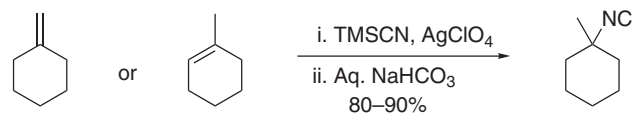
3.21.1.1.1 The alkylation and alkynylation of cyanides

The synthesis of isocyanides by alkylation typically involves AgCN. The conversion of alkyl iodides into alkyl isocyanides upon treatment with AgCN was the first method for the generation of isocyanides. Recently, this chemistry has been expanded to trimethylsilyl cyanide (TMSCN). Initial studies showed that tertiary alcohols and halides can be converted into their corresponding isocyanides upon treatment with TMSCN in the presence of ZnX_2 (X = I, Br, Cl), followed by TBAF <1998TL1911>. Subsequent investigations revealed that silver salts ($AgClO_4$, $AgBF_4$, and AgOTf) were more effective than zinc salts, and that hydrolysis could be performed using $NaHCO_3$ instead of TBAF <2001S437>. An S_N1 pathway was postulated, with an intermediate that possesses a cationic isocyanide functional group still bound to the TMS group, which only dissociates upon hydrolysis (Scheme 1).



Scheme 1

Similar methodology was applied to the conversion of alkenes into isocyanides <1999SL288>. The selectivity followed Markovnikov's rule in which the isocyanide functionality was found at the more substituted position of the former alkene (Equation (1)). It was postulated that the silver cation activated the alkene toward nucleophilic attack. As such, only tertiary isocyanides were formed.



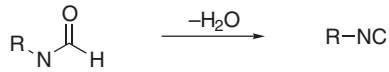
(1)

3.21.1.1.2 The reaction of primary amines with dichlorocarbene (the Hofmann carbylamine reaction)

Despite the earlier popularity of the Hofmann carbylamine reaction, only a few examples have been reported recently. Diethyl (*o*-isocyanophenylmethyl)phosphonate was generated from the amine upon treatment with aqueous KOH and $BnEt_3NCl$ (a phase-transfer catalyst, PTC) in a $CH_2Cl_2/CHCl_3$ mixture. Addition of NaOH to a $CHCl_3$ solution of 1,3-diamino bicyclo-[1,1,1] pentane (1-staffane) results in the formation of isocyanide 1-staffane derivatives <1993CCC89>. This route has also proven to be favorable in the synthesis of polyisocyanides <1996ICA(242)115, 1998L3071, 2001EJO655>. In addition, isocyanides bearing a nitroxyl functional group have been synthesized from the corresponding amines, albeit in low yields <2004OL695>. In the latter example, a PTC was necessary to effect the transformation.

3.21.1.1.3 α-Eliminations from formic acid derivatives of primary amines

The most utilized method for generating isocyanide compounds is still the dehydration of *N*-monosubstituted formamides (Equation (2)).



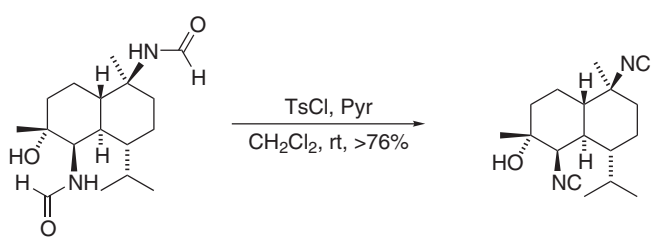
(2)

Several different reaction conditions have been utilized, and phosgene derivatives are the most common dehydrating agents. For instance, phosgene was used in combination with triethylamine in the synthesis of an isocyanide bearing a nitroxyl functional group <2004OL695>. However, it is still more common to use the less toxic disphosgene and triphosgene derivatives. Disphosgene is generally used in combination with triethylamine in either THF or CH_2Cl_2 and these reactions are usually performed at low temperatures, from 0 to −78 °C <2003CEJ704, 1996S975, 2000S1101>. *N*-Methylmorpholine (NMM) has also been used in combination with disphosgene in CH_2Cl_2 <2001OL3301, 2001TL6271>. Triphosgene appears to only be used in CH_2Cl_2, with triethylamine being the most common base <1996JOC8750, 1998S991, 2001JOC4200>. In addition, Yamada and co-workers <2002JPS(A)399> have reported using triphosgene without the presence of an obvious base.

Phosphorus-based dehydrating agents have also been developed. The phosphorus reagent can be either in the plus three or plus five oxidation state. With regard to the latter, $POCl_3$ is a very common dehydrating agent of *N*-monosubstituted formamides in the presence of a tertiary amine such as NEt_3 or Pr^i_2NEt. In the synthesis of solid-supported isocyanides, the reactions can either be performed in CH_2Cl_2 <2003TL2367> or under solvent-free conditions using a $POCl_3/Pr^i_2NEt$ reaction mixture <2001TL2269, 2001SL1263>. Homogeneous conditions have been developed using a $POCl_3/NEt_3$/THF system <1996TL8113, 1999TL5633, 2001BCJ1109, 2003OL3759, 2003SL1153> or a $POCl_3/NEt_3/CH_2Cl_2$ system <1994JOC7752, 1995AG(E)914, 1997AG(E)2372, 2002S1017, 2002TL1009, 2002TL4067, 2003S1171>. The use of Pr^i_2NEt in conjunction with $POCl_3$ is not as common; however, this combination has been effective in $CHCl_3$ <1993MI923> and CH_3NO_2 <1998EJO1511>. A $POCl_3$, pyridine, and $CHCl_3$ reagent mixture has also been reported <1996TL3491>.

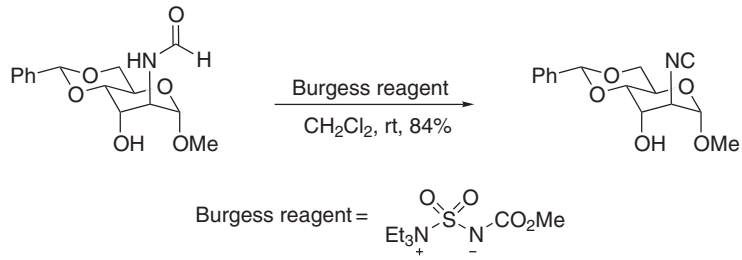
With regard to trivalent phosphorus-based systems, a $PPh_3/NEt_3/CBr_4$-based system was used for the synthesis of glucopyranosyl isocyanides from their corresponding formamides <2000SL1253>. Carbon tetrachloride is the solvent of choice in the PPh_3/NEt_3-mediated dehydration of solid-supported formamides to isocyanide derivatives <1996TL751, 1998TL5469>. A series of boron-substituted methyl isocyanides was also generated using similar methodology (*vide infra*) <1995TL2109>.

Sulfur-based dehydrating systems have also been utilized. A TsCl/pyridine/CH_2Cl_2 combination was used in the synthesis of Kalihinol A and Kalihinol C, naturally occurring bisisocyanides (Equation (3)) <2001OL1825, 2004OL1123>. Polymer-supported sulfonyl chloride in the presence of pyridine was used for the conversion of formamides into their corresponding isocyanide compounds <2002TL7201>. Trifluoromethanesulfonic anhydride (Tf_2O) was used in conjunction with NEt_3 for the synthesis of sulfide-substituted isocyanides <1996BCJ1763>.



(3)

Perhaps the most recent addition to the library of potential formamide dehydrating systems was the use of the Burgess reagent for the conversion of a wide range of formamides into isocyanides, including sugar derivatives possessing unprotected secondary alcohols (Equation (4)) <1998JCS(P1)1015, 2001JIB43>. This reagent was found to be very functional group tolerant and can be used for the synthesis of a wide variety of isocyanide compounds (*vide infra*).

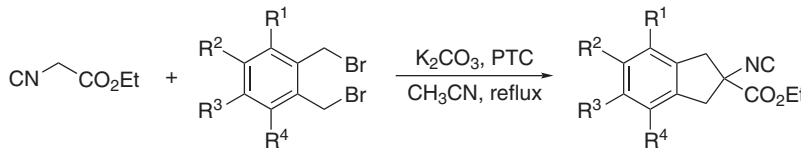


(4)

3.21.1.1.4 Further elaboration of isocyanide

Deprotonation of an α-hydrogen atom on an isocyanide compound is still a common method for further functionalization of isocyanides. Recently, α-lithiated benzyl isocyanide has been treated with alkyl iodides (methyl iodide, benzyl bromide, and cyclohexyl bromide) to yield the respective disubstituted isocyanide compounds <1996AG(E)640>. In addition, α-lithiation of isocyanides allows for the generation of new isocyanide compounds that can be used in Wittig–Horner–Wadsworth–Emmons reactions <1996S511> and in regioselective ring opening of β-epoxy-isocyanides <1997CC2389>. In addition, an α-lithiated isocyanide complex was used in the synthesis of 1,3-diamines from chiral aziridines <1999TL1001>. These reactions will be discussed in greater detail in the appropriate section.

Ethyl and methyl isocyanoacetates can also be highly functionalized, again due to the acidic α-hydrogen atom. As such, weaker bases such as K_2CO_3 have often been used. This methodology has been applied to the synthesis of α-amino acids via the corresponding α-isocyanoesters (Equation (5)) <1997BMCL2719, 1997TL3561, 1997TL9031, 2000JOC1359, 2003TL1347> and toward the synthesis of (±)-Kainic acid <1996JOC7116, 1996SL60>.



(5)

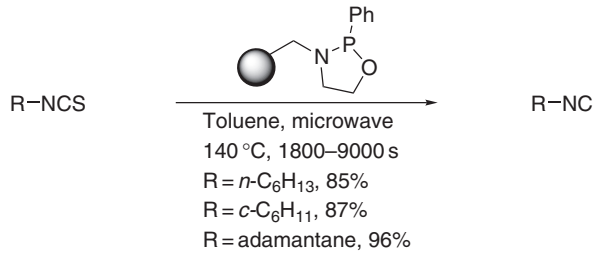
The potassium salt of isocyano acetic acid is another good reagent for the synthesis of new isocyanide compounds as this reagent can undergo esterification with alkyl halides. ω-Olefin isocyanides have been generated in moderate-to-good yields <2003OL1047> and a variety of polymer-bound isocyanides have also been produced <2003SL2410, 2003TL7015>.

3.21.1.1.5 Use of organometallic isocyanides

No further examples of reactions in this area have been reported since COFGT (1995). The use of TMSCN in the synthesis of isocyanides has been discussed in Section 3.21.1.1.1.

3.21.1.1.6 Reduction of isocyanates, isothiocyanates, isoselenocyanates, and isocyanide dihalides

No new methods for the reduction of isocyanates have been reported since COFGT (1995). However, isocyanides have recently been generated by the reduction of isothiocyanates and isoselenocyanates. The reduction of isothiocyanates was mediated using a polymer-supported [1,3,2]-oxazaphospholidine to give isocyanides in good yields (Equation (6)) <2002BMCL1813>. This method is an extension of earlier work in which the unstable 3-methyl-2-phenyl-[1,3,2]oxazaphospholidine was used to reduce both isocyanates and isothiocyanates; however, no mention of isocyanate reduction was made with the polymer-supported system.

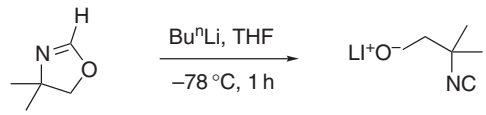


(6)

Reduction of isocyanide dihalides can be performed by direct chemical reactions or electrochemically. PPh_3 is effective at reducing isocyanide difluorides in the synthesis of perfluorinated aliphatic isocyanides <1995IC3114>. Alkyl isocyanides can be generated electrochemically from the corresponding isocyanide dichlorides in a polar medium <1999T9631, 2002TL1405>.

3.21.1.1.7 *Miscellaneous methods*

A few new methods have been developed to generate isocyanide compounds. Treatment of oxazoline with *n*-BuLi results in the *in situ* formation of the alkoxo isocyanide complex (Equation (7)), which can react with electrophiles to form more complicated isocyanides (see subsequent related sections) <1999T7411, 2002OL1167, 2004SL41>.



(7)

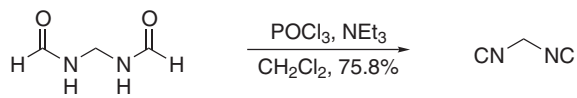
3.21.1.2 Aliphatic Isocyanide Synthesis

3.21.1.2.1 *Saturated isocyanide synthesis*

Dehydration of formamides is a common route into saturated isocyanide compounds. The most notable example of this is the use of the Burgess reagent <1998JCS(P1)1015>. Good yields were obtained for the conversion of cyclohexyl formamide and *n*-octaneformamide into the respective isocyanide compounds (89% and 82%, respectively). This reaction required dry CH_2Cl_2 and either stoichiometric, freshly prepared Burgess reagent or excess (up to 2.0 equiv.) Burgess reagent, presumably due to the moisture sensitivity of this compound.

Solid-state drying agents have also been utilized for the synthesis of saturated isocyanide compounds. Cyclohexyl formamide was dehydrated to the isocyanide compound in 95% yield by polymer-supported sulfonyl chloride in the presence of 50 equiv. of pyridine in CH_2Cl_2 <2002TL7201>. Cyclohexyl isocyanide was also formed in 87% yield from the corresponding isothiocyanate via the polymer-supported [1,3,2]oxazaphospholidine reducing agent with microwave irradiation at 140 °C <2002BMCL1813>. This procedure was also applied toward the synthesis of *n*-octyl isocyanide and adamantyl isocyanide (see Equation (6)).

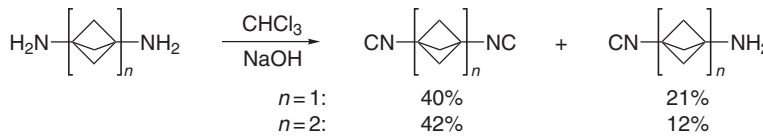
The structurally simple diisocyanomethane was obtained from the low-temperature dehydration of bis(formylamino)methane with a $POCl_3/NEt_3/CH_2Cl_2$ reaction mixture (Equation (8)) <1997AG(E)2372>. Prior to this, the diisocyanomethane was only detected by chemical derivatization, which is partially due to its thermal instability. This compound is only stable at temperatures below −10 °C, above which it decomposes explosively.



(8)

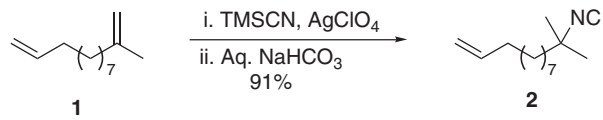
Terminal isocyanides of [*n*]-staffanes ($n = 1, 2$) have been synthesized from their corresponding amino compounds in the presence of NaOH in $CHCl_3$ (Equation (9)) <1993CCC89>. Only mixtures of the diisocyanide and amino-isocyanide were obtained under the reaction conditions

(2 h at room temperature). Attempts at longer reaction times did not increase the yield of the diisocyanide. 1,12-Diisocyanododecane was synthesized using similar methodology <1996ICA(242)115>.



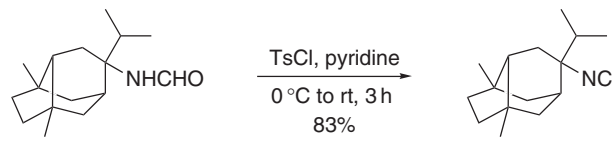
(9)

Kitano and co-workers <1998TL1911, 1999SL288, 2001S437> have utilized a TMSCN/$AgClO_4$ mixture in the synthesis of several tertiary aliphatic isocyanide compounds. This reagent mixture works for both the conversion of tertiary alcohols and halides into isocyanides and the reduction of alkenes to isocyanides. The latter reaction appears to be chemoselective: treatment of diene **1** with TMSCl, $AgClO_4$ in dry CH_2Cl_2 resulted in the formation of isocyanide **2** exclusively (Equation (10)).



(10)

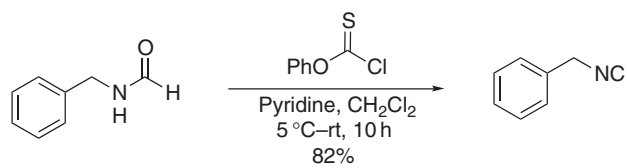
Natural product 9-isocyanoneopupukeanane, a marine natural product found in the sponge *Ciocalypta*, was synthesized by the dehydration of the corresponding formamide with TsCl in pyridine (Equation (11)) <1999JOC8965>.



(11)

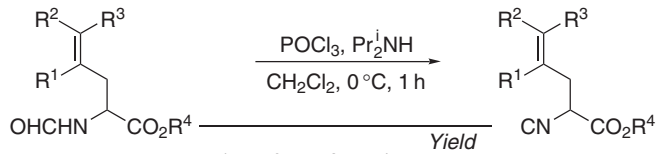
3.21.1.2.2 β and More remotely unsaturated isocyanides

The most common method of generating β and more remotely unsaturated isocyanides is still the dehydration of *N*-formamides. This method has been applied to a variety of different compounds, from isocyano peptides to polymer-supported isocyanides. Two new dehydrating agents have been utilized in the synthesis of these types of compounds. The Burgess reagent is effective in transforming a wide variety of remotely unsaturated aliphatic formamides into the corresponding isocyanide derivatives <1998JCS(P1)1015> beta- and phenyl chlorothionoformate has been found to be effective at transforming simple formamides into isocyanide compounds (Equation (12)) <1999TL747>.



(12)

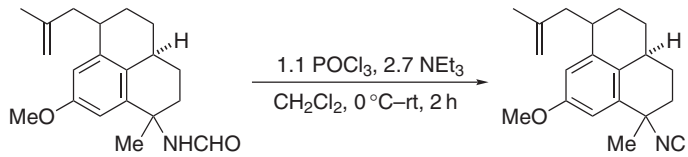
Phenylalanine-derived formamides can be converted into the corresponding isocyanide compounds by dehydration with either a $POCl_3/NEt_3$ system <2003OL3759, 2003SL1153> or a triphosgene-based system <2002JPS(A)399>. γ-Alkenyl and alkynyl isocyanides can also be generated by the dehydration of the precursor formamide (Equation (13)) <1994JOC7752>. In addition, 9-isocyanofluorene can be made via the dehydration of the corresponding formamide <2003OL3759>.



R^1	R^2	R^3	R^4	*Yield* (%)
H	H	H	Bu^t	93
H	H	H	Et	>30
H	Me	Me	Et	84
Me	H	H	Bu^t	96

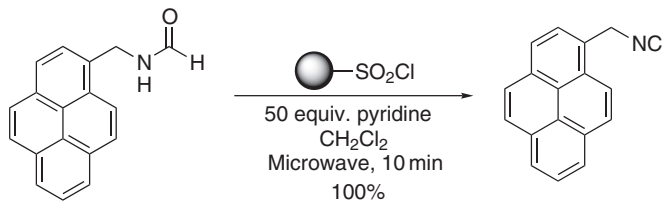
(13)

The synthesis of structural analogs of marine diterpenoids, naturally occurring isocyanides, was achieved by dehydrating the formamide precursors with $POCl_3$ (Equation (14)) <2002TL1009>.



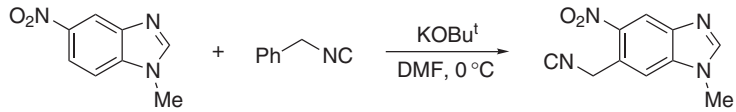
(14)

A solid-supported sulfonyl chloride resin has also been used to generate remotely unsaturated aliphatic isocyanide compounds <2002TL7201>. This reaction was most effective when microwave irradiation was used with a large excess of pyridine present, with 100% conversion of formamides into isocyanide compounds observed for several remotely unsaturated formamides (an example is shown in Equation (15)).



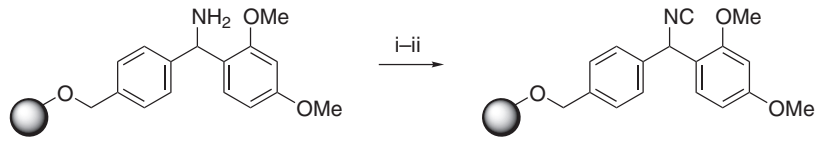
(15)

Deprotonation of phenylthiomethyl isocyanide with $KOBu^t$ and subsequent treatment with nitroarenes results in the formation of *o*- and *p*-substituted nitro arenes. This chemistry was initially discussed in COFGT (1995); however, it has been expanded recently to include heteroaromatic compounds (Equation (16)) <1998JCR(S)14>.



(16)

Isocyanide functional groups can also be directly bound to a polymer support. Two different types of remotely unsaturated polymer-supported isocyanides have been developed recently. The amine-based Rink resin can be readily modified to the corresponding formamide, which is dehydrated with $POCl_3$ in the presence of *i*-Pr_2NEt in CH_2Cl_2 (Equation (17)) <2001TL2269>. Wang-based amino acid resin can also be used to support isocyanides <1996TL751, 2001SL1263>. All of these isocyanide resins can be used in multicomponent reactions.

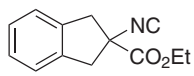
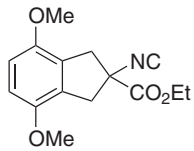
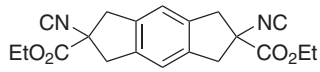
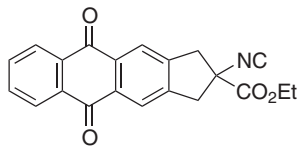
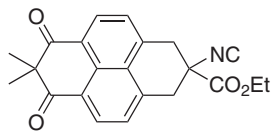
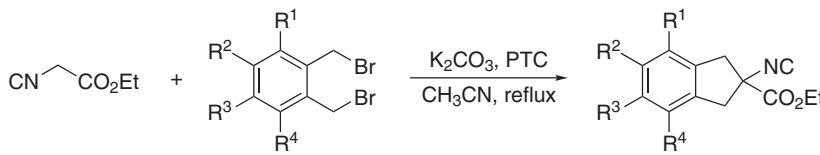


(17)

i. HCO_2H, diisopropylcarbodiimide, pyridine, CH_2Cl_2; ii. $POCl_3$, DIPEA, 0 °C to rt, 6 h

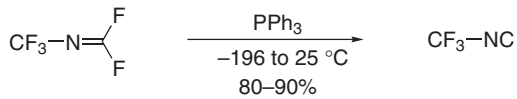
The derivatization of ethyl isocyanoacetates in the synthesis of remotely unsaturated isocyanides is increasing in popularity, presumably due to the increasing number of benzylic, allylic, and propargyl bromides available. Ethyl isocyanoacetate can be alkylated with α,α'-dibromo-*o*-xylene derivatives in the synthesis of cyclic α-amino acid derivatives (Table 1) <1997BMCL2719, 1997TL9031, 2000JOC1359>. Moderate-to-good yields were obtained for all reported modifications, and the resulting isocyanide compound was readily converted into the α-amino acid via acid hydrolysis. Under similar reaction conditions, 1,6-diynes can be synthesized upon treatment of propargyl bromide with ethyl isocyanoacetate <1997TL3561>.

Table 1 Examples of cyclic isocyanide compounds

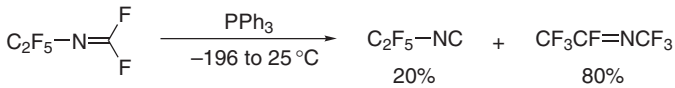
Isocyanide	*Yield* (%)
	93
	57
	42
	42
	40
	

3.21.1.2.3 Halo-substituted isocyanides

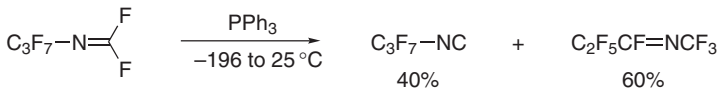
Only a few examples of aliphatic halogenated isocyanides were found in the primary literature. Three different fluorinated isocyanides were generated via the defluorination of difluoromethanimines with PPh_3 (Equations (18)–(20)); however, for the fluorinated ethyl and propyl derivatives, isomerization to fluorinated imines was observed to be a competing reaction <1995IC3114>.



(18)

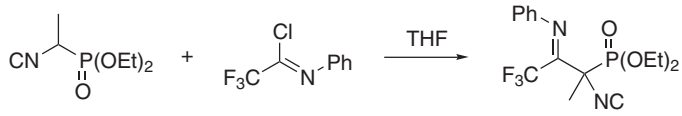


(19)



(20)

The synthesis of another fluorinated isocyanide compound was reported by Yuan and co-workers. α-Lithiation of 1-isocyanoethylphosphonate, followed by the addition of *N*-phenylfluoroacetimidoyl chloride, resulted in the formation of 1-isocyano-2-iminophosphonate (Equation (21)) <1996S511>.

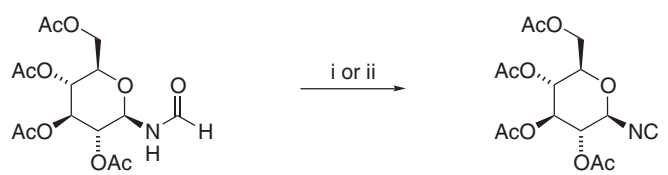


(21)

Finally, dehydration of *N*-(1-phenylsulfanyl-2,2,2-trifluoroethyl)formamide with Tf_2O/NEt_3 in CH_2Cl_2 resulted in the formation of the corresponding isocyanide <1996BCJ1763>. $POCl_3$ was not effective in this transformation as decomposition of the formamide precursor was observed. This method was also used in the synthesis of the pentafluorophenyl derivative.

3.21.1.2.4 Aliphatic isocyanides bearing an oxygen-based functional group

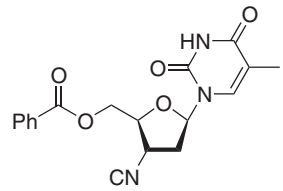
This is perhaps the largest class of aliphatic isocyanides. As such, there have been multiple approaches toward the synthesis of these types of compounds. There are no recent examples of complexes containing an oxygen atom directly bound to the isocyanide nitrogen. However, there have been some important developments on α-oxygenated isocyanides, particularly in the area of sugar chemistry. For instance, a fully protected *N*-formyl-α-D-ribofuranosylamine derivative could be dehydrated with $POCl_3/i\text{-}Pr_2NH$ <1993MI923>. Ichikawa and co-workers have described two methods for the generation of glucosyl isocyanide from the formamide precursors, and they found that the β-glucosyl derivative could be generated without epimerization at the C-1 position (Equation (22)) <2000SL1253, 2001JOC4200>.



(22)

i. PPh_3, CBr_4, NEt_3, CH_2Cl_2, –20 °C, 79%;
ii. Triphosgene, NEt_3, CH_2Cl_2, 90%

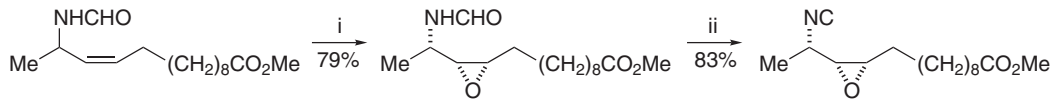
The Burgess reagent has also been used in the synthesis of amino sugar derivatives, such as shown in Equation (4), and isocyano-substituted nucleosides **3** <1998JCS(P1)1015>.



3

There are a large number of β-oxygenated isocyanide derivatives. Kalihinol diterpenoid derivatives, which possess two isocyanide functional groups and one β-hydroxyl group, are generated upon treatment of the precursor bis-formamide with TsCl, pyridine, and CH_2Cl_2 (Equation 3) <2001OL1825, 2004OL1123>. Baldwin has expanded on epoxy-isocyanide chemistry to include acyclic systems. Epoxidation of a *Z*-vinyl formamide with *m*-chloroperbenzoic acid results in the formation of epoxy-formamide, which can be dehydrated into the β-epoxy-isocyanide in relatively good yields (Scheme 2) <1997CC2389>.

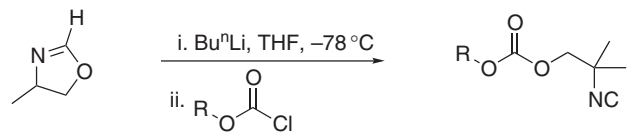
The diisocyanide, 2,2′-(ethylenedioxy)bis(ethyl isocyanide), was synthesized via the Hofmann carbylamine reaction from the parent diamine <2001EJO655>.



i. mcpba, CH_2Cl_2, ii. Tf_2O, Pr^iNEt, CH_2Cl_2, –78 °C

Scheme 2

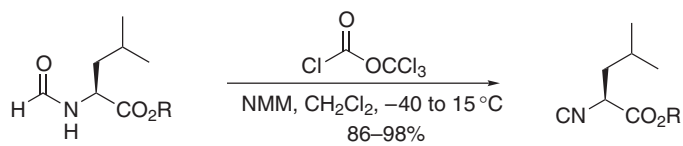
The β-carbonate derivatives are commonly generated from treatment of β-alkoxo-isocyanide complexes with chloroformates (Equation (23)). These "convertible" isocyanides have been investigated as the carbonate functional group allows for modification after the isocyanide undergoes an Ugi four-component reaction. Thus, a range of β-carbonate isocyanide complexes have been generated <1999T7411, 2004SL41>, and this functionality has been added to solid support <2002OL1167>.



(23)

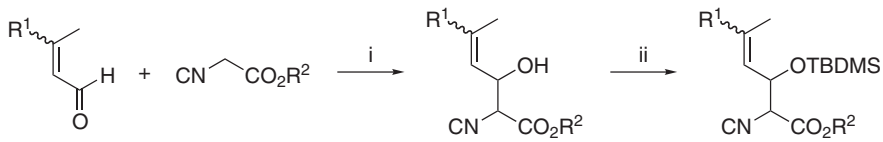
R = Me, Et, allyl, Bn, Ph; upto 80% yield

β-Ester isocyanides are a very common class of isocyanide derivatives. There are two general routes into these compounds—the dehydration of *N*-monosubstituted formamide derivatives and the *C*-alkylation of readily available isocyanoacetates. The former method is used in the synthesis of an isocyanide-modified Wang resin <2001SL1263>. In addition, the former is a general method of transforming amino acids (via the formamide intermediate) into isocyanide acetates <1998S991>. Specifically, leucine isocyanide derivatives were obtained upon treatment of the formamide ester precursors with diphosgene and NMM (Equation (24)) <2001TL6271> and phenylalanine derivatives were obtained upon treatment of the corresponding formamide esters with triphosgene <2002JPS(A)399>.



(24)

Bachi and co-workers have generated lithiated isocyanoacetates and treated the resulting carbanion with aldehydes to give isocyanide-substituted hydroxyl esters (Scheme 3) <1995JOC6242, 1996JOC7116>. These compounds were immediately silylated to prevent elimination of water.

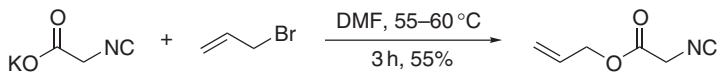


i. Bu^nLi, THF, –74 °C; ii. TBDMSOTf, 1,6-lutidine, CH_2Cl_2

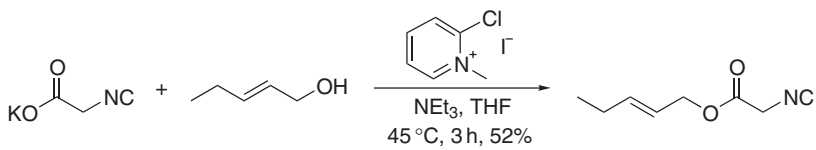
R^1 = Me, R^2 = Et, 69%
R^1 = CH_2SEt, R^2 = Bu^t, 50%
R^1 = CH_2SBu^t, R^2 = Bu^t, 85%

Scheme 3

Potassium salts of isocyanocarboxylic acids are also a versatile tool for the synthesis of a variety of isocyanoacetates as treatment of the carboxylate salt with a variety of alkyl halides, or even primary alcohols in the presence of 2-chloro-1-methylpyridinium iodide, will result in the formation of a library of ester functionalities (see Equations (25) and (26) for specific examples) <2003OL1047>. This methodology has also been utilized in the synthesis of solid-supported isocyanides <2003TL7015, 2003SL2410>.

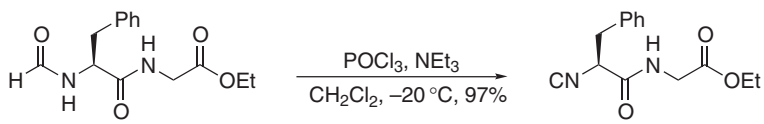


(25)



(26)

Aliphatic isocyanides that are substituted in the β-position with an amide functional group (*N*-alkyl isocyanoacetamides) can also be generated using similar methodology to that outlined above. The Burgess reagent is effective at transforming simple dipeptides into isocyanide derivatives <1998JCS(P1)1015>. The $POCl_3/NEt_3$-mediated synthesis of isocyanopeptides has been extensively studied and the scope of this reaction has been explored (Equation (27)) <2002TL4067, 2003SL1153>. In addition, *N*-alkyl isocyanoacetamides can also be generated from their formamide precursors by using a diphosgene/Et_2NH or triphosgene/NEt_3 combination <2001OL3301, 1996JOC8750>.



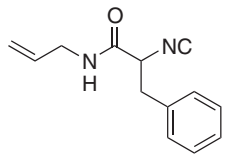
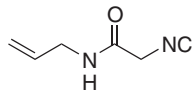
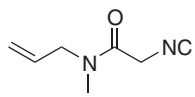
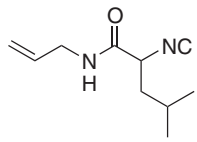
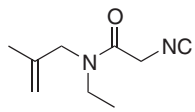
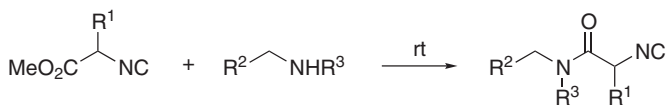
(27)

Dömling and co-workers <2003OL1047> have taken advantage of the reactivity of primary and secondary amines with methyl or ethyl isocyanoacetic acid (Table 2). This approach can be used to make a wide variety of *N*-alkyl isocyanoacetamides.

3.21.1.2.5 Aliphatic isocyanides bearing a sulfur-based functional group

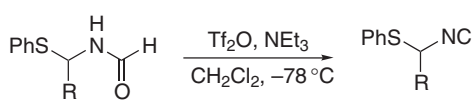
There are a variety of different aliphatic isocyanides bearing a sulfur-based functional group. Ethylthio and *t*-butylthio remotely substituted isocyanides were generated upon treatment of the

Table 2 Examples of *N*-alkyl isocyanoacetamides

Isocyanide	*Yield* (%)
	40
	95
	83
	10
	42
	

corresponding ω-ethylthio-*t*-butylthio-dimethylacrylaldehyde with the lithium enolate of *t*-butyl isocyanoacetate (see Scheme 3) <1996JOC7116>.

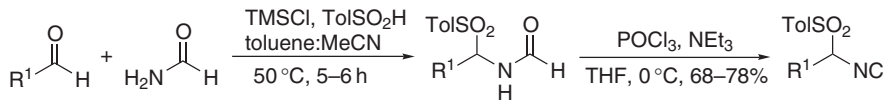
β-Phenylsulfanyl isocyanides are generated upon treatment with Tf_2O/NEt_3 in CH_2Cl_2 (Equation (28)) <1996BCJ1763>. Good yields were obtained for all isocyanides, although the trifluoromethyl derivative readily trimerized under concentrated conditions.



R	*Yield* (%)
CF_3	79
Ph	71
$PhCH_2CH_2$	79
C_6F_5	76

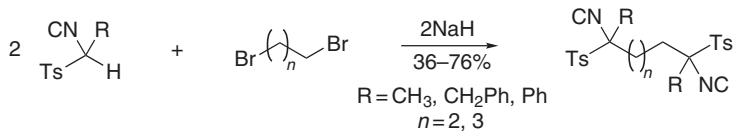
(28)

Sulfone derivatives have been synthesized via a variety of different pathways, most commonly from the dehydration of the formamide precursors. The utility of the tosylmethyl isocyanides (TosMICs) has only recently been realized and this has inspired research into generating TosMIC derivatives. Sisko and co-workers have developed a simple protocol for the synthesis of a range of substituted TosMICs (Scheme 4) <1996TL8113>. A variety of aldehydes can be used, and the resulting isocyanides were obtained in moderate-to-good yields.



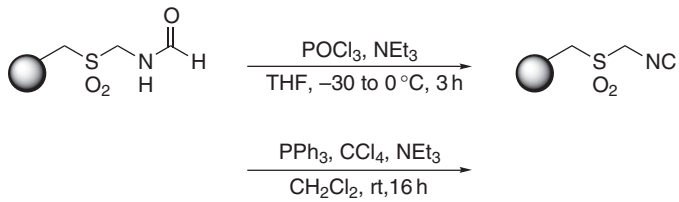
Scheme 4

TosMIC derivatives can also be converted into bisisocyanides. Deprotonation of TosMIC with NaH followed by treatment with a dibromoalkane results in the formation of a symmetrical TosMIC dimer (Equation (29)) <1999PHA412>. Asymmetrical dimers could also be generated using similar methodology.



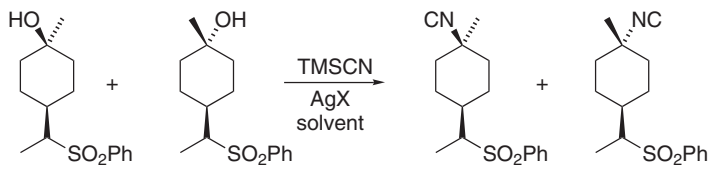
(29)

A solid-supported TosMIC was also generated from the Tentagel-SH resin (Equation (30)) <1999TL5633>. A $PPh_3/CCl_4/NEt_3$ reagent system was found to be more convenient than the $POCl_3$-based system for the dehydration of the formamide precursor.



(30)

Isocyanide sulfones have been used in the synthesis of antifouling compounds <2002JCS(P1)2251>. In this example, a tertiary alcohol was converted into an isocyanide upon treatment with TMSCN in the presence of AgX salts (X = ClO_4, BF_4, Equation (31)). The product ratio **4**:**5** was dependent upon the reaction conditions, with perchlorate salts and the more polar solvent nitromethane giving the largest ratio of **5**. In addition, the perchlorate salts also gave the highest product yields.



(31)

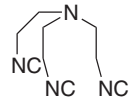
AgX	*Solvent*	*Yield* (%)	*Ratio* (**4**:**5**)
$AgClO_4$	$MeNO_2$	90	8:92
$AgClO_4$	CH_2Cl_2	88	11:89
$AgBF_4$	CH_2Cl_2	48	30:70

3.21.1.2.6 Aliphatic isocyanides bearing an Se- or Te-based functional group

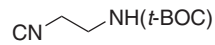
No examples of this functionality could be found in the primary literature.

3.21.1.2.7 Aliphatic isocyanides bearing a nitrogen-based functional group

A variety of different aliphatic isocyanides bearing a nitrogen-based functional group have been discussed in preceding sections (see *N*-alkyl isocyanoacetamides in Section 3.21.1.2.2). Isocyanides bearing an amino functionality have been reported. Aminoisocyanides of *n*-staffanes have been generated via the Hofmann carbylamine reaction (see Equation (9)) <1993CCC89>. This methodology was also used to generate tris-(2-isocyanoethyl)amine **6** <1998L3071>. Xu and co-workers have synthesized *N*-*t*-BOC-aminoethyl isocyanide **7** from ethylenediamine via the *N*-*t*-BOC-aminoformamide. In this, a $POCl_3/NEt_3/CH_2Cl_2$ system was utilized (Equation (32)) <2003S1171>. Some *t*-BOC-deprotected products were observed due to the hydrogen chloride produced, and reaction conditions had to be altered in order to minimize the deprotection.

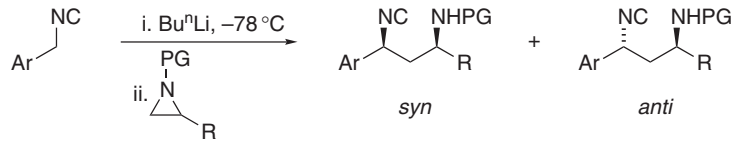


6



7

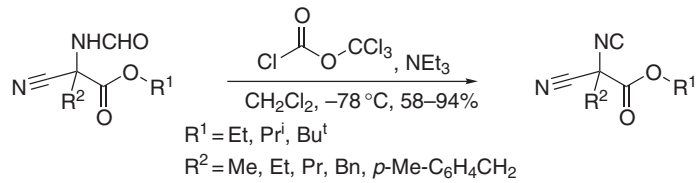
N-Protected 3-isocyanoamines can be generated by the treatment of α-lithiated benzylic isocyanides with *N*-protected (Ts or diphenylphosphinoyl (DPP)) aziridines (Equation (32)) <1999TL1001>. The *syn*:*anti* ratio was dependent upon the R group as well as the protecting group; however, the diastereomers could be easily separated using column chromatography. The DPP-protected aziridine was less reactive than the Ts-protected counterpart and slightly different conditions were used to effect the transformation.



R	*PG*	*syn*:*anti*	*Yield* (%) (*syn* + *anti*)
Bn	Ts	60:40	91
Pr^i	Ts	70:30	77
$CH_2CH(CH_3)_2$	Ts	60:40	65
Bn	DPP	60:40	81
Pr^i	DPP	80:20	60
$CH_2CH(CH_3)_2$	DPP	50:50	80

(32)

Substituted isocyanoacetonitriles have also been generated. The parent molecule was generated from the corresponding formamide upon treatment with $POCl_3$ and NEt_3 in CH_2Cl_2 <1995AG(E)914>. Subsequently, a variety of ester-substituted isocyanoacetonitriles were also synthesized using similar methodology. In these cases, disphosgene was used as the dehydrating agent (Equation (33)) <1996S975>.

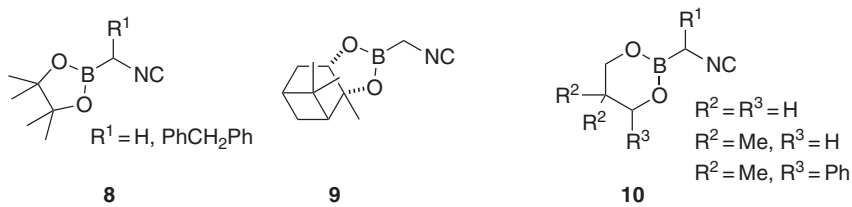


(33)

A similar methodology was used to generate isocyanoacetontriles bearing an α-phosphonate instead of an ester functional group <2000S1101>.

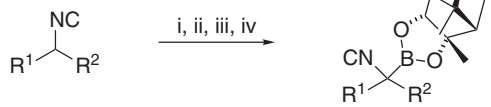
3.21.1.2.8 Aliphatic isocyanides bearing other substituents

Isocyanoboronic ester derivatives have been developed recently. Van Leusen and co-workers synthesized a series of 1-isocyanoboronic ester compounds (of types **8**–**10**) from formamide precursors <1995TL2109>. $POCl_3$ and phosgenes were not effective at dehydrating the formamide precursor and a $PPh_3/CCl_4/NEt_3/CH_2Cl_2$ system was employed. This method does appear limited to boron substituents and most of the isocyanoboronic esters could not obtained in pure form.



8 **9** **10**

Priestley and Decicco <2000OL3095> synthesized a series of α,α-disubstituted 1-isocyanoboronic esters from α-lithiation of aliphatic isocyanides followed by treatment with triisopropylborate (Equation (34)).

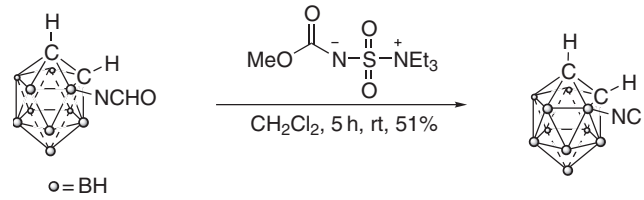


R	R^1	Yield (%)
$-CH_2CH_2-$		33
Me	Me	2
$-CH_2(CH_2)_3CH_2-$		14

(34)

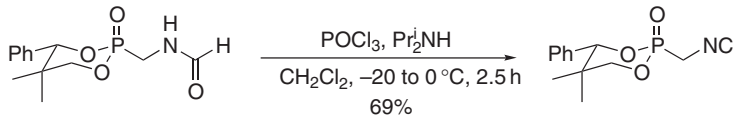
i. Bu^nLi, THF, −78 °C, 30 min; ii. $B(OPr^i)_3$, −78 °C to rt, 14 h; iii. $NaHSO_4$; iv. (+)-pinanediol, ether

Carborane derivatives of isocyanides have also been generated by the dehydration of the corresponding formamide with Burgess reagent (Equation (35)) <2001JIB43>.



(35)

A chiral isocyanomethylphosphonate compound was generated from dehydration of the corresponding formamide precursor using a $POCl_3/Pr^i_2NH$ (or NEt_3) reaction mixture (Equation (36)) <1998EJO1511>. Both the racemic and the enantiomerically pure (2(*S*),4(*S*))-(−)-isomer were generated using this methodology. The *trans*-isomer, in which the methyl isocyanide functional group lies in the axial position, was observed upon either heating the *cis*-isomer to 100 °C or by treating the *cis*-isomer with KF in DMSO.



(36)

3.21.1.3 α,β-Unsaturated Isocyanides

3.21.1.3.1 General methods

The synthesis of α,β-unsaturated isocyanides has received considerably less attention than their saturated counterparts. As such, only six different methods have been reported since COFGT (1995).

The general methods are:

(i) the dehydration of α,β-unsaturated formamides;
(ii) deprotonation and further elaboration of isocyanides and α,β-unsaturated isocyanides;
(iii) β-elimination of functionalized isocyanides;
(iv) reduction of isoselenocyanates;
(v) photochemical methods; and
(vi) pyrolysis of organometallic isocyanides.

In contrast to COFGT (1995), no examples of base-promoted ring opening of heterocycles or isomerization of allyl isocyanides were found in the primary literature.

(i) The dehydration of α,β-unsaturated formamides

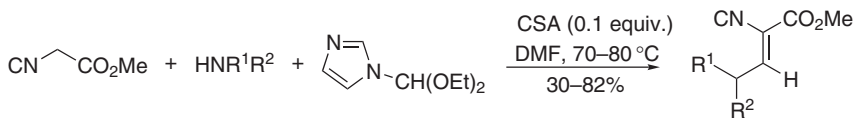
The dehydration of α,β-unsaturated formamides remains the most common method for the synthesis of α,β-unsaturated isocyanides. In contrast to the saturated version, only a handful of dehydrating systems have been employed with $POCl_3$ and trifluoromethanesulfonic anhydride (Tf_2O) as the most popular dehydrating agents.

For instance, a Tf_2O/pyridine combination was used in CH_2Cl_2 in the synthesis of (–)-Isonitrin B <1998JA13285>. Tf_2O was also used with Pr^i_2NEt and dimethyldioxirane for the synthesis of a highly functionalized epoxy α,β-unsaturated isocyanide complex (*vide infra*) <1996CC41> and Smith synthesized a number of vinyl isocyanides using similar methodology <2000JCS(P1)641>.

The synthesis of a series of 3-substituted methyl 3-bromo-2-isocyanoacrylates (BICA) has been acheived from their formamide precursors with a $POCl_3/NEt_3$ dehydrating system <1995S1365, 1995TL257>.

(ii) Deprotonation and further elaboration of isocyanides and α,β-unsaturated isocyanides

A very efficient route to a variety of methyl β-(*N*,*N*,-dialkylamino)-α-isocyanoacrylates was found upon treating methyl isocyanoacetate with a secondary amine, *N*-formylimidazole diethyl acetal, and a catalytic amount of CSA (Equation (37)) <1998TL4255, 2002TL6897>. This route allowed for the synthesis of a range of new isocyanides.



(37)

Numani and co-workers explored the chemistry of BICA. It was found that isopropyl-substituted BICA was substituted upon treatment with benzylhydrosulfide <1995TL257>. Baldwin converted β-epoxy-isocyanides into the corresponding enol upon treatment with a strong base <1997CC2389>. Van Leusen showed that phosphonate-substituted isocyanosteroids can be deprotonated and induced to undergo Wittig–Horner–Wadsworth–Emmons reactions with aldehydes (*vide infra*) <1993JOC3687>. These reactions will be discussed in greater detail in the following sections.

(iii) Reduction of isocyanates, isothiocyanates, isoselenocyanates, and isocyanide dihalides

No examples of the reduction of isocyanates, isothiocyanates, or isocyanide dihalides in the synthesis of isocyanides were found in the primary literature. However, vinyl isoselenocyanates can be reduced by either PPh_3 or $P(OEt_3)$ to the corresponding isocyanides in moderate-to-good yields when heated to 80 °C for 24 h <1995AG(E)1627>. Interestingly, vinyl isothiocyanates were unreactive under similar reaction conditions.

(iv) β-Elimination from functionalized isocyanides

Armstrong has popularized the use of cyclohexenyl isocyanide as a "convertible" isocyanide for use in the Ugi four-component condensation reaction <1995JA7842, 1996JA2574>. This isocyanide, initially reported by Ugi (see COFGT (1995)), is generated from the sequential dehydration/elimination (of HCN) from *N*-(1-cyanocyclohexyl) formamide using $KOBu^t$, triphosgene, DABCO in CH_2Cl_2.

(v) Photochemical methods

Photolysis of imines is a new route into α,β-unsaturated isocyanides. However, the choice of imine is important as they either need to be very sterically constrained <2003TL3781> or possess a leaving group that is stable as a radical species <1996TL9337>.

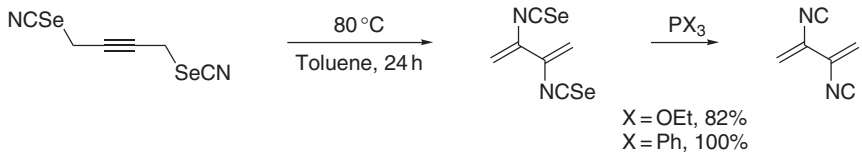
(vi) Pyrolysis of transition metal isocyanides

A series of α,β-unsaturated isocyanides can be generated via pyrolysis of transition metal isocyanide complexes <1998AG(E)2879, 2001CEJ881>. This method has led to the synthesis of a variety of unusual isocyanides including cyanoisocyanoacetylene and ethynyl isocyanide.

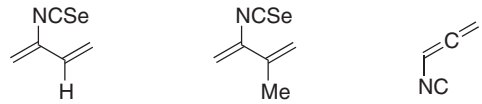
3.21.1.3.2 Isocyanides bearing an α,β-double bond

(i) With no further substituents

A variety of α,β-unsaturated isocyanides can be generated via the deselenizations of selenocyanates, which are generated from prop-2-ynyl selenocyanates (Scheme 5) <1995AG(E)1627>. This method was used to generate both vinyl isocyanides (**11** and **12**) and an allenyl isocyanide **13**.

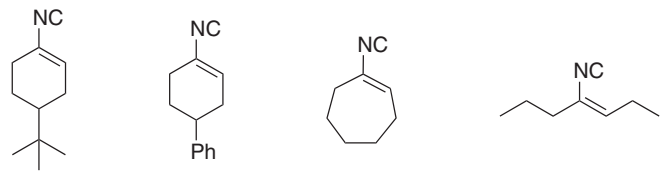


Scheme 5



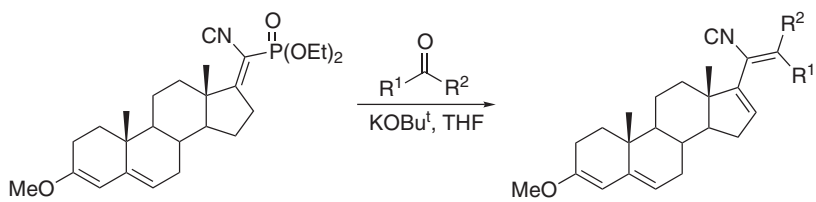
11 **12** **13**

As previously discussed, cyclohexenyl isocyanide is generated from the sequential dehydration/elimination (of HCN) from *N*-(1-cyanocyclohexyl) formamide using $KOBu^t$, triphosgene, DABCO in CH_2Cl_2 <1995JA7842>. In addition, a series of vinyl isocyanides (e.g., **14**–**17**), for use in radical cascade reactions, were generated via dehydration from the corresponding formamide precursors <2000JCS(P1)641>.



14 **15** **16** **17**

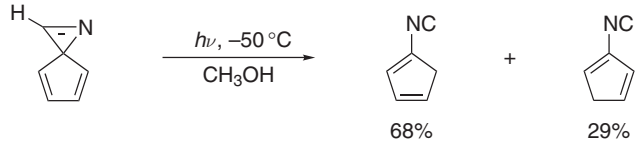
Phosphonate-substituted isocyanosteroids can be converted into α,β-unsaturated isocyanides upon treatment with $KOBu^t$ in the presence of an aldehyde (Equation (38)) <1993JOC3687>. By varying the aldehyde, a series of α,β-unsaturated isocyanides was generated.



(38)

R^1	R^2	Yield (%)	(*E*)/(*Z*)
H	H	96	
H	Me	96	14/86
H	Bu^n	81	7/93
Me	Me	87	
H	$(CH_2)_2CO_2Et$	71	13/87
H	$CH{=}CH{-}Pr^n$	83	9/91

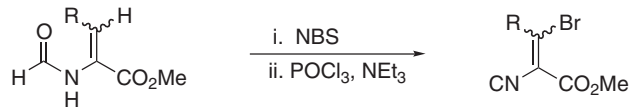
Photolysis was also used in the generation of cyclopentadienyl isocyanides. Photolysis of a spirocyclic aziridine in aprotic solvents at low temperatures (−40 to −60 °C) results in the formation of a mixture of cyclopentadienyl isocyanides (Equation (39)) <2003TL3781>. This reaction can also be performed thermally at 50 °C under dilute conditions.



(39)

(ii) With halo-substituents

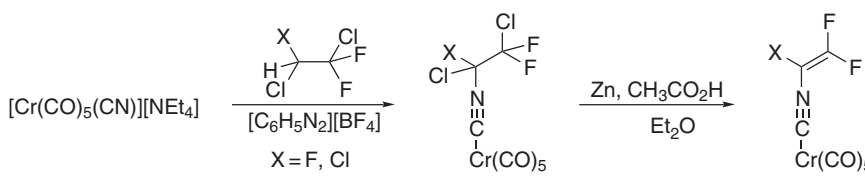
As discussed in COFGT (1995), a variety of BICA as can be generated from the corresponding 3-substituted methyl-2-(formylamino)acrylates (Equation (40)) <1995TL257>. This chemistry was expanded to include a few more substituents.



(40)

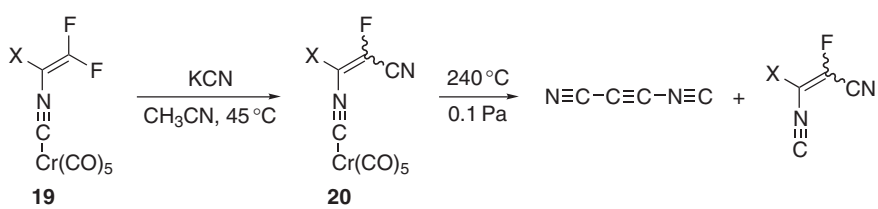
R = $CH_2CH(CH_3)_2$, $CH(CH_2CH_3)_2$, cyclohexyl, Ph, 4-Cl(C_6H_4)

Organometallic complexes can also be used to generate α,β-unsaturated isocyanides with halo-substituents. A pentacarbonyl(cyano)chromate complex can be converted into a halogenated ethyl isocyanide complex upon treatment with halogenated ethanes (Scheme 6 and **18**) <1998AG(E)2879, 2001CEJ881>. Compound **18** is then dehalogenated to form the 2,2-difluoro-substituted ethenyl isocyanide complexes **19**.

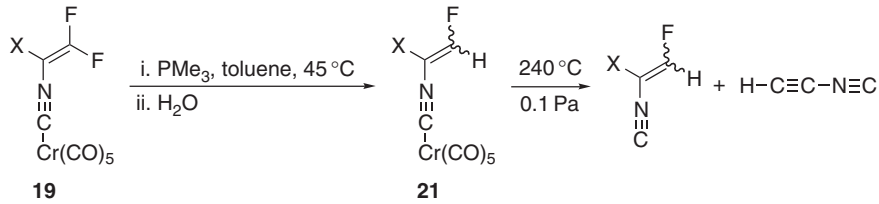


Scheme 6

Compound **19** can be attacked by nucleophiles, such as cyanide or trimethylphosphine, yielding new chromium-isocyanide complexes (compounds **20** and **21**, Schemes 7 and 8 respectively). Upon pyrolysis of these complexes, new conjugated isocyanide complexes are generated.



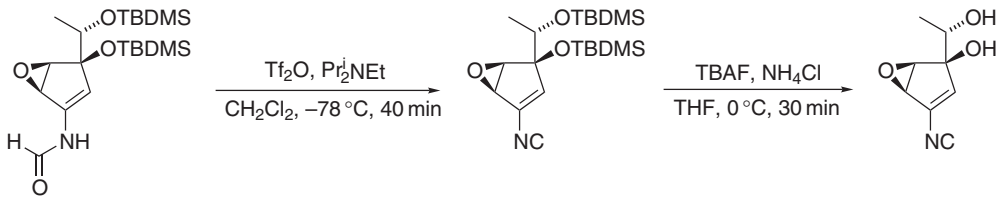
Scheme 7



Scheme 8

(iii) With oxygen-based substituents

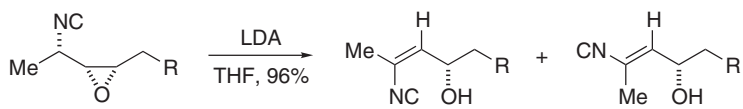
Epoxy-isocyanides are a naturally occurring motif. As such, the synthesis of α-epoxy-isocyanides is desirable, with the most facile route into such compounds via α,β-unsaturated isocyanides. Using this methodology, the synthesis of (–)-isonitrin **B** was successful (Scheme 9) <1998JA13285>. The intermediate formamide was converted into an α,β-unsaturated isocyanide using $Tf_2O/i\text{-}Pr_2NEt$ reaction mixture. The alcohol protecting groups were then removed in good yields to give the desired product.



Scheme 9

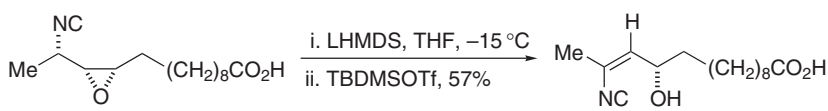
Baldwin and co-workers attempted a one-pot conversion of α,β-unsaturated formamide into an α-epoxy-isocyanide and, in simple systems, the desired products were obtained <1996CC41>. However, in more complex system (±)-trichoviridin, only an α,β-unsaturated isocyanide was found in the reaction mixture.

β-Epoxy-isocyanides can be readily converted into the corresponding α,β-unsaturated isocyanides upon treatment with base in aprotic media (Equation (41)) <1997CC2389>. If protic media is used, then rearrangement to an α,β-unsaturated ketone is observed.



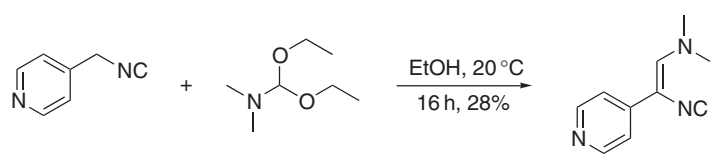
(41)

This methodology was then used in the synthesis of desepoxyaerocyandin. However, the hydroxy-α,β-unsaturated isocyanide decomposed and so the alcohol was protected *in situ* as a *t*-butyldimethyl silyl ether (Equation (42)).



(42)

In a route similar to the CSA-mediated route described above (Equation (37)), Dömling synthesized 2-dimethylamino-1-(4-pyridyl)-1-ethenyl isocyanide from the corresponding benzylic isocyanide and *N*,*N*-dimethyl formamide diethyl acetal (Equation (43)) <2002TL6897>.



(43)

3.21.1.3.3 Isocyanides bearing and α,β-aryl or hetaryl substituent

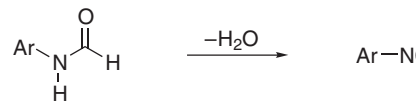
(i) General methods

As with previous literature surveys, the most common method for the generation of aryl isocyanides is the dehydration of formamide precursors as displacement reactions used in the synthesis of aliphatic and α,β-unsaturated isocyanides are not possible due to the aromatic ring. In contrast with COFGT (1995), methods that included the deprotonation of arylimidates and aryl heterocycles, abnormal Beckmann rearrangements, or ring-cleavage reactions of heterocyclic compounds were not found in the primary literature. The general methods for the synthesis of aryl isocyanides are listed below:

(i) dehydration of formamides;
(ii) the Hofmann carbylamine reaction;
(iii) reduction of isocyanates, isothiocyanates, isoselenocyanates, and isocyanide dihalides; and
(iv) photochemical methods.

These methods are discussed in more detail below:

(a) The dehydration of aryl formamides. The dehydration of aryl formamides is the most common method for the generation of aryl isocyanides (Equation (44)). A similar range of reagents that were used for aliphatic isocyanides are used in the synthesis of their aryl counterparts.



(44)

Phosgene derivatives are commonly used, although phosgene itself has only been used a couple of times, either in combination with NEt_3/CH_2Cl_2 <2000S429> or in combination with $NEt_3/CHCl_3$ <1996H(43)471>.

Diphosgene has been used in the presence of a variety of different tertiary amines. The most frequently used base is NEt_3 in CH_2Cl_2 <1996JOM(526)149, 2002JOM(662)70, 2003CEJ704>; however, DABCO and pyridine have also been utilized <1996CL185, 1999JOC336>.

Triphosgene is another efficient dehydrating agent. In contrast to diphosgene and phosgene, triphosgene has only been used in combination with NEt_3 and CH_2Cl_2 <1996TL7099, 1999JOM(577)223, 2003T2497>.

The most utilized dehydrating agent is $POCl_3$. This has been used in the presence of NEt_3 in THF <1998CL551, 1998JA11880, 2001BCJ1109, 2001H(55)973, 2002JA11940, 2003TL4733> or in the presence of *i*-Pr_2NH in CH_2Cl_2 <1999TL6325, 2002JA13668, 2003OL3277>.

Two other dehydrating systems have also been used. PhOC(S)Cl was shown to effectively dehydrate simple formamides to isocyanides in the presence of pyridine and CH_2Cl_2 <1999TL747>. A $PPh_3/CCl_4/NEt_3/CH_2Cl_2$ system was used in the synthesis of a solid-supported isocyanide <1998TL7227>.

(b) The Hofmann carbylamine reaction. The Hofmann carbylamine reaction is still used in the synthesis of aryl isocyanides. In these reactions, a $KOH/CHCl_3$ reaction mixture is employed in refluxing CH_2Cl_2 with benzyltriethylammonium chloride as the PTC <1996ICA(242)115, 2001SL1403>.

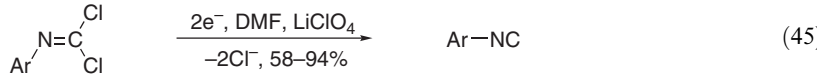
(c) Reduction of isocyanates, isothiocyanates, isoselenocyanates, and isocyanide dihalides. Aromatic isothiocyanates can be converted into isocyanides using a polymer-supported [1,3,2]-oxazaphospholidine. As with the corresponding alkyl systems, this reaction was found to be most effective in the microwave at 140 °C for 1800 s <2002BMCL1813>. Aryl isocyanides can also be generated electrochemically from the corresponding isocyanide dichlorides in a polar media <1999T9631>.

(d) Photochemical methods. Imines can be used as a source of isocyanides under certain conditions. As such, Ito reported the synthesis of aryl isocyanides from the photolysis of bis(organosilyl)imines in the presence of CCl_4 in C_6D_6 <2000JOC624>.

(ii) Aryl isocyanides

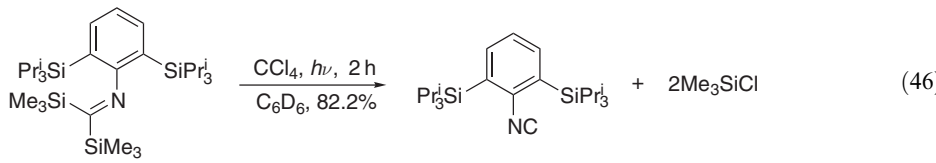
Aryl isocyanides bearing nonreactive substituents can be generated using a number of different methods. In addition to the dehydration of aryl formamides <1999TL747>, the reduction of isothiocyanates was achieved using a polymer-supported [1,3,2]-oxazaphospholidine (see Equation (6)) <2002BMCL1813>. However, the scope of this reaction was not explored as only aliphatic- and chloro-substituted aryl isothiocyanates were reduced.

Simple aryl isocyanide dichlorides were reduced to aryl isocyanides electrochemically (Equation (45)) <1999T9631>. A variety of chloro-substituted aryl isocyanides, in addition to *p*-fluoro, -bromo, -cyano, and ethyl-ester-substituted aryl isocyanides, were generated. The reduction of nitro-substituted aryl isocyanides dichlorides was unsuccessful, potentially due to an initial electron transfer into the nitro functional group.



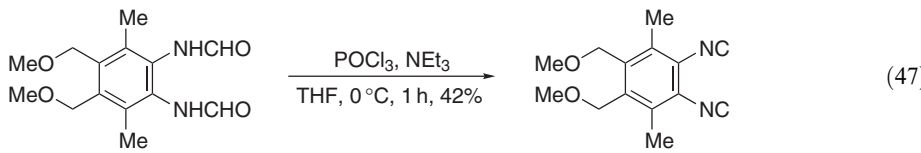
(45)

One novel synthesis of simple isocyanide compounds is the photolysis of bis(organosilyl)imines in the presence of CCl_4 (see Equation (46) for a specific example) <2000JOC624>. After 2 h, a complete conversion of the imine was observed, with only minor by-products found within the reaction mixture. This reaction was presumed to occur via radical intermediates.



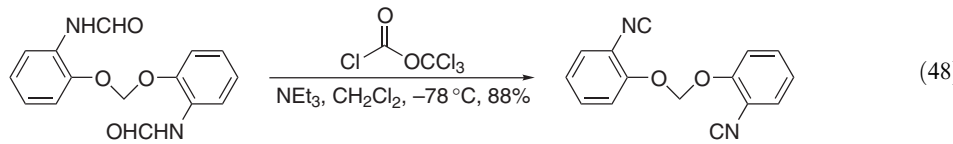
(46)

1,2-Diisocyanobenzene derivatives were generated via dehydration of the corresponding formamide precursor (Equation (47)) <1998JA11880>. In addition to the 4,5-bis(methoxymethyl)-3,6-dimethyl-substituted 1,2-diisocyanobenzene, the 4- and 5- positions were also substituted with (phenylmethoxy)methyl or (2-methyoxyethoxy)methyl functional groups.



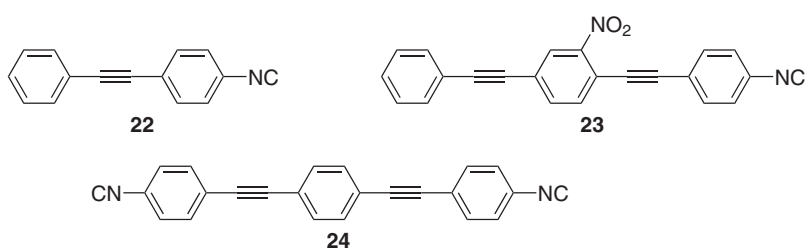
(47)

Hahn and co-workers synthesized a diisocyanide compound that possesses two isocyano-substituted aromatic rings linked by a methylenedioxy functional group (Equation (48)) <1996JOM(526)149>. Again, dehydration of the formamide precursor was the method of choice.



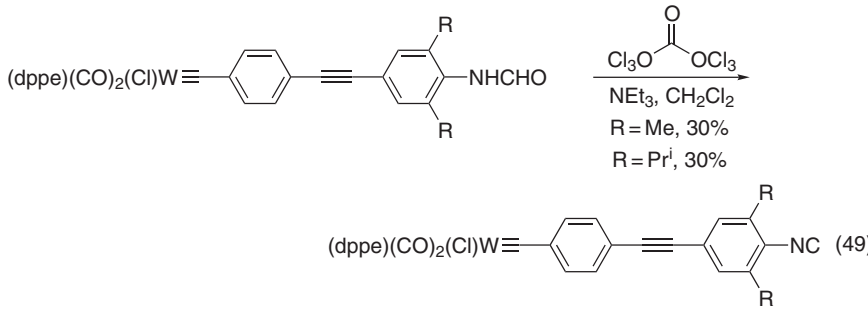
(48)

The 4,4′-biphenyldiisocyanide compound was synthesized by Kubiak and co-workers using the Hofmann carbylamine reaction <1996ICA(242)115>. This same paper also reported the synthesis of 4,4′-*p*-terphenyldiisocyanide and 1,4-di(4-isocyanophenylethynyl)-2-ethylbenzene. Other *p*-acetylide-substituted aryl isocyanides have also been generated via dehydration of formamide precursors. For instance, Tour and co-workers <2003T2497> synthesized a series of isocyano oligo(phenylene ethynylene)(s) such as **22**–**24** <2003T2497>.



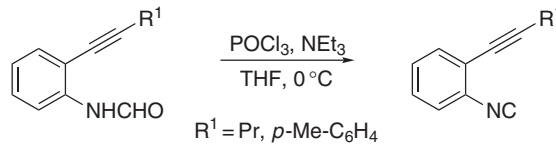
22 **23** **24**

Two unsaturated alkylidyne ligands bearing a terminal isocyanide have also been generated directly on a tungsten metal center (Equation (49)) <1999JOM(577)223>.

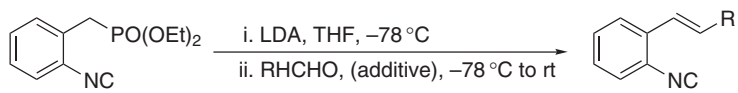


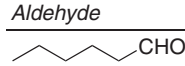
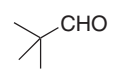
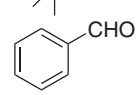
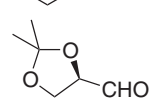
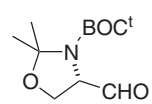
Kobayashi and co-workers synthesized a series of substituted 1-isocyano-2-(2-lithio-2-methoxyethenyl)benzenes from formamide precursors upon treatment with $POCl_3$ and NEt_3 <2003TL4733>.

2-Alkenyl- and alkynyl aryl isocyanides are useful precursors in the synthesis of functionalized indoles. As such, several groups have developed routes to these isocyanides. The most common method is the dehydration of the corresponding formamide precursor. 2-Isocyanocinnamates were generated using either a triphosgene/NEt_3/CH_2Cl_2 reaction mixture <1996TL7099> or a phosgene/NEt_3/CH_2Cl_2 reaction mixture <2000S429>. A number of 2-alkynyl-substituted aryl isocyanides were also generated from their formamide precursors using $POCl_3$ as the dehydrating agent (Equation (50)) <2002JA11940, 2003OL3277, 1999TL6325>.



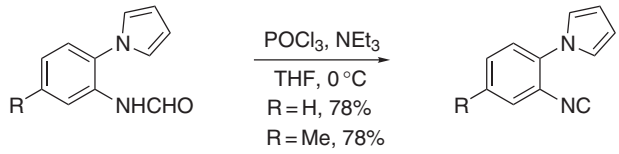
The other route into 2-alkenyl aryl isocyanides has been developed by Fukuyama and co-workers <2001SL1403>. Diethyl (*o*-isocyanophenylmethyl)phosphonate was synthesized from the arylamine precursor using the Hofmann carbylamine reaction. The phosphonate could then undergo a Wittig–Horner–Wadsworth–Emmons reaction with a variety of aldehydes to generate a range of 2-alkenyl aryl isocyanides (Equation (51)).



Aldehyde	*Additive*	*Yield* (%)
		87
		93
		90
	HMPA (5 equiv.)	80
	HMPA (5 equiv.)	78

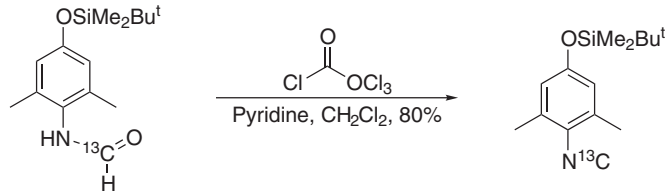
(51)

Nitrogen-substituted aryl isocyanides have been generated via the dehydration of formamide precursors. For instance, treatment of *N*-formyl-2-azidoaniline with diphosgene in the presence of NEt_3 in CH_2Cl_2 results in the formation of 2-azidophenyl isocyanide. 1-(2-Isocyanophenyl)pyrroles have been synthesized by treating the corresponding formamide precursors with a $POCl_3$/NEt_3 reaction mixture in THF at 0 °C (Equation (52)) <1998CL551, 2001BCJ1109, 2001H(55)973>.



(52)

A diphosgene/pyridine mixture was used in the synthesis of a ^{13}C-labeled isocyanide for use in the total synthesis of [2-^{13}C]D-*ribo*-C_{18}-phytosphingosine (Equation (53)) <1996CL185>.



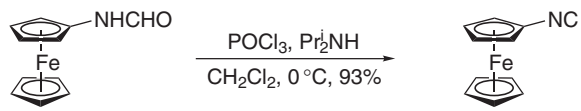
(53)

Other silylated aryl isocyanides have also been synthesized from their formamide precursors including 2-(trimethylsiloxymethyl)phenyl isocyanide and 2-(tri-*t*-butylsiloxymethyl)phenyl isocyanide <2002JOM(662)70, 1999JOC336>.

A thio-substituted aryl isocyanide, 2-isocyanothioanisole, was generated by treating 2-formylaminothioanisole with a phosgene/NEt_3/$CHCl_3$ reaction mixture at −10 °C to 0 °C <1996H(43)471>.

Polymer-supported aryl isocyanides have also been developed. Hulme and co-workers used the Wang resin as a basis for a supported aryl isocyanide, using PPh_3, NEt_3, and carbon tetrachloride in CH_2Cl_2 to dehydrate the formamide precursor <1998TL7227>.

Isocyanoferrocene was generated from ferrocenyl formamide using exactly 1 equiv. of $POCl_3$ in the presence of Pr^i_2NH in CH_2Cl_2 (Equation (54)) <2002JA13668>. This compound had previously been generated via irreproducible methods.



(54)

3.21.2 ISOCYANIDE ANALOGS WITH A HETEROATOM OTHER THAN NITROGEN

As with COFGT (1995), there are still no examples of isocyanide analogs RX═C, where X = phosphorus, arsenic, antimony, or bismuth. The phosphorus analog has been implicated as an intermediate that can be generated at low temperatures. Weber <2003EJI1843> has written an extensive review on the subject which discusses several studies that have attempted to trap out isophosphocyanides and theoretical calculations on isophosphocyanides.

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Biographical sketch

J. Robin Fulton: Born in Wichita, Kansas and moved to Seattle, Washington at age 11. She obtained a B.S. in chemistry and a B.S. in biochemistry from the University of Washington in 1995 and her PhD, under the direction of Professor R. G. Bergman, in 2000 from the University of California, Berkeley. After spending a period at the University of Colorado studying environmental chemistry, she moved to the University of Bristol to work in the laboratories of Professor V. K. Aggarwal in 2002. She then moved in September 2003 to King's College London as a temporary lecturer and will take up a permanent position at the University of Sussex in September 2004, where she will spend her first two years as a Leverhulme Early Career Fellow.

Comprehensive Organic Functional Group Transformations 2
ISBN (set): 0-08-044256-0

Volume 3, (ISBN 0-08-044254-4); pp 705–730